

## INTESTINAL MICROBIOTA, METABOLIC SYNDROME AND MEDITERRANEAN DIET: PATHOPHYSIOLOGICAL MECHANISMS AND NEW POTENTIAL THERAPEUTIC APPROACHES

Calabrò Ferdinando <sup>1</sup>, Lorello Giuseppe <sup>1</sup>, Morace Carmela <sup>2</sup>, D'Ambrogio Lucio <sup>1</sup>, Amoroso Luigi <sup>1</sup>, Squadrito Giovanni <sup>2</sup>, Marini Herbert Ryan <sup>2</sup>

<sup>1</sup> Department of Medical Sciences, Internal Medicine Division, University Hospital “G. Martino”, Messina, Italy

<sup>2</sup> Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy

Human intestinal microbiota (IM) is defined as the microorganisms community present in the gastrointestinal system, which plays a crucial role in metabolic syndrome onset (MS) <sup>[1]</sup>.

A reduction in *Proteobacteria*, *Streptococcus*, *Enterococcaceae* and *Clostridium* was observed in favor of a greater presence of *Bifidobacteriaceae* and *Akkermansia* and this latter is significantly related to an improvement in MS; additionally, the increase in the *Firmicutes/Bacteroidetes* ratio is associated with a worsening in MS and body weight, while the presence of *Lactobacillus reuteri* V3401 correlates with a reduction in interleukin-6 and soluble vascular cell adhesion molecule-1 <sup>[2,3]</sup>.

Recent evidence showed that the occurrence of *Muciniphila* species is associated with insulin sensitivity reduction <sup>[4]</sup>, as well as *Klebsiella pneumoniae* is related to development of non-alcoholic fatty liver disease, *Ruminococcus* to obstructive sleep apnea syndrome and *Enterobacter cloacae* B29 to obesity. Moreover, the pancreas and sensitive insulin tissues can be influenced by some muropeptides and/or other degradation products of IM, that cross the intestinal barrier (post-biotic products).

Interestingly, about 60% of the variations in IM populations are attributable to feed and the Mediterranean dietary (MD) pattern is directly correlated to an increase in bacterial species considered positive for health <sup>[5]</sup>.

Intestinal dysbiosis and metabolic syndrome	
<i>Bilophila wadsworthia</i>	Diet rich in saturated fatty acid predisposes to the development of this species with pro-inflammatory phenomena in the colon
<i>Bifidobacteriaceae</i>	Increased in Bifidobacteria/E. coli ratio is associated with a high adherence to MD
<i>Akkermansia Muciniphila</i>	Intestinal barrier protection, immunotolerance and insulin resistance improvement
<i>Klebsiella pneumoniae (variant HiAlc Kpn)</i>	Related to an increased risk of Non-NAFLD development
<i>Enterobacter cloacae B29</i>	Related to an increased risk of Obesity development
<i>Firmicutes</i>	Increased in Firmicutes/Bacteroidetes ratio is associated with a worsening in MS and body weight
<i>Faecalibacterium prausnitzii</i>	Short chain fatty acids production and increased anabolic activities in bone and muscle
<i>Lactobacillus reuteri V3401</i>	Reduction in interleukin-6 and soluble vascular cell adhesion molecule-1

### Main nutritional principles of the mediterranean diet effective on intestinal microbiota

- Soluble fibers
- Short-chain fatty acids (acetate, propionate, butyrate)
- Olive oil: Oleic acid, Oleupein, Tyrosol, Hydroxytyrosol, Oleocanthal, Oleoylethanolamine
- Resveratrol
- Silymarin
- Citrus fruits: Naringenin, Apigenin, Hesperidin, Capferolo, Quercetin, Ellagic acid, Rosmarinic acid
- $\beta$  - Glucans

At this purpose, the production of short-chain fatty acids (acetate, propionate and butyrate) due to the fermentation of soluble fibers by the IM, is able to fortify the gastro-intestinal barrier and increase satiety <sup>[5]</sup>. Furthermore, oleic acid also appears to have positive effects on bacterial transmigration and inflammatory response induced by lipopolysaccharide, arousing interest in experimental models of sepsis treatment <sup>[6]</sup>. Therefore, by acting on the main modifiable factors regarding the balance between IM and the host organism, it is possible to strengthen the homeostasis and health of both systems <sup>[7]</sup>.

The aim of this presentation is to review the mechanisms of interaction between IM and MD and their effects on MS, thus opening up new avenues for research and novel therapeutic approaches.

### References

1. Guarner F and Malagelada JR. Gut flora in health and disease. *Lancet* 2003; 361: 512–19;
2. Tenorio-Jimenez C, et al. *Lactobacillus reuteri* V3401 reduces inflammatory biomarkers and modifies the gastrointestinal microbiome in adults with metabolic syndrome: the PROSIR study. *Nutrients* 2019;11: E1761;
3. Schertzer JD and Lam TKT. Peripheral and central regulation of insulin by the intestine and microbiome. *Am J Physiol Endocrinol Metab.* 2021;320(2): E234-E239;
4. Bishehsari F, Voigt RM, Keshavarzian A. Circadian rhythms and the gut microbiota: from the metabolic syndrome to cancer. *Nat Rev Endocrinol.* 2020;16(12):731-739;
5. Garcia-Mantrana I et al. Shifts on Gut Microbiota Associated to Mediterranean Diet Adherence and Specific Dietary Intakes on General Adult Population. *Front. Microbiol.* 2018, 9, 890;
6. Hou Y et al. FABP5 Deficiency Impaired Macrophage Inflammation by Regulating AMPK/NF-KB Signaling Pathway. *J. Immunol.* 2022, 209, 1–14;
7. Seon MJ et al. Circulating GLP-1 Levels as a Potential Indicator of Metabolic Syndrome Risk in Adult Women. *Nutrients.* 2021;13(3):865.