

# The role of IgG hypersensitivity in the pathogenesis and therapy of depressive disorders

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Depressive episodes are associated not only with changes in neurotransmission in the central nervous system, but also may lead to structural changes in the brain through neuroendocrine, inflammatory, and immunological mechanisms. The aim of this article is to present a new hypothesis connecting the inflammatory theory of depression with IgG food hypersensitivity and leaky gut syndrome. This new potential pathway that may mediate the pathogenesis of depression implies the existence of subsequent developmental stages. Overproduction of zonulin triggered, for example, by gliadin through activation of the epidermal growth factor receptor and protease-activated receptor causes loosening of the tight junction barrier and an increase in permeability of the gut wall ('leaky gut'). This results in a process allowing larger molecules that would normally stay in the gut to cross into the bloodstream and in the induction of IgG-dependent food sensitivity. This condition causes an increased immune response and consequently induces the release of proinflammatory cytokines, which in turn may lead to the development of depressive symptoms. It seems advisable to assess the intestinal permeability using as a marker, for example, zonulin and specific IgG concentrations against selected nutritional components in patients with depression. In the case of increased IgG concentrations, the implementation of an elimination-rotation diet may prove to be an effective method of reducing inflammation. This new paradigm in the pathogenesis of depressive disorders linking leaky gut, IgG-dependent food sensitivity, inflammation, and depression is promising, but still needs further studies to confirm this theory.

**Keywords:** Depression, Leaky gut, IgG hypersensitivity, Zonulin, Inflammatory theory of depression, Gluten sensitivity

## Introduction

Depression is a heterogeneous psychiatric disorder with multifactorial aetiology and therefore needs improved integration models, based on behavioural studies, sociology, and neuroscience to better reflect both the complexity and variety of mood disorders.<sup>1</sup> Among the factors deserving special attention are biological ones, including psychoneuroendocrinology and psychoimmunology, posing a bridge between strictly biological and psychological approaches.<sup>2</sup> More and more evidence indicates that depressive episodes are associated not only with changes in neurotransmission in the central nervous system (CNS), but also may lead to structural changes in the brain through

neuroendocrine, inflammatory, and immunological mechanisms.<sup>3-5</sup> Different factors potentially connected with systemic inflammation in depression are taken into consideration; these include psychosocial stressors, poor diet, physical inactivity, obesity, smoking, altered gut permeability, atopy, dental caries, sleep, and Vitamin D deficiency.<sup>6</sup>

The aim of this article is to present a new hypothesis connecting the inflammatory theory of depression with IgG food hypersensitivity and leaky gut syndrome (LGS).

## Inflammatory theory of depression

Among many theories of depression, the cytokine (macrophage) theory of depression, first demonstrated in 1991 by Robert Smith,<sup>7</sup> has aroused much interest among researchers. It is assumed that changes in behaviour, typical of depression, are the result of the

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interaction of proinflammatory cytokines produced in the peripheral and/or CNS with the neuroendocrine system. This leads to activation of the hypothalamic-pituitary-adrenal (HPA) axis and elimination of tryptophan, a serotonin precursor (as a result of activation of indole 2,3-dioxygenase, an enzyme that converts tryptophan into kynurenine).<sup>8</sup>

Cytokines are a large group of more than 100 regulatory proteins, proinflammatory and anti-inflammatory mediators, which can be considered immune regulating hormones that regulate growth, proliferation, and cell activity.<sup>9</sup> A wide range of biological activities of cytokines known so far includes pyrogenic activity, hyperalgesic activity, the effect on energy balance in the body by changing the appetite level and metabolism, modulation of the autonomic nervous system activity, the effect on the functioning and structure of the cardiovascular system, mood lowering effects, increased drowsiness, and the regulation of hormones, and other cytokines.<sup>10</sup> Cytokines are also signalling molecules involved in a diverse set of physiological roles with extensive cross-talk.<sup>11,12</sup>

The increase in the proinflammatory cytokine concentration and their effects on the CNS contribute to the development of neuropsychological and somatic depressive symptoms.<sup>13</sup>

Many studies conducted so far have shown elevated levels of proinflammatory cytokines in the serum of patients with a major depressive episode. In these studies, multiple cytokines such as tumour necrosis factor (TNF- $\alpha$ ), interferon- $\gamma$ , interleukin IL-1 $\beta$ , IL-2, IL-4, IL-6, IL-8, and IL-10 were taken into account. Two recent meta-analyses confirmed the importance of higher interleukin-1, -6, and TNF- $\alpha$  levels in the serum of patients with depression.<sup>14,15</sup> Elevated levels of these cytokines in the cerebrospinal fluid of depressive patients were also shown in numerous studies.<sup>16,17</sup> The importance of elevated C-reactive protein is highlighted<sup>18,19</sup> in the absence of clearly consistent findings with regard to other cytokines.<sup>15</sup> An interesting phenomenon, confirming the link between the inflammatory process and depression symptoms, is the co-occurrence of depression with inflammatory diseases such as asthma, chronic obstructive pulmonary disease, diabetes, allergy, and rheumatoid arthritis.<sup>20</sup>

Immunostimulatory treatment using interferon-alpha (IFN-alpha) in hepatitis C or cancer (melanoma, leukaemia) shows that this treatment is associated with much higher rates of depression as compared to those of the general population.<sup>21</sup> Among patients receiving IFN-alpha, the percentage of depressed individuals is nearly 45%.<sup>22</sup> Further evidence on the important role of proinflammatory cytokines in the pathogenesis of depression is provided by a study demonstrating that the concentration of inflammatory cytokines correlates positively with the

severity of depressive symptoms,<sup>23</sup> while antidepressive treatment and clinical improvement leads to reduction of proinflammatory cytokine concentration in patients with depression.<sup>10</sup> A meta-analysis of 22 studies evaluating the relationship between the efficacy of antidepressant medication in the treatment of depression and levels of inflammatory markers showed that the use of antidepressive drugs (especially serotonin-specific reuptake inhibitors) was associated with decreased levels of IL-1 $\beta$  and IL-6.<sup>24</sup>

It has been established that Proinflammatory cytokines may contribute to the development and progression of depression through the following pathways:

1. Pathological activation of the immune response, including the acute-phase reaction as well as changes occurring early in response to tissue damage: this reaction is manifested, among other things, with a sharp increase in the production of many proteins, including acute phase proteins: the C-reactive protein, alpha-1 acid glycoprotein, and  $\alpha$ -chymotrypsin, together with changes in their structure.<sup>25,26</sup>
2. Changes in neurotransmitter systems: inflammatory cytokines can cross the blood-brain barrier, using both the space with increased permeability and the active transport principle. The migration of cytokines to the CNS can trigger various psychopathological changes,<sup>27</sup> i.e., due to the influence of changes in the synthesis, reuptake, and metabolism of neurotransmitters involved in the regulation of mood such as dopamine, serotonin, or glutamate.<sup>28-30</sup> It turns out that cytokines can cause a decrease in the availability of serotonin, with an increase in concentrations of neurotoxic tryptophan metabolites via 2,3-dioxygenase indoleamine activation. Substances produced during the catabolism of tryptophan (called TRYCATs) may adversely affect the behaviour processes. For example, kynurenine elicits anxiety and depressive behaviour.<sup>31,32</sup> Toxic metabolites of tryptophan are also produced under the influence of tryptophan 2,3-dioxygenase, activated by cortisol,<sup>33</sup> whose concentration is often increased in depression.<sup>34</sup> Dopamine is also a neurotransmitter whose concentration and availability is reduced under the influence of cytokines in selective areas of the brain.<sup>35</sup> Another process, also disrupted in depression, is associated with the capacity of cytokines to increase glutamate release, which consequently leads to an increase in glutamate transmission, and finally results in enhanced generation of free radicals. An important consequence of the increased glutamatergic transduction is also reduced production of the nerve growth factor (brain derived neurotrophic factor (BDNF)). Increased glutamate neurotransmission and BDNF reduced levels lead to changes in neuronal plasticity.<sup>36</sup>
3. The effect on the HPA axis and release of corticotropin-releasing hormone (CRH) and adrenocorticotrophic hormone (ACTH): proinflammatory cytokines

intensify noradrenergic neurotransmission and activate the HPA axis.<sup>37</sup> HPA hyperactivity has been proposed as the neurobiological basis of major depression.<sup>38</sup> It is well documented that patients with major depressive disorder have elevated plasma cortisol levels as well as decreased sensitivity to external dexamethasone and CRH.<sup>39</sup>

4. The processes described above, expressed in immunological and glandular malfunctions and neurotransmitters dysregulation, can lead to brain cell loss and reduction in neurogenesis. According to the latest views on the pathogenesis of depression, stress factors can cause atrophy of hippocampal cells (as a result of hypercortisolism caused by HPA axis hyperactivity) and impairment of neurogenesis in predisposed subjects.<sup>40</sup>

Although there is a growing body of evidence supporting the importance of inflammation and immune activation in at least part of the population of depressive patients,<sup>3,15,18,41</sup> the role of inflammation and inflammatory processes similar to those described in cases of schizophrenia<sup>42</sup> requires further investigation in depression as do potential issues governing the integrity of the intestinal barrier via sulphonation,<sup>43</sup> tight-junction (TJ) modulators,<sup>44</sup> the contributing role of pathogenic agents,<sup>42</sup> and IgG food hypersensitivity.<sup>45</sup>

### Leaky gut and IgG hypersensitivity

There is an increasing number of reports on the role of the gastrointestinal tract in the pathogenesis of depression.<sup>46</sup> One of the factors leading to a systemic inflammatory response is increased intestinal permeability, also called leaky gut syndrome (LGS). LGS is a dysfunction of the intestinal barrier, resulting from damaged connections between enterocytes.<sup>47</sup> These connections – intercellular tight junctions (TJs) – are protein complexes, with junctions between enterocytes that are the structural basis for the epithelium barrier.<sup>48</sup> They play two fundamental roles, serving as: (1) a gate that regulates the passage of ions, water, and other molecules through the paracellular route; and (2) a fence that blocks the lateral diffusion within the plane of the membrane of lipids and proteins, thereby maintaining the polarized distribution of lipids and proteins between the apical and basolateral plasma membrane domains.<sup>49</sup> TJs also control the balance between the body's immune tolerance and response to antigens. Proteins that make up TJs – zonulin, occludin, and claudins, modulate the permeability of the described connections.<sup>50,51</sup> We already know much about the structure of TJs, but relatively little is known about their physiological and pathophysiological modulation.

Zonulin is a precursor of acute phase protein-haptoglobin 2. This protein controls paracellular

permeability through the epidermal growth factor receptor<sup>52</sup> and protease-activated receptor (PAR)-2.<sup>44,53</sup> The main role of zonulin is to regulate the flow of molecules from the intestinal lumen by loosening TJs.<sup>44,54</sup>

It has been shown that overproduction of zonulin can be triggered by exposure to bacteria,<sup>53,55,56</sup> drugs,<sup>53</sup> stress,<sup>57</sup> or foods.<sup>53</sup> For example, the dietary protein gliadin, which is a class of proteins present in wheat and several other cereals within the grass genus *Triticum*, binds to the CXCR3 receptor, leading to MyD88-dependent zonulin release and increased intestinal permeability.<sup>53,56,58</sup> This, in turn, may result in higher serum concentrations of the proinflammatory cytokines, free radicals, and others.<sup>59</sup> The bowel dysfunction could, through a TJ opening, induce immune activation which could contribute to mitochondrial dysfunction and finally result in oxidative stress.

It remains unclear whether gliadin-induced zonulin activation is a specific reaction, that is whether gliadin-dependent activation of the zonulin system requires interaction of gliadin with a specific enterocyte receptor(s), or is a consequence of an unspecific response.<sup>60</sup> A possible gliadin mechanism of action may lead to a zonulin-mediated increase in actin polymerisation and intestinal permeability. Enterocytes exposed to gliadin physiologically react by secreting zonulin into the intestinal lumen. While in normal intestinal tissues this secretion is self-limited in time, the zonulin system in gut tissues of subjects with coeliac disease (CD) is chronically upregulated, leading to a sustained increase in intestinal permeability to macromolecules, including gliadin, from the lumen to the lamina propria, and ultimately to intestinal permeability, immune, and autoimmune disorders.<sup>60</sup> Increasing evidence points to possible connections between autoimmune diseases, such as coeliac disease or type 1 diabetes, and an earlier increase in intestinal permeability, where, apart from a genetic predisposition and environmental factors, impairment of the intestinal barrier function must occur.<sup>61,62</sup> The hypothesis about the dysregulation of the zonulin release system, which triggers the disease mechanism, immunological impairment of the gut wall with increased intestinal permeability combined with exposure to non-specific antigens, e.g. dietary or bacterial factors may result in chronic inflammation or autoimmune disease in genetically predisposed subjects.<sup>53,61–63</sup>

Zonulin impact on intestinal permeability depends on time of administration and dosage. These results were confirmed independently *in vivo* in intestinal permeability assay, wherein zonulin induced a significant, reversible increase in the gastric mucosal permeability of the duodenum and small intestine.<sup>44</sup> Zonulin can

be used as a biomarker of impaired gut barrier function for several autoimmune, neurodegenerative, and tumour diseases and can be a potential therapeutic target for the treatment of these devastating conditions.<sup>44</sup>

However, it should be stressed that other factors, for instance commensal bacteria<sup>64</sup> or glycated and lipoxidated proteins and peptides,<sup>65</sup> may also disturb the gut immune homeostasis, leading to LGS, chronic immunological overactivation, and low-grade inflammation. Advanced glycation end products constitute a group of heterogeneous compounds, whose high concentrations in the body may be linked to activation of a specific receptor called RAGE and substantially exaggerate and prolong an inflammatory condition.<sup>65</sup> Production of similar compounds is facilitated by foods undergoing high-temperature processing and may adversely affect bowel receptors or exert an impact on systemic inflammation.<sup>65,66</sup>

The other proteins that play an important role in regulating the intestinal barrier by modulating the permeability of tight junctions are tight junction-associated MARVEL proteins (with occludin being the best studied member of this protein family), junctional adhesion molecules, and more than 20 members of the claudin family.<sup>67,68</sup> It is likely that claudins interact with many proteins.<sup>69,70</sup> Better understanding of these interactions may provide insight into the entire cycle of TJ regulation.<sup>71</sup> For example, the results of some studies<sup>72,73</sup> demonstrate increased intestinal claudin expression in response to milk protein components. Occludin in turn was first identified as an integral membrane protein connected with TJs in chickens<sup>74</sup> and in mammals.<sup>75</sup> These proteins interact with the actin cytoskeleton via TJ adaptor proteins like zonula occludens, which are membrane-associated guanylate kinase inverted, and cingulin.<sup>67</sup>

The factors aggravating TJs functioning are, i.a., psychological stress (increasing levels of CRH), proinflammatory cytokines, bacterial dysbiosis, nuclear transcription factor NFκB (involved in the cellular response to stimuli—stress, cytokines, free radicals, antigens), oxidative stress, and others.<sup>45,59</sup> In their study on mice, Riba *et al.*<sup>76</sup> found that stress from maternal separation induces irritable bowel-like syndrome connected with increased paracellular intestinal permeability and visceral hypersensitivity in adult offspring, but also causes a specific IgG response to soluble food antigens.

Selective permeability due to loss of intestinal barrier is observed, i.a., in coeliac disease, inflammatory bowel disease, obesity, atopic dermatitis, food hypersensitivity, diabetes, sarcoidosis, neoplastic diseases, cystic fibrosis, and also in autism.<sup>5,77,78</sup>

There is a growing interest in the role of microbiota in the maintenance of proper TJ functioning, the

brain–gut axis, and in the development of psychiatric disorders.<sup>79</sup> The effect that intestinal bacteria has on CNS and, consequently, psychiatric disorders are multidirectional, and is based primarily not only on cytokine levels modulation, tryptophan metabolism, but also on intestinal permeability.<sup>45,80</sup> Autochthonic bacteria are an important component in reducing levels of proinflammatory cytokines and in maintaining intestinal barrier continuity. This is the reason why bacterial dysbiosis can lead to TJ unsealing. Increased intestinal permeability allows bacterial lipopolysaccharides to penetrate into the blood. In depression, significantly elevated levels of IgM and IgA antibodies against gram-negative enterobacteria lipopolysaccharides were found.<sup>5</sup> This observation is very important because metabolites of certain bacteria not only adversely affect the functioning of the CNS but also penetrate into the blood. A perfect example is the study of Naseribafrouei *et al.*<sup>81</sup> They showed that the *Oscillibacter* type strain, found in depression patients, has a homolog of neurotransmitter GABA – valeric acid as its main metabolic end product.<sup>81</sup> This mechanism may contribute to the psychopathology of depression.

The type of diet can also contribute to LGS development, either by mechanical TJ damage or by having a negative effect on microbiota balance. A study by Drago *et al.*<sup>56</sup> shows that gliadin containing foods may lead to increased gut permeability. Gliadin activates zonulin signalling irrespective of the genetic expression of autoimmunity, which leads to increased intestinal permeability to macromolecules.<sup>56</sup>

Taken together, many factors contribute to LGS, which is the reason why intestinal bacteria (autochthonous microflora; microbiota) and incompletely digested nutrients move from the intestinal lumen into the blood. This condition leads to the activation of the immune system,<sup>82</sup> which may initiate production of specific IgG antibodies against nutrients, and consequently, the development of food hypersensitivity, which is delayed and IgG-dependent.<sup>83</sup> Inflammation, emerging as a consequence of this process, is chronically sustained by repeated consumption of allergenic foods.<sup>46,84–86</sup> The role of specific IgG antibodies has been confirmed in coeliac patients where IgG-dependent delayed reaction to gluten occurs.<sup>87,88</sup>

The delayed nature of the reaction is a considerable diagnostic obstacle that makes it impossible for the patient to identify the factor causing the allergy. This results from the characteristics of IgG-dependent responses. While IgE antibodies are responsible for acute, immediately appearing allergic reactions, IgG-dependent reactions take much longer to develop.<sup>89,90</sup> These antibodies play a significant role in shaping the body's normal immune response.

Specific IgG-food-antigen complexes activate the complementary system and phagocytic migration, degrading the immune complex.<sup>91</sup> The immune system can be activated where the immune complex is formed at the binding site of the receptor, e.g. in the choroid plexus CNS, renal glomerular basement membrane, blood vessel walls, etc. Production of proinflammatory cytokines (IL-1, IL-6, and TNF- $\alpha$ ), proteolytic enzymes, and free radicals – damaging the surrounding tissue – is observed. Sustained inflammation can be an initiating factor in the development of chronic diseases.<sup>91–93</sup> As mentioned above, intestinal barrier discontinuity resulting in elevated levels of proinflammatory cytokines has been reported in patients with depression.

It is worth mentioning that type II hypersensitivity reaction (cytostatic–cytotoxic reaction) does not lead to the development of a chronic inflammation state and, consequently, is not involved in depression development and/or its maintenance. In this reaction, IgM/IgG antibodies bind to the antigens and join complement fractions. As a result, cytolysis of the effector cell is observed.

### Gluten sensitivity and depression

Only recently has coeliac disease been separated from gluten sensitivity (non-coeliac gluten sensitivity, NCGS) and gluten allergic reactions (IgE-mediated).<sup>94</sup> According to the consensus document developed in 2012, a spectrum of gluten-related disorders includes three main forms of gluten reactions: allergic (e.g. food allergy), autoimmune (e.g. coeliac disease, dermatitis herpetiformis, and gluten ataxia), and possibly immune-mediated (e.g. NCGS).<sup>95,96</sup>

CD is a chronic immune-mediated enteropathy triggered by gluten ingestion in subjects who have genetic compatibility of the HLA DQ2 or DQ8 haplotype.<sup>97</sup> This disorder affects one percent of the general population and is characterized by villous atrophy, crypt hyperplasia, and increased intraepithelial lymphocytes.<sup>94,98</sup>

Classic CD manifestations (but only in 50 per cent of patients) are severe diarrhoea and consequent weight loss with failure to thrive due to severe intestinal malabsorption. All the other cases are clinically atypical, associated, for example, with anaemia, osteoporosis, musculoskeletal and neurological disorders, endocrinopathies, or skin diseases.<sup>99</sup>

NCGS is a relatively new term for conditions in which symptoms are triggered by gluten ingestion, in the absence of coeliac-specific antibodies and of classical coeliac villous atrophy, with a variable presence of first generation anti-gliadin antibodies.<sup>100</sup>

The Human Leukocyte Antigen (HLA) classification is not particularly useful in the NCGS diagnosis process (only 50% of positive DQ2/DQ8 outcomes)

and, moreover, anti-gliadin antibodies in the first generation of the IgG class tend to be positive in subjects with gluten sensitivity.<sup>96,101,102</sup>

Unfortunately, despite the fact that NCGS occurs six times more frequently than CD, the majority of research has not separated these two disorders.<sup>103</sup> Although there is some evidence connecting CD with neurologic and psychiatric symptoms,<sup>94</sup> there have been very few studies so far examining connections between NCGS and mental disorders. In the mainstream of this trend, there is Fasano's group research, focused on possible links between NCGS and schizophrenia, identifying a biomarker and a subsequent diagnostic tool for the condition of gluten sensitivity and the role of the timing of gluten introduction in CD pathogenesis in infants.<sup>44</sup>

Biesiekierski<sup>104</sup> confirmed the existence of NCGS in patients with irritable bowel syndrome in a randomized, double blind, placebo-controlled trial. The role of intestinal barrier dysfunction was confirmed in patients suffering from autism.<sup>105</sup>

There is still a lack of studies on the importance of leaky gut and IgG food allergy in the pathogenesis of depression. Gluten sensitivity or intolerance has been mentioned only in a few reports so far. For example, Carta *et al.*<sup>106</sup> found that major depressive disorder, dysthymic disorder, and adjustment disorders were more common in a group of coeliac patients as compared to the controls. Ludvigsson *et al.*<sup>107</sup> achieved similar results with regard to depression, but prevalence of CD in patients diagnosed with bipolar disorder was similar to the controls. Ruuskanen *et al.*<sup>108</sup> in their research found that the elderly population with gluten sensitivity was more than twice as likely to have depression as compared to the elderly sample without gluten sensitivity.

Carr,<sup>95</sup> in turn, described a case of an 11-year-old girl who had been on a gluten-free diet since early childhood due to health issues associated with wheat consumption. At the age of 10 she had to consume a wheat-containing diet for a week. After this short period, her mood dropped suddenly, and she also claimed that she had wanted to kill herself. Her parents immediately changed her diet back to a strictly gluten-free diet and after several days her mental state improved significantly. In the pilot study, Peters *et al.*<sup>109</sup> evidenced that even short-term gluten exposure in patients with NCGS can cause symptoms similar to depression.

### The role of IgG-based elimination diet in the therapy of depression

There is some evidence confirming the fact that the quality of diet has an influence on leaky gut syndrome, immune functioning and systemic inflammation in depressive patients.<sup>6</sup> For example, whole grain foods

include fibre and beta glucans that can probably modulate immune functioning.<sup>110</sup>

Other dietary immunomodulating factors of considerable current interest to mental health researchers include prebiotics and probiotics.<sup>111</sup> The effectiveness of prebiotics in promoting the growth of strains of beneficial bacteria, e.g. bifidobacteria in the gut, has been demonstrated by some studies. Namely, it has been argued that the use of prebiotics leads to a favourable change in intestinal microbiology, reduces intestinal inflammation, and alleviates symptoms, e.g. atopic eczema, irritable bowel syndrome.<sup>112,113</sup> There are more and more reports about the positive effect of such strains of bacteria as *Streptococcus thermophilus* or *Lactobacillus acidophilus*, and even probiotic *Escherichia coli* Nissle 1917, which protect the intestinal barrier against harmful factors by reducing the symptoms of leaky gut.<sup>114,115</sup>

Various potential immunomodulating factors improving tightness of the intestinal barrier also include amino acid L-glutamine, which has been confirmed by some studies demonstrating its positive effect on intestinal enterocytes as well as its power to reduce leaky gut.<sup>115,116</sup>

Present in curry powder, curcumin is another compound with a beneficial immunomodulating effect, potentially reducing inflammatory condition and oxidative stress related to the activity of tight junctions.<sup>117</sup>

Tight junction damage between enterocytes leads to increased intestinal permeability that causes absorption of undigested proteins in small intestine and higher levels of specific IgG antibodies as a consequence.<sup>86</sup>

The essential treatment in this case should be implementation of an appropriate diet. An elimination-rotation diet may be a good choice in patients with IgG food allergy in many diseases (e.g. migraine<sup>118,119</sup>). This type of diet relies on elimination of foods identified as causing allergic reactions and rotation in taking a certain type of food (only for one day and then a three-day interval). Such rotation reduces the risk of occurrence hypersensitivity to food products that have been well tolerated before.<sup>120</sup>

Most publications connecting intestinal permeability with mental disorders refer to studies on autism spectrum disorders. Demonstration of efficacy of gluten and casein-free diets in patients suffering from autism<sup>105,121–124</sup> has resulted in attempts to use this type of therapeutic proceedings in other mental disorders, including depression. So far, studies on the connection of a gluten-free diet and depression have involved depressive subjects only with coeliac disease (CD). For example, Corvaglia *et al.*<sup>125</sup> reported several cases of patients with CD who had been unsuccessfully treated with antidepressants and whose depressive symptoms improved with a gluten-free

diet. Pynnonen *et al.*<sup>126</sup> also achieved similar results in adolescents with CD. It may be assumed that elimination of a factor causing inflammation (gluten) contributes to mental health improvement also in patients experiencing NCGS and depression. So far there have been no studies that take into consideration a gluten-free diet in depressive patients with NCGS.

## Conclusion

The presented new hypothesis assumes existence of a new potential pathway that may mediate the pathogenesis of depression, which implies the existence of subsequent developmental stages. Overproduction of zonulin triggered by, e.g. gliadin<sup>60</sup> through activation of the epidermal growth factor receptor and protease-activated receptor (PAR)-2 causes loosening of the TJ barrier and an increase in permeability of the gut wall ('leaky gut'). This results in a process allowing larger molecules that would normally stay in the gut to cross into the bloodstream and in induction of IgG-dependent food sensitivity.<sup>127,128</sup> This condition causes an increased immune response<sup>93,129</sup> and consequently induces the release of proinflammatory cytokines,<sup>15</sup> which in turn may lead to the development of depressive symptoms.<sup>130</sup>

In view of the foregoing considerations, it seems advisable to assess the intestinal permeability using as a marker, e.g. zonulin, occludin, and specific IgG concentrations against selected nutritional components in patients with depression. In the case of increased IgG concentrations, the implementation of an elimination-rotation diet may prove to be an effective method of reducing inflammation. It is necessary to evaluate the concentration of all subclasses of specific IgG (IgG 1–4) using validated research tools, by a quantitative method.

This new paradigm in the pathogenesis of depressive disorders linking leaky gut, IgG-dependent food sensitivity, inflammation and depression is promising, but still further studies are needed to confirm this theory. Another field of interest, i.e. elimination diets in depression treatment, requires well-designed clinical trials to check their utility.

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