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XI International Conference on Immunonutrition 2018: ISIN

Immunonutrition in Health and Disease

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Abstracts

Guest Editors
Laurence S. Harbige, London
Philip C. Calder, Southampton

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Introduction to the XI International Conference on Immunonutrition 2018

Annals of Nutrition & Metabolism

Immunonutrition (in its widest context) or nutritional immunology can be defined as the "scientific study of the processes by which essential nutrients maintain, or other diet constituents† affect, the normal physiology of the immune system and the extent to which these processes are altered by deficiency, overnutrition, supplementation and disease." Nutrition is essential for innate and adaptive immunity and the hosts ability to initially resist pathogens and to fight established infection. Undernutrition in relation to protein and micronutrients is still a major contributor to mortality and morbidity due to infectious diseases, particularly in developing countries. Similarly in developed countries overnutrition and its associated metabolic disorders e.g. obesity and type 2 diabetes contribute to the burden of disease and have become a worldwide epidemic. Inflammation is an underlying pathological mechanism in many chronic non-communicable diseases and is one disease factor which is modifiable by diet and nutrition. Advances in understanding the roles of fatty acids, vitamins (e.g. A, C, D, E) and minerals (e.g. iron, zinc, selenium) in immune function continue to be made at the molecular and cellular levels. The relationship of nutrition to epigenetic, conception and intergenerational effects on immune and inflammation biology are also beginning to emerge. Research is also exploring the complex interactions of nutrients with the microbiota and host immunity and their roles in both the early developing and the aging immune systems. Science is also about application and immunonutrition is no exception, it continues to deliver new treatments and public health measures to improve human and animal health. Interactions between nutrition and immunity are therefore very much relevant today as they were in the latter half of the last century when they were beginning to be scientifically studied and recognised.

†*includes prebiotics, probiotics, phytochemicals, food allergens etc*

Under the leadership of Ascensión Marcos the first immunonutrition course was held in Madrid in 1994 and thereafter international courses were held mainly in Spain (1998, 1999, 2001, 2003, 2005 and 2007) and Latin America (Argentina-2003, Brazil-2004, Mexico-2006, Ecuador-2010, Mexico-2011, Venezuela-2012). In 2007 the International Forum for Immunonutrition Education and Research (i-FINER) group was established to exchange knowledge among senior scientists and academics and to support younger researchers, with the first workshop held in Valencia, Spain in 2007. Since 2007 a workshop has been annually organized by i-FINER in several different countries (Argentina-2008, Spain-2009, Ecuador-2010, Mexico-2011, Spain-2012, Spain-2013, Italy-2014, Brazil-2015, and Mexico-2016). In 2014 i-FINER was renamed the International Society for Immunonutrition (ISIN) after the 7th International Immunonutrition Workshop in Brindisi, Italy. Given this long history of workshops etc, ISIN celebrated the 10th Anniversary of these events in Madrid (Spain) in 2017. The ISIN international conference on immunonutrition comes to London (UK) for the first time in September 2018 and has become one of the world's most important meetings for researchers and students working on the interactions between nutrition, immunity, infection and inflammation. The conference includes 28 invited speakers and session chairs from 12 countries. The opening special lecture focuses on the global impact of immunonutrition and the closing special lecture on the immunology of asthma. The other invited lectures are divided into 11 sessions covering traditional and emerging topics:

Molecular and cellular roles of nutrients in the immune system
Immunometabolism
Nutrition and inflammation
Micronutrients and immunity
Fats, immunity and inflammation
Phytochemicals, immunity and inflammation
Nutrition and infectious disease
Microbiota and immune health
Obesity, immunity and inflammation
Nutrition and immunosenescence
Nutrition and immune-development

In this special supplement in the Annals of Nutrition and Metabolism, 26 invited lecture abstracts plus 26 delegate abstracts presented at the XI International Conference on Immunonutrition are included. The International Society for Immunonutrition is indebted to several companies and organisations that have collaborated (with no involvement in the scientific affairs) in the organization of this event, such as Bayer, DSM, Yakult UK, Ysonut, Nutrition Society and London Metropolitan University. Finally, we would very much like to thank the conference organizing committee for all their hard work and the ISIN scientific committee for all its support and continued work on behalf of the society.

Laurence S. Harbige and Philip C. Calder
Presidents, XI ISIN International Conference on Immunonutrition and on behalf of the ISIN Board

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Annals of Nutrition & Metabolism

Molecular and Celular Roles of Nutrients in the Immune System

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Zinc and the Immune System

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Since the discovery of zinc deficiency in the 1960s, data suggesting the importance of zinc for the development and function of the immune system strongly increased [1]. Symptoms such as lymphopenia, decreased ratios of T helper cells to cytotoxic T cells, decreased natural killer (NK) cell activity, altered monocyte cytotoxicity and increased susceptibilities to infections are some of many hallmarks of zinc deficiency [2]. Benefits of zinc supplementation in preventing inflammatory diseases such as sepsis and acute lung injury have recently been found [3].

During long term zinc deficiency, development of innate immune cells seems to be prioritized on cost of the adaptive immune cells, and polarization of macrophages seems to be altered [4]. In regard to the adaptive immune system, zinc was found to be decisive for lineage commitment of especially T cells, not only affecting the balance between Th1 and Th2 responses but also for the development of Tregs and Th17 cells [5–7]. Moreover, B cell development and functions such as antibody production are altered [4, 8, 9]. Those data form the basis for the usage of zinc to improve organ survival after transplantation and to alter allergic reactions.

Molecular mechanisms underlying the strong effects that zinc homeostasis has on immune functions comprise its structural as well as catalytic importance for over 300 enzymes. For example via its effect on phosphatase and kinase activities zinc regulates intracellular signaling [10]. Also, epigenetically active enzymes are affected, thus zinc availability can influence histone and DNA modifications as well as the DNA structure [6, 11, 12] Zinc's role in protein-protein interaction as well as transcription factor binding to the DNA represents another example.

Current data strongly suggest benefits of balancing zinc homeostasis, especially preventing zinc deficiency, and the therapeutic use of zinc to normalize disruptions in immune responses.

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Keywords: Zinc, Immunobiology, Nutritional Immunology, Epigenetics, Hematopoiesis.

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Immunometabolism

380/55
Immunometabolic Adaptation in Pregnancy

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Maternal metabolic adaptation during pregnancy – evidenced by adipose tissue accretion in early pregnancy then increasing insulin resistance and lipolysis as pregnancy progresses1 – supports growth of the fetal-placental unit. Insulin resistance manifests around 12 – 14 weeks becoming more pronounced as pregnancy progresses2. Placental hormones likely have a role by modifying expression of energy substrate transporters, enzymes and signalling molecules1, 3, 4. Dynamic readjustment of immune homeostasis also is a feature of pregnancy with modified function of multiple leukocyte subsets described5. Pregnancy success is associated with heightened Th2 and Treg activity but dampened Th1 and Th17 with the converse in adverse pregnancy outcomes6. Altered activity of CD8+ T and NK cells is linked to heightened susceptibility of pregnant women to respiratory viruses and increased disease severity7. Innate immune adaptation also occurs8.

The impact of cellular metabolism on cell phenotype and function is a burgeoning area of immunology9, 10. Glycolysis and/or de novo fatty acid synthesis are linked to the proliferation and effector function of various T cell populations whereas fatty acid catabolism is important for the development of CD8+ T cell memory and CD4+ Treg11-13. Lipid metabolism appears particularly important for controlling the Treg/Th17 cell balance13. Cellular metabolism also shapes macrophage effector function with fatty acid oxidation (FAO) associated with polarisation to alternatively-activated anti-inflammatory M2 rather than classically-activated pro-inflammatory M1 macrophages14. Tolerogenic DCs at the maternofetal interface have elevated FAO pathway proteins and activity compared to mature pro-inflammatory DCs15. These studies highlight that reprogramming of leukocyte cellular metabolism could explain many of the functional adaptations that occur in pregnancy: down-regulation of glycolysis – especially if accompanied by up-regulated FAO – would generate leukocyte phenotypes and functional profiles reminiscent of those described by many investigators to favour pregnancy success. Our early results support such a metabolic adaptation by maternal peripheral blood leukocytes16.

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T Cell Metabolism: Nutrients, Signals, and Function

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Changes in nutrition can influence immunity. Both under- and over-nutrition are associated with impaired protective immunity and vaccine response, as well as altered susceptibility to autoimmune disease. T cells play an important role in nutritionally regulated immune responses, and changes in T cell metabolism can influence function. We have found that T cells from both undernourished and diet-induced obese mice and humans have cellular metabolic changes that contribute to impaired immunity. We have also identified nutritionally regulated hormones, such as leptin and insulin, as key players in regulating immunometabolism and function. We now seek to identify methods by which we can improve immunity through modulation of cellular metabolism.

Conflict of Interest: The author has no conflicts of interest.
Keywords: Nutrition, obesity, T cells, metabolism, leptin.

Nutrition and Inflammation

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Fatty Acids as Triggers and Modulators of Inflammation

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Inflammation contributes to a range of human diseases. Inflammation involves a multitude of cell types, chemical mediators, and interactions. Experimental studies suggest that some saturated fatty acids may directly trigger inflammation. Omega-6 (n-6) polyunsaturated fatty acids are precursors to some of the chemical mediators of inflammation like prostaglandins and leukotrienes. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are omega-3 (n-3) fatty acids found in oily fish and fish oil supplements. EPA and DHA are able to partly inhibit a number of aspects of inflammation including leucocyte chemotaxis, adhesion molecule expression and leucocyte-endothelial adhesive interactions, production of eicosanoids like prostaglandins and leukotrienes from the n-6 fatty acid arachidonic acid, and production of inflammatory cytokines. In addition, EPA gives rise to eicosanoids that often have lower biological potency than those produced from arachidonic acid and both EPA and DHA give rise to anti-inflammatory and inflammation resolving mediators. Thus increasing abundance of n-3 fatty acids reduces inflammation and creates an environment favouring its resolution. Mechanisms underlying these actions of n-3 fatty acids include altered cell membrane phospholipid fatty acid composition, disruption of lipid rafts, inhibition of activation of the pro-inflammatory transcription factor nuclear factor kappa B so reducing expression of inflammatory genes, activation of the anti-inflammatory transcription factor peroxisome proliferator activated receptor ? and binding to the G protein coupled receptor GPR120. These mechanisms are interlinked, although the full extent of this is not yet elucidated. Animal experiments demonstrate benefit from n-3 fatty acids in a range of models of inflammatory conditions including arthritis, inflammatory bowel disease and endotoxemia. Human trials demonstrate benefit of oral n-3 fatty acids in some inflammatory diseases, with the strongest evidence in arthritis. There is growing interest in whether these effects of n-3 fatty acids may be useful in controlling the chronic low-grade inflammation that accompanies cardio-metabolic disease.

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Nutrition & Inflammatory Signalling Pathways: The Possible Involvement of FAMPs

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An immune response, also to nutritional antigens, is the resultant of a complex interplay between its initiator (the antigen), possible adjuvant factors, and the various immunological cellular and organismal responses.

There is much debate on e.g. the physiological relevance of the many quantifiable markers in e.g. blood or on cell surfaces, on progression and possible modulation of immune responses. On the one hand this can be related to the enormous genetic and phenotypic variability of humans, to insufficiently stringent definition of immune-related (adverse) health effects, and probably also the enormous variability in nutrition-contained antigens and the effect of food processing on their antigenicity.

Very different cellular immune parameters are involved in the initiation and eventual resolution of an immune response. The later events in immune responses are for sure characterised by a high variability. The initiation of an immune responses may be equally relevant, however, to determine eventual physiological and clinical effects. Better comprehension and the development of tools for intervention of such early cellular mechanisms may ultimately lead to options to better deal with the consequences and possible need for modulation of full-blown immune responses.

Processing of proteins does have an effect on their antigenicity. Modified protein structure is an important factor in DAMP-signalling, and also in the preparation of proteins for pharmaceutical purposes care is taken to minimise e.g. shear-related damage to their structure. Also for food proteins, processing-related structural alterations impacts their immunogenicity. This phenomenon will be discussed with allergic responses to peanut or milk proteins as examples, and leads to the postulation of the Food-processing Associated Molecular Pattern (FAMP-)concept.

Micronutrients and Immunity

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Vitamin C, Immunity and Infection

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Vitamin C was identified in the early 20th century in the search for the substance, the deficiency of which caused scurvy. In the early literature, scurvy was directly linked to pneumonia, implying that vitamin C might influence infections. Starting in the 1930s, some German and US physicians proposed that vitamin C might be beneficial in the treatment of pneumonia. So far, 3 controlled trials have reported that vitamin C prevented pneumonia, but the

participants of the trials were special such as schoolchildren during the WW-II and military recruits. Thus, those findings cannot be extrapolated to the general population. The effect of vitamin C on the common cold has been studied extensively. Although the vitamin has not prevented colds in the general population, it has halved the incidence of common colds in 5 randomized trials (RCTs) with participants under heavy short-term physical stress. Regularly administered 1 g/day or more of vitamin C shortened the duration of colds by 8% in adults and by 18% in children, indicating a physiological effect. Furthermore, 2 RCTs compared the efficacy of 2 different vitamin C doses and both found that the higher dose, 6 and 8 g/day, was twice as effective in reducing the duration of the common cold than the lower dose of 3 and 4 g/day. Most common cold studies used just 1 g/day of vitamin C, which may have biased the estimate of efficacy downwards. The practical importance of therapeutic vitamin C in common cold treatment is open. RCTs with vitamin C doses over 8 g/day are needed to estimate the maximal efficacy in common cold treatment. The effects of vitamin C are not limited to the common cold and pneumonia. Over 100 animal studies indicate that vitamin C may alleviate or prevent infections caused by diverse bacteria, viruses, and protozoa.

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The Effect of Supplementation on Immune Function in the Elderly: A Double-Blinded, Randomized Control Trial

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The elderly frequently lack adequate zinc, vitamin C and vitamin D, and this may contribute to age-related decline of the immune system and increased infection. We hypothesized that supplementation with vitamins C, D and zinc could change immune function in the elderly. To test this hypothesis, we treated healthy adults 55 and older with either Redoxon VI (n = 21) or an identical placebo (n = 21) supplement for 12 weeks. Prior to and after treatment, we collected heparinized blood to i) test for whole blood bacterial killing against Staphylococcus aureus and ii) measure neutrophil phagocytosis and production of reactive oxygen species (ROS). We expected that Redoxon VI would increase these activities. We measured plasma levels of vitamin C and serum levels of zinc and vitamin D prior to and after 12 weeks of supplementation. After 12 weeks supplementation, Redoxon VI recipients showed significantly increased levels of zinc and vitamin C, but not vitamin D. We did not observe an increase in whole blood killing or phagocytosis in the Redoxon VI treated participants, but we did observe increased ROS production. Interestingly, we also observed a statistically significant decrease (~4-fold in days x severity) in severity and length of self-reported illness in the Redoxon VI participants versus placebo. Further refinement of assays for measuring functional outcomes and larger study populations should improve detection of changes in immune function after supplementation. Taken together, our findings suggest that the overall effect of multivitamin and mineral supplementation improves some aspects of immune function and possibly decreases the rate of illness and its severity in an older adult population.

Acknowledgements: We thank Jaewoo Choi and Scott Leonard of the Linus Pauling Institute for measuring vitamin C levels.

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Conflict of Interest: Adrian F. Gombart has consulted for Bayer Consumer Care AG in the past in regards to the role of vitamin D on immune function, but unrelated to the Redoxon VI.

Authorship: MLF and MBL performed experiments and analyzed data. SU enrolled participants, collected samples and coordinated the study. GB performed statistical analysis of the data. AFG designed the study, performed experiments, and analyzed data.

Fats, Immunity and Inflammation

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Omega-6 Fatty Acids in Inflammation and Autoimmunity: Time for a Kuhnian Paradigm Shift

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The paradigm that Omega-6 polyunsaturated fatty acids (PUFA) are pro-inflammatory is paradoxical (notwithstanding antioxidant protection or excessive intakes) and is primarily based on the classical role of eicosanoids in early (onset) inflammation [1]. The in vivo evidence does not support the generalisation that Omega-6 PUFA are pro-inflammatory [1]. Studies in autoimmune and chronic inflammation animal models of Rheumatoid Arthritis (RA) and Multiple Sclerosis (MS) have demonstrated protective effects of the Omega-6 PUFA [1] particularly gamma-linolenic acid (GLA, 18:3 n-6). Re-analysis of clinical trials supplementing linoleic acid (LA, 18:2 n-6) in MS showed reduced relapse severity and in mildly affected patients reduced disease progression. In ad-

dition, recent clinical trials in MS using GLA alone or in combination with other fatty acids have reported beneficial clinical effects [2–4]. Similarly three clinical trials in RA with GLA supplementation have also shown clinically beneficial effects [5]. Experimental rodent and non-human primate studies have demonstrated reduced atherosclerotic lesions and cardiovascular protection with Omega-6 PUFA. Furthermore, several meta-analyses and EPIC-Norfolk findings show Omega-6 PUFA reduce the risk of Coronary Heart Disease, although some studies have shown no associations. Proposed mechanisms of action of Omega-6 PUFA include reduced production of pro-inflammatory TNF?, IL-1β, IL-6, IL-8, MCP-1, MIP-1? and ICAM-1 expression and upregulation of anti-inflammatory TGFβ. These effects appear to be mediated by the binding to nuclear transcription factors such as PPAR and/or via metabolism to eicosanoids such as PGJ2, LXA4, PGE1, PGE2 and PGI2 which can mediate immuno-regulatory, anti-inflammatory and resolution-like effects. In conclusion, a paradigm shift is required to fully understand the role of Omega-6 PUFA in inflammation, autoimmunity and disease.

Conflict of Interest: The author is a named inventor on patents for the treatment of neurodegenerative conditions.

Keywords: Omega-6 PUFA, immune and inflammatory biology, experimental models, clinical trials.

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Omega-3 Fatty Acids and Resolution of Inflammation

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Inflammation is a coordinated host response that when self-limited is protective. Many cell types upon activation produce mediators that regulate the physiological function of inflammation. Arachidonic acid derived mediators that include the leukotrienes, prostaglandins and thromboxane orchestrate the initiation of the inflammatory response. Termination or resolution of inflammation is also appreciated to be an active response coordinated by a novel genus of lipid mediators coined as specialized pro-resolving mediators (SPM). These mediators actively control leukocyte responses counter-regulating the production pro-inflammatory signals, promote leukocyte phenotype switch from inflammatory to protective and orchestrate tissue cellular trafficking. Using mass spectrometry-based structure elucidation we recently identified four new mediator families that regulate the progression of inflammation as well as fine tune the host response to clear the invading pathogens, repair and regenerate damaged tissues in tissues during ongoing infectious-inflammation. These include the thirteen series resolvins (RvT) and the protectin conjugates in tissue regeneration (PCTR). Failure to engage these protective pro-resolving pathways is implicated in the etiopathogenesis of many inflammatory diseases including infections, cardiovascular disease and neurological disease. Using a targeted mass spectrometry-based approach, measuring the flux down each of the major bioactive metabolomes we recently found that lipid mediator profiles from both experimental systems and humans provide an insight into the body's inflammation-resolution status. Using this lipid-mediator profiling approach we have recently investigated the relationships between circulating SPM concentrations and cellular responses in healthy volunteers following omega-3 fatty acid supplementation. We also assessed the relationship between the concentrations of these molecules in the cerebrospinal fluids and outcome following treatment in patients with meningeal tuberculosis. Results from these studies demonstrated a link between SPM-concentrations and outcome suggesting that functional lipid mediator profiling may represent a novel useful tool in patient stratification and to also assess treatment responsiveness. Thus, these results indicate that resolution-based personalized medicines may be useful in both preventing and treating diseases with an inflammatory component.

The Mediterranean Diet, Immunity and Inflammation

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Flavonoids and Allergy

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The allergy prevalence has increased during the last decades and nutrition could have played a role in this fact. New dietary habits, as well as environmental factors among others, could be involved in this rise in allergic prevalence as well as worsening their symptomatology. On the contrary, particular bioactive compounds present in the food may help both to prevent the onset or to modulate the severity of this disease. The flavonoids arise, among some other potential functional components, as modulators of allergy by several mechanisms.

Flavonoids, are secondary plant products present in foods such as seeds, nuts, grains, spices and derived beverages. Flavonoids have emerged as potential therapeutic agents in cardiovascular diseases, chronic inflammation and cancer [1] and, in the last years, data about their effects on allergies have emerged [2].

In vitro studies have demonstrated that certain flavonoids, besides their antioxidant and anti-inflammatory actions, have the ability to down-modulate specific IgE-derived degranulation of mastocytes, as well as the associated cytokine and eicosanoids release. In addition, in vivo studies in experimental models have also showed inhibition of eosinophil accumulation, regulation of the Th1/Th2 balance and in general a decrease in inflammatory mediators' production. Finally, although just a few evidences exist, some clinical and epidemiological studies suggest that an increase in flavonoid intake could be beneficial for allergic diseases such as asthma and rhinitis.

A better understanding of mechanisms and more human clinical trials to substantiate the anti-allergic efficacy of flavonoids are still required.

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Keywords: Flavonoids, polyphenols, allergy, immunity, IgE.

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Beer, Immune System and Microbiota

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Although the scientific literature is vast about a harmful element of our diet, such as alcohol and the damage of its consumption on organs and metabolism, the Baltimore study made a change in 1926 revealing a U-shaped relationship between the amount of alcohol intake and the rate of total mortality, showing a decreasing effect on mortality when moderate alcohol is consumed in comparison with non-consumption or excessive intake. Since then, increasing evidence suggests that light to moderate amounts of polyphenol-rich alcoholic beverages like wine or beer could have health benefits, by decreasing the risk of cardiovascular disease (CVD) mortality when moderate alcohol is consumed compared with non-consumption or excessive intake. Scientists have long debated the effects of alcohol on the immune system, showing that high doses of alcohol consumption can directly suppress a wide range of immune responses, being associated with an increased incidence of a number of infectious diseases. However, moderate alcohol consumption seems to have a beneficial impact on the immune system compared to alcohol abuse or abstinence. Therefore, the link between alcohol consumption, immune response, as well as infectious and inflammatory processes remains not completely understood. With this in mind, it is important to realize that other factors, unrelated or indirectly related to immune function, like drinking patterns, beverage type, amount of alcohol, or gender differences, will affect the influence that alcohol consumption may have on the immune system. In addition, moderate consumption of alcohol has been also associated with higher gut bacteria diversity, while the habit of consuming a high amount of alcohol significantly modifies the microbiota compared to a moderate daily consumption.

Nutrition and Infectious Disease

380/66
Vitamin D and Respiratory Infections

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Vitamin D metabolites support innate antimicrobial and antiviral immune responses in humans, and vitamin D deficiency associates with susceptibility to diverse respiratory infections across the lifespan. In this presentation I will review the latest findings of meta-analyses of individual participant data from clinical trials, which indicate a potential role for vitamin D supplementation in the prevention of acute respiratory infections and asthma exacerbations, and in the treatment of pulmonary tuberculosis. I will also present new data suggesting that Mycobacterium tuberculosis, the

causative organism of tuberculosis, may itself dysregulate vitamin D metabolism. Thus, vitamin D deficiency may be a consequence, as well as a cause, of respiratory infection.

380/77
Iron and Infection

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Iron is required for the growth of almost all infectious organisms but is also needed for host immune function. The iron regulatory hormone hepcidin controls both total body iron levels and the distribution of iron. Hepcidin expression is regulated by the balance of several signals, chief among them being iron status, inflammation, and erythropoietic drive. Interestingly, iron appears to be the only nutrient that is controlled by a hormone that responds both to nutrient levels and to infection, underscoring the importance of iron in host-pathogen interactions. Furthermore, hepcidin is evolutionarily related to microbicidal defensins that target bacteria and yeast infections. Here I will discuss the role of hepcidin and iron in infectious diseases and the immune response. Emerging evidence is revealing marked heterogeneity in how hepcidin is regulated during different types of infection, and the effect of hepcidin and altered iron distribution on the progression of infections is also highly variable. One of the best-studied infections in this field is malaria. Epidemiological evidence in humans shows that iron is a critical determinant for the outcome of malaria, and experiments in mice show that hepcidin controls growth of the liver-stage of *Plasmodium* infection. Ongoing work is examining how iron availability and hepcidin influence the *Plasmodium* blood-stage, development and recovery from anaemia, and malarial transmission. The innate immune response to most infections (including malaria) involves an acute and profound hepcidin-mediated decrease in serum iron levels. Furthermore iron deficiency is the most common micronutrient deficiency worldwide; recent genetic evidence links lack of iron acquisition by lymphocytes from serum to severe immunodeficiency. Therefore, a currently underappreciated important aspect of iron and hepcidin in the context of infection is that iron levels may directly regulate the adaptive immune response.

Microbiota and Immune Health

380/67
Microbiota & GALT

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The effects of early-life factors on neonatal development using a piglet model of human infants. I am especially interested in how the environment and early nutrition impact on the microbiota, and the interactions which occur at the host-microbe interface in response to these factors. We have previously demonstrated that exposure to different types of farm environments influence both local antigen presentation, and levels of Tregs in the gut mucosa. We have also shown that high-hygiene environments during the neonatal period direct T-cell differentiation at the mucosa surface, probably reducing the potential for immune regulation. We also explore early nutritional supplementation and have shown that observed affects can be driven by earlier dietary regimes. Here, both the composition and metabolic activity of the early microbiota can be modified, and these changes are linked to altered host metabolic and immune phenotypes. The process of weaning destabilises the microbiota and we have demonstrated that intervention at this time can impact on immune and metabolic development, and on the pattern of initial intestinal colonisation. Importantly, many of the change we have characterised are sustained beyond the period of intervention, and thus may impact on longer-term host health. Specifically, the first day or two of life, and weaning, are critical points of developmental plasticity and appear to offer windows of opportunity in which interventions have greater potential to promote longer term health than if delivered at other times of life. Our work is especially relevant to infants who are at increased risk of developing metabolic and immunological disorders in later life due to factors such as caesarean births and early antibiotic therapy.

380/12
Probiotic Interaction with Host Immunity

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The gastrointestinal tract is the most active microbiologically ecosystems and play a crucial role in the Mucosal Immune System (MIS). Probiotic microorganisms stimulate the Immune System and send signals to: 1) the intestinal epithelial cells and the immune cells associated, to the intestine; 2) the Paneth cells to produce antimicrobial sustances The interactions induce the production of different cytokines from the immune cells with MIS activation. We demonstrate: a) probiotics stimulate the mucosal immunity increasing the number of IgA +intestinal cells, activity

of T cells, and induce inmunomodulation by IL10 b) We determined the importance of the probiotic viability c) the interaction with the epithelial cell and macrophages, is Toll like receptors (TLRs) dependent d) probiotics induce an increase in goblet and Paneth cells e) favor the innate immune response, where macrophages and DCs play an important role, without induce an inflammatory response, favoring the expression of regulators proteins to minimize the NFkB activation avoiding proinflammatory cytokines f) probiotics are effective in Salmonella infection by increase of microbicidal activity of macrophages g) In malnutrition models improves the histology of intestine and thymus and the Immune System functionality h) In respiratory allergy model, a PFM diminished the levels of IgE with Th1 balance, favoring the IgG instead of IgE. In conclusion probiotic and PFM have an important role in the functionality of the MIS and in the mechanisms of immunoregulation.

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Authorship: Dr Perdigon conceived the idea. Drs Carolina Maldonado and Silvia Cazorla performed the experiments.

All the authors discused the results and approved the present.

Keywords: Probiotic, Fermented milk, Gut immune system, mechanisms involved.

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Obesity, Immunity and Inflammation

380/68

Why Obesity Is an Inflammatory Disease

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The concept of adipose tissue plasticity is well known, as is the fact that a positive energy balance drives increased adiposity in vivo. Less well accepted or indeed understood, are the molecular mechanisms that couple nutritional cues to titrated adipose tissue expansion and those that negatively regulate adipose tissue plasticity particularly under physiological and/or patho-physiological conditions. When one considers the possibility that there may be a limit in the extent to which adipose tissue can expand, it is plausible that surpassing such limits can have significant metabolic consequences. Could the mechanisms involved in regulating adipose tissue function and plasticity hold the key to reversing obesity-related metabolic dysfunction in the face of over-nutrition? Our laboratory has been investigating candidate signalling networks that are likely to be important local regulators of adipose tissue expansion. Some of these will be introduced and discussed.

Keywords: Obesity, adipogenesis, metabolic syndrome, signalling.

380/69

Adipose Tissue as an Inflammatory Focus

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Obesity is associated with a state of low grade, chronic inflammation – this is the current consensus within the scientific community. We also agree that this inflammatory status leads to insulin resistance and higher cardiovascular risk. Inflammation is, in consequence, the link between obesity and other chronic non-communicable conditions such as diabetes, coronary-heart disease, cancer, or dementia.

What is the origin of inflammation in obesity? The adipose tissue, obviously, as obesity results from adipose tissue excess and dysfunction. Unravelling the mechanisms that initiate inflammation in adipose tissue is key to understanding the etiopathogenesis of obesity, and it provides a source of potential therapeutic targets to alleviate obesity's comorbidities. Research into the physiology of mammalian adipose tissue, especially in the last two decades, has revealed a fascinating aspect of this organ, namely its close association with the immune system, to the point that some authors consider it as an immune organ [1, 2]. Immune cells populate the stromal-vascular (i.e. non-adipose) fraction of the tissue, regulating adipocyte metabolism

differently under normal conditions or in obesity. Adipocytes in turn modulate immune cell functions by secreting adipokines such as leptin, adiponectin, or visfatin, and other inflammatory molecules like chemerin, acute phase proteins, complement factors, and typically immune proteins like cytokines and chemokines [3]. More recently, attention has turned into another cell type within the stromal-vascular fraction of the tissue, the adipose stem cells, which seem to present anti-inflammatory activity [4].

So what makes the cells in the adipose tissue initiate an inflammatory response in the first place? The main trigger is adipocyte stress, and three different, non-mutually exclusive pathways have been proposed to explain this phenomenon: hypoxia, oxidative stress, and endoplasmic reticulum stress5. They all share the occurrence of hypertrophied adipocytes that struggle to cope with a nutrient-overloaded environment, consequence of a chronic positive energy balance.

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Nutrition and Immunosenescense

380/70
Probiotics and the Ageing Immune System

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Influenza is a major cause of death in older people and while vaccination offers a prophylactic solution for preventing infection and associated complications, immunosenescence significantly impairs vaccine efficacy. Potential adjuvants and dietary strategies to improve the immune response to influenza vaccines are therefore of interest, particularly in older people.

Emerging evidence suggests that the resident gut microbiota plays an influential role in shaping antiviral defenses and modulating the outcome of viral infections and this forms the basis for the hypothesis that pre- and probiotics may modulate responses to infection or vaccination.

Trials investigating the use of probiotics in prevention of common respiratory illnesses have produced mixed results, although a recent systematic review concluded that they significantly reduce episodes of acute URTI and antibiotic usage in infants and young to middle-aged adults. Response to vaccination is increasingly being used as a surrogate for the response to infection because it can provide information on the immunomodulatory effects of dietary components. The majority of studies investigating the impact of probiotics on responses to vaccination have been conducted in healthy adults, and some show modest effects of probiotics. Since ageing is associated with reduced biodiversity and compromised stability of the gut microbiota, as well as immunosenescence, older individuals may derive particular benefit from intervention with pre- and/or probiotics.

This presentation will describe recent work illustrating how the immune system in young and older subjects responds differently to probiotics, both in vitro and in vivo. Studies investigating the influence of probiotics on respiratory infections and on the immune response to vaccination will be reviewed, and proposed underlying mechanisms will be discussed.

380/71
Vitamin E and the Ageing Immune System

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Ageing is associated with significant changes in immune system, a state often termed as immunosenescence, which has been implicated in the observed higher rates of morbidity in, and mortality from, infection in the elderly. While many immune functions are affected by aging, the defects in T cells are the most pronounced and best characterized. Nutritional intervention has been proposed to be helpful in delaying/reversing immunosenescence, which is well exemplified in the case of vitamin E. Studies in several species of animals show that vitamin E deficiency impairs immune function, which can be corrected by vitamin E repletion. Although vitamin E deficiency is rare in humans, increased intake above recommended levels has been shown to enhance T cell function, particularly in the aged animals and humans. Vitamin E-induced enhancement of immune functions has significant clinical implication as evidenced by the findings that vitamin E supplementation is associated with both enhanced resistance to respiratory infections in aged mice and older adults. The mechanistic studies have revealed that vitamin E's immuno-modulating effects involve both its direct effect of enhancing T cell activation and effector function, and its suppressing effect on production of prostaglandin E2, a T cell-suppressing lipid mediator known to be increased with aging. Together, these findings have provided evidence at the cellular and molecular levels to help understand how vitamin E improves immune function and increase host resistance to infection.

Keywords: Aging, immunity, infection, vitamin E.

Nutrition and Immune Development

380/72
Breast Milk Oligosaccharides and the Developing Immune System

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The immune system of the newborn infant is functionally immature and naïve. Human milk contains bioactive carbohydrates, lipids and proteins that stimulate neonatal innate and adaptive immune development, which can have long-term health implications [1]. Research over the past decade has defined the complexity and bioactivity of the oligosaccharides in human milk (HMO) and other species' milk. The concentrations, structural diversity and degree of fucosylation of HMO is greater than milk oligosaccharides of other species, particularly bovine milk from which many infant formulae are produced [2]. Immune-related functions of HMO include protecting the infant from pathogenic infections, facilitating the establishment of the gut microbiota, promoting intestinal development, and stimulating mucosal and systemic immune maturation. Many of these actions are exerted through carbohydrate-carbohydrate interactions with pathogens or host cells [3, 4]. This presentation will summarize the immune functions of HMO and will review the findings of randomized clinical trials of 2-fucosyllactose (2'-FL) and lacto-N-neotetraose (LNnT) supplementation to infant formula on clinical outcomes, including immune and microbiome development [5–7].

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380/73
Breast-Feeding, Microbiota and Immune Development in Early Life

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The first 1000 days of a human life – the period from conception to the age of 2 years – is a key period during which the immune system is trained and immune fitness/resilience status is set. This early life programming of immunity is substantially influenced by the interaction of the intestinal microbiota and the host mucosal immune system. The development of a stable microbiome and the immune system is a concomitant process. The impact of breastfeeding on this development of the infants' immune system can be explained by different mechanisms:

1. Direct immunomodulatory effects of specific milk components
2. Effect through changing the composition and activity of the gut microbiota.

Breast milk contains high levels of factors that can help the development of a healthy immune system early in life such as immunoglobulins, cytokines, lactoferrin, non-digestible oligosaccharides (prebiotic fibers) and even unique microbes. Extensive amount of studies have indicated that breast-feeding is associated with the prevention of non-communicable diseases (NCDs) such as asthma and allergy, but also auto-immunity. Moreover, reduced early life gut microbial diversity has been associated with a higher risk of NCDs even with consequences for the brain.

380/74
Gene-Environmental Interactions in the Onset and Progression of Asthma

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Although a simple concept of reversible bronchoconstriction, asthma is a complex disorder of chronic inflammation and remodelling punctuated by exacerbations driven by a range of environmental interactions including virus infection, air pollution and diet. Asthma has become an epidemic, affecting 155 million individuals in the world. The most likely reason for rising trends relates to various aspects of the Western Lifestyle, especially in the developed and developing world. Most asthma begins in childhood and in genetically susceptible individuals is triggered by repeated viral infections causing bronchiolitis especially human rhinoviruses. These serve as "danger signals" to direct antigen presenting dendritic cells to instruct T cells along a differentiation pathway involving the pro-allergic cytokines L-3, -4, -5, -13 and GM-CSF. Viruses and other insults, recognised by the epithelium as danger signals, lead to the release of the alarmins IL-33, IL-25 and TSLP

which polarise the immune response towards the Type 2 (allergic) response. Once established, T cells instruct B cells to switch from IgM to IgE synthesis. An alternative mechanism for activating Type-2 immunity is via T2 innate lymphoid cells implicated in the non-allergic eosinophilic forms of asthma. Many genome-wide screens for asthma have now been carried out and identified asthma susceptibility genes many of which are preferentially expressed in the epithelium (e.g. IL1RL1 and IL18R1, HLA-DQ, IL33, SMAD3 and ORMDL3/GSDMB) and implicated in the innate immune response, while others are shared with those of other atopic diseases. Early life exposure to farm animals and some household pets is protective against allergy via exposure to high concentrations of microbial products that induce a state of tolerance. This occurs via interaction with the many pathogen recognition receptors on the epithelium and DCs deviating the immune response away from T2 immunity. An alternative explanation is through microbial induction of protective metabolites such as the short fatty acid butyrate.

Annals of Nutrition & Metabolism

Molecular and Cellular Roles of Nutrients in the Immune System

380/20
In Vitro Immunomodulating Effect of Quinoa and Hemp Proteins

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Dietary proteins, in addition to being instrumental in a wide range of nutritional and biological processes, can also be precursor of peptides able to influence a number of regulatory systems, including the immune system [1, 2]. While proteins from many commonly consumed food commodities have been investigated for their potential to serve as precursors of peptides with immunomodulating properties, studies on emerging protein sources, such as those from quinoa and hemp, are sparse. Therefore, the objective of this research was to evaluate the immunomodulatory capacity of quinoa and hemp proteins using a cell model system. Proteins were first isolated from quinoa and hemp seeds by alkaline extraction and the resulting protein isolates were submitted to in vitro gastrointestinal (GI) digestion. Both digested proteins were able to significantly ($P < 0.05$) suppress the production of nitric oxide and the pro-inflammatory cytokine TNF-α in lipopolysaccharide (LPS)-stimulated RAW 264.7 macrophage cells. Conversely, an increased IL-6 secretion was observed following the treatment of the cells with the digests. The samples had no effect on the macrophage cell viability. Findings from this research show that peptides with immunomodulatory properties can be generated during GI digestion of quinoa and hemp proteins and suggest the potential of these proteins as functional food ingredients with health benefits.

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Conflict of Interest: None.

Authorship: I. M. E Lacroix designed the study, I.M. E. Lacroix and A. de Vries performed the experimental work and data analysis and I. M. E. Lacroix wrote the abstract.

Keywords: Quinoa, hemp, bioactive peptides, nitric oxide, cytokines.

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Immunometabolism

380/35
Overtraining and Exhausting Exercise Alter Redox Status, Composition and Functionality of Lymphoid Tissues in Rats

Camps Bossacoma, M.[1]*; Estruel-Amades, S.*[1]*; Garcia-Cerdà, P.*[2]*; Massot Cladera, M.*[1]*; Periz, M.*[2]*; Castell Escuer, M.*[1]

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Although moderate exercise produces beneficial effects, intense physical activity alters the immune system (1). The aim of this study was to establish the influence of overtraining and exhausting exercise on oxidative stress and spleen and thymus lymphocyte composition and functionality in rats. Overtraining was induced with two exhausting tests (on Monday and Friday) plus three trainings per week for 5 weeks. At the end, rats were classified into overtrained (T), exhausted (T-E) and 24 h post-exhaustion (T-24E) groups. Reactive oxygen species (ROS) production from peritoneal macrophages and superoxide dismutase (SOD) and catalase activities in spleen and thymus were assessed. Moreover, lymphocyte composition and function were also determined. Regarding the results, exhaustion increased ROS production. Overtraining and exhausting exercise decreased SOD activity in spleen and thymus. Moreover, spleen catalase activity was reduced in the T-E group. Overtraining increased spleen T/B and decreased Th/Tc cell proportion ratios, whereas reduced spleen NK and NKT cell proportions. No changes in thymus were observed by overtraining. Nevertheless, exhaustion decreased the proportion of mature thymocytes and the proportion of spleen NK and NKT cells. These changes in spleen cells were maintained in the T-24E group together with a lower proportion of TCR?β+ and TCR??+ cells. Spleen T- and B-cell proliferation rate was higher after exhaustion, modifying the cytokine profile released. These results showed that overtraining and exhaustion alter the redox status, which are associated with changes in lymphocyte composition and function. Therefore, it could be of interest to test an antioxidant food component in this model.

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Conflict of Interest: None.

Authorship: M.C. and M.C-B designed the study; S.E-A., P.G-C., M.M-C, M.P. and M.C-B. carried it out, P.G-C. analysed the data; M.C-B and P.G-C. wrote the abstract.

Keywords: Catalase, exhausting exercise, overtraining, spleen, superoxide dismutase.

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Effects of Overtraining and an Exhausting Exercise on the Mucosal Immune System in Rats

Estruel-Amades, S.; Ruiz-Iglesias, P.; Camps Bossacoma, M.; Pérez-Cano, F.; Castell Escuer, M.; Massot Cladera, M.

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Intense physical exercise has been shown to induce gastrointestinal complaints and negative effects on the mucosal-associated lymphoid tissue (MALT) [1, 2]. The aim of this study was to seek MALT biomarkers showing alterations induced by overtraining and exhausting exercise in rats. For this purpose, 4-week-old female Wistar rats undertook high-intensity endurance training on a treadmill for 5 weeks. At the end, rats were distributed into three groups: overtrained (samples obtained 24 h after a regular training), exhausted (samples obtained immediately after an exhaustion test) and 24 h post-exhaustion (samples obtained 24 h after the exhaustion test). A sedentary group was used as a control. Changes in mucosal SIgA content (intestinal and salivary), intestinal permeability and mesenteric lymph nodes (MLN) composition and function were assessed. The results showed a negative correlation between the performance in the final exhaustion test and the content of IgA in salivary glands and gut washes 24 h after this test. At this time, intestinal permeability tended to increase with respect to the overtrained group. Regarding MLN composition, the overtraining raised the proportion of T cells, which decreased their proliferative capacity but increased the secretion of proinflammatory cytokines. The exhaustion reduced the proportion of TCRγδ+CD8αα+ cells in favour of TCRγδ+CD8αβ+ cells and increased the secretion of IFNγ, TNFα, IL-2 and IL-6. In conclusion, the overtraining and exhaustion models achieved in this study produce a disruption in the MALT that can be characterized by quantifying the mucosal IgA concentration. These models can be useful for testing preventive nutritional interventions.

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Conflict of Interest: None.

Authorship: M.M-C, M.C. and F.P-C. conceived and designed the experiments; S.E-A., P.R-I. and M.C-B carried out the experiments; S.E-A., P.R-I. and M.M-C analysed the data; P.R-I. and M.M-C wrote the abstract and M.C. and F.J.P-C reviewed it.

Keywords: Exhausting exercise, mucosal IgA, intestinal permeability, mesenteric lymph nodes.

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Nutrition and Inflammation

380/6

The Effect of Obesity on Adipose Tissue Fatty Acid Composition and Lipid Mediators, and their Response to Chronic Marine Omega-3 Fatty Acid Supplementation

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Obesity is linked with increased inflammation that enhances risk of type-2 diabetes and CVD. We assessed the effect of obesity on AT fatty acid (FA) composition, lipid mediators, and response to chronic omega-3 fatty acid supplementation. AT biopsies were collected pre- and post-12 week supplementation with 1.1 g EPA + 0.8 g DHA/day or corn oil. The composition of FA in the total lipid extract (TLE) of AT from 37 normal weight and 45 obese subjects was assessed by gas chromatography and the concentration of lipid mediators by GC-MS.

Obese subjects had higher proportions of AT AA, EPA, DPA, eicosapentaenoylethanolamine (EPEA), arachidonoylethanolamine (AEA), PGE2, and 5-HETE ($P < 0.05$), and lower concentrations of many oxo-octadecadieonic acids, hydroxyeicosatetraenoic acids, prostaglandins, lipoxins, EPA derived resolvins and glycerol-esters, hydroxydocosahexaenoic acids, and FA ethanolamines of saturated FA ($P < 0.05$ all) than normal weight subjects (NWS).

Chronic supplementation with EPA+DHA increased AT EPA, DPA, DHA ($P < 0.01$), EPEA, docosahexaenoylethanolamine, EPA

glycerol-ester and 14-HDHA in NWS ($P < 0.05$), and EPA and 8-iso-PGF2α in obese subjects ($P < 0.006$). EPA+DHA supplementation decreased AEA, 1-20-4-glycerol-ester and 14,15-dihydroxyeicosatetraenoic acid in NWS ($P < 0.05$), and 2-AG, glycerol-esters of 16.1 and 18.1, 12-HETE, LTE4, HXA3, and RvE3 in obese subjects ($P < 0.05$).

These data suggest dysregulation of lipid signalling in AT in obesity, and in the incorporation and utilization of EPA+DHA for synthesis of anti-inflammatory lipid mediators. EPA+DHA are able to modulate synthesis of EPA, DHA and AA derived lipid mediators but obesity may involve resistance to these effects particularly in endocannabinoid synthesis.

Acknowledgements: In collaboration with The Department of Adipose Biology, Institute of Physiology of the Czech Academy of Sciences, Prague for lipid mediator laboratory analyses.

Financial Support: This research was supported by the European Commission (grant number 244995).

Conflict of Interest: Philip Calder is an advisor to Pronova BioPharma, Aker Biomarine, Smartfish, Sancilio, Solutex, Dutch State Mines, Cargill and Danone/Nutricia.

Authorship: Helena Fisk conducted processing of adipose tissue for lipid mediator extraction, lipid mediator data integration and analysis, fatty acid data analysis, all statistical analyses and wrote the abstract.

Rob Ayres conducted processing of adipose tissue for fatty acid composition.

Ondrej Kuda and Jan Kopecky supervised all aspects of lipid mediator extraction and measurement by UPLC-MS/MS. Ondrej Kuda performed all lipid mediator measurements by UPLC-MS/MS.

Philip Calder was responsible for designing the study and supervising all aspects of the reported work.

Keywords: Omega-3 fatty acids, adipose tissue, lipid mediators, inflammation, obesity.

References

N/A.

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Comparison Between Different Branched-Chain Amino Acids Supplementation Protocols on Cytokines Synthesis in Lipopolysaccharide-Stimulated Macrophages

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This study aimed to compare two branched-chain amino acids (BCAA) supplementation protocols on cytokines synthesis in LPS-stimulated RAW 264.7 macrophages. Cell cultures were distributed into five groups: CTL – DMEM without BCAA supplementation (0.8 mmol/L of each BCAA); LEU – DMEM supplemented with leucine (1.2 mmol/L); ISO – DMEM supplemented with isoleucine (1.2 mmol/L); VAL – DMEM supplemented with valine (1.2 mmol/L) and LIV – DMEM supplemented with leucine, isoleucine and valine (1.2 mmol/L of each BCAA). These groups followed two different treatment protocols: in acute supplementation (AS), cells were treated with CTL or BCAA media and LPS (1 μg/mL) stimuli for 24 hours. In chronic supplementation (CS), cells were treated with CTL or BCAA media for 24 hours and, after this period, the media was replaced and these cells were stimulated with LPS (1 μg/mL) for another 24 hours. IL-6, IL-10 and TNF-α cytokines were quantified by ELISA. In AS, all supplemented groups had a higher concentration of IL-10 compared to CTL ($p < 0.05$). In CS, there was an increase in IL-10 concentration in all supplemented groups when compared to CTL ($p < 0.001$) and in ISO compared to LEU and LIV ($p < 0.01$). There was also an increase in IL-6 synthesis in ISO, VAL and LIV compared to CTL ($p < 0.05$) and in ISO compared to LEU ($p < 0.01$). CS shows to be more effective in increasing IL-10 synthesis than AS. Additionally, isoleucine plays a promising role in the modulation of cytokine synthesis when administered before and not only during the inflammatory state.

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Financial Support: This work is supported by the São Paulo Research Foundation (A.B., grant number 2016/11360-6), (A.Y.C., grant number 2016/22789-3), (J.T., grant number 2016/04910-0).

Conflict of Interest: The authors declare that they have no conflict of interest.

Authorship: This study is conducted by A.B., with the collaboration of A.Y.C. in the assays. The laboratory is provided by R.A.F. and P.B. Technical support and supervision of the work are carried out by MMR and JT. This abstract was revised by A.Y.C. and M.M.R.

Keywords: Branched-chain amino acids, macrophages, inflammation, cytokines.

References

N/A.

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Late Supplementation with Branched-Chain Amino Acids in Lipopolysaccharide-Stimulated Macrophages Does Not Change Inflammatory Parameters

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[1]Department of Food and Experimental Nutrition, University of São Paulo, Brazil; [2]Department of Clinical Analysis, University of São Paulo, Brazil; [3]Department of Nutrition, University of São Paulo, Brazil

Objective: This study aimed to evaluate the late supplementation with branched-chain amino acids (BCAA) in LPS-stimulated RAW 264.7 macrophages on prostaglandin E2 (PGE2), cytokines and nitric oxide synthesis.

Methods: Cell cultures were distributed into five groups: CTL – DMEM without BCAA supplementation (0.8 mmol/L of each BCAA); LEU – DMEM supplemented with leucine (1.2 mmol/L); ISO – DMEM supplemented with isoleucine (1.2 mmol/L); VAL – DMEM supplemented with valine (1.2 mmol/L) and LIV – DMEM supplemented with leucine, isoleucine and valine (1.2 mmol/L of each BCAA). Groups were treated with CTL medium and LPS (1 μg/mL) for 24 hours. After this period, the CTL medium was removed and the CTL or BCAA media was added. These cells were re-stimulated with LPS (1 μg/ml) for another 24 hours. PGE2 was quantified by enzyme immunoassay kit, the cytokines IL-6 and TNF-α were quantified by ELISA and indirect NO was measured by Griess reaction.

Results: There was no statistically significant difference between the groups.

Conclusion: BCAA supplementation after the LPS-inflammatory state induction does not influence the synthesis of inflammatory mediators.

Acknowledgements: N/A.

Financial Support: This work is supported by the São Paulo Research Foundation (A.B., grant number 2016/11360-6), (J.T., grant number 2016/04910-0).

Conflict of Interest: The authors declare that they have no conflict of interest.

Authorship: This study is conducted by A.B., with the collaboration of R.R. in the assays. The laboratory is provided by R.A.F. and P.B. Technical support and supervision of the work are carried out by M.M.R. and JT. This abstract was revised by R.R. and M.M.R.

Keywords: Branched-chain amino acids, inflammation, nitric oxide, cytokines, prostaglandin.

References

N/A.

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Late Supplementation with Branched-Chain Amino Acids in Lipopolysaccharide-Stimulated Macrophages Does Not Change Inflammatory Parameters.

Bonvini, A.[1]*; Raizel, R.*[1]*; Fock, R.*[2]*; Borelli, P.*[2]*; Rogero, M.*[3]*; Tirapegui, J.*[1]

[1]Department of Food and Experimental Nutrition, University of São Paulo, Brazil; [2]Department of Clinical Analysis, University of São Paulo, Brazil; [3]Department of Nutrition, University of São Paulo, Brazil

Objective: This study aimed to evaluate the late supplementation with branched-chain amino acids (BCAA) in LPS-stimulated RAW 264.7 macrophages on prostaglandin E2 (PGE2), cytokines and nitric oxide (NO) synthesis.

Methods: Cell cultures were distributed into five groups: CTL – DMEM without BCAA supplementation (0.8 mmol/L of each BCAA); LEU – DMEM supplemented with leucine (1.2 mmol/L); ISO – DMEM supplemented with isoleucine (1.2 mmol/L); VAL – DMEM supplemented with valine (1.2 mmol/L) and LIV – DMEM supplemented with leucine, isoleucine and valine (1.2 mmol/L of each BCAA). Groups were treated with CTL medium and LPS (1 μg/mL) for 24 hours. After this period, the CTL medium was removed and the CTL or BCAA media was added. These cells were re-stimulated with LPS (1 μg/ml) for another 24 hours. PGE2 was quantified by enzyme immunoassay kit, the cytokines IL-6 and TNF-α were quantified by ELISA and indirect NO was measured by Griess reaction.

Results: There was no statistically significant difference between the groups.

Conclusion: BCAA supplementation after the LPS-inflammatory state induction does not influence the synthesis of inflammatory mediators.

Acknowledgements: N/A.

Financial Support: This work is supported by the São Paulo Research Foundation (A.B., grant number 2016/11360-6), (J.T., grant number 2016/04910-0).

Conflict of Interest: The authors declare that they have no conflict of interest.

Authorship: This study is conducted by A.B., with the collaboration of R.R. in the assays. The laboratory is provided by R.A.F. and P.B. Technical support and supervision of the work are carried out by M.M.R. and JT. This abstract was revised by R.R. and M.M.R.

Keywords: Branched-chain amino acids, inflammation, nitric oxide, cytokines, prostaglandin.

References

N/A.

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Diet as a Moderator in the Association of Adiposity and Sedentary Behavior with Inflammatory Biomarkers in European Adolescents

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Aim: Our aim is to demonstrate that a healthy diet might attenuate the inflammation related to adiposity or sedentary behavior, whereas an unhealthy diet may increase the effects.

Methods: In 618 adolescents (13–17 y) of the European HELENA study, data was available on body composition, a set of inflammation markers, and food intake determined by a self-administered computerized 24 h-recall. A 9-point Mediterranean diet Score and an antioxidant-rich diet Score were used as dietary parameters and tested as moderator. Total body fat was represented by the sum of six skinfold thicknesses and central adiposity by waist circumference. A set of inflammation-related biomarkers was used as outcome: a pro/anti-inflammatory interleukins ratio, TGFβ-1, C-reactive protein, TNF-α, 3 cell adhesion molecules, 3 types of immune cells, alanine-transaminase (ALT), gamma-glutamyltransferase (GGT), and homocysteine. Sedentary behavior was reflected by self-reported screen time. Multiple linear regression analyses tested moderation by diet in the association of adiposity and sedentary behavior with inflammation. Analyzes were adjusted for age, sex, country, puberty, socioeconomic status and parental education.

Results: Both diet scores, Mediterranean and antioxidant-rich diet, were significant protective moderators in the effect of adiposity on the pro/anti-inflammatory interleukins ratio, TGFβ-1, GGT, and ALT; and in the effect of sedentary behavior on ALT (P = 0.014; P = 0.027) and pro/anti-inflammatory ratio (P = 0.001; P = 0.004).

The set of low-grade inflammatory markers was used as outcome:

- interleukins in an inflammatory ratio for adiposity ((IL-1 + IL-2 + IL-6)/(IL-4 + IL-5 + IL-10));
- cytokines in an inflammatory ratio for sedentary behavior (IL-6, IL-10, TNF-α, TGFβ-1);
- C-reactive protein;
- 3 cell-adhesion molecules (sVCAM-1, sICAM-1, sE-selectin);
- 3 cardiovascular risk markers (GGT, ALT, homocysteine);
- 3 immune cell types (white blood cells, lymphocytes, CD3).

They were measured as follow:

Blood samples were collected from fasting in a randomly selected one-third subset of the total HELENA study population. The methodology for blood collection, transport and analysis was standardized among all participating centers. All analyses were executed by certified laboratories. CRP was measured in serum by immunoturbidimetry (AU2700 biochemistry analyzer, Olympus, Watford, UK). Serum cytokines were determined using the High Sensitivity Human Cytokine MILLIPLEXTM MAP kit (Millipore Corp., Billerica, MA, USA) and collected by flow cytometry (Luminex-100 v.2.3, Luminex Corporation, Austin, TX, USA). WBC counts were determined with automated blood cell counters. Lymphocytes were measured in the Immunonutrition laboratory at the Spanish National Research Council after incubated with monoclonal antibodies (BD Biosciences, San José, CA, USA). The serum adhesion molecules was analyzed through commercial ELISA kit (Diaclone, France). ALT and GGT levels were measured in serum using standard protocols with the clinical chemistry system RxL (Dade Behring, Schawalbach, Germany). Homocysteine was measured by competitive immunoassay (Immulite 2000, DPC Biermann GmbH, Bad Nauheim, Germany).

Conclusion: A higher adherence to the Mediterranean diet or an antioxidant-rich diet may attenuate the onset of oxidative stress signs associated with adiposity and sedentary behavior, whereas a poor diet seems to increase inflammation.

Acknowledgements: Thanks to the European Community Sixth RTD Framework Programme (Contract FOODCT-2005-007034), which supported this study.

Financial Support: The HELENA Study was carried out with the financial support of the European Community Sixth RTD Framework Programme (Contract FOODCT-2005-007034).

Conflict of Interest: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Authorship: A. Arouca formulated the research question, has analyzed the data and wrote a draft of the paper. N. Michels helped in formulating the research question, analyzing the data and did editing of the first draft. N. Michels and S. De Henauw are co-supervisor and supervisor of A. Arouca; L.A. Moreno was coordinator of the HELENA project. All other authors were involved in the HELENA project (coordinator or data collection). A. Marcos was responsible for the inflammatory parameter analyses. I. Huybrechts developed the Mediterranean diet Score. M. Gonzalez-Gross was responsible for the complete blood sampling and collection. All authors have read the draft and agreed on the final version.

Keywords: Low-grade inflammation, overweight, sedentary behavior, Mediterranean diet, interaction.

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Gamma-Linolenic and Pinolenic Acids Exert Anti-Inflammatory Effects in Cultured Human Endothelial Cells Through their Elongation Products

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Plant-derived polyunsaturated fatty acids (PUFAs) gamma-linolenic acid (GLA) and pinolenic acid (PIN) may provide sustainable land-based sources of bioactive fatty acids.

Anti-inflammatory effects of GLA and PIN were compared to EPA and DHA in cultured EA.hy926 cells. Cells were treated with PUFAs (25 and 50 μM) for 48 hours prior to stimulation with tumour necrosis factor for 24 hours. FAs were incorporated into EA.hy926 after 48 hours, with significant increases in elongation products; dihomo-gamma-linolenic acid (DGLA) from GLA and eicosatrienoic acid (ETrA) from PIN. Pre-treatment with PUFAs (25 and 50 μM) had differential effects on inflammation depending on PUFA and cytokine examined. Interleukin (IL)-6 and monocyte-chemoattractant protein (MCP)-1 were significantly reduced after treatment with either EPA or DHA at 25 μM and 50 μM with GLA and PIN treatment significantly reducing MCP-1 at 50 μM. Soluble intracellular adhesion molecule (sICAM)-1 concentrations were significantly reduced by all four PUFAs at 25 and 50 μM. Anti-inflammatory effects of GLA and PIN were possibly due to their elongation products, therefore silencing of ELOVL5 was explored. ELOVL5 siRNA significantly inhibited the production of DGLA and ETrA in EA.hy926 cells pre-treated with GLA and PIN (50 μM). Furthermore significant decreases in sICAM-1, MCP-1 or IL-6 were not l seen after pre-treatment with GLA or PIN in ELOVL5 siRNA silenced EA.hy926 cells.

GLA and PIN demonstrate some anti-inflammatory effects in this model system but are less potent than EPA or DHA. Anti-inflammatory effects of GLA and PIN may be due to their elongation metabolites; DGLA and ETrA.

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University of Southampton.

Conflict of Interest: None.

Authorship: N/A.

Keywords: Polyusaturated fatty acids, gamma-linolenic acid, pinolenic acid, anti-inflammatory, endothelial cells.

References

N/A.

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Effect of Supplementation with Polyphenol-Rich Extract of Passiflora Ligularis on the Risk Factors of Metabolic Syndrome in a Murine Model

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The present study was focused on evaluating the effect of polyphenols rich extract from Passiflora ligularis (Granadilla) on the risk factors of metabolic syndrome. Twenty-eight overweight induced Wistar rats were exposed to a two week 30% rich in sucrose diet. The animals were distributed in a completely randomized experimental design, forming a 2x3 +1 factorial model (2 sources of extract rich in polyphenols from Passiflora ligularis and Camellia sinensis, 3 supplementation dose in drinking water 2.0, 2.5, and 3.0 g/l and 1 control group. After 42 days, analyzed variables were food and water consumption, weight gain, blood glucose, cholesterol and serum triglycerides, and percentage of ethereal feces extracts. A sample of liver was taken to determine the degree of hepatic steatosis by means of histological analysis. Results showed effect of polyphenol extract addition with relation to variables weight gain and lipid percentage in feces ($p < 0.05$). The extract of Camellia sinensis statistically reduced water consumption in comparison to the control group. For serum variables, significant glucose reduction was observed in the rats fed with doses of 2.5 and 3.0 g/l of the extract rich in polyphenols from Passiflora ligularis. In both sources of polyphenol-rich extracts, the highest dose reduced triglycerides levels ($p = 0.05$).

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Financial Support: The authors are grateful for the contribution granted by the Universidad de Manizales (Manizales, Colombia) as a result of the Internal Call for Research 2014-II.

Conflict of Interest: Authors manifest that there is no direct or indirect relationship, commercial or industrial connections that generate any conflict of interests derived from the present work.

Authorship: Doctors Ángel-Isaza and Narvaez-Solarte (Veterinarians) where in charge of the animal-related proceedings throughout the project. Doctor Gonzalez-Correa and J.C. Carmona-Hernandez were dedicated to all the methodology concerning polyphenol extraction and quantification. All authors contributed equally to the drafting, editing and data management.

Keywords: Granadilla, green tea, anti-inflammatory, metabolism.

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Association Between Plasma Polyphenols and Chronic Low-Grade Inflammation: A Cross-Sectional Data Analysis

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Polyphenols have been suggested to exert anti-inflammatory properties by animal studies, yet results from human research have been inconsistent. Studies using plasma biomarkers for assessment of polyphenol intake are particularly scant. We aimed to explore the associations between plasma concentrations of total polyphenols, polyphenol subgroups and 35 individual polyphenol compounds and the state of chronic low grade inflammation as measured by high-sensitivity C-reactive protein (hs-CRP). A cross-sectional data analysis was performed using 315 predominantly healthy participants in the European Prospective Investigation into Cancer and Nutrition cohort with available measurements of plasma polyphenols and hs-CRP. Cross-sectional associations were investigated across quartiles of polyphenol concentrations using multivariable-adjusted logistic regression for CRP ≥3 mg/L. Higher plasma concentrations of total polyphenols, phenolic acids and lignans were associate with 29%, 28% and 29% lower odds of elevated CRP (95% confidence intervals: 50%-1%; 89%-28%; 48%-2%, respectively. Odds ratios (OR-s) also decreased consistently across quartiles of flavonoids and tyrosols. In the class of flavonoids, daidzein was inversely associated with elevated CRP (OR = 0.66, 95% CI 0.46–0.96). Among phenolic acids, statistically significant associations were observed for 3,5-dihydroxyphenylpropionic acid (OR = 0.58, 95% CI 0.39–0.86), 3,4-dihydroxyphenylpropionic acid (OR = 0.63, 95% CI 0.46–0.87), ferulic acid (OR = 0.65, 95% CI 0.44–0.96), and caffeic acid (OR = 0.69, 95% CI 0.51–0.93). The odds of elevated CRP were significantly reduced for hydroxytyrosol (OR = 0.67, 95% CI 0.48–0.93). To the best of our knowledge, this is the first study to investigate the relationship between a large set of plasma polyphenols and CRP concentrations.

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Financial Support: N/A.
Conflict of Interest: None to declare.
Authorship: KA designed the research ad supervised statistical analysis and data reporting; AS initiated and conducted laboratory analyses on polyphenol measurements; RZ-R, SR and MJ provided critical comments, LMH. performed the statistical analyses and writing of the results.
Keywords: Polyphenols, plasma biomarkers, chronic low-grade inflammation, C-reactive protein, epidemiological data analysis.

References

N/A.

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Dietary Inflammatory Index Score and Colorectal Cancer Risk Markers Associated with Inflammation and WNT Signalling

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Chronic inflammation is associated with increased disease risk, including colorectal cancer (CRC), and both inflammation and CRC risk may be modulated by diet. Abnormal WNT signalling is causal for the development of CRC. The aim of this study was to investigate relationships between the inflammatory effects of diet, assessed using a Dietary Inflammatory Index [1], and markers of CRC risk that are associated with inflammation and the WNT signalling pathway.

We used biological samples and dietary data from 75 healthy participants recruited to the DISC Study [2]. DII score was calculated using food frequency questionnaire data and included 29 food parameters. Systemic inflammation was assessed by quantifying high-sensitivity C-reactive protein (hsCRP) and local (large bowel) inflammation using faecal calprotectin. Expression of WNT pathway genes and regulatory microRNAs by qPCR, SFRP1 methylation by pyrosequencing and colonic crypt proliferative state were assessed in colorectal mucosal biopsies.

Mean DII score was 0.143 (−4.186–4.964) and mean hsCRP and faecal calprotectin concentrations were 3.6 mg/L and 46.5 mg/kg, respectively. We observed a significant positive relationship between DII score and hsCRP ($\rho = 0.295$, $p = 0.011$). DII score also correlated positively with expression of AXIN2 ($\rho = 0.358$, $p = 0.003$), CTNNB1 ($\rho = 0.390$, $p = 0.001$) and GSK3β ($\rho = 0.317$, $p = 0.011$). These are WNT pathway-related genes that are upregulated in CRC.

The findings from this study provide evidence for detrimental effects of a pro-inflammatory diet (greater DII score) on markers

on inflammation and on WNT pathway-related markers of CRC risk. This suggests that WNT signalling may be a mechanism through which diet modulates CRC risk.

Acknowledgements: We acknowledge the DISC Study team (Ian T Johnson, Nigel J Belshaw, Michael Bradburn, Seamus Kelly, Naomi Willis, Iain McCallum and Long Xie) and DISC Study participants. We thank Aycil Ozturan and Betul Kocaadam for processing of the dietary data. We acknowledge that the DII score was devised and calculated by James Hebert, Nitin Shivappa and Michael Wirth.

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Conflict of Interest: None.

Authorship: FCM and JCM designed research; FCM, AO, BK, MW, NS conducted research; FCM analyzed data; FCM and JCM wrote the abstract.

Keywords: Colorectal cancer, WNT signalling, dietary inflammatory index, inflammation.

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Circulating Leptin in Healthy Nigerian Females Is Positively Associated with Insulin But Not in Healthy Nigerian Males

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Objective: To investigate cytokine and fatty acid status in healthy Nigerian male versus female subjects.

Methods: Fasting blood samples were obtained from 11 males and 17 female subjects with similar body mass index (BMI kg/m^2). Plasma choline phosphoglyceride fatty acid composition (C14-C22), fasting plasma glucose (FPG), fasting plasma lipids (FLP), insulin and cytokines (Adiponectin, Resistin, Leptin, IL-1β, IL-4, IL-10, IL-8, IL-6, IL-12, TNF-α, IFN-γ, TGF-1β, MCP-1) were measured.

Results: Males had a small but significantly higher age compared with the females (56.36 ± 1.47 years vs. 51.71 ± 1.58 years; p = 0.04) but had similar FPG (4.51 ± 0.24 mmol/L vs. 4.74 ± 0.21 mmol/L; p = 0.49), compared to females. The BMI was similar in both sexes (22.92 ± 3.14 kg/m^2 vs. 26.01 ± 2.48 kg/m^2; p = 0.45). Only C18:3n-3 was significantly higher in the females (0.22 ± 0.04%) compared with males (0.13 ± 0.02), p = 0.04. Similarly, only leptin and insulin were higher in the females (35.30 ± 12.41 ng/ml vs. 948.83 ± 372.57 ng/ml, p = 0.02; 191.25 ± 47.82 pg/ml vs. 443.86 ± 103.02, p = 0.04). There was no difference between males and females for other cytokines measured. Inclusion of all samples showed Leptin vs. insulin correlation r = 0.52, p = 0.005.

Conclusion: Leptin appears to be associated with increased secretion of insulin in Nigerian females but not in Nigerian males. This gender difference in healthy Nigerians may be significant in the metabolic origin and pathogenesis of DM2 in Nigeria.

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Conflict of Interest: None to declare.

Authorship: All authors participated in the design and operational aspects of the study.

Keywords: Plasma leptin, plasma fatty acids, Plasma insulin, Healthy Nigerian subjects, gender differences.

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Fatty Acid Status of Sudanese Patients with Drug-Resistant Epilepsy

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Introduction: Epilepsy affects over 50 million people worldwide and accounts for approximately 1% of the global burden of disease [1]. Patients are treated with epileptic drugs [2]. About 30% of patients do not respond to treatment and continue to have seizures [3, 4]. The pathophysiology of epileptic seizures is not well understood. However, chronic inflammation is thought to play a critical role [5, 6]. There is evidence that chronic inflammation is stimulated by saturated (palmitic and stearic) and omega 6 (linoleic and arachidonic) fatty acids [7, 8].

Aim: To investigate if drug resistant epileptic patients (DRE) have an abnormal fatty acid profile indicative of pro-inflammatory activity.

Subjects and Methods: Patients with DRE (n = 15) and healthy subjects (n = 15) matched for age and gender were recruited from the University of Khartoum Teaching Hospital, Sudan. Fasting blood specimen, 5 ml, was collected for plasma phosphatidyl-choline fatty acid assessment.

Results: The DRE patients compared with their healthy counterparts had higher stearic (18.3 ± 3.1% vs. 15.7 ± 2.1%, p = 0. 001), palmitic (23.2 ± 5.6% vs. 21.3 ± 3.8%, p < 0.05) and total saturated (42.2 ± 5.5% vs. 38.0 ± 3.5%, p = 0. 001) fatty acids. In contrast, they had lower levels of linoleic (LA, 19.8 ± 3. 5% vs. 22.5 ± 4.2%, p = 0. 001) and arachidonic (AA, 8.2 ± 2.6% vs. 11.4 ± 2.7%, p = 0. 001) acids.

Conclusion: The omega-6 fatty acid findings suggest an accelerated elongation of LA to AA and a subsequent conversion of the latter to its pro-inflammatory metabolites (PGE2 and LTB4) in the patients. This abnormality is indicative of a chronic inflammatory state.

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Authorship: Nada Abuknesha: Conducted laboratory analysis, statistical analysis and data interpretation.

Dr Fatma A. S. Ibrahim : Recruited, followed patients, collected clinical data, and conducted statistical analysis.

Dr Inaam M. Mohmed : Recruited patients and collected clinical data.

Dr Ahmed A. Daak : Recruited patients and coordinated the implementation of the trial.

Professor Kebreab Ghebremeskel: Formulated the research question, designed and initiated the study, carried out data interpretation. Professor Mustafa I. Elbashir: Supervised patients recruitment and coordinated the implementation of the trial.

Keywords: Drug-resistant epilepsy, seizures, inflammation, fatty acids.

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Effect of Acute Ingestion of Sucralose on Glucose Tolerance and Monocyte Subpopulations in Healthy Young Adults

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The objective of this study was to evaluate the effect of acute exposure to 48 mg of sucralose in a single dose on mononocyte subpopulations as well as inflammatory and migratory capacity, studying its association with glucose, insulin, glucagon, peptide concentrations C incretins (GIP and GLP-1) in healthy young adults, subjected to an oral glucose tolerance curve of 180 minutes with measurements every 15 minutes. It is a cross-sectional, double-blind, placebo-controlled clinical trial with two groups, each with 25 healthy volunteers.Our results show that in patients with sucralose consumption the concentrations of insulin, peptide C and the determination of HOMA-IR were greater at 30, 90 to 180 min compared with the placebo group; with a tendency of GIP and GLP-1 to increase at 30 and 60 min. Significantly in the exposed group, the percentage of classical monocytes increased along with the expression of CD11c and CX3CR1; visceversa the percentage of intermediate and non-classical monocytes decreased, with an increase in the expression of CD11c and CCR2 as well as a decrease in CD206 and CX3CR1. These data suggest that sucralose consumption is associated with an inflammatory profile in circulating human monocytes with greater migratory tissue capacity as well as alterations in insulin response and decreasing their sensitivity as secretion is probably enhanced by incretins. This may bef risk for the development of insulin resistance and a harmful product for patients from an early age.

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Conflict of Interest: None.

Authorship: Angelica Yunuel Gómez Arauz: support during the design of the protocol, coordination and supervision of the protocol during the taking of samples, with subsequent analysis of flow cytometry and hormone determinations by ELISA. Galileo Escobedo: Participated directly in the coordination of flow cytometry and ELISA assays for the determination of levels of hormones, and inflammatory monocytes in study volunteers, before and after acute exposure to sucralose. In addition, Dr. Escobedo participated in the design of the study, the discussion of the results, the training of human resources.

Keywords: Sucralose, proinflammatory monocytes, Tissue migration, insulin sensitivity.

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Micronutrients and Immunity

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Effect of Vitamin D and n-3 Supplementation on Cytokines in Adults with Type 2 Diabetes Mellitus

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According to the WHO, there are more than 346 million individuals with type 2 diabetes mellitus (T2DM). There is evidence supporting that chronic inflammation caused by obesity is a risk factor for the development of T2DM, all the mechanisms involved are not well understood. Vitamin D constitutes a predictor of cardiovascular disease, while n-3 fatty acids have shown beneficial effects on glucose/insulin metabolism in T2DM. The objective was to evaluate the effect of a vitamin D and n-3 supplementation protocol on cytokines in Mexican adults with T2DM. Fifty patients with T2DM were randomly allocated to a placebo (cornstarch) or supplement (800 IU vitamin-D + 520 mg n-3) group; baseline and 24-week anthropometric and biochemical evaluations were done. Analyses used were t-test, U-Mann-Whitney or Wilcoxon and ANOVA depending on the type of data. IL-1β, IL-6, IL-8, TNF-α, IFN-γ and MCP-1 decreased in both groups ($p < 0.01$), while IL-10 decreased only in the placebo group ($p < 0.01$). ANOVA showed that IL-1β, IL-8, IL-10 and TNF-α had a significant ($p < 0.05$) effect of type of supplement, due to a decrease in the placebo group, while significance in IL-12 and MCP-1 was due to a decrease in the supplemented group. No clear effect of the supplementation protocol can be observed at this point. All subjects were being treated with metformin, glibenclamide or their combination, which may have attenuated the effect. Further research is needed to clarify the effect of a combination of vitamin D and n-3 fatty acids on the inflammatory profile in T2DM.

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Conflict of Interest: The authors declare no conflict of interests.

Authorship: All authors participated in the development of the project and the writing and revision of the abstract.

Keywords: Type 2 diabetes mellitus, vitamin D, n-3 PUFA, citokoines, adipokines.

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Correlation of Plasma Vitamin D with Phagocytosis in Elderly Care Home Residents

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Background: Vitamin D is a liposoluble nutrient which exerts pleiotropic actions. Its role through the different stages in life has been described, and more physiological effects and interactions continue to be understood. Ageing is a heterogeneous process associated with a progressive decline in morphology and physiologic functionality. Bone status, gastrointestinal homeostasis, immune decline, enhanced low grade inflammation and frailty risk are all affected by ageing. This could be improved by vitamin D.

Objectives: Here, the association between vitamin D status and some immune parameters in elderly residents of care homes was investigated.

Methods: An immunoenzymatic assay for total 25-hydroxy vitamin D3 (hereafter called VitD) was performed on a Beckman Coulter Dxl 800. Full blood count analyses included quantification of immune cell populations performed on a Beckman coulter. Phagocytic analyses were done using E. coli fluorescently labelled using flow cytometry (BD FACSCalibur). Active populations of neutrophils and monocytes was gated.

Key Findings: Mean plasma VitD concentration was 61.8 nmol/l (n = 120). 53.3% of subjects were vitD deficient (defined as plasma levels below to 50 nmol/L) while 14.8% were insufficient (defined as plasma levels between 50 and 74 nmol/L). VitD concentration was not associated with full blood count or with neu-

trophil phagocytosis. However vitD concentration was positively associated with phagocytic activity of blood monocytes (r = 0.186, p = 0.042, n = 120).

Conclusions: Plasma VitD is associated with monocyte phagocytic activity in elderly care home residents. VitD supplementation might enhance monocyte phagocytosis.

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Conflict of Interest: We declare no conflict of interest.

Authorship: Calder and Castro-Herrera formulated the research question. The authors contributed equally in the designing of the study.

Keywords: Vitamin D, Phagocytic function, elderly population, monocytes.

References

N/A.

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Role of Hesperidin on the Intestinal Immune System of Young Healthy Rats

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The biological activity of flavonoids in human or animal health, such as their anti-inflammatory (1), anti-diabetic (2) properties as well as their modulatory effects on the immune system, have been widely described. Hesperidin, the main flavanone found in citrus fruits, has shown a vast number of biological properties, including its immune-modulatory role (3). The aim of this study was to establish the effect of oral hesperidin administration on the intestinal immune system in young healthy animals. Three-week-old Lewis rats were orally administrated with 100 or 200 mg hesperidin per kg of body weight, three times per week for four weeks. Mesenteric lymph node lymphocyte (MLNL) composition and functionality, assessed by the cytokine pattern, were determined. Furthermore, cytokines presented in small intestine washes as well as the intestinal and serum levels of IgA were quantified. Hesperidin administration modified the MLNL composition by increasing the relative proportion of TCRαβ+ lymphocytes at the expenses of B cells. However, no differences were seen in the cytokine pattern released by MLNL after anti-CD3/CD28 stimulation. Hesperidin administration was able to increase the IgA content and to decrease interferon-γ and monocyte chemotactic protein-1 concentrations in the small intestine. Nevertheless, no effects on serum IgA concentrations were found. In conclusion, these results show the immunomodulatory actions of hesperidin on the intestinal immune system, playing a role in the gut homeostasis maintenance by increasing intestinal IgA.

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Conflict of Interest: None.

Authorship: M.C-B. M.C., and F.J.P.C. designed the study, S.E.A., M.M-C. and M.C-B. performed the experiments, S.E.A. and A.F. analysed the data, S.E.A. and M.C-B wrote the abstract.

Keywords: Flavanone, flavonoids, immunoglobulin A, intestinal immunity, polyphenol.

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The Impact of Smoking Habit on White Blood Cells in Healthy Elderly Adults

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Cigarette smoking is one of the most important modifiable risk factor for atherosclerosis, chronic diseases and immune function alterations [1]. The aim of this study was to evaluate the effect of tobacco habits on white blood cell (WBC) counts, together with other possible confounding factors in healthy elderly subjects. This is an observational, cross-sectional study, of volunteers between 55 and 85 y. with BMI <30 and free of major disease. Information on lifestyle, socioeconomic status (SES) and health was collected through specific interviewer-administered questionnaires. Three groups were established: 1) smokers (S, N = 28), former smokers

(FS, N = 62) and non-smokers (NS, N = 63). A univariate linear model adjusted by age, sex, SES, prevalence of chronic disease, alcohol and tobacco habits, BMI and physical activity (PA; METS-min*wk-1) was performed, and in a second model only those that showed a significant effect were kept (gender, SES, tobacco and PA). Chi-square test showed that gender distribution was not different across tobacco consumption categories. The variability in total WBC, and differential counts was mainly influenced by gender and tobacco consumption. Pair-wise comparison with Bonferroni test showed that leukocytes and absolute number of neutrophils and monocytes were higher in S than in FS and NS groups ($P < 0.05$ all). A correlation was found between both, leukocyte and neutrophil numbers, with number of cigarettes per day ($P < 0.01$ both). In addition, leukocytes and all WBC type counts, except lymphocytes, were higher in men than in women. Conclusion: Smoking habit is related to a higher number of innate immune cells in healthy elderly adults.

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Conflict of Interest: The authors declare no conflict of interest.

Authorship: A.M., E.N. were responsible of the conception and design of the research. I.S.M and L.E.D. carried out the study. E.N and L.E.D analysed the data and wrote the article.

Keywords: Tobacco, leucocytes, elderly, innate immunity.

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Fats, Immunity and Inflammation

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Beneficial Effects of PARAISO Yogurt on Digestive Symptoms, Nutritional and Immunological Profile

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Introduction: Scientific studies show that the consumption of probiotics is beneficial in diseases affecting the gastrointestinal tract. PARAISO is a natural dietary supplement, consisting of lactobacillus of probiotic action, with high protein, high content of calcium, phosphorus, magnesium and potassium, besides stimulates the immunity. Their daily consumption is significant in the improvement of gastrointestinal and allergic symptoms.

Objective: To evaluate the beneficial effects of probiotic yogurt PARAISO.

Materials and Methods: Prospective longitudinal study of patients with digestive manifestations and alterations in nutritional status, who attended the probiotic yogurt consultations of LABIOFAM Business Group and consumed yogurt for 6 months. All medical records were reviewed and a medical history was designed for the collection of information. According to the nature of the variables, were used Mc Nemar, wilcoxon and paired t test for evaluating the evolution of nutritional variables, the lipid and immunological profile and clinical symptoms.

Results: The intestinal malabsorption syndrome predominates as main diagnosis. Diarrhea predominated (154; 56%) and the improvement was statistically significant ($p = 0.000$). 55.6% of the patients started with a moderately nourished state, at 6 months the majority improved significantly ($p = 0.000$). Weight increased significantly ($p = 0.034$). The values of cholesterol ($p = 0.017$) and triglycerides decreased slightly. It is estimated that 97.39% to 99.91% of patients consuming yogurt paradise, can tolerate the supplement.

Conclusions: PARAISO is beneficial in the improvement of digestive symptoms, nutritional status indicators, lipid and immunological profile.

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Conflict of Interest: No conflict of interest.

Authorship: N/A.

Keywords: Probiotic yogurt, lipid profile, immunological profile, dietary supplement.

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EPA and DHA Habitual Intake Is Associated with Pro-Inflammatory Cytokines in Mexican Population with and Without Type 2 Diabetes Mellitus

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Background: Factors including stress, inactivity and adiposity can increase the secretion of pro-inflammatory cytokines, the serum concentrations of which have been associated with low-grade

chronic inflammation and several diseases including type 2 diabetes mellitus (T2DM). There is evidence of beneficial effect of polyunsaturated fatty acids (PUFA) EPA and DHA in patients with chronic inflammatory diseases.

Objective: To investigate the relationship between habitual EPA and DHA intake and circulating pro-inflammatory cytokines in patients with and without T2DM in the State of Mexico.

Methods: We conducted a cross-sectional study of 240 subjects divided into four groups; normal weight (NW), overweight (OW), T2DM normal weight (T2DMNW) and T2DM overweight (T2DMOW). Anthropometric, biochemical, and pro-inflammatory biomarkers (IL-1, IL-6, TNF-α, IFN-γ) were measured. Differences between groups were tested using ANOVA. Multivariate linear regression analysis was performed.

Results: We found in T2DMOW group, significantly higher IL-1 (69.6 ± 0.2 pg/mL vs 37.3 ± 0.5 pg/mL in T2DMNW, 5.9 ± 0.2 pg/mL in OW, and in NW 0.8 ± 0.2 pg/mL) and IL-6 (22.4 ± 0.3 pg/mL vs 7.9 ± 0.8 pg/mL in T2DMNW, 3.9 ± 0.2 pg/mL in OW, and in NW 1.6 ± 0.3 pg/mL); negative associations between EPA intake and serum IL-6 ($\beta = -0.241$ $p = 0.001$) and DHA intake and serum IL-6 ($\beta = -0.384$ $p = 0.001$) was observed.

Conclusions: Mexican subjects with T2DM and overweight had higher serum pro-inflammatory cytokine concentrations than subjects with T2DM and normal weight; EPA and DHA intake appears to be inversely related to serum IL6 and it could therefore be a useful dietary therapeutic option to increase the intake of EPA and DHA in T2DM subjects to lower the circulating IL-6 concentration.

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Authorship: All authors participated in the development of the project and the writing and revision of the abstract.

Keywords: Type 2 Diabetes Mellitus, pro-inflammatory cytokines, EPA intake, DHA intake.

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Supplementation with Omega 3 in Olive Oil Diet. Study in Experimental Model

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The objective was to analyze the effect of diet containing olive oil, as fat source, with and without the supplementation with omega 3, on serum and thymus' fatty acid profiles of growing rats. Weanling Wistar rats received during 10 days normocaloric diet and fat was provided by olive oil (O group). The other group received the same diet supplemented with 24 mg/day of fish oil (OS group). Control group (C) received diet AIN'93. Serum and thymus fatty acids profiles were determined by gas chromatography. Statistical analysis used ANOVA and Dunnett test. Results were (%Area): SERUM: OLEIC O:23.44 ± 3.68c; OS:18.31 ± 2.22b; C:10.60 ± 2.01a. LINOLEIC O:12.44 ± 1.65b; OS:12.98 ± 4.31b; C:18.27 ± 2.81a; alfa-linolenic (ALA) O:0.30 ± 0.09b; OS:0.32 ± 0.08b; C:0.92 ± 0.34a; EPA O:0.65 ± 0.17a; OS:1.63 ± 0.49b; C:0.80 ± 0.23a; DHA: O:1.57 ± 0.58a; OS:4.00 ± 1.70b; C:1.33 ± 0.19a. THYMUS: OLEIC O:21.54 ± 5.92; OS:24.40 ± 5.04; C:18.22 ± 3.23. LINOLEIC O:5.90 ± 0.56b; OS:6.5 ± 0.61b; C:10.89 ± 2.18a; ALA O:0.27 ± 0.02b; OS:0.30 ± 0.07b; C:0.49 ± 0.19a; EPA O:0.49 ± 0.28; OS:0.50 ± 0.13; C:0.50 ± 0.12; DHA: O:0.47 ± 0.10a; OS:0.70 ± 0.12b; C:0.52 ± 0.16a. Media that didn't present a letter (a,b) in common, were different ($p < 0.05$).

In sera, O and OS groups showed lower ALA and linoleic acids levels and higher oleic acid levels, compared to C. The results suggest that olive oil exacerbated omega 9 family with diminution of essential fatty acids. OS group presented high levels of EPA and DHA.

In thymus, O and OS groups showed lower levels of ALA and linoleic acids than C. OS group only increased DHA.

Fish oil supplementation increased DHA levels on serum and thymus, not modifying essential fatty acid low levels. EPA increase only in serum. The results suggest that dietary lipids provoked changes in serum and thymus fatty acids profiles.

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Conflict of Interest: All the authors declared to have no Conflict of Interest.

Authorship: Slobodianik Nora.

Keywords: Thymus, Fatty acid, omega 3, olive oil.

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Relationship Between Visfatin Levels and Nutritional Status in Adolescents with and Without Down Syndrome

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Objective: This study was aimed to evaluate a possible relationship between fatness and visfatin levels (as a cardiovascular marker) in adolescents with and without Down Syndrome (DS).

Methods: Two groups of adolescents (95 DS, 44.2% girls, and 113 controls, 47.8% girls), aged 11–18 years-old, were recruited into the UP&DOWN Study. Height, weight, waist circumference, triceps and subscapular skinfold thicknesses were measured and visfatin levels were analyzed. Body mass index (BMI), waist-to-height ratio (WHtR) and body fat percentage (Slaughter's equation) were calculated. The following subgroups were created according to their BMI (underweight, normal weight, overweight or obesity), abdominal obesity (when WHtR ≥0.51 in boys and ≥0.50 in girls, or not), body fat percentage (normal range <20% or excess of body fat ≥20%) and visfatin detection levels (<0.156 ng/mL or ≥0.156 ng/mL). Student's t and chi-square tests were performed.

Results: DS adolescents showed higher BMI, WHtR and body fat percentage than the control group ($p < 0.001$). In the total sample, 64.5% showed visfatin levels below the detection limits. Visfatin was only detected in 44 (38.9%) controls and 23 (24.2%) DS adolescents. A higher percentage of adolescents with DS and with high levels of body fat showed undetectable levels of visfatin ($p = 0.003$ and $p = 0.017$ respectively). However, DS participants within visfatin detectable group showed higher visfatin levels than controls ($p = 0.019$).

Conclusions: In view of these results, the relationship between fatness and vistafin should be deeply analyzed, not only in general population [1, 2] and overweight youth [3], but also in DS adolescents.

Acknowledgements: To the adolescents who participated in this study, as well as to their parents and families.

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Conflict of Interest: The authors declare no conflict of interests.

Authorship: N/A.

Keywords: Visfatin levels; adolescents; Down syndrome.

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Plasma Phosphatidylcholine Saturated and Monounsaturated Fatty Acids in Healthy Nigerian and Mexican Subjects

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Background: We earlier compared saturated fatty acids (SFAs) and monounsaturated fatty acids (MUFAs) in Nigerian and Mexican type 2 diabetics1, but such comparison haven not been reported in healthy subjects of these populations.

Objective: Compare SFAs and MUFAs in Nigerian and Mexican healthy subjects.

Methods: Nigerian (n = 33) and Mexican (n = 50) subjects fasting plasma were analysed for phospholipid (PC) fatty acids by GLC, and mean % fatty acids compared in healthy subjects.

Results: C17:0 – C22:0 SFAs were higher in Nigerians (C17:0; 0.42 ± 0.12 vs. 0.34 ± 0.06, p = 0.001, C18:0; 17.57 ± 2.43 vs. 14.99 ± 1.20, p = 0.001, C20:0; 0.14 ± 0.08 vs. 0.08 ± 0.06, p = 0.001, C22:0; 0.12 ± 0.10 vs. 0.07 vs. 0.03, p = 0.026). C15:0 was higher in Mexicans (0.14 ± 0.05 vs. 0.08 ± 0.04, p = 0.001. C14:0 (0.25 ± 0.10 vs. 0.21 ± 0.13, p = 0.134), C16:0 (29.48 ± 2.20 vs. 29.04 ± 4.22, p = 0.582) and the MUFAs (C16:1n-7, C18:1n-9 and C18:1n-7) were not significantly different in both population. C18:1n-9/C18:0 ratio was higher in Mexico subjects (0.89 ± 0.18 vs. 0.76 ± 0.23, p = 0.006) but C16:1n-7/C16:0 was similar in both groups (0.02 ± 0.01 vs. 0.02 ± 0.01, p = 0.144).

Discussion: The study shows that despite similar high carbohydrate consumption in both countries, there are differences in FAs profile which could be due to other environmental or genetic factors.

Acknowledgements: We thank the clinicians and nurses who helped us obtain blood samples in both countries.

Financial Support: This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Conflict of Interest: None to declare.

Authorship: All authors participated in the design and operational aspects of the study.

Keywords: Fatty acids profile, Healthy subjects, Nigerians, Mexicans, plasma saturated and monounsaturated fatty acids.

Reference

1 Oghagbon E, Harbige LS, Valdes-Ramos R, Guadarrama-López AL: Plasma phosphatidylcholine saturated and monounsaturated fatty acids in Nigerian and Mexican type 2 diabetes mellitus patients. Ann Nutr Metab 2017;71:31–79.

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Comparison of n-3 plasma phosphatidylcholine (PC) fatty acids in healthy Nigerian and Mexican subjects

Oghagbon, E.[1]*; Chowdhry, B.*[2]*; Ghebremeskel, K.*[3]*; Valdés-Ramos, R.*[4]*; Guadarrama-López, A.*[4]*; Harbige, L.*[3]

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Background: Long chain n-3 FAs are affected by diet and genetic factors, but the impact of these factors has not been compared between Nigerian and other countries. This study compared the n-3 fatty acid profile in Nigerian and Mexican healthy subjects who largely consume a high carbohydrate and low-fat diet.

Objective: Compare VLCn-3PCFAs in Nigerian and Mexican healthy subjects.

Methods: Nigerian (n = 33) and Mexican (n = 50) subjects fasting plasma were analysed for phospholipid (PC) fatty acids by GLC, and mean % fatty acids compared in the subjects.

Results: The plasma PC C18:3n-3 was higher in the Mexican subjects (0.33 ± 0.11 vs. 0.17 ± 0.13, p = 0.001). The longer chain n-3 fatty acids were higher in Nigerian subjects compared with Mexicans; C20:5n-3 (0.81 ± 0.72 vs. 0.37 ± 0.59, p = 0.004, C22:5n-3; 0.69 ± 0.27 vs. 0.43 ± 0.13, p = 0.001, and C22:6n-3; 4.11 ± 1.77 vs. 1.14 ± 0.46, p = 0.001. Similarly, C20:5n-3/C18:3n-3 ratio was higher in Nigerian subjects compared to Mexicans (7.43 ± 9.36 vs. 1.32 ± 2.75, p = 0.001).

Discussion: The study suggests that despite similar high carbohydrate consumption in both countries, Nigerians maybe consuming more dietary longer chain n-3 or are better at converting the parent n-3 FA to their longer chains.

Acknowledgements: We thank the clinicians and nurses who helped us obtain blood samples.

Financial Support: This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Conflict of Interest: None to declare.

Authorship: All authors participated in the design and operational aspects of the study.

Keywords: Healthy subjects, Nigerians, Mexicans, plasma PC n-3 fatty acids.

Reference

1 Oghagbon E, Harbige LS, Valdes-Ramos R, Guadarrama-López AL: Plasma phosphatidylcholine saturated and monounsaturated fatty acids in Nigerian and Mexican type 2 diabetes mellitus patients. Ann Nutr Metab 2017;71:31–79.

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Associations of Maternal Immune Response, Methylmercury and Polyunsaturated Fatty Acids at 28 Weeks Gestation

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Maternal methylmercury (MeHg) exposure may be associated with immune response during pregnancy. In the high fish-eating Seychelles Child Development Study Nutrition Cohort 2, we examined the association of maternal MeHg, polyunsaturated fatty acids (PUFA), and immune markers (Th1:Th2; TNF-α, IL-1β, IFN-γ, IL-2, IL-4, IL-5, IL-10, MCP-1, TARC, SFlt-1, VEGFD, CRP and IL-6) at 28 weeks gestation. Linear regression examined associations between MeHg exposure and immune markers with and without adjustment for PUFA. In all models, as MeHg concentrations increased the Th1:Th2 ratio, total Th1 and individual Th1 (IL-1β, IL-2, TNF-α) concentrations decreased. MeHg was not associated with total Th2 cytokines but was associated with a decrease in IL-4 and IL-10. MeHg was positively associated with TARC and VEGFD and negatively associated with CRP. There was a significant interaction between MeHg and the n-6:n-3 ratio, with MeHg associated with a larger decrease in Th1:Th2 at higher n-6:n-3 PUFA ratios. The n-3 PUFA were associated with lower CRP, IL-4 and higher IFN-γ. The n-6 PUFA were associated with higher IL-1β, IL-2, TNF-α, IL-4, IL-10, CRP and IL-6. Maternal MeHg was associated with markers of immune function at 28 weeks gestation. A significant interaction between MeHg and the n-6:n-3 ratio on the Th1:Th2 ratio suggests that the n-3 PUFA may mitigate any immunosuppressive associations of MeHg. The n-3 and n-6 PUFA were associated with suppressive and stimulatory immune responses, respectively. Overall, the associations were of small magnitude and further research is required to determine the clinical significance.

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Conflict of Interest: The authors declare they have no conflicts of interest.

Authorship: Emeir M McSorley1, Alison J Yeates1, Maria S Mulhern1, Edwin van Wijngaarden2, Katherine Grzesik2, Sally W Thurston2, Toni Spence1, William Crowe1, Philip W Davidson2,

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PWD, GJM, CFS and JJS conceived and designed the SCDS; EMS, AJY, MSM, EvW and JJS conceived and designed this research. EMS, AJY MSM, TS and WC conducted the reserach. KG, SWT and GEW perfromed the statistical analysis. EMS, AJY, EvW and JJS interpreted the data. EMS and AJY drafted the manuscript. All authors have read and contributed to the final version.

Keywords: Methylmercury; n-3 PUFA; pregnancy; immune function, Th1, Th2, cytokines.

References

N/A.

Phytochemicals, Immunity and Inflammation

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Antioxidant and Anti-Inflammatory Effects of Dietary Polyphenols on a Cellular Model for Intestinal Epithelia

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Dietary polyphenols are widely known by its antioxidant property. However, few reports have confirmed this notion by measuring redox impact in living cells and even less connect the antioxidant impact with an anti-inflammatory effect.

By expressing HyPer, a redox biosensor in Caco-2 cells, we monitored the biological impact of five polyphenols [quercetin, 5 μM; kuromanin, 5 μM; caffeic acid, 10 μM; neochlorogenic acid, 5 μM and procyanidin B1, 5 μM] on redox state in the cytoplasm of living cells. Complementary to this approach, we examined if these polyphenols contribute to the generation of Caco-2 monolayer along with TNF-α secretion and interleukin mRNAs abundance by ELISA and qPCR, respectively.

Quercetin and neochlorogenic acid (24 h) showed significant decrease in basal measurements of HyPer (control: 0.837 ± 0.007; Quer: 0.748 ± 0.012 and Neo: 0.770 ± 0.014). By exposing transiently control cells to 50 ?M H2O2, HyPer signal increased by 39 ± 2%. Cells treated with procyanidin, caffeic acid and kuromanin elicited significant reduction in the biosensor signal (23 ± 3; 25 ± 3 and 29 ± 3, respectively). Upon exposure to 500 μM of H2O2 by 30 minutes we detected increases in the abundance of mRNAs for TNF-α of 57 ± 18 fold, whereas for IL-6 it was 6 fold.

Further experiments in Caco-2 monolayers with transepithelial electrical resistance values over 300 Ω*cm^2 have been useful to investigate the connection between redox impact and inflammatory response measured by secreted cytokines.

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Conflict of Interest: None.

Authorship: MH: She did most of the experimental work, cell culture and monolayer maintenance was under her responsibility. She participates in data analysis and interpretation of results.

VK: She was involved mainly in biosensor measurements, data analysis and interpretation. She also help with adenovirus production and cell culture labours.

NT: He participated in qPCR determinations, supervising sample quality, interpretation data and planning experiments.

OP: he contributed with the experimental design, data analysis, writing of results and data discussions and supervising students and colaborators.

Keywords: HyPer Biosensor, Caco-2 cells, TEER, Cytokines, Real-time.

References

N/A.

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Immunomodulatory Effect of Consumption of Andalusian White Wine in Elderly Men with High Risk Cardiovascular

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Background and Aims: Light to moderate alcohol consumption has a protective effect on atherosclerosis (1). The aim of this study was to evaluate the effects of Andalusian white wine (AWW) and gin (without polyphenol) on circulating endothelial progenitor cells (EPC) and the expression of inflammatory cytokines and chemokines related to atherosclerosis in elderly men with high cardiovascular risk.

Methods: This study was an open, randomized, controlled, crossover trial, on 38 high risk male volunteers between 55–80 years of age who were randomized to receive 30 g of ethanol/day as AWW or gin for 21 days. Expression of EPC were assessed by cytometry at baseline and after 21 days, and plasma of inflamma-

tory biomarkers, determined by Luminex assays. The volunteers maintained their dietary habits and physical activity throughout the study.

Results: Compared to gin, EPC increased significantly by ? 39% after 21 days of AWW intervention. We observed changes in plasma cytokine and chemokine concentrations after the 21 days AWW and gin interventions. In addition, following the AWW intervention a significant decrease in VCAM-1 ($p = 0.012$), ICAM-1 ($p = 0.020$), IL-8 ($p = 0.048$) and IL-18 ($p = 0.048$) concentrations was observed. Finally, IFN-γ concentrations significantly decreased after both AWW and gin intake ($p \leq 0.046$; both).

Differences between groups showed a significant improvement of IFN-α ($p = 0.027$), MCP-1 ($p = 0.042$), IL-18 ($p = 0.037$) and VCAM-1 values ($p = 0.035$) after AWW compared to gin.

Conclusions: The light to moderate consumption of AWW, due to its polyphenolic compounds, could have protective and immunomodulatory effects on atherosclerosis in elderly men with high CVR.

Acknowledgements: We thank the participants for their enthusiasm and compliance with the study protocol. We also thank the Government of Andalucía for covering part of the expenses of the trial and the Fundación para la Investigación del Vino y la Nutrición (FIVIN) for their donation of the alcoholic beverages used in the study. CIBEROBN is an initiative of ISCIII, Spain.

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Conflict of Interest: None of the authors declare any conflict of interest related to the study.

Authorship: PhD student in Nutrition/Nutritionist.

Keywords: Cardiovascular risk, atherosclerosis, polyphenols, wine, inflammatory biomarkers.

Reference

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Glycyrrhizin Inhibits High-Mobility Group Box 1 Protein Released from Damaged Intestinal Epithelia and Antigen Sensitization

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Objective: Glycyrrhizin (GL) isolated from licorice root is an inhibitor of high-mobility group box 1 protein (HMGB1) and has anti-inflammatory activities. Cholera toxin (CT) is a potent mucosal adjuvant, and oral administration of antigens plus CT induces antigen-specific immune responses including CD8+ cytotoxic T lymphocytes [1] as well as IgA production [2] in intestinal mucosa; however, mechanisms for the induction of these immune responses remain unknown. In this study, we examined whether the oral CT-administration triggers intestinal cell death and HMGB1 release and whether GL inhibits the HMGB1 released from damaged intestinal epithelia and antigen sensitization.

Key Findings: We observed a significant decrease of viable intestinal epithelial cells (IECs) that were EpCAM+ CD45- by oral administration of CT in mice. Dying Annexin V+ 7-AAD+ EpCAM+ IECs were significantly increased by oral CT. HMGB1 levels were significantly increased in fecal extracts after oral CT. Oral CT induced enhancement of expression of co-stimulatory molecules such as CD80 and CD86 on intestinal dendritic cells (DCs) involved in antigen presentation. Intravenous or oral treatment with GL, an HMGB1 inhibitor, significantly suppressed the fecal HMGB1 levels, the expression of CD80 and CD86 on intestinal DCs, and antigen presentation of DCs enhanced by the oral CT-administration [3]. Actually, GL-treatment significantly suppressed OVA-specific fecal IgA production and delayed-type hypersensitivity induced by oral CT in mice.

Conclusions: The oral CT-administration triggers the death of IECs, HMGB1 release from the damaged IECs, and antigen sensitization. GL inhibits the HMGB1 release and the antigen sensitization.

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Authorship: A. Wakabayashi was responsible for formulating the research questions, designing the study, carrying it out, analysing the data and writing the article.

M. Shimizu was responsible for carrying the study out.

E. Shinya was responsible for designing the study.

H. Takahashi was responsible for formulating the research questions and writing the article.

Keywords: Glycyrrhizin, high-mobility group box 1 protein, intestinal epithelia, antigen sensitization, cholera toxin.

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Effect of Mango (Mangifera indica L.) By-Product on the Immune System of Scholar Children

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Mango (Mangifera indica L.) by-product is rich in dietary fiber and phytochemicals with prebiotic activity, suggesting an immunomodulatory effect. This randomized, double-blind, parallel and placebo-controlled study aimed to evaluate the effect of mango by-product on the immune response of healthy scholar children during upper-respiratory and gastrointestinal tract infections. Eighty children (6–8 years old) randomly received either ground mango by-product dissolved in water (2.5 g/50 mL) or mango flavored water for two months. Mango by-product supplementation significantly ($p < 0.05$) decreased the incidence rate of congested nose, dry cough, and abdominal inflammation, as well as the duration of abdominal inflammation symptom. These health beneficial effects were associated with increased levels of serum IL-18, IL-4, FASL, MCP-1, and RESISTIN, and decreased levels of G-CSF, MIF, MIP-1a, PAI-1, and RAGE, indicating the activation of the innate and adaptive immune system during upper-respiratory and gastrointestinal infection episodes. Moreover, mango by-product immunomodulatory activity was associated with its high content of soluble dietary fiber, extractable polyphenols like myricetin 3-O-glucoside, ellagic acid, and mangiferin, as well as non-extractable polyphenols like ellagic acid, 3-7-dimethylquercetin, and secoisolariciresinol. Therefore, mango by-product is an interesting source of bioactive compounds with protective effects on immune-mediated inflammatory response.

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Conflict of Interest: None.

Authorship: IFPR and MAAL designed the study, GGM participated in the interventions study, GGM and JAEM carried out the protein array analysis. All authors participated in the data analysis and interpretation.

Keywords: Mango, by-product, immune system, protein array, bioactive compounds.

References

N/A.

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Lycium Intricatum: Phytochemical Study and Evaluation of Antioxidant Activity

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The aim of this work is to study the antioxidant power of Lycium Intricatum, a genus of flowering plants in the nightshade family, Solanaceae found only in some subtropical regions and especially in Morocco [1]. Although it is a source of phytochemicals with high added value, this plant remains underutilized.

This work provides data on the composition of the plant in polyphenols and flavonoid and its antioxidant power. Determination of total phenol content in Lycium Intricatum, calculated in terms of Gallic acid equivalents (GAE) showed that the extracts are rich in these compounds with a significant heterogeneity of these levels depending on the organ. The fruits of Lycium intricatum are very rich in total polyphenols (2208 μg/mg) compared to extracts from other organs. In addition, leaf extracts come in second place with a polyphenol content in the range of (1993 μg/mg). As for the stems, they include the lowest levels of these molecules (1370 μg/mg). Flavonoids dosing results in fruits, leaves and stems reveal respectively the following values: 63.64 μg/mg; 640.73 μg/mg and 72.50 μg/mg. these data show that the leaves are the richest in flavonoids. The antioxidant assessment, performed using the DPPH free radical scavenging method [2], indicated that the methalonic extracts have moderate antioxidant activity. These extracts could therefore be an alternative to certain synthetic additives. From these results, it has been shown that L. intricatum has great potential as a source of natural antioxidant that can replace the use of synthetic substances.

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Conflict of Interest: None.

Authorship: Bouaouda realized the experimental part as identification of polyphenol and flovonoid and she wrote the article. Taki evaluated the results and he corrected the manuscript for publication, Kettani analyzed the data and shared ideas and proposals. All authors read and approved the final manuscript.

Keywords: Lycium intricatum, polyphenols, Flavonoids, antioxidant activity.

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Anti-Inflammatory Activity of Mexican Negro Jamapa Bean (Phaselous vulgaris) in Murine RAW264.7 Macrophages

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A polyphenol rich diet may prevent the development of stress and inflammation associated disorders such as diabetes, cardiovascular diseases and cancers [1, 2]. Legumes have been associated with anti-inflammatory properties in vitro and in vivo which may be linked to their polyphenol content [3, 4], yet, detailed information about the anti-inflammatory activity of beans, in particular processed beans, is still scarce. The aim of this study was to evaluate the potential of cooked Mexican Negro Jamapa beans (P. vulgaris) to modulate inflammation by assessing inflammatory gene expression RAW264.7 macrophages, a cellular model of inflammation. RAW264.7 macrophages were incubated with methanolic extracts of cooked beans (10–100 μg/mL) and subsequently stimulated for 6 h with 100 ng/mL of lipopolysaccharide (LPS) to elicit an inflammatory response. Expression of inflammatory markers (interleukin 6 (IL-6), interleukin 1 beta (IL1β) and nitric oxide synthase (iNOS) was assessed using real time PCR. The Negro Jamapa cooked bean extract showed a moderate anti-inflammatory effect by reducing mRNA levels of IL6 (by 18% at 50 μg/mL and 20% at 100 μg/mL), IL1β (16% at 100 μg/mL) and iNOS (16% at 100 μg/mL) ($p < 0.05$) in comparison with cells treated only with LPS. Sinapic acid, a phenolic acid identified in the bean extract, decreased mRNA levels of IL6 at concentrations of 10 μM and 50 μM by 27.64% and 22.84%, respectively, which may indicate that this compound could partially be responsible for the attenuation of inflammation. To conclude, bean consumption may only have a moderate effect to attenuate inflammation.

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Conflict of Interest: None.

Authorship: LMPH, CO, MM, CB designed the research, LMPH and KN performed the experiments. LMPH, KN and CB analysed the data, LMPH drafted and CO, MM and CB finalised the article.

Keywords: Bean polyphenols, processing, inflammation, macrophage.

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Inhibitory Effects of Withaferin a and Withania Somnifera on Macrophage Inflammation

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Inflammation has been recognized as an important contributor to the pathogenesis of a number of disorders such as diabetes, cardiovascular and neurodegenerative disease, and cancer. As a consequence, there is continuing interest in identifying plant bioactive compounds with anti-inflammatory properties that could prevent inflammation or support therapeutic approaches. The current study aimed to investigate the contribution of withaferin A, a lead compound in extracts of Withania somnifera, a traditional Indian herb, to the LPS-induced inflammatory response in RAW264.7 macrophages, a cellular model of inflammation. RAW264.7 macrophages were incubated with increasing concentrations of withaferin A (0.5–5 μM) and Withania somnifera extract (1–50 μg/ml), stimulated with LPS to elicit an inflammatory response evaluated using real time qPCR, ELISA and Western Blotting methods. We observed a strong dose-dependent reduction in pro-inflammatory markers such as IL-6, IL-1beta and iNOS which was supported by reduction of nuclear p65 protein indicating modulation of redox-regulated NFkB signalling pathway activation. Further results show a strong induction of Nrf2 (nuclear factor E2-related factor 2) signalling and increased expression of its target genes heme oxygenase 1 (HO-1) and gamma glutamyl cysteinyl synthase (GCLC) through both, Withania somnifera extract and withaferin A. Our results confirm the effectiveness of withaferin A towards attenuation of inflammation. Further experiments are underway to demonstrate functional consequences of Withaferin A and Withania somnifera on LPS-induced changes of phagocytosis activity in macrophages.

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Authorship: KN and CB designed the study. KN performed the experiments; KN and CB analysed the data and wrote the abstract.

Keywords: Withania somnifera, withaferin A, inflammation, phagocytosis.

References

N/A.

Nutrition and Infectious Disease

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Calprotectin Modulates Bacterial Metabolism During Clostridium Difficile Infection

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Nutrient metals are necessary for the survival of all organisms, but it is unclear how host control of metal abundance influences the microbiota in the intestines. Clostridium difficile is a bacterial pathogen that induces inflammation characterized in part by the release of calprotectin, which binds and sequesters nutrient metals to limit their availability. The consequences of immune mediated nutrient sequestration on pathogen and microbiota survival are unknown. To determine how calprotectin drives changes to the microbiota, a mouse model of C. difficile infection (CDI) was used. Interestingly, during CDI there were significant differences in the relative abundances of the microbiota between wild type and calprotectin deficient mice. We thus hypothesized that calprotectin influenced C. difficile and microbiota niche selection by limiting nutrient metal availability. To test this hypothesis, C. difficile responses to calprotectin were first examined using RNA sequencing. In response to calprotectin-mediated zinc limitation, C. difficile metabolism shifts towards proline fermentation. The ability to ferment proline enhances C. difficile growth in vitro and provides a fitness advantage during CDI, suggesting that calprotectin released during infection alters C. difficile's metabolic niche and improves pathogen survival. Next, to understand the mechanisms responsible for calprotectin-mediated shifts in microbiota abundances, future work will test how nutrient metal limitation changes the growth and metabolic output of fecal isolates. This information will improve our understanding of the functional consequences to changes in the nutrient landscape of the gut.

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Authorship: CAL and EPS were responsible for the experimental design, implementation, analysis, and writing/editing of the presented work. JPZ and RJK were involved in carrying out experiments and editing the presented work. AW was involved in data analysis and editing of the presented work.

Keywords: Nutritional immunity, Clostridium difficile, microbiota, zinc.

References

N/A.

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2'-Fucosyllactose Prevents Rotavirus Diarrhoea in Suckling Rats by Preventing Microbiota Alteration and Boosting Toll-Like Receptors

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Human milk oligosaccharides are involved in early life intestinal development, by influencing the intestinal microbiota and the immune system, among others (1). The most abundant oligosaccharide, 2'fucosyllactose (2'FL), represents ~30% of the total in human milk and has shown potential to provide protection against rotavirus (RV) infection.

The aim of this work was to investigate the impact of 2'FL on microbiota-host crosstalk and gut microbiota composition during RV-induced diarrhoea in suckling rats.

Lewis rats were daily administered with 2'FL from days 2–16 of life and on day 5 the RV was administered intragastrically. Faecal samples were collected daily for clinical evaluation of diarrhoea. On day 8, corresponding to the peak of diarrhoea, half of the animals were sacrificed in order to assess the intestinal Toll-like receptors (TLRs) expression. On day 16, the faecal microbiota composition was assessed by 16S rRNA sequencing and the caecal short-chain fatty acids (SCFAs) were quantified by HS-GC-MS.

2'FL supplementation reduced severity, incidence and duration of diarrhoea. RV infection increased intestinal TLR2 expression and altered intestinal microbiota composition, by reducing several genera, such as Staphylococcus and Streptococcus, and promoting the colonization with Proteobacteria. Moreover, RV reduced caecal SCFA. However, the supplementation with 2'FL boosted TLR5 and TLR7, prevented the RV-induced microbiota alteration, promoted the colonization of new species and increased the caecal SCFA butyrate.

The supplementation with 2'FL in early life ameliorates RV diarrhoea. The increased TLRs expression and the prevention of RV-induced microbiota alteration are suggested to be part of mechanisms involved in such amelioration.

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Conflict of Interest: K.K. and J.G. declare that they are employees of Danone Nutricia Research.

Authorship: F.J.P-C., M.J.R-L., M.C., and K.K. conceived and designed the experiments; I.

A-B., F.J.P-C., M.J.R-L. and M.M-C. carried out the experiments, analysed the data and wrote the abstract; the rest of the authors reviewed it.

Keywords: 2'-fucosyllactose, rotavirus, diarrhoea, TLR, microbiota.

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Microbiota and Immune Health

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Interrelation Between Chronic Consumption of Sweeteners, GALT Lymphocytes and the Small Intestine Microbiota of CD1 Mice

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Sweeteners are additives that provide sweetness, their use is not toxic to health, and however it has been observed that they exert diverse effects in some cellular ways. The intestinal microbiota plays an important role in the regulation of host metabolism, which is related to the digestion of food, energy supplements and the development of the immune system. The aim is to relate the chronic consumption of sweeteners on the lymphocytes of GALT with the composition of the small intestine microbiota in CD1 mice. We used 72 CD1 mice divided into 3 groups: (a) basal, (b) intermediate and (c) final. The Groups b and c were divided into 4 subgroups (Control, Sucrose, Stevia and Splenda). The sweetener was diluted in water and administered for 5 hours a day with food and water without sweetener ad libitum. The sediment of the intestinal content was inoculated in enriched culture media, the 16S rRNA gene was amplified for the identification of the microbiota. Sucralose and Stevia showed a higher percentage of CD19 + B cells and IgA + plasma cells in Peyer's plate at the end of treatment. In lamina propria IgA + cells increased their production in all study groups. The genera that predominated were: Bacillus that was present in 7 groups, Pseudomonas that was presented in 4 groups and Staphylococcus was present in 3 groups. Sweeteners modulate the proliferation of lymphocytes in the intestinal mucosa and modify the composition of the intestinal microbiota increasing bacterial diversity.

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Conflict of Interest: The authors declare not have conflict of interests.

Authorship: N/A.

Keywords: Sweeteners consumption, microbiota, small intestine.

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380/27

Effect of a Multivitamin and Fibre Mixture on Immunity and Microbiota of Adult Rats

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The aim of this study was to establish the effects of a nutritional multivitamin and mineral supplementation together with two different dietary fibres on the intestinal immune system in adult rats. For this purpose, female and male 9-week-old Wistar rats were distributed into four experimental groups (n = 10/group): one constituted the REF group, another group received a daily supplement based on a food matrix with proteins, vitamins and minerals (V), and two other groups received this supplement enriched with inulin (V+I) or acacia fibre (V+A). Body weight, food intake, and faecal pH and humidity were evaluated throughout the study. At the end, faecal and caecal content samples were collected to evaluate intestinal IgA and microbiota composition by ELISA and sequencing techniques, respectively [1, 2]. No significant differences on body weight, food intake, faecal pH and humidity were observed due to dietary intervention. Regarding intestinal immune response, the V+I supplementation increased the faecal IgA content compared to the REF and V groups ($p < 0.05$). Although no changes were observed in the V group, both V+A and V+I supplementations increased Firmicutes and Actinobacteria phylum proportions, which were associated with a higher presence of Lactobacillus and Bifidobacterium spp. Overall, the supplements tested in this study present differential effects, whereby V+I shows intestinal immune enhancement, while the V+A has stronger prebiotic activity.

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Authorship: F.J.P-C., M.J.R-L., M.C., A.F. and M.M-C conceived and designed the experiments; M.M.-C., F.J.P-C. and I.A-B. carried out the experiments, analysed the data and wrote the abstract; A.F., M.C., M.J.R-L. and F.J.P-C., reviewed it.

Keywords: Prebiotic fibre, inulin, acacia fibre, intestinal IgA, microbiota.

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Lactobacillus Fermentum CECT5716 Administration in Rats During Gestation and Lactation Improves Immune Quality of Milk

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Babies are born with an immature immune system unable to cope with all the environmental hazards, such as for instance pathogens. Human milk contains many immune factors (i.e. immunoglobulins, cytokines or antimicrobial proteins) that help the newborn fight these threats. There is evidence that probiotics may help improve the immune quality of human milk, but such proof remains scarce.

The objective of the study was to investigate whether the daily administration of Lactobacillus fermentum CECT5716, a strain isolated from human milk with immunomodulatory effects (1), during rat gestation and lactation periods can impact the immune quality of milk.

Lewis rats were administered daily either with Lactobacillus fermentum CECT5716 or vehicle during the three weeks of gestation and the first two weeks of lactation. At the end of the study, plasma and milk were obtained in order to analyse the content of immunoglobulins and cytokines by Luminex®. Moreover, IgA was determined by ELISA in faeces, gut wash, mesenteric lymph nodes and mammary glands. The supplementation with the probiotic did not affect the concentration of cytokines but changed the immunoglobulin profile, showing a tendency to increase IgG2a in plasma and milk. Moreover, in the probiotic group the amount of IgA in milk was increased twofold ($p < 0.05$) and a tendency to higher IgA levels was detected in all other samples analysed.

In conclusion, the supplementation with Lactobacillus fermentum CECT5716 during rat gestation and lactation periods may beneficially impact the immune quality of milk, and therefore may confer higher immunological protection to their offspring.

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Authorship: F.J.P-C., M.J.R-L., M.C., and A.F. conceived and designed the experiments; I.

A-B, F.J.P-C, M.J.R-L. and M.M-C. carried out the experiments, analysed the data and wrote the abstract; M.J.R-L. and F.J.P-C., reviewed it.

Keywords: Probiotic, milk, lactation, cytokines, immunoglobulins.

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Immunological Effects of Prebiotic B-GOS® on Adult Peripheral Blood Mononuclear Cells

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Trans-galactooligosaccharides (GOS) are non-digestible fibres showing a bifidogenic effect on the gut microbiota (1). Supplementation with GOS is associated with a reduction in gastrointestinal disorders (2), lower airway-responsiveness (3) and better immune functions (4). The aim of this study is to assess a direct, non-prebiotic interaction between GOS and adult peripheral blood mononuclear cells (PBMCs). Our hypothesis is that *in vitro* culture of PBMCs with Bimuno® galactooligosaccharide (B-GOS®) will not have adverse effects upon viability, but may alter cell counts and secretory cytokine production. PBMC from healthy donors ($n = 5$) were incubated for 24 h, 48 h and 72 h with Bimuno® galactooligosaccharide (B-GOS®) or mitogens. Cell counts, viability measurements and supernatant collection were performed. Two-way ANOVA followed by Bonferroni *post-hoc* test were used to evaluate the effects of stimulation time and concentration. Incubation of PBMCs with B-GOS® did not significantly affect cell counts. PBMC well tolerated culture with B-GOS®, with viability above 80%. No statistically significant effects were observed upon interferon-γ (IFN-γ) production. However, there was a highly variable IFN-γ production among PBMCs stimulated with the highest concentration of B-GOS® for 72 h (288.8 pg/mL ± 479.6) compared with minimal production at other conditions (under 16.3 ± 15.7 pg/mL) and those achieved with PMA + ionomycin (152.2 ± 142.3 at 72 h). We are now assessing a full profile of cytokine production and investigating which cell types are responsible for these preliminary observations.

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Conflict of Interest: None.

Authorship: S. D. F. carried out the experiments and drafted the abstract. P. C. C. and C. E. C. were involved in designing and coordination of the study and revising the abstract critically.

Keywords: Prebiotics, Galactooligosaccharides, PBMCs, Cell culture, IFN-γ.

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380/53
Association Between Probiotic Fermented Milk (PFM) Consumption and Bifidobacterium Species in Healthy Adults

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Probiotic fermented milk (PFM) consumption has been related to beneficial effects on maintaining a healthy gut microbiota, although evidence in healthy adults is inconclusive. Therefore, this study was aimed to assess the influence of PFM consumption on the gut microbiota in 260 healthy adults (51% males; 25–45 years), neither suffering from any chronic disease nor following medical treatment. PFM consumption habits on a weekly basis were analyzed by a questionnaire including Lactobacillus and Bifidobacterium-enriched PFM products. Gut microbiota was analyzed through 16S rRNA gene amplicon sequencing (V3+V4 gene regions. MiSeq 2x250 Illumina) and taxonomic analysis. Taxa differential abundance between groups was analyzed by general linear models and Man-Whitney U test for parametric and non-parametric variables, respectively. Chi-square test for species-occurrence analysis and Spearman correlation for variables association were used. There were 175 subjects classified as non-consumers (NC) and 85 as PFM consumers (Bifidobacterium-enriched [B-PFM, n = 71] and Lactobacillus-enriched [Lb-PFM, n = 14]). PFM consumers showed higher Bifidobacterium levels (P = 0.028) compared to NC, which could be attributed to the increased levels of B. animalis (P < 0.001), B. pseudolongum (P < 0.001), B. thermophilum (P < 0.001), B.magnum (P < 0.001), B. merycicum (P < 0.001) and B. dentium (P = 0.045). Specifically, the proportion of positive subjects detected for each species was higher in B-PFM consumers compared to NC (P < 0.001), and the relative abundances were also positively correlated with the number of B-PFM consumed (P < 0.001). In conclusion, PFM showed species-specific effects and could be potential candidates to maintain a healthy gut microbiota, as observed in the increased Bifidobacterium levels.

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Keywords: Probiotic fermented milks, healthy adults, Bifidobacterium, gut microbiota.

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Differences in Bacterial Genus Depending on the Body Mass Index of Healthy Adults

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Gut microbiota effects on energy harvesting and fat storage are well known, but existing evidence on healthy adults is scarce. Therefore, this study was aimed to assess the influence of the body mass index (BMI) on the bacterial genus composition of 261

healthy adults (51% males; 25–45 years), neither suffering from any chronic disease nor following medical treatment. Height (Soehnle) and body weight without shoes and with light clothing (Tanita BC 601) were taken for body mass index calculation [BMI = weight (kg)/height (cm)^2]. Gut microbiota was analyzed through 16S rRNA gene amplicon sequencing (V3+V4 gene regions. MiSeq 2x250 Illumina) and taxonomic analysis. After propensity score matching of confusion factors (age and gender), 152 subjects were included. Taxa differential abundance among groups were analyzed by Kruskal Wallis and Man-Whitney U tests for pairwise comparisons, considering significant those q values <0.05 by the Storey method. There were 57 subjects classified as normoweight (BMI = 20–25 kg/m^2), 79 as overweight (BMI = 25–30 kg/m^2) and 16 as obese (BMI = 30–35 kg/m^2). Obese subjects showed higher levels of the Firmicutes Lactobacillus and Weissella compared to overweight ($q = 0.003$ and $q < 0.001$, respectively) and normoweight (both $q < 0.001$), as well as lower Lachnospira compared to normoweight ($q = 0.027$). Normoweight showed higher levels of the Bacteroidetes Pedobacter and Hymenobacter compared to overweight ($q = 0.004$ and $q = 0.005$) and obese ($q < 0.001$ and $q = 0.002$). This study confirms the well-known relation between high body mass and changes in Firmicutes or Bacteroidetes members. However, the Firmicutes genera showed different behaviors depending on the BMI, highlighting the importance of exploring specific genera within the same bacterial group and their roles in human metabolism.

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Conflict of Interest: None.

Authorship: N.R., A.G, L.D. and B.V. carried out the experimental part of the study, N.R., A.M. and E.N. wrote the abstract and A.M. and E.N. designed and supervised the study.

Keywords: Body mass index, healthy adults, gut microbiota.

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Nutrition and Immune Development

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Knowledge and Management of Food Allergy Among Pre-School Child Caregivers in Ogun State. Nigeria

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Background and Objectives: Investigating the knowledge and management of food allergy among child caregivers is one of the ways of reducing infant mortality as the severe case of this immunological response can lead to life threaten situations. This study assessed the knowledge and management of food allergy among child caregivers in Ogun State, Nigeria.

Methods: Descriptive survey using multisampling technique was adopted to select eight-two (82) child caregivers from the study area. A validated Food Allergy Knowledge and Management Questionnaire (FAKMQ) was used for data collection. Knowledge and management scale of 0–10 was adopted and categorized high: ≥7, moderate: 4.0–6.9 and poor: 0–3.9. Data collected were analyzed using descriptive statistic and t test at $p = 0.05$.

Results: Results revealed that respondents had low knowledge on common food allergy among children (2.5 ± 0.4), signs and symptoms of food allergy (3.2 ± 0.9), factors that increase the risk of having food allergy (2.2 ± 0.6). The knowledge on the differences between food allergy and food intolerance (1.20 ± 0.2) and severe allergic reactions (anaphylaxis) (2.0 ± 0.3) were also low. Respondents were also found to have poor management of allergic reactions in children (2.15 ± 0.8). A significant difference between knowledge and management of food allergy among child caregivers was established.

Discussion and Conclusion: knowledge and management of food allergy was poor among child caregivers, therefore, regular training should be organized for caregivers to increase their knowledge on food allergy by reviewing past occurrences to identify better ways of management.

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Authorship: Awofala A.A was one of the biostatisticians that helped the validating the questionnaire and analyzing the statistical results.

Keywords: Food Allergy, Management, Caregivers.

References

N/A.

380/23

Functionality of Spleen Lymphocytes from Suckling Rats Is Modulated by Breast Milk Growth Factors

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Immune response is functionally deficient and less competent during the first days of life compared with adults [1]. Breast milk contains growth factors (GF) that seem to contribute to the maturation of the immune system in early life [2]. The aim of this study was to determine whether transforming growth factor (TGF) β2, epidermal growth factor (EGF) and fibroblast growth factor 21 (FGF21), present in breast milk, were able to influence the functionality of the developing systemic immune system during suckling period. For this, newborn Wistar rats were randomly distributed into four experimental groups: reference, TGF-β2, EGF and FGF21. Rats were daily supplemented by oral gavage with these GF since the day of birth until the end of the suckling period (day 21). At days 14 and 21 of life, spleen lymphocytes were isolated, cultured and their proliferative ability as well as their cytokine secretion patterns were evaluated. The results show that the supplementation with EGF and FGF21 has a trend to promote the spleen lymphocytes proliferative ability at 21 days. Regarding cytokine production, FGF21 was the only supplementation able to induce some changes in comparison to the reference group. Specifically, in the FGF21 group, the production of TNF-α was reduced at day 14, and that of IFN gamma at day 21, inducing a decrease of IFN gamma/IL-4 ratio. These results evidence that FGF21 is the most active growth factor tested, suggesting that its immunoregulatory effects may contribute to the development of systemic immune system in early life.

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Authorship: A.F., F.J.P-C. and M.C. designed the study; P.T-C., B.G-P., and M.A-G. carried out the experiments and analyzed the data; P.T-C. wrote the abstract; A.F., F.J.P-C. and M.C. reviewed it.

Keywords: Growth factors, suckling rat, proliferation, spleen lymphocytes, cytokines.

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Epidermal Growth Factor Promotes the Intestinal Barrier Maturation of Preterm Rats

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The neonatal immune system is immature and prematurity magnifies this state, provoking severe deficiencies and specifically, the intestinal function is highly affected [1]. The breastfeeding, due to its rich composition in bioactive components such as growth factors, has a key role promoting intestinal and immune maturation [2]. The aim of this study was to determine whether the supplementation with epidermal growth factor (EGF) -present in breast milk-was able to enhance intestinal barrier maturation in premature rats. For this purpose, preterm Wistar rats were daily supplemented with EGF during the first ten days of life. Preterm (PT) and term (T) groups receiving vehicle were used as controls. At 10 days, the intestinal permeability was evaluated, small intestine (SI) was weighted and measured and morphometric variables from SI histological sections were analyzed after PAS staining. Concerning the intestinal permeability, the results demonstrated differences between PT and T groups ($p < 0.05$). Interestingly, the EGF supplementation was able to reverse prematurity state, reaching levels equivalent to those of the T group ($p < 0.05$ vs. PT group). Regarding the histological study, the size of the goblet cells present in the intestinal epithelium was lower in the PT group ($p < 0.05$ vs. T), whereas EGF administration prevented such effect ($p < 0.05$ vs. PT). No differences were observed in the rest of morphometric variables assayed. Overall, these results revealed the ability of EGF to improve the prematurity status of the intestine as well as the capacity to accelerate the maturation of the intestinal barrier function.

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Authorship: MA-G, FJP-C and AF designed the study; PT-C, CD-C, LM-M and MA-G. carried out the experiments and ana-

lyzed the data; P.T-C, CD-C and MA-G wrote the abstract; FJP-C and AF reviewed it.

Keywords: EGF, suckling rat, prematurity, goblet cells.

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Lactobacillus Paracasei Supplementation Effect on the Intraepithelial Lymphocytes Composition in Rat Early Life

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Although the health benefits caused by probiotics when they are consumed in adequate amounts have been widely claimed [1, 2], these effects are strongly strain-dependent [3, 4]. Moreover, early life is a critical stage in the immune system development [5]. In the present study we aimed if the supplementation with two different strains of Lactobacillus paracasei, LP-ORD0681 and LP-ORD0712, in this window of time could be able to promote the intestinal immune system maturation. To achieve this purpose, newborn Wistar rats were daily supplemented with LP-ORD0681 or LP-ORD0712 throughout the first 28 days of life. Not supplemented animals were used as a reference (REF) group. At the end of the study, intraepithelial lymphocytes (IEL) from small intestine were obtained and purified to determine their composition by multiple immunofluorescence staining and the subsequent flow cytometry analysis. The main subsets found in this effector intestinal compartment were NK > TCR??????TCR????? NKT lymphocytes. The results showed that LP-ORD0681 was able to increase significantly the TCR???CD4+ population and had a tendency to rise the NK CD8+ cell proportion with respect to REF group. Regarding LP-ORD0712 supplementation, it induced an increase in the percentage of IEL expressing the isoform CD8?, typical from the intestine ($p < 0.05$ vs REF group). In conclusion, these results demonstrated that these probiotic supplementations in rat early life induce several strain-dependent changes in the IEL composition that could contribute to the intestinal immune system development.

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Conflict of Interest: The authors -MCDA, JAMM, and MR-P- declare that they are employees of the company Laboratorios Ordesa.

Authorship: AF, FJP-C, MCDA, JAMM and MR-P conceived and designed the experiments; MA-G, AF and FJP-C, carried out the experiments and analysed the data, MA-G and AF wrote the abstract; MCDA, JAMM, MR-P and FJP-C reviewed it.

Keywords: Probiotic, early life, rat, immunonutrition, IEL composition.

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Immune System Development in a Rat Model of Prematurity for Immunonutrition Studies

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At birth, the immune system of neonates is immature and it develops during the first stages of life [1]. This immaturity is more acute in the preterm newborn [2]. Nutrition has a key role promoting the development of the immune system [3]. The aim of the present study was to establish representative biomarkers of innate and adaptive immunity to evaluate the maturity of the immune system on a premature rat model. The model is achieved by the performance of a caesarean one day before its normal delivery. For this purpose, body and organs weight and blood cell composition were determined. To evaluate the functionality of the intestinal epithelial barrier, the permeability to fluorescent dextran was measured in vivo. Furthermore, the phagocytic activity of blood leukocytes (innate immunity) and plasmatic Ig (adaptative immunity)

were assessed. The animals that were born in preterm conditions had a lower red blood cell count but a higher count of leukocytes than the full-term ones. Regarding the permeability assay, preterm rats had lower intestinal permeability than those born at term. Although there were no changes in the granulocytes ability to phagocyte, preterm monocytes revealed less capacity. Finally, preterm rats showed lower IgG and IgM plasma concentration, without changes in IgA. Overall, these results show that prematurity carries an immature immune system that can be reflected in the different biomarkers here established. Moreover, this experimental model could be an essential tool for studies focused on nutrition to promote the development of the immune system in preterm rats.

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Authorship: A.F., F.J.P-C., M.A-G and M.J.R-L conceived and designed the experiments; B.G-P., P.T-C. and M.A-G carried out the experiments and analysed the data, B.G-P. wrote the abstract; A.F., F.J.P-C., M.A-G and M.J-R-L. reviewed it.

Keywords: Premature model, suckling rat, intestinal permeability, phagocytosis, immunoglobulin.

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Intrauterine Growth Restriction Induced by Maternal Low-Protein Diet During Pregnancy Is Associated with Alterations of Intrathymic Thymocyte Distribution in Offspring

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Background: Intrauterine growth restriction (IUGR) is associated with precocious thymic atrophy. We previously demonstrated that atrophy predominates in the cortex area, consistent with a reduced cortico-medullar ratio. However, the underlying thymic subsets alterations induced by IUGR remain poorly described. We aimed to characterize alterations of thymocytes subsets at adulthood in rat offspring born after IUGR.

Methods: Sprague-Dawley rat dams were exposed to normal (control, CTRL) or low protein diet (LPD, 9% casein) during gestation to induce IUGR. At postnatal day (PND) 60, the expression of autoimmune regulator (AIRE) protein on medullary thymic epithelial cells (mTECs) was assessed by Western-blot on frozen thymuses. At PND 180, the offspring thymuses were isolated, stained for CD3, CD4, CD8, CD25 and CD44 expression and analyzed by flow cytometry (LSR-II, Becton Dickinson).

Results: The distribution of the CD4–/CD8– (double negative, DN), CD4+/CD8+ (double positive, DP), CD4+/CD8– and CD4–/CD8+ thymocytes was significantly altered between CTRL (n = 4) and LPD diet fed (n = 6) rats. In addition, the AIRE expression in mTECs was significantly reduced in the IUGR offspring.

Conclusion: LPD-induced IUGR is associated with abnormal thymocytes maturation, with decreased proportions of DN and CD8+ thymocytes subsets in adulthood. In addition, a decreased expression of AIRE suggests an altered function of mTECs in IUGR-exposed offspring. Altogether, our findings highlight potential mechanisms of programmed autoimmune diseases associated with IUGR exposure. The potential consequences of such anomalies deserve further investigations. These findings suggest that early life nutrition may have lifelong consequences to the immune system.

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Authorship: N/A.

Keywords: Developmental immunologic programming, Early-life nutrition, Thymic function.

References

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380/43

Probiotic Ganeden BC30 Promotes Innate Immune Response in Mexican Children After 3 Months of Consumption

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Probiotic effects on adult people have been widely evaluated, however few studies in children have been conducted. This age group is very interesting because this is when infections and respiratory diseases are most prevalent. The aim of this study was to evaluate the immune response of healthy school-age children supplemented with a commercial probiotic (Ganaden BC30). A total 80 Mexican children both sexes were randomly allocated in the

treatment (BC30) or control (placebo) group. The study was double blinded. Children in each group received a sachet either with the probiotic BC30 or placebo on a daily basis for 3 months. Children aged from 5 to 7 years, of which girls represented 58.2 mm Hg and boys 41.8%. Data collected included anthropometrics, diet, blood collection for analysis of immune response markers, and the occurrence of respiratory and infectious diseases. After 3 months BC30 significantly decreased serum levels of TNF-α, CD163, G-CSF, ICAM-1, IL-8, IL-6,IL-1b and increased PF4. G-CSF was positively correlated with TNF-α (r = 0.476). ICAM-1 reduction was associated with innate immune response and correlated with TNF-α, IL-6 and Il-1b. Consumption of probiotic BC30 was effective at activating the innate immune system of the children, as demonstrated by changes in proteins such as IL-6, TNF-α and IL-1b.

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Authorship: IFPR, KD and MAAL designed the study, IFPR and MAAL conducted the intervention study, IFPR and JAEM carried out the proteomic analysis, IFPR and MAAL analyzed the data.

Keywords: Probiotic, Bacillus coagulans, immune system, upper-respiratory tract infections, gastrointestinal tract infections.

References

N/A.

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Antioxidant Capacity of the Plasma Lipid-Soluble Fraction in Anorexia Nervosa Patients During a One-Year Follow-Up

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Few studies have indicated changes in the antioxidant status in anorexia nervosa (AN); however, it has been suggested that malnutrition alters antioxidant capacity in AN patients. The objective of the study was to determine the baseline status and evolution of the antioxidant capacity of the lipid-soluble fraction of blood plasma (ACL) in patients with AN. The relationship between the changes in the ACL and anthropometry parameters (Z-score of BMI) was studied in 16 female adolescents, 8 diagnosed with AN (14.13 ± 1.12 years) in their first episode, paired for age and socioeconomic level to 8 healthy controls. Measurements were made at three time points: on admission (AN0), one month (AN1) and after one year (AN12). ACL was measured after hexane extraction using chemoluminescence (Photochem, Analytikjena). Recovery of the BMI Z-score was observed throughout the follow-up (AN0 = −1.49 ± 0.64; AN1 = −0.59 ± 0.26; AN12 = −0.11 ± 0.63, ANOVA, $p < 0.05$). No significant changes were observed in the ACL after the improvement of the BMI Z-score in the group of patients with AN (AN0 = 3.03 ± 0.83; AN1 = 2.76 ± 1.21; AN12 = 2.79 ± 0.78 ng/μL), nor in comparison with the control group (2.96 ± 1.11 ng/μL). Finally, a comparison of two sets of ACL measurements according to the corresponding BMI Z-score value (>-1 vs. ≤-1) did not show differences either. In conclusion, the results obtained do not show a significant influence of the nutritional status in the ACL of patients with short term AN.

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Conflict of Interest: None.

Authorship: A.M, M.G. and E.N. designed and supervised the study. J.C., S. G-M and E.N. carried out the experimental part of the study; P.A., A. E. and M. G. recruited and followed the patients; J.C. and E.N. analysed the data and wrote the article.

Keywords: Antioxidant capacity, anorexia nervosa, lipid-soluble fraction of blood plasma.

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