ROLE OF EXOGENOUS DIETARY ADVANCED GLYCATION END PRODUCTS (AGES) IN THE CROSS-TALK MECHANISMS LINKING DIET, MICROBIOTA AND METABOLIC INFLAMMATION

Debora Collotta[1], Alessia Sofia Cento[2], Fausto Chiazza[1], Roberta Verta[1], Thomas Henle[3], Friederike Manig[4], Michael Hellwig[4], Giulia Gaudioso[5], Francesca Fava[6], Kieran Tuohy[5], Manuela Aragno[2], Raffaella Mastrocola[2], Massimo Collino[1]

[1]Department of Drug Science and Technology, University of Turin., Turin - Italy, [2]Dept. of Clinical and Biological Sciences, University of Turin, Turin - Italy, [3]Technische Universität Dresden, Germany, Dresden - Germany, [4]Technische Universität Dresden,Germany, Dresden - Germany, [5]Fondazione Edmund Mach, San Michele all'Adige - Italy, [6]Fondazione Edmund Mach, San Michele all'Adige - Italy

Introduction: Advanced glycation end products (AGEs) are a heterogeneous group of irreversible products resulting from nonenzymatic glycation between reducing sugars and free amino groups of proteins, nucleic acids, or lipids. Modern diets are largely heat-processed and as a result contain high levels of AGEs, highly oxidant compounds, which have been recently suggested to contribute to the high incidence of cardiometabolic diseases. However, their pathogenic role in diet-related metabolic derangements has not yet been clearly elucidated. Thus, this study aims to investigate the effects of an AGE-enriched diet (AGE-D) on gut microbiota composition and function as well as on the development of metabolic inflammation ("metaflammation"), deepening the molecular pathways activated by AGEs chronic exposure in different organs and tissues.

Materials and methods: C57BL/6mice were randomly allocated into the following dietary regimens: Control Diet (CD, n=24) and AGE-enriched Diet (AGE-D n=20) for 22weeks. AGE-D was prepared replacing casein (200 g/kg of diet) by an equal amount of modified casein where 10% of arginine was glycated with MG-H1(methylglyoxal 5-hydro-5-methylimidazolone) for a total of 4umol of MG-H1per g of diet. Faeces were collected using metabolic cages (18h starving) at week 0, 11and 22for fecal DNA extraction and 16SrRNA analysis through Illumina MiSeq using V3-V4targeted primers. After 22weeks of dietary manipulation, mice were killed, plasma, urine, tissues and organs were collected. Glucose, lipid and inflammatory profiles were determined. To evaluate kidney function, albumin-to-creatinine ratio (ACR) was evaluated.

Results: AGE-D chronic administration did not significantly affect metabolic parameters such as body weight, lipid profile, fasting blood glucose and glucose sensitivity. Interestingly, AGE-D caused a significant reduction in the blood levels of two important components of the incretin system, GIP (CD 588± 21pg/ml vs. AGE-D 503± 29pg/ml, $p < 0.05$) and GLP-1(CD 138± 13pg/ml vs. AGE-D 90 ± 18pg/ml, $p < 0.05$). AGE-D led to an increase in the systemic inflammatory profile (IL-1β and IL-17) and in the levels of plasminogen activator inhibitor 1(PAI-1; CD 1536± 143pg/ml vs. AGE-D 2015± 142pg/ml, $p < 0.05$), a marker of cardiovascular risk. Immunohistochemistry analysis showed an increased accumulation of AGEs and upregulation of AGE Receptor in salivary glands and gut of AGE-D mice. Besides, AGE-D mice showed a significant kidney function impairment, based on data on ACR (CD 0.067± 0.017vs. AGE-D 0.674± 0.152pg/ml, $p < 0.05$). The effects of local AGEs accumulation on microbiome community structure will be described.

Conclusions: Our data suggests that despite the poor impairment of systemic metabolic profiles, chronic exposure to dietary exogenous AGEs evoked a significant unbalance in the incretins axis and a robust increase in markers of metabolic inflammation. Notably, these effects were associated to partial reshape of the intestinal microbiota structure.