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Review Article

What Markers are Activated in Gut Dysbiosis?

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Abstract

Although new markers of gut dysbiosis appear every day, they continue to be a necessary find, since applying much more expensive studies, such as metagenomics and others, are not entirely consistent.

However, we should not disregard the clinic, as it is considered a stable instrument of medical assistance, since not all patients can afford and undergo through expensive studies. This is due to the lack of these medical practices worldwide and their tendency to stay in large research centers. Undoubtedly, making these processes more affordable is one of the priorities, in order to democratize the various genomic studies.

In this review we try to describe, even if briefly, a large number of markers, with the aim for them to be determined by users and used as excellent support in diagnosis, a crucial goal for caring for human health.

Keywords: *Dysbiosis (Dys); Gut Dysbiosis (DG); Short Chain Fatty Acids (SCFA); Microbiome (Microb); Intestinal Microbiota (IM)*

Introduction

Dysbiosis (Dys) of the microbiota has been considered as the alterations in its composition, quantity, diversity and metabolic activity [1]. Having this disturbance poses negative consequences for human health, through the increase in the abuse of antibiotics, chemotherapy and changes in diet [2], through alteration of host mechanisms [3].

Dys (dysbacteriosis) is defined as the "imbalance of the microbiota that can be caused by various etiologies or by a mismatch of the same, which translates multiple alterations and, consequently, diseases" [4].

It can appear as a result of tumors or immunological alterations [5].

It has also been noted that, in part, it is a phenomenon induced by inflammation [6].

Gut dysbiosis (DG) is known as the imbalance of microorganisms at the intestinal level. It can happen because of a number of reasons, for example the use of antibiotics [7].

In this work we try to show which markers are activated by these processes, in order to provide an additional tool to diagnose this frequent phenomena. And in this way, help preserve a healthy microbiome (Microb), from the early stages of life; an increasingly understandable concept, which is oriented with metabolomic studies, which reveal neuro-signalers or neuro-transmitters [8].

Since Dys serves as a guide to pathological processes when *Clostridioides difficile* appear, the fecal microbiota transplantation has been pronounced a safe and effective treatment. Continuing through, the consideration of gravity of the ratio between *Firmicutis/Bacteroidetes* should be similar. Any alteration points towards disease [9].

Increased markers of systemic inflammation have been observed in obese individuals; in these same patients there is reduced bacterial diversity [10].

The metabolites generated by the microbes can be used as diagnostic markers, both in disease status and in IM Dys (Intestinal microbiota dysbiosis). Among them, the short chain fatty acids (SCFA), secondary bile acids and fecal calprotectin stand out; although there are others less known such as trimethylamine-N-oxide, 3-indoxylsulfate, hippurate, sodium benzoate, secreted immunoglobulins, zonulin. These last two best known; p-cresylsulfate, human β-defensin-2 and chromogranin A. There are others such as p-hydroxybenzoate, p-hydroxyphenylacetate; dihydroxyphenyl propionate. Tartarate, citramalate and arabinitol. Tryptophan, phenylalanine and tyrosine. Finally, these are useful in the determination of markers: Anti-trypsin alpha-1, eosinophil protein X, beta-glucuronidase and pancreatic elastase [11].

Yu L and contributors [12], analyze forty five studies to choose bacterial markers in colorectal cancer, to evaluate their use as predictive and make evident the association between microbial species and the predictive value in colorectal cancer, another marker.

Next, we analyze the markers, in search of their efficiency, in order for the user to determine which of them would be preferred at that given moment, and especially provide support to those places where there are no medical centers. With this publication, these places can resort to any of these markers, and based on clinical experience, choose a single marker that provides congruent evidence to the diagnosis of intestinal dysbiosis.

SCFA (Short chain fatty acids): It is essential to identify the interaction between them, IM and bile acid metabolism, to understand their role in the carcinogenesis of gastric, colon, and liver cancer. Generally, butyric, acetic, and propionic are determined.

Acylcarnitines: Acylcarnitines are fatty acid metabolites that play an important role in many pathways of cellular energy metabolism. These include metabolic disorders, cardiovascular disease, diabetes, depression, neurological disorders, and certain types of cancer. The drug L-carnitine, approved by the US Food and Drug Administration, along with the short-chain acylcarnitines (acetylcarnitine and propionylcarnitine), are now widely used as a dietary supplement. These are dietary interventions or supplements for many powerful indications [13].

Bile acids: The article by Chattopadhyay I, and Cols [14], points out how deoxycholic acid and metabolites from intestinal bacteria that contribute through inflammation and oxidative DNA damage to hepatocellular and colon cancer. This makes bile acids a marker in carcinogenesis.

Fecal calprotectin: In the article by Shaw KA, and her group [15], they demonstrate the importance of fecal calprotectin in determining IBD (Inflammatory bowel disease) in children, evaluating IM through repeated stool samples. Undoubtedly, fecal calprotectin is a good marker in determining intestinal dysbiosis tests to assess metabolic function.

Trimethylamine-N-oxide: TMAO (trimethylamine N-oxide) is formed after eating choline-containing foods. It is produced by IM. There is an intimate link between its elevation and the risk of presenting Atherosclerosis: an inflammatory lesion of the vascular endothelium [16].

3-indoxyl sulfate: It presents as one of the easiest biomarkers to detect in urine while its elevation translates Dys as being significantly higher in individuals with Parkinson's disease [17].

Hippurate: Pallister T and contributors determine the presence of Hippurate and other metabolomic markers in patients after eating fruit, and consider that the reduction of bacterial diversity and expansion of Proteobacteria are a phenomenon that produces various diseases. The Microb is a mediator of the dietary impact, both in the metabolic state and in health [18].

Sodium benzoate: It is used as an antifungal preservative and is effective against yeast and bacteria. Growing evidence implies that food additives might be closely related to IBD, but the molecular mechanisms involved are still only faintly understood [19].

Immunoglobulins: In celiac disease, the increase of IgA makes it relevant and can be determined as a marker of this disease [20]. Decreased secretory IgA reveals immunosuppression and allergies, or congenital IgA deficiency or watery stools, due to constant diarrhea.

Zonulin: It has been determined as a marker of intestinal permeability and dys. Analyzes have been carried out to determine polycystic ovarian syndrome, both in urinary levels and hormonal and metabolic parameters. Their results states that metabolic factors and not the Syndrome itself, are determinants of Dys in pre-menopausal women [21].

P-cresyl sulfate: As the prototype of protein-bound uraemic toxin to which toxic biochemical and biological effects have been attributed, and having a complex process to eliminate dialysis, it has been used as a marker in severe renal processes [22].

Human β-defensin-2: Antimicrobial peptide that acts against infections. And that can be used with marker in Dys. It can be induced by pre-inflammatory cytokines, as well as pathogen-specific molecules [23].

Chromogranin A: This protein is located in endocrine cells. It is used as a tumor marker and is occasionally increased with certain endocrine tumors, small cell lung cancer, and prostate cancer. Chromogranin A can be used to assess for new onset of cancer [24].

P-hydroxybenzoate: This urinary organic acid, marker of Dys, is quite acceptable in gastrointestinal or toxicological processes. As it rises on par with other acids such as cresol, hydroxyphenylpropionate, 3,4-dihydroxyphenylpropionate, indica, and D-lactate, which had not been considered, it generally affects treatments directed at microbial overgrowth, performed by introducing favorable microorganisms that restore the intestinal mucosa [25].

P-hydroxyphenylacetate: In search of new markers of Dys that guide various pathologies, p-hydroxyphenylacetate was welcomed. The foregoing includes conditions as recent as Covid-19, as they are associated with alterations in the function and composition of the IM. It must not be forgotten that the most frequent damages that occur in Dys are decreased bacterial diversity, excessive growth of harmful microbiota, and loss of beneficial microbiota. This requires the search for new therapeutic and diagnostic routes, such as biotics, intestinal microbiota transplantation and new markers [26].

Dihydroxyphenyl propionate: Propionate is the most widely used preservative in sliced bread. It is a metabolite product of the hydrogenation of caffeoylquinic acids, which is produced in normal human biofluids, with potent antioxidant properties [27].

Eosinophil protein X: In allergic intestinal inflammation processes, this component is present and aids in providing a diagnosis, especially in monitoring inflammatory activity [28].

Beta-glucuronidase and pancreatic elastase: Patients with chronic pancreatitis have a severe reduction in bacterial diversity. With an increase in *Enterococcus, Streptococcus* and *Escherichia coli*, and a decreased in SCFA-producing bacteria [29] the marker of exocrine or secretory pancreatic function causes of pancreatic insufficiency. That being said, other stimuli include prolonged stress and insulin resistance.

Anti-trypsin alpha-1: Glycoprotein of 52 kD, made up of a chain of 394 amino acids and 3 carbohydrate side chains. In order to diagnose the deficit of this marker, it must be carried out in all patients with COPD [30]. It can be elevated in the DG. Likewise, this increase in alterations in intestinal permeability is observed in gut inflammatory processes and in the loss of proteins through the enteric route.

Beta-glucuronidase: The glucuronide acid component of Beta-glucuronidase is a substance at the liver level binds with different metabolites, allowing liver detoxification. The enzyme beta-glucuronidase, found in the digestive tract in high concentrations, is produced by some of the intestinal bacteria (*Escherichia coli, Enterococcus* spp, *Lactobacillus* spp) [31].

Conclusion

- The most consistent markers of Dys are a decrease in the diversity of the microbiota and an expansion of *Proteobacteria* [32].
- The determination of butyric acid, SCFA, and calprotectin are crucial markers to determine metabolic function.
- The clinic continues to be a strong ally of DG markers.
- SCFA and bile acids are the most important markers in the detection of various types of Dys.

Conflicts of Interest

The authors declare that they do not have affiliation or participation in organizations with financial interests.

Ethical Approval

This report does not contain any study with human or animal subjects carried out by the authors.

Informed Consent

The authors obtained informed, written consent from the patients, in order to develop this article.

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