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Intestinal Permeability and Zonulin : Key Connections to Understanding the Impact in Diseases Systemic

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Abstract:- Zonulin, recognized since 1993 as a marker of intestinal permeability and response inducer inflammatory when found increased, has been a topic of discussion in the last two decades. This work Update the community scientific about this problematic and its association with diseases non - communicable chronicles. Through searches In PubMed, Redalyc and Google Scholar, 238 articles were identified, of which which were 20 references were selected, published between 2005 and 2024. The alteration of intestinal permeability, influenced by factors like zonulin and inflammation, affects the axes intestine-liver and intestine-kidney, exacerbates diseases chronicles such as kidney failure and damage hepatic. In addition, the imbalance in the intestinal microbiota, it facilitates the translocation of bacteria and toxins. Therapies as prebiotics, probiotics and supplements nutritional they can restore the intestinal barrier and modulate inflammation, improving he management and treatment of these conditions.

Keywords:- *Intestinal Microbiota, Intestinal Permeability, Zonulin, Probiotics, Prebiotics.*

I. INTRODUCTION

"All diseases begin in the intestine ' ' declared Hippocrates more than two thousand years back to doing allusion to the theory of the humors Postulated in Ancient Greece. Today, this premise becomes relevant due to the advances in Intestinal Genomics, Proteomics and Transcriptomics, establishing that the alteration of the barrier function of the mucosa of this organ, provide a context that favors the antigen trafficking and with it an answer immunological in the host tissues. (1)

Due to the great responsibility of the system digestive to separate and discriminate which substances food will be absorbed and defended against colonization by a variety of microorganisms, an army is required cellular capable of carrying out such functions, being considered so like an organ immunologically privileged. These groups Cell phones are found divided as follows: a) Tissue Lymphoid associated with Intestine he which includes: Peyer's patches, follicles lymphoid isolated, the appendix and the nodules lymphatics mesenteric; and b) Cells effectors: meeting in the Sheet Own with the lamina lymphocytes own and the lymphocytes intraepithelial. (2)

The colon is the section further colonized tract digestive and has been estimated to contain 70 % of the microbiome human. The intestinal microbiota is essential for the maintenance of microbial homeostasis and epithelial barrier function, regulation of metabolism and tolerance immunological. In condition of eubiosis, the intestinal barrier is compartmentalized effectively with the bacteria in the lumen, benefiting from a reinforced intestinal barrier, response immunological specific and memory, and the production of molecules beneficial synthesized by the intestinal microbiota. (3)

However, in dysbiosis condition, the function of junction barrier narrow is altered, which generates an increase in intestinal permeability, producing the translocation of microorganisms and molecules that lead to the response inflammatory whose intensity It depends on the type and prevalence of bacteria pathogenic. From this way, the response is triggered immune, activating the mediators proinflammatory such as cytokines, interleukin - 6 and tumor necrosis factor that damage cells epithelial and their junctions. (3)

The intestinal barrier can be split in three well-differentiated zones, from the outermost to the innermost: the mucous layer. the layer epithelial and the lamina own. The Closest to the intestinal lumen is a layer thick mucus, whose mucus goes away compacting as it approaches the next layer. Act as a protective barrier to prevent the entry of pathogens or substances harmful toward the interior. In she is found harboring the commensal intestinal microbiota, the acids chain fatty acids short, the fiber dietetics, the peptides antimicrobials, enzymes and defense molecules. (4)

Once After crossing the mucous layer, you reach the epithelial layer, where some folds called crypts. In the case of the intestine slim also It has some projections, villi intestinal. These villi have as function ease the process of nutrient absorption. Said layer is characterized for a high regeneration power of three to seven days. At the level cellular, predominate the enterocytes, but are also found cells goblet cells, Paneth cells, M cells, enteroendocrine cells. The last layer is the sheet own where there are cells immune cells that will be responsible for regulating the response immune, by controlling what is pathogenic or harmful to the organism. (4)

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Between the cells of the epithelium are the junctions narrow or *Tight Junction* (TJ*)* that are responsible for regulating the intracellular passage of macromolecules. Zonulin is the protein endogenous acting as modulator physiological of *TJ*. It was discovered by Alessio Fasano, doctor gastroenterologist specialized in intestinal permeability, while was investigating the creation of the cholera vaccine. This protein, through his anchoring to receptors membrane - specific, active a cascade of signs that give as result a loss in the organization of the *TJ*. This destructuring leads to increased permeability of the pathway paracellular. It is a reversible process, when zonulin stop signaling, the *TJ* return to their structure initial. (4)

The intestinal microbiota has four functions main. The function metabolic is related to the production of acids chain fatty acids short, the balance between the oxidation of acids fatty and lipogenesis, and the synthesis of vitamins. The function Immunological is related to the activation of T lymphocytes, the production of immunoglobulins by the B cells, cytokine release proinflammatory and immunoregulatory, and the secretion of hormones, neuropeptides and neurotransmitters. These processes occur from the recognition of the called patterns molecular associated with pathogens through the pattern recognition receptors. The other two functions the main components of the microbiota are the physiological and the barrier. The first of these It has to do with "turnover" or rotation cellular, linked to the apoptosis process and the second is related to the maintenance of the intestinal barrier function that has to do with the passage of products metabolic, system components immune and hormones from the intestinal lumen to the torrent sanguine. (5)

Each There is more and more evidence that the Gut microbiome and gut dysfunction play a role important in the development of diseases cardiovascular. In the patients with hypertension, atherosclerosis and heart failure cardiac is observed dysbiosis, an imbalance of populations microbial. The models experimental reveal interactions important between the microbiota, the intestinal barrier and the function immune in These and others diseases. (6)

According to the author, intestinal health is a central axis in physiology human, as evidenced by the paper critical to the intestinal barrier in regulating antigen transit and modulating immune. The intestinal microbiota, housed mostly in the colon, acts as key mediator in homeostasis through functions metabolic, immunological and barrier, in addition to producing acids chain fatty acids short and regular the balance between lipogenesis and acid oxidation fatty. However, dysbiosis, characterized due to an imbalance in the populations microbial, destabilizes are functions and generates an increase in intestinal permeability.

Among the elements that regulate the intestinal barrier, the junctions' Tight *junctions* (TJ) play a key role. Zonulin, a key protein in this process, modulates TJ reversibly, affecting permeability paracellular. This disturbance in the intestinal barrier is related to a cascade of events pathological including inflammation systemic, disease development metabolic such as obesity, insulin resistance and more recently, diseases cardiovascular. For all the above, the researcher reviews the literature existing to give answer to the following ask scientific:

How affects the modulation of the intestinal microbiota by administering probiotics and prebiotics to intestinal permeability in individuals with dysbiosis and their relationship with markers inflammatory systemic?

II. METHODOLOGY

Between November - December 2024 were databases examined electronic literature scientific medical (Redalyc, Google Scholar and PUBMED) to investigate the articles eligible in the last two decades (2005 - 2024). The search terms in the databases employees were: "intestinal microbiota", "intestinal permeability", "zonulin", "probiotics" and "prebiotics". They were included the articles available in English and in Spanish. They were 338 studies selected carried out in humans, 318 were excluded and only useful for research 20 articles that included he job complete and answered the question scientific. The evidence was included because it was relevant and currently current of the effects modulators of intestinal permeability. They were used the methods analysis theorists synthesis and the method inductive deductive.

- *Development*

Intestinal permeability, regulated in part for protein zonulin, plays a fundamental role in intestinal and systemic health. Its disruption promotes inflammation chronic, obesity and insulin resistance, conditions related to alterations metabolic and systemic. In this context, the axis intestine-liver is particularly relevant, since increased intestinal permeability facilitates the translocation of endotoxins and mediators inflammatory, exacerbating diseases hepatic and metabolic. This relationship is part of the grand theory unified gut, which connects gut health to multiple systems corporals.

Other axis important is the intestine-kidney, whose dysfunction during chronic kidney disease (CKD) evidence a connection bidirectional between intestinal microbiota, inflammation systemic and alterations metabolic. The consequences include the progression of CKD and the appearance of complications as stress oxidative and dysfunction immune. To address these imbalances, treatment strategies focus in restore the integrity of the intestinal barrier by probiotics, prebiotics, zonulin modulators and modifications dietary. These interventions not only improve intestinal permeability, but also mitigate the effects negatives in key organs such as he liver and the kidneys. Below are details the milestones further important related to intestinal permeability.

- *Factors Intestinal Permeability Modifiers*

For reasons didactics are divided the stimuli that affect intestinal permeability in factors external and internal. Next, they will be described some factors external. The intestinal flora plays a role important in the metabolism and absorption of molecules, allowing his entry into the interior of the body.

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These bacteria luminal constitute true defenses that prevent the effects of microorganism's pathogens in the intestinal mucosa. Disturbances in the balance of the normal intestinal microbiota (dysbiosis) result in the overgrowth of microorganisms harmful and in the release of a variety of mediators with potential antigenic as endotoxins and patterns molecular associated with pathogens that contribute to increased intestinal permeability associated with local and systemic inflammation. (7)

These changes allow the access of molecules as lipopolysaccharides, patterns molecular associated with pathogens, bacterial DNA, adhesins and invasins, whose release in the portal circulation triggers the response immunological of the liver, inducing defense mechanisms and damage elimination; as well as repair mechanisms that can to be maintained in the medium and long term. The mediators' pro-inflammatory agents produced at the luminal level induce changes in the organization of protein junctions narrow. The synthesis of tumor necrosis factor alpha, mediated via NF - kB, increases parallel to intestinal permeability when they occur paintings inflammatory at the intestinal level. (7)

This alteration coincides with modifications in the expression levels and distribution of junctional proteins narrow such as ZO-1 and occludin; in addition to TNF-α showing effects *in vitro* on the state of phosphorylation and activity of junctional proteins narrow. On the other hand, side, the growth factor platelet - derived gestational age (PDGF) promotes the release of neutrophils adhered to the vascular endothelium with the consequent synthesis of oxide nitric and radicals free in models' animals; by favoring by as well as local vasodilation and intestinal permeability. Finally, the luminal concentration of gases such as he oxide nitric and others molecules air pollutants from sources inhalation or food intake contaminated, activate stress pathways oxidative with effects harmful on the cells of the intestinal epithelium. (7)

Studies recent indicate that, in addition to water and salt homeostasis and nutrient digestion and absorption, another Key function of the intestine is to regulate the antigen trafficking environmental factors across the host mucosal barrier. The junctions narrow intestinal are responsible for the traffic paracellular macromolecules and therefore contribute to the balance between tolerance and response immune to non- self-antigens. Although there is considerable knowledge about the ultrastructure of junctions narrow intestinal, relatively little is known about his regulation pathophysiological leading to local and/or systemic inflammation. Technologies capable of restoring the function of the intestinal barrier and therefore the traffic suitable antigens, can represent an approach innovative to prevent and/or treat diseases immune-mediated in which the Increased intestinal permeability appears to be an integral part of its pathogenesis. (8)

Among the various stimuli intestinal potentials that can trigger the release of zonulin, exposure of the intestine thin to bacteria and gluten are the two triggers that have been identified so far. In addition to the exhibition bacterial, we have demonstrated that gliadin, the main protein wheat staple, also affects the intestinal barrier function by releasing zonulin by interacting with the chemokine receptor CXCR3. (8) In As for the factors that have been seen to be able to increase this protein, they highlight dysbiosis (alteration of the intestinal microbiota), due to the release of enterotoxins that can trigger some pathogens, and gluten. Others factors include the toxic as alcohol and some medicines. (4)

Although, it could be hypothesizing a mechanism unidirectional in where intestinal dysbiosis induces intestinal permeability and thus translocation bacterial that allows infiltration bacterial, by inducing a answer inflammatory and the triggering the pathogenesis of obesity, could not assert this is not found mediated previously or in parallel by the action of the acids chain fatty acids short or others metabolites bacterial. Possibly both mechanisms in the intestinal microbiome of the obese are seen induced, since feedback is viable positive between both paths as long as intestinal dysbiosis is not attenuated, all by the role defined for the characteristic intestinal endotoxemia in obese population and that precisely promotes inflammation chronic low- grade and induction of increased intestinal permeability. (1)

In Summary, according to the author of the work, intestinal permeability is influenced by a variety of factors external and internal, which affect the integrity of the intestinal barrier and its ability to regulate the trafficking of molecules between the intestinal lumen and the system circulatory. Dysbiosis, or imbalance of the intestinal microbiota, plays a central role, as it promotes, he growth excessive microorganisms pathogens that release endotoxins and patterns molecular associated with pathogens. These molecules activate answers local and systemic inflammation, by compromising the joints narrow intestinal epithelium.

Additionally, factors as he consumption of gluten, alcohol and certain medications, along with exposure to pollutants environmental and stress oxidative, also contribute to intestinal barrier dysfunction. Among these stimuli, highlights zonulin, a protein regulator of unions narrow, whose release can be triggered by enterotoxins bacterial and components dietary like gliadin. This knowledge underlines the importance of strategies therapeutic focused in restore microbial homeostasis and intestinal barrier integrity to prevent diseases immune-mediated and metabolic.

- *Zonulin, Intestinal Inflammation, Obesity and Insulin Resistance*

A new paradigm was described in 1993 by the discovery of zonula occludens 1 (ZO-1) as the first component of the TJ complex which is now this compound by more than 150 proteins, and includes occludin, claudins, junctional adhesion molecules, tricellulin and angulins. However, despite the big advances in the knowledge on the composition and function of unions intercellular, the mechanisms by the which are regulated They are still not understood by complete. One of the main advances in understanding the role of intestinal permeability in health and disease has been the discovery of

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zonulin, the only modulator physiological of intestinal permeability described so far. (9) In the same year in which ZO-1 was discovered, it was identified increased intestinal permeability in a subset of first- degree relatives of people with Crohn's disease. (10)

The studies led to the discovery and characterization of zonulin as the only one protein human discovered to date that is known to reversibly regulate intestinal permeability by modulating the junctions intestinal intercellular. Through the analysis serum proteomics humans, has been identified recently zonulin as pre- haptoglobin (HP2), a molecule that, to date, has only been considered as the inactive precursor of HP2 , one of the two variants genetics (along with HP1) of human HPs . The data suggest that pre HP2 , a protein multifunctional that, in its chain shape unique intact (zonulin), regulates intestinal permeability through proteinase activating receptor 2 (PAR2) , while in its double-split chain form act as a Hb scavenger .(8)

The two main ones zonulin release triggers that have been described so far are bacteria and gliadin. It is well described that many pathogens enteric are capable of producing enterotoxins that affect binding narrow intestinal tract of the host. In addition to enterotoxins, several have been shown pathogens enteric, including *Escherichia coli* commensal, *laboratory E. coli, E. coli* virulent and *Salmonella typhi*, cause a zonulin release from the intestine when applied to the apical surface. (11)

After the release of zonulin, the intestine showed increased permeability and disassembly of ZO-1 from the junctional complex narrow. Gliadin is the other trigger that has been described to release zonulin. While it is not understood by complete the signaling cascade complete that follows the binding of gliadin to CXCR3 and leads to the release of zonulin, has been shown to be dependent on MyD88. Gliadin also can provoke a release of zonulin and cytokines proinflammatory of the macrophages similar to the response observed after the exhibition bacterial. (11)

In circumstances physiological There is strict control of mucosal antigen trafficking, which, in conjunction with cells immune specific and mediators of chemokines and cytokines, leads to anergy and, therefore, to mucosal tolerance. The production inadequate of a greater amount of zonulin causes a loss functional barrier function, with the consequent antigen trafficking inappropriate and uncontrolled that triggers a answer immune innate by part of the compartment immune submucosal. If this process continues, it is unleashed a answer immune adaptive which causes the production of cytokines proinflammatory, including IFN -γ and TNF-α, which cause Greater opening of the road paracellular to the passage of antigens, which creates a circle vicious. (11)

It is known that several stimuli affect the cytoskeleton and therefore induce changes in permeability paracellular. This is mediated mostly by phosphorylation of MLC by MLCK affecting F - actin fibers in the F- actin ring prejunctional. In particular, it is known that IFN -γ, TNF and *Escherichia coli* enteropathogenic induce an increase MLCK dependent in permeability paracellular. (12)

The evidence suggests that there is a association between cow 's milk and DM1, but maybe he approach is misplaced state. Disruption of intestinal permeability affects oral tolerance, and is usually accompanied by antigenic loads high. Therefore, it has been proposed that a subject with susceptibility genetics and a “leaky gut,” he has the underlying problems and should be considered when evaluating cow 's milk and others antigens associated with the disease. This intestinal leak has been associated with low Claudin levels and Zonulin elevation, allowing the passage of antigens toward he space subepithelial. In In this context, cow 's milk is accompanied by gliadin (gluten) as molecule food-related diabetes. (2)

Evidence recent suggest a possible role of intestinal permeability in obesity. In patients obese, the intestinal permeability parameters are correlated with risk factors for the syndrome metabolic, inflammation induced due to obesity and liver disease non -alcoholic fatty acid. More recently, it has been reported that zonulin this associated with insulin resistance associated with obesity. Interestingly, zonulin circulating increased with the body mass index, the relationship waist hip, insulin in fasting, the triglycerides in fasting, the acid uric acid and IL-6. This last observation is of particular interest as it suggests that the relationship between insulin sensitivity and zonulin circulating could be mediated by the Increased circulating IL-6 related to obesity. (8)

It has recently been shown that obesity this associated with inflammation chronic. In a mouse model obese, it was observed increased intestinal permeability and absorption of macromolecules. In addition, patients obese they run the risk of developing complications secondary to their obesity, such as high cholesterol, type 2 diabetes, coronary heart disease, high blood pressure and stroke. Three studies they have demonstrated that the level serum zonulin increases in subjects obese in compared to non- obese individuals. It has been shown a correlation between bacteria totals and the levels serum zonulin levels. It is suggested that the intestinal microbiota may cause an increase in the zonulin levels, with the consequent Abnormal intestinal permeability to endotoxin (lipopolysaccharide - LPS) and, in last instance, microinflammation observed in obesity. (11) Figure 1 mentions the mechanisms related between the modulation of the intestinal microbiota in the pathogenesis of obesity.

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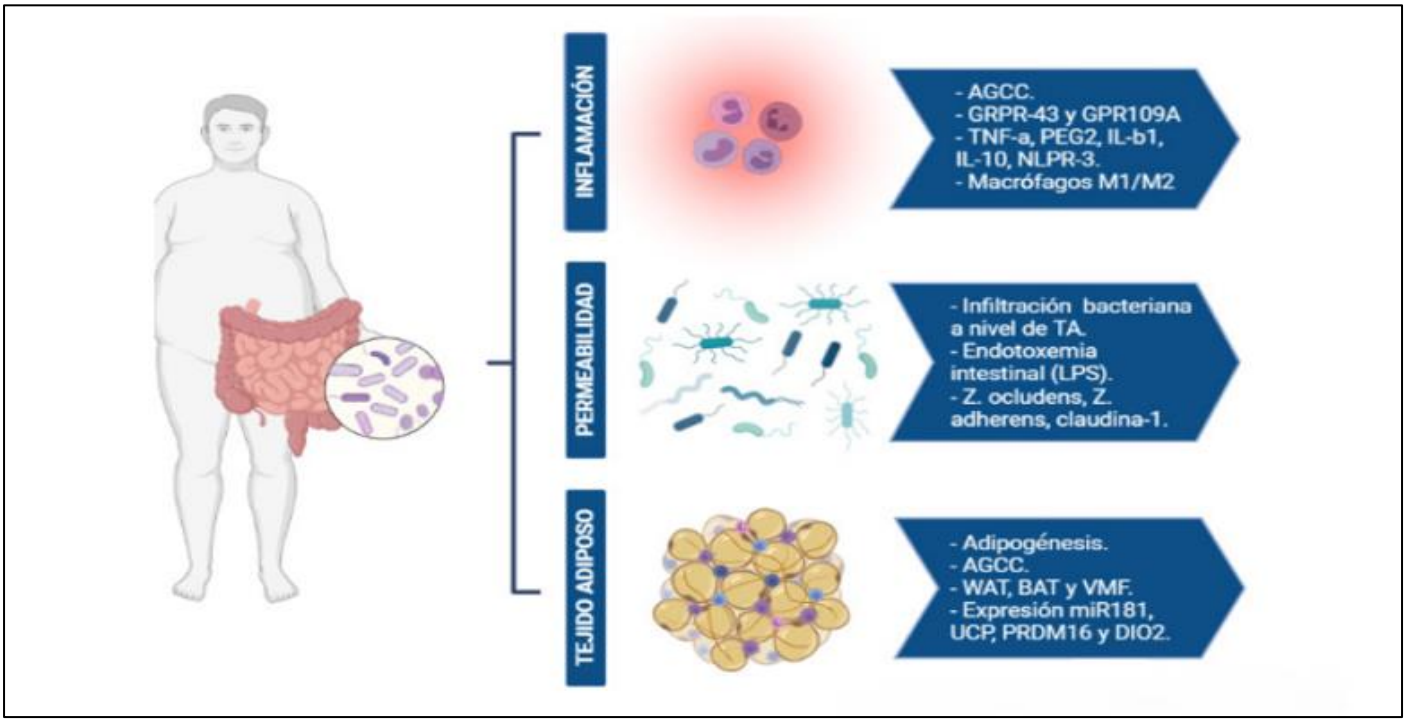

Fig 1 Modulation of the Intestinal Microbiota in the Pathogenesis of Obesity

Various methods they have allowed the assessment of intestinal permeability : first, the molecules probe ingested by oral route (one assessment functional direct route of the epithelial barrier , specifically the route paracellular); second , endotoxins circulating [lipopolysaccharide (LPS) and LPS-binding protein] , zonulin serum (which is a modulator of the binding narrow intestinal) or the acid binding protein levels fatty intestinal ; these measurements reflect he damage to the epithelium and constitute evaluations indirect barrier pathways. Zonulin are proteins 47 kDa paracrine released by several lines cell phones in the body, including cells epithelial covering he intestine thin. (13)

During the last decade, a particular effort has been made in the identification of biomarkers reliable capable of assessing intestinal permeability in blood. One of the first proteins identified with results promising was zonulin, an analogue human endogenous toxin enterotoxin bacterial zonula occludens. It has been proposed that zonulin modulates intestinal permeability by dismantling the complexes binding proteins narrow in the intestinal epithelium. Zonulin is a precursor of haptoglobin -2 and belongs to the haptoglobin family of phase - 2 reaction proteins. acute. (12)

From the perspective of the author of this research, it is considered that the discovery of ZO-1 in 1993 not only represented a milestone in understanding unions narrow, but established a paradigm that connects the regulation of the intestinal barrier with processes immunological and metabolic complexes. This analysis includes the evolution of knowledge in around the TJ and, specifically, the impact of zonulin as key modulator in intestinal permeability. This work highlights as a disturbance in the barrier function can trigger answers immune uncontrolled, leading to conditions such as Crohn's disease, type 1 diabetes, and obesity.

Recognize this bond allows the researcher advance in the identification of biomarkers and strategies therapeutics to intervene in these processes. In addition, the comprehensive perspective that is adopted It aims not only to elucidate the mechanisms underlying, but also to identify new opportunities for the prevention and management of these entities. This approach intends contribute significantly to the understanding of how intestinal barrier regulation can influence in health systemic.

- *Effect of Intestinal Permeability on the Axis Intestine-Liver*

The study of intestinal permeability gains importance in function of its potential to induce a answer liverwort adaptive aimed at maintaining homeostasis against antigens from the portal circulation. The factors External and internal gases that reach the portal circulation are transported to the liver and distributed in the spaces sinusoidal. These molecules are able to activate a series of signaling cascades that induce answers proinflammatory and profibrogenic. Effects that occur after his interaction with the receivers Toll type (*Toll-like receptors*, TLR) present in the cells mesenchymal of the liver like Kupffer cells. (7)

In answer , said cells synthesize and release mediators proinflammatory such as IL-1β and TNFa , as well as by fibrogenic TGF β1 and PDGF, which secondarily They promote both a answer inflammatory sustained (the release of factors antiapoptotic through the expression of proteins of the family Bcl -2) as the transformation of cells stellar liverwort (main) liver fibroblasts) of a state quiescent to a state activated in the one they produce a greater amount of matrix extracellular with characteristics structural that can be more complex. (7)

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In this context, species reactive oxygen species originated in the hepatocytes damaged, and as a consequence of the hyperactivity of the NADPH oxidase of the Kupffer cells, they amplify proliferation or apoptosis stimuli that determine the destination cell phone when involving NF-kB and JNK signaling pathways. The minor ZO-1 expression at the intestinal level appears be associated with diseases that present with increased intestinal permeability, for example the disease celiac, as the presence of liver non -alcoholic fatty acid, according to reports Preliminary and observations early cross - sectional. (7)

Nowadays there are different non- invasive techniques that allow the study of the permeability of the intestinal barrier, as well as the progression of damage hepatic. The administration oroenteral substances as carbohydrates that pass through the intestinal epithelium, reach the circulation systemic and are excreted by via urinary, is a method useful for noninvasive evaluation of the intestinal absorption area. The use of mannitol, validated by methods chromatographic with parameter adjustment, allows assess he degree of intestinal permeability in children with diarrhea. (7)

On the other hand side , it is possible assess he Intestinal damage due to overpopulation of intestinal flora through the concentration of D- Lactate or lipopolysaccharides in blood , since certain metabolites originate in the intestinal microbiota that it has enzymes required in the metabolism of these molecule , unlike the mammals and their levels are associated with modifications concomitant intestinal flora and intestinal permeability , such as in the case of ischemia , burn and necrotizing pancreatitis acute . Noninvasive assessment of damage progression hepatic is performed by determining different molecules involved in the damage mechanisms as the α- SMA, desmin, GFAP markers that denote the presence of cells stellar liverwort in a state of greater activity fibrogenic; or components direct from the matrix extracellular as he acid hyaluronic, collagen types I, III, IV and laminin, as well as adhesion molecules vascular cell reflecting neoangiogenesis. (7)

From the author 's perspective, the research on intestinal permeability highlights his paper in the answer adaptive liverwort against antigens from the portal circulation, essential for maintaining homeostasis. The factors external and internal transported to the liver activate signaling cascades through receptors, triggering answers inflammatory and fibrogenic. In addition, the species reactive oxygen species amplify are signs, and alterations as the minor Intestinal ZO-1 expression is associated with diseases as he liver non- alcoholic fatty acid. This comprehensive analysis of the interactions between intestinal permeability and damage hepatic, provides new prospects for the handling such circumstances.

- *The Grand Theory Unified Intestine*

This is how it was communicated he Increased intestinal permeability (two to five times with respect to the normal value) observed versus : situations that determine a Breakdown of the mucous barrier (ingestion of non -steroidal anti-inflammatory drugs , alcoholism , renal failure , etc.); agents luminal aggressive (infections intestinal such as giardiasis, shigellosis , salmonellosis , etc.); deficiency syndromes immunological (immunodeficiency virus) human , hypogammaglobulinemia , etc.); and miscellaneous (cystic fibrosis , diabetic diarrhea , quiescent Crohn's disease , etc.).(14)

When considering are same situations in terms of intestinal inflammation, an increase was found uniform between two and eight times with respect to the normal value. Both situations, alteration of intestinal permeability and intestinal inflammation could then be considered as interdependent. Thus, they postulate that whatever the etiology of most intestinal diseases, thin, all they share a mechanism common final pathogen dominated by the interaction permeability-inflammation determined for the answer immunological in front of agent's luminal aggressive bacteria that access the mucosa through an increase in intestinal permeability. (14)

In the framework of this study showed that various conditions, such as the use of anti-inflammatory drugs, infections intestinal or deficiencies immunological, they increase intestinal permeability. At the same time, an increase was observed uniform in intestinal inflammation and suggests that both situations are tightly related. These findings support the idea that, regardless of the cause, many bowel diseases slim They share a mechanism common where the interaction between permeability and inflammation plays a central role.

- *Alterations in the Axis Intestine-Kidney during Chronic Kidney Disease*

Various conditions present in the patients with chronic kidney disease are associated with the development of alterations in the permeability of the intestinal barrier and in the intestinal microbiota, among which the loss of renal function, toxicity stand out uremic, the use frequent antibiotics, the consumption decreased fiber in feeding and lowering fluid intake. Intestinal permeability is seen committed due to a decrease in the expression of the proteins that make up the junctions narrow intestinal, thereby causing translocation of microorganisms and antigens food. The intestinal microbiota suffers changes in his composition, increases the families with the capacity to synthesize urea, acid uric and others compounds as indoles and phenols, the which They cross the intestinal barrier due to its dysfunction. (15)

Maintaining the intestinal epithelial barrier is essential to prevent the translocation of antigens and bacteria presents in the intestinal lumen. Its integrity depends on maintaining the balance of enterocytes, so as of the unions present among said cells, called unions narrow, whose structures protein form membrane - spanning fibrils plasma and interact with cell proteins surrounding. Intracellularly, proteins interact with the actomyosin ring surrounding he enterocyte. These proteins consist into two types of trepaspaninas, called occludin and claudin, which interact in the cytoplasm with the protein family called zonula occludens, which this composed by three variants (ZO-1, ZO-2 and ZO-3). The interaction between these proteins forms a barrier between a cell and

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another, protects the body from the passage of toxins and microorganisms and regulates also he transport paracellular ions, water and others solutes. (15)

They have been identified different mechanisms causing the decrease of said proteins, highlighting he increase in urea concentrations in the intestine, hydrolyzing to ammonium hydroxide, the which causes erosion of the intestinal barrier and decrease in the resistance electric transepithelial. Erosion of the intestinal barrier causes the stimulation of leukocytes, producing cytokines inflammatory locally, causing retraction and endocytosis of proteins mentioned. Intestinal dysbiosis, defined as the alteration in the composition of the intestinal microbiota, is present in various diseases non - communicable chronic diseases, including type 2 diabetes mellitus, obesity and chronic kidney disease. (15) Figure 2 shows the causes and consequences of the alterations in the axis intestine-kidney during chronic kidney disease.

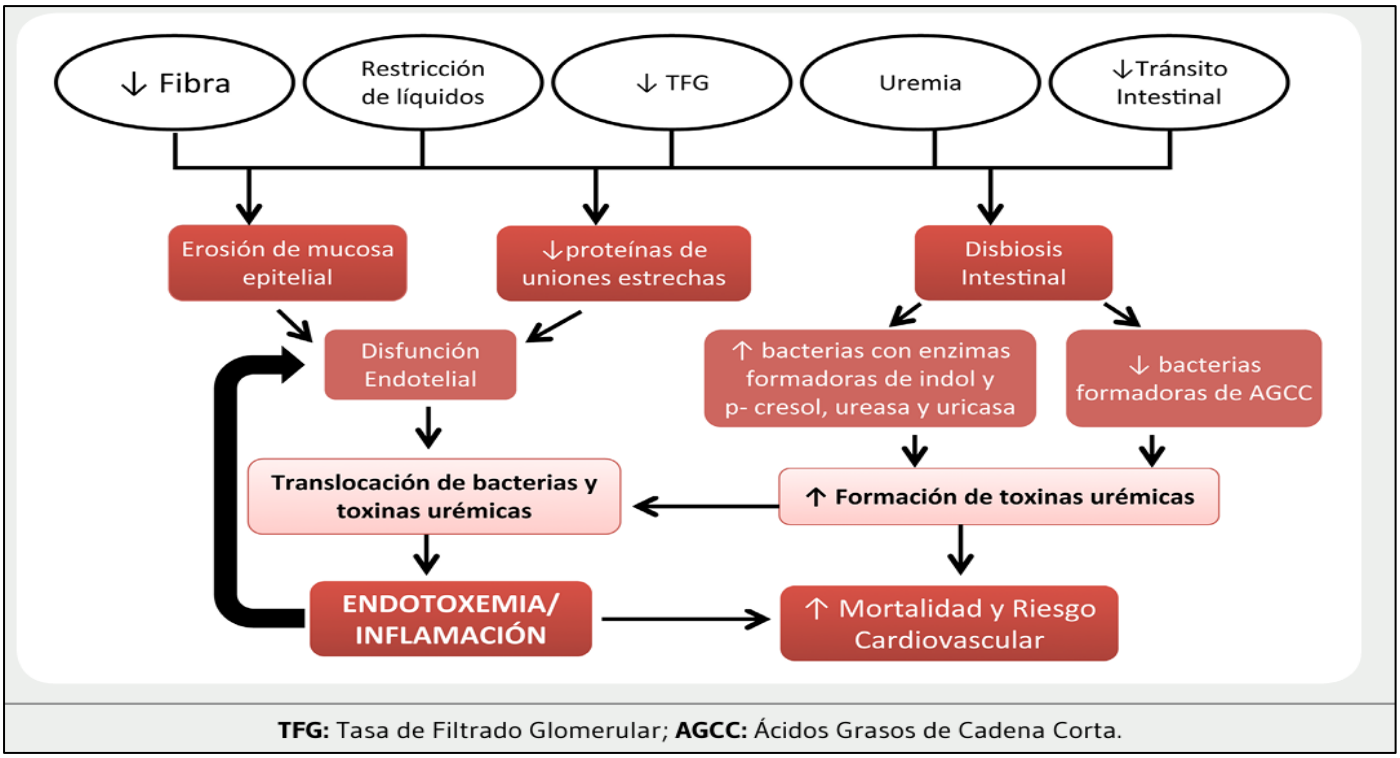

Fig 2 Causes and consequences of alterations in the axis intestine-kidney during chronic kidney disease
Source: Taken from Alterations in he axis intestine-kidney during chronic kidney disease: causes, consequences and treatment proposals. Rev Esp Nutr Hum Diet. 2017;21(2):174-183

In abstract, the figure illustrates as various factors, such as reduced fiber in the diet, fluid restriction, decreased glomerular filtration rate, uremia, and altered intestinal transit contribute to the development of endotoxemia and inflammation. Initially, they generate erosion of the epithelial mucosa, a Decrease in junction proteins narrow, causing dysfunction endothelial. In parallel intestinal dysbiosis increases the proliferation of bacteria toxin producers as indole, p-cresol and urea and decreased bacteria acid - forming chain fatty acids short. These toxins uremic aggravate he intestinal damage and promote the translocation of bacteria towards circulation.

The process described flows into in the translocation of bacteria and toxins uremic, generating a state of inflammation systemic known as endotoxemia. This increases the risk of mortality and disease cardiovascular due to the effects negatives of toxins uremic and inflammation persistent. According to the author 's interpretation, the interaction complex between factors dietary, functional and metabolic that contribute to a circle vicious intestinal damage, inflammation and complications systemic in people with kidney failure or other diseases chronicles.

➢ *Treatment Alternatives in Conditions Compromised Intestinal Permeability*

In the conditions management associated with a compromised intestinal permeability, it is essential to explore alternatives therapeutics that restore the integrity of the intestinal barrier and modulate the responses inflammatory associated. These strategies include Interventions nutritional, the use of prebiotics, probiotics and symbiotics, as well as approaches pharmacological aimed at reducing inflammation and promoting the regeneration of the intestinal epithelium. In addition, the personalization of the treatment in function of etiology underlying and the state the patient 's clinical care is key to ensuring results effective and sustainable. This section includes the options therapeutic available, when highlighting his applicability and effectiveness in different contexts clinical.

It starts this analysis, with one of the measures fundamentals: follow a *feeding anti-inflammatory*, rich in foods that contain compounds anti-inflammatory, such as omega-3, curcumin, ginger and garlic. It is also important take Vitamin and mineral supplements to ensure that you receive a amount adequate nutrients. Fat consumption must

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be moderate, in relation to others food groups, and prioritize always those unsaturated (fruits) dried, olive oil extra virgin, avocado, fish blue). (16)

Fiber consumption is one of the *few* Interventions dietary with evidence of strengthening the intestinal barrier in health. Influences in the barrier by altering the microbiota and/or the integrity of the mucous layer and the fermentation products (acids) chain fatty acids short). (16) The fibers Dietetics are divided in fibers soluble and insoluble. Insoluble fiber includes cellulose, some hemicellulose and lignin. Soluble fiber includes wheat dextrin, pectin, gums, β- glucan, psyllium and fructans, as well as like some hemicellulose. These Fibers are derived from grains, fruits, vegetables and legumes. Generally, fibers insoluble are poorly fermented by the microbes intestinal, but probably They promote the rate of intestinal transit and therefore reduce the amount of time available for fermentation. bacterial colonic of undigested food. (17)

Fruits *and vegetables* contain metabolites as polyphenols, including flavonoids and stilbenes. The protection mechanisms include the improvement of the intestinal barrier function and the inhibition of intestinal dysbiosis. Due to its part , glutamine is the L-alpha -amino acid further abundant in the blood human . It can be synthesized and obtain from the diet and enters in protein synthesis or in the pathways energetic. It has been shown his protective effect on the integrity of the tissues, inflammation and intestinal permeability in patients with irritable bowel syndrome and Crohn 's disease. This is achieved with the Bone broth consumption and supplementation specific glutamine. (16)

Vitamin *D* administered to patients with Crohn's disease (2000 IU/day) for three months is associated with an improved permeability in the gastroduodenal tract through a sucralose test. The supplement food zinc carnosine seems protect the intestinal barrier through an answer proliferative. Today it is known that the effect of abuse chronic alcohol abuse he Increased intestinal permeability may persist further beyond the cessation of its intake. (16) The treatment of intestinal permeability is based mostly in avoid big sugar and fat amounts and implementation of FODMAP (oligosaccharides fermentable, disaccharides, monosaccharides and polyols), prebiotics, probiotics, fibers, glutamine, acids chain fatty acids short, quercetin and metformin. (18)

Resveratrol belongs to the group of compounds stilbenes. It is abundant in plants and products vegetables, such as grapes, peanuts and red wine. Resveratrol supplementation restores the expression of TJ proteins, such as ZO-2, occludin, JAM-A, claudin - 3, claudin -4, and claudin -7, and mitigates the levels increased lipopolysaccharide binding protein plasma. Inulin is an oligosaccharide or polysaccharide (depending on the length of its chain) that is present in sources vegetables as wheat, barley and garlic. In a study done in volunteers' men healthy, the participants who took inulin during eight weeks They had a relationship lactulose / mannitol and zonulin serum significantly further lows and levels higher levels of GLP-2 in the mucosa. (13)

Glutamine is an L-alpha *amino* acid, the further abundant in the blood human. Glutamine is necessary for several functions in the body, including protein synthesis, as well as a source of energy. Glutamine can be synthesized by the bodies and also can obtained from the diet. The actions glutamine proposals in the cells intestinal are protection against apoptosis and stress cellular, anti -inflammation and maintaining the integrity of intestinal tissue, as well such as enhanced expression of binding proteins narrow and glutamine correction synthase reduced associated with the increased expression of miR -29a in the intestinal mucosa of patients with diarrhea - predominant irritable bowel syndrome. There are multiple foods and supplements high in glutamine, including meats, fish, eggs, nuts, beans, and milk. (13)

Glutamine is an amino acid that plays a role in intestinal physiology and in the multiple management diseases intestinal, promoting the proliferation of enterocytes, regulating the binding proteins narrow, by suppressing the signaling pathways proinflammatory and protect cells against apoptosis and stress cellular during conditions pathological. From this in this way, glutamine is essential for reducing intestinal permeability and for the stability of the intestinal barrier. (3)

Prebiotics are defined as indigestible ingredients of the foods that affect beneficially to the host by stimulating selectively he growth and/or activity of one of the species of bacteria that already are established in the colon, or a number limited from them and, therefore, consequently, they improve the health of the host. Prebiotic supplementation has been used as strategy to reduce he syndrome uremic, by contributing to increased nitrogen excretion in the stool fecal matter, in addition to reducing the production of toxins uremic in the intestine. (15)

Among the prebiotics further studied in the patient with chronic kidney disease is found in agave inulin, fructooligosaccharides and the galactooligosaccharides. Knowing the alterations intestinal presents in this type of patients and their consequences, have been studied various strategies therapeutics with the capacity to modulate the composition of the intestinal microbiota and the overgrowth of microorganisms (probiotics, prebiotics, symbiotic and modifications) dietary, and reduce the absorption of toxins uremic in the intestine. (15)

The *agents Probiotics* are microorganisms alive that are administered in quantities controlled, resist the effects of degradation digestive and upon reaching he intestine favor he balance of the microbiota, they possess effects anticarcinogenic and suppose benefits both metabolic as for health In general of the individuals who consume. Sayings effects protectors explained because the probiotics promote the repair of the intestinal barrier, inhibit apoptosis of the enterocytes, reestablish the unions narrow at level epithelial and control the intestinal absorption of ammonium.

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Therefore, they are able to regulate the translocation bacterial and control he ingress of endotoxins, molecules hepatotoxic and mediators proinflammatory derived from harmful intestinal flora. (7)

Different studies clinical they have shown the benefit of the probiotics in the comprehensive disease management liverwort chronicle in its different scenarios clinical: liver non- alcoholic fatty acid, damage hepatic alcoholic, encephalopathy hepatic and portal hypertension. However, more is required Essays clinicians to establish a formal recommendation in disease treatment guidelines liverwort chronicle. (7)

However, it is not explored he mechanism behind the effect beneficial of the probiotics about the health benefits. Especially in the elderly, not revealed completely and it is debatable how supplementation probiotic improvement he Leaky gut, inflammation and interaction intestine brain. Probiotics modulate mainly the intestinal microbiota, by producing several metabolites, which confers health benefits. (19) They are found prebiotics in many foods with this type of fiber, such as by example he underripe banana and probiotics in food fermented as he sauerkraut, pickles, yogurt and kefir. (16)

The question is whether medicine can discover ways to care ailments acute (the which constitute he start of imbalance) with means further moderate, which promote and improve the natural reaction of the system immunological in instead of suppressing it with medication chemicals strong that may damage it irreparably. Apparently, the defense mechanism in its set has a “superior” intelligence that is capable of maintaining a balance optimal under any stress. But, under certain conditions, the body cannot overcome and neutralize the stressor while he problem is found on one level peripheral, this puts in risk his general well-being and transfers the defense to a level deeper by mobilizing defenses to an organ or system deeper and therefore more important; of this way is marked the “beginning” of a disease chronic degenerative. (20)

In conclusion, according to the evidence obtained, the treatment of conditions associated with a compromised intestinal permeability has to focus in strategies that promote the restoration of the integrity of the intestinal barrier and the modulation of inflammation. Interventions as he fiber consumption dietary, prebiotics and probiotics, as well such as supplementation with glutamine and vitamin D, have proven to be tools effective in improving bowel function and reducing the effects harmful associated with this dysfunction. The personalization of these therapies, having in take into account the needs patient - specific and characteristics particulars of the disease underlying, is key to ensuring best results in intestinal and systemic health. This, in addition to offering solutions specific, could foster an approach further holistic and preventive in the disease management chronicles related to intestinal permeability.

III. CONCLUSIONS

- Intestinal dysbiosis, by altering the balance of the microbiota and promote the growth of pathogens, contributes significantly to increased intestinal permeability. This imbalance promotes the release of endotoxins and molecules pathogens that trigger answers inflammatory, compromise the integrity of the joints epithelial and, by hence, the barrier function of the intestine.
- The discovery of zonulin established a crucial link between unions narrow, the regulation of the intestinal barrier and the processes immunological and metabolic that can trigger answers immune uncontrolled, which contributes to the development of diseases systemic.
- The alteration of intestinal permeability, through the decrease in the expression of zonulin, favors the transport of antigens to the liver, which activates signaling cascades inflammatory and fibrogenic, causing diseases liverwort as he liver non -alcoholic fatty acid.
- Increased intestinal permeability, caused by factors as anti-inflammatory, infections or deficiencies immunological, is tightly related to intestinal inflammation, suggesting a mechanism common in various bowel diseases slim.
- Factors as unhealthy diet and intestinal dysbiosis promote endotoxemia and inflammation, damaging the intestinal mucosa and promoting the translocation of bacteria and toxins. This increases the risk of disease cardiovascular and mortality in people with kidney failure or other diseases chronicles.
- Treatment of intestinal permeability should focus in restore the barrier and modulate inflammation, by using fiber, prebiotics, probiotics and supplements as glutamine and vitamin D. Customize are therapies improvement the results and promotes an approach preventive in diseases chronicles.

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