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Research Article

NEW THERAPEUTIC APPROACHES FOR CHRONIC DISEASES ON THE RISE: THE IGUBAC DIET®

Ismael San Mauro Martin., Elena Garicano Vilar and Sara López Oliva

Research Centers in Nutrition and Health. Paseo de la Habana, 43. 28036, Madrid, Spain

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ABSTRACT

Chronic diseases are recognized as a major health challenge. Given the population projections which predict a doubling of the elderly population over the next 30 years, this will give rise to a significant increase in chronic diseases. *IGUBAC Diet*® (Inflammatory Gut-Brain Axis Control Diet) is an evidence-based personalized diet focused in the relationship between nutrition, inflammation and the gut-brain axis. After treating more than 100 patients with fibromyalgia, irritable bowel syndrome, autism or attention-deficit/hyperactivity disorder in CINUSA Clinic (Spain), modulation and correction of the usual symptoms are achieved in 100% of patients after following the diet at least for 2 months.

INTRODUCTION

IGUBAC Diet® (Inflammatory Gut-Brain Axis Control Diet) is an evidence-based personalized diet focused in the relationship between nutrition, inflammation and the gut-brain axis (Carabotti, Scirocco, Maselli, & Severi, 2015).

It is based in 5 different pillars: 1) low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) and 2) gluten-free (Ali & McCarthy, 2014; Catassi *et al*., 2015; Chaves-Carballo, 2003; Isasi *et al*., 2014; Langhorst *et al*., 2012; Marí-Bauset, Zazpe, Mari-Sanchis, Llopis-González, & Morales-Suárez-Varela, 2014; Marum, Moreira, Tomas-Carus, Saraiva, & Guerreiro, 2017; Nigg & Holton, 2014; Pelsser *et al*., 2009; L Rodrigo, Blanco, Bobes, & de Serres, 2013; Luis Rodrigo, Blanco, Bobes, & de Serres, 2014; San Mauro-Martín, Garicano-Vilar, Collado-Yurrita, & Ciudad-Cabañas, 2016; Sonuga-Barke *et al*., 2013; Whiteley *et al*., 2010; Wiles, Northstone, Emmett, & Lewis, 2009), 3) low histamine and other amines or inflammatory molecular intermediaries (Alstadhaug, 2014; Amon *et al*., 1999; Bachelet, Levi-Schaffer, & Mekori, 2006; Enko *et al*., 2016; Fitó *et al*., 2007; Gazerani, Pourpak, Ahmadiani, Hemmati, & Kazemnejad, 2003; Hamada *et al*., 2013; Lugović-Mihić, Seserko, Duvancić, Situm, & Mihić, 2012; Maintz & Novak, 2007; San Mauro Martin, Brachero, & Garicano Vilar, 2016; Slim, Calandre, & Rico-Villademoros, 2015; Weissler, Mekori, & Mor, 2008), 4) preservative free (Arnold, Lofthouse, & Hurt, 2012; Donaldson, Speight, & Loomis, 2001; Keifer & Firestone, 2007; Nigg, Lewis, Edinger, & Falk, 2012; Wender, 1986) and 5) natural food (Alves *et al*., 2013; Fadus, Lau, Bikhchandani, & Lynch, 2017; Ghasemian, Owlia, & Owlia, 2016; Gupta *et al*., 2013; Merchant & Andre, 2001).

The *IGUBAC Diet*® has been probed by CINUSA Clinic (Spain) ("CINUSA Group," n.d.) in the treatment of rheumatic diseases, such as fibromyalgia (FM) or irritable bowel syndrome (IBS), in adults; and neurodevelopmental disorders, such as autism or attention-deficit/hyperactivity disorder (ADHD), in children.

The human gut harbors microbiota which has a wide variety of microbial organisms, which are mainly symbiotic and important for well-being. However, an alteration in normal commensal gut microbiome (dysbiosis) with an increase in pathogenic microbes, impacts homeostasis/health (Mak A. Daulatzai, 2015).

Dysbiosis is underpinned by dysfunctional bidirectional "Gut-Brain Axis" pathway. Pathogenic gut microbiota is known to upregulate gut- and systemic inflammation (due to

Corresponding author:* **Ismael San Mauro Martin
Research Centers in Nutrition and Health. Paseo de la Habana, 43. 28036, Madrid, Spain

lipopolysaccharide from pathogenic bacteria and synthesis of pro-inflammatory cytokines); they enhance energy harvest, cause obesity, insulin resistance, and dysfunctional vago-vagal gut-brain axis (Mak Adam Daulatzai, 2014). Conceivably, the above cascade of pathology may promote various pathophysiological mechanisms, neuroinflammation, and cognitive dysfunction. Hence, dysbiosis, gut inflammation, and chronic dyshomeostasis are of great clinical relevance.

Fibromyalgia and rheumatic diseases

FM is a chronic rheumatic disease producing widespread pain, accompanied by other symptoms such as depression, anxiety, fatigue, or sleep disturbances. In Spain, 2.4% of the population over 20 years of age suffer from it, with a greater presence in women in a 21:1 ratio. Its etiology is unknown and there are no effective treatments. The pathophysiological sign is a sensitized or hyperactive central nervous system that leads to greater gain in pain and sensory processing. In addition, other pathophysiological mechanisms such as mitochondrial dysfunction, oxidative stress, inflammatory component and neuroendocrine disorders must be taken into account (Pareja *et al*., 2015).

Other studies have investigated the frequency of presentation of gastrointestinal symptoms in fibromyalgia in a nonspecific approach describing several gastrointestinal complaints frequently reported by these patients such as abdominal pain, dyspepsia and bowel changes, among others. Several underlying mechanisms that require further investigation could serve as potential explanatory hypotheses for the appearance of such manifestations. These include sensitivity to dietary constituents such as gluten, lactose or FODMAPs or alterations in the brain-gut axis as a result of small intestinal bacterial overgrowth or subclinical enteric infections such as giardiasis (Slim *et al*., 2015).

Results in research suggest that diet can have a potential therapeutic role in the balance of FM syndrome. One possible dietary approach could be to restrict FODMAPs (Fermentable, Oligo-Di-Mono-saccharides And Polyols) as part of a multidisciplinary treatment of FM (Marsh, Eslick, & Eslick, 2016). FODMAPs are composed by, poorly absorbed, short-chain carbohydrates, including excess free fructose, lactose, polyols, fructo-oligosaccharides, and galacto-oligosaccharides. Literature suggests a possible common cause, responsible by both FM and IBS. Common characteristics between them: both are characterized by functional pain, not explained by biochemical or structural abnormalities, with predominance in females, associating with life-stressing and complain of sleep disturbances and fatigue (Marum *et al*., 2017). A low FODMAP diet was already found to alleviate gastrointestinal disorders and symptoms of IBS (Gibson & Shepherd, 2010; Marsh *et al*., 2016) and by comparison, as about 70% of FM patients report IBS symptoms (Kurland, Coyle, Winkler, & Zable, 2006), we hypothesized that low FODMAPs diet may have some therapeutic benefit on FM symptoms.

Other authors (Slim *et al*., 2017) have also proposed dietary interventions for FM treatment using a restricted gluten, lactose or FODMAPs diet in FM patients with gluten sensitivity symptoms, obtaining benefits in the outcomes.

Gluten sensitivity that does not fulfil the diagnostic criteria for celiac disease is a frequent and treatable condition with a wide spectrum of manifestations that also overlap with the manifestations of FM, including chronic musculoskeletal pain, asthenia, and irritable bowel syndrome (Isasi *et al*., 2014). Nonceliac gluten sensitivity may be an underlying cause of FM syndrome; therefore we also hypothesized that a gluten-free diet could ameliorate FM symptoms.

Neuroinflammation in FM has biological contributions including gastrointestinal dysbiosis, vitamin D deficiency, and mitochondrial dysfunction. These independent contributions commonly co-exist, and each of these is synergistic with the others in the promotion of peripheral and central hyperalgesia (Vasquez, 2016).

Chronic pain has been associated with lipopolysaccharide (LPS)-stimulated proinflammatory cytokines (particularly IFN-γ and TNF). The gastrointestinal tract is the most abundant source of LPS, systemic absorption of which is increased by small intestine bacterial overgrowth and increased intestinal permeability. LPS promotes muscle mitochondrial impairment, peripheral hyperalgesia, and central sensitization (Littlejohn, 2015).

Human clinical trials have shown that vitamin D supplementation can alleviate inflammation (Timms *et al*., 2002), intestinal hyperpermeability (Raftery *et al*., 2015), fibromyalgia pain (Wepner *et al*., 2014) and other neuromusculoskeletal pain. Vitamin D reduces experimental microglial activation (Hur, Lee, Kim, & Cho, 2014), a component of neuroinflammation and central sensitization.

Mitochondrial dysfunction may be triggered by gastrointestinal dysbiosis via LPS, D-lactate, hydrogen sulfide, and inflammation; mitochondrial dysfunction exacerbates and perpetuates microglial activation and glutaminergic neurotransmission (Nguyen *et al*., 2011), thereby promoting pain sensitization centrally while also contributing to muscle pain peripherally.

Perspective from *IGUBAC Diet*® in CINUSA Clinic: After treating more than 100 patients with this condition, we observed a significant reduction in the usual symptoms of these patients after following the diet for 2 months. Great results are obtained in: headache, fatigue, muscle aches, digestive problems (abdominal pain, bloating, gas, and gastritis), sleep disturbance and skin problems, such as hives.

Attention-deficit/hyperactivity disorder

Attention deficit hyperactivity disorder (ADHD) is one of the most commonly diagnosed neurobehavioral disorders in childhood, and it often lasts into adulthood. It is characterized by a difficulty in maintaining voluntary attention to activities, both academic and in daily tasks, coupled with lack of impulse control. Boys are more likely to have ADHD than girls, and higher rates of ADHD in younger age groups have been observed in studies of children and adolescents. The worldwide pooled prevalence of ADHD is reported to be 3.4% (San Mauro Martín *et al*., 2017).

Limited, but growing, clinical evidence comes primarily from associations of gut microbial composition and function to behavioral and clinical features and brain structure and function. Converging evidence suggests that the brain and the gut microbiota are in bidirectional communication. Observed dysbiotic states in depression, chronic stress, and autism may

reflect altered brain signaling to the gut, while altered gut microbial signaling to the brain may play a role in reinforcing brain alterations (Martin & Mayer, 2017).

Proposed ADHD environmental risk factors include heavy metal and chemical exposures such as lead, mercury, organochlorine, organophosphates, and phthalates, as well as nutritional and lifestyle/psychosocial factors (Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015).

The treatments that have been proposed for ADHD over the years include several kinds of dietary interventions, including single nutrient supplements, multinutrient supplements, supplementation with omega-3 fatty acids, and others. Among the most enduring ideas has been the use of a food restriction or food elimination diet (Nigg & Holton, 2014).

The effect of diet and dietary supplements is unclear, but considerable evidence suggests that dietary factors are associated with childhood behavioral disorders such as ADHD. Low levels of copper, iron, zinc, magnesium, and omega-3 fatty acids have been reported in children with ADHD and sugar, artificial food colorants, and preservatives are associated with an increased risk of ADHD (Cormier & Elder, 2007; Millichap & Yee, 2012). Based on the statements above *IGUBAC Diet*® is preservative free and involves natural food.
Perspective from *IGUBAC Diet*® in CINUSA Clinic: The benefit obtained from the diet in our children with ADHD results in greater attention, fewer absences, less irritability, and better digestive health.

Autism

Autism spectrum disorders (ASD) are a group of developmental disabilities, clinically characterized by difficulties with reciprocal social interactions; verbal and nonverbal communication deficiencies; and restricted, repetitive, and stereotyped behaviours and interests. According to a publication analysing 2008 data (Baio, 2012), the prevalence has increased to 11.3 per 1000 people, and it is notably more common in men (ratio 4:1).

The gut microbiota influences brain development and behaviors through the neuroendocrine, neuroimmune and autonomic nervous systems (Wang *et al*., 2017). Environmental factors (especially gut dysbacteriosis) are involved in the development of ASD, and as many as 70% of autistic patients exhibit gastrointestinal tract-related symptoms; therefore, it is thought that ASD is associated with impairment of the gut-brain axis (Mayer, Padua, & Tillisch, 2014). The majority of autistic patients have diarrhea, abdominal pain, constipation, gastroesophageal reflux, and other gastrointestinal symptoms (Zhu *et al*., 2017).

The bidirectional microbiota-gut-brain axis acts mainly through neuroendocrine, neuroimmune, and autonomic nervous mechanisms. Application of modulators of the microbiota-gut-brain axis, such as probiotics, helminthes and certain special diets, may be a promising strategy for the treatment of ASD (Li & Zhou, 2016).

The most commonly alternative treatments used is the gluten-free, casein-free diet (Whiteley *et al*., 2010). The elimination of gluten implies the exclusion of all food items containing wheat, oats, barley or rye, that is, all flours, bread, rusks, pasta, pastries, and other bakery products made with these cereals, while the elimination of casein means no intake of dairy products: milk, including breast milk, yogurt, cheese, butter, cream or ice cream, among others. On the other hand, in relation to children with autism spectrum disorders, these diets involve significant changes to their routine and such changes can, in themselves, affect their eating behaviours (Marí-Bauset *et al*., 2014).

The most commonly cited theory to justify adoption of a gluten-free, casein-free diet is related to neurotransmitters and concerns the release of peptides with an opioid activity in the intestines (Amidon & Lee, 1994). After digestion, certain types of proteins could cross the intestinal mucosa intact (Daniel, 2004), if this were more permeable than normal. If these peptides, transported by the bloodstream, were to cross the blood-brain barrier and reach the central nervous system in large quantities, it would affect brain functioning (Janecka, Staniszewska, Gach, & Fichna, 2008). The hydrolysis of proteins from cereals and milk would generate exogenous neuropeptides (exorphines) such as gluteomorphins from gluten and beta-casomorphins from casein.

Perspective from *IGUBAC Diet*® in CINUSA Clinic: There are different approaches for autistic children due to the differences between the treated stages. The stages range from lack of mobility, speech, self-injury, and no control of sphincters; through communication and response by pictograms, mainly calm behavior and without injury or injury to third parties; to the evolution in language, psychomotricity, and behavior. Thus, in each of the stages, a qualitative and quantitative benefit has been observed, both in the approximation and evolution of a stage with greater depth and commitment of behavior and physiological as well as in an improvement in the language and the use of pictograms, social participation, injuries, etc. In addition, direct and objective biological measures are taken as number of stools, stool consistency, weight and height, and their percentiles.

Gastrointestinal disorders

Despite the benign prognosis of functional gastrointestinal disorders (FGID), the health-related quality of life in these patients can be affected significantly by their symptoms (Spiegel *et al*., 2009).

Bidirectional brain-gut interactions play an important role in the regulation of many vital functions in health and disease, namely through signaling from gut-microbiota to brain and from brain to gut-microbiota by means of neural, endocrine, immune, and humoral links (Carabotti *et al*., 2015).

In health, brain-gut interactions are crucial in the regulation of digestive processes, in the modulation of the gut-associated immune system, and in the coordination of the overall physical and emotional state of the organism (sleep, stress, anxiety) with activity in the gastrointestinal (GI) tract. The importance of bidirectional brain-gut interactions in GI illness is increasingly recognized, most prominently in the area of functional GI syndromes such as IBS, and functional dyspepsia (Mayer & Tillisch, 2011).

The effects of central nervous system on microbiota composition are likely mediated by a perturbation of the normal luminal/mucosal habitat that can be restored by the use

of probiotics and possibly by diet. In clinical practice, an example of this interaction is constituted by FGID, in particular IBS, now considered a microbiome-gut-brain-axis disorder.

IBS could be governed by elevated circulating pro-inflammatory cytokines, IL-6 and IL-8, acting either locally or on the brain-gut axis. This pro-inflammatory cytokines may be involved in the exaggerated activation of the hypothalamic-pituitary-adrenal axis and thereby promote a coordinated central response to stress, such as GI inflammation and dysfunction. In this sense, *IGUBAC Diet*® aims to reduce that inflammation state.

Perspective from *IGUBAC Diet*® in CINUSA Clinic: Modulation and correction of the usual symptoms such as gas, abdominal pain, spasms, gastritis, reflux, constipation, diarrhea, stool consistency and bloating are achieved in 100% of patients.

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