MET-CONF 24

A HOT TOPIC IN METABOLIC DYSFUNCTION

2ND CONFERENCE OF THE DOCTORAL PROGRAM
IN METABOLISM – CLINICAL AND EXPERIMENTAL

BOOK OF

ABSTRACTS

25th October 2024

U.PORTO

FM UP

PROGRAM

8h30-9h00 — **Registration**

9h00-10h30 — **New trends in systemic inflammation**

Glycans and immune-regulatory networks | Joana Gaifem (i3S)

The interplay between EDCs and inflammatory biomarkers | Diana Teixeira (CHRC & NMS)

Targeting immune dysfunction in ageing | João Pedro Magalhães (University of Birmingham)

Chair: Henrique Almeida (i3S & FMUP) + PhD Student PDMCE

10h30-11h00 — **Opening Session**

José Castro Lopes (Vice-rector UP)
Raquel Soares (Director of PDMCE)
João Tiago Guimarães (Coordinator of Bioch. Unit)
Juliana Morais (PhD Student)

11h00-11h30 — **Coffee Break & Posters Session**

11h30-12h30 — **Oral Communications**

12h30-14h00 — **Lunch**

14h00-15h30 — **The microbiome-inflammation axis: truth or dare?**

Human microbiome: still a hot topic? | Alexandre Almeida (University of Cambridge)

Chronic Pain: is microbiome saving your gut feeling? | Joana Ferreira-Gomes (i3S & FMUP)

Fetal programming and Inflammation: is microbiome a wild card? | Marta Selma-Royo (Institut d'Investigacions Biomèdiques August Pi i Sunyer)

Chair: Benedita Sampaio-Maia + PhD Student PDMCE

15h30-16h00 — **Speed Talks**

16h00-16h30 — **Coffee Break & Posters Session**

16h30-18h00 — **Debate**

A debate about metabolically healthy obesity: facts and fantasies

Joana Araújo (ISPUP)
Gil Faria (FMUP)

Chair: Davide Carvalho + PhD Student PDMCE

18h00-18h30 — **Concluding Remarks**

Altamiro da Costa Pereira (Dean of FMUP)
Scientific Committee

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PLENARY SESSION

New trends in systemic inflammation

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Changes in the glycosylation of circulating IgG predict future Crohn's

Joana Gaifem, i3

Joana Gaifem is a biologist focusing on mucosal immunology, microbiome, and glycosylation. She holds a degree in Biology (2009) from the Faculty of Sciences of the University of Porto, a Master's in Environmental Contamination and Toxicology (2011) from ICBAS, University of Porto, and a PhD in Ageing and Chronic Diseases (2019) from the School of Medicine, University of Minho. During her PhD, her work focused on deciphering the microbiome and metabolic factors contributing to protection or susceptibility in Inflammatory Bowel Disease (IBD).

Joana joined i3S in 2019 as a post-doctoral researcher in the Immunology, Cancer & Glycomedicine group (funded by FCT-CEEC2020). Her research primarily centers on elucidating the impact of mucosal glycosylation alterations on the gut microbiota and immune response. Additionally, she explores how precision nutrition can act as a preventive approach to avoid the transition from health to inflammation. In 2022, Joana received an ESCMID research grant to explore the impact of glycans on gut microbiota and IBD. In 2023, she was awarded an ECCO Grant to investigate whether a glycan-based diet can help regulate the immune system and gut microbiome. Recently, Joana has been studying predictive serum markers of Crohn's Disease, revealing a new potential for serum autoantibodies in the health-to-disease transition. Her ultimate goal is to develop strategies for predicting and preventing IBD.

Abstract

Inflammatory bowel disease (IBD) is a complex set of chronic inflammatory disorders from the gastrointestinal tract, with a significant impact in patients' quality of life due to the early onset of the disease and the substantial morbidity associated with frequent relapses and the absence of an efficient treatment. IBD pathogenesis has been defined as an inappropriate inflammatory response triggered by environmental factors and the gut microbiota in a genetically susceptible host. Still, the precise etiology remains unclear. In CD, evidence shows a preclinical period where immunological changes occur before symptoms, starting years before diagnosis. Understanding this phase can aid in predicting and preventing the disease. Analysis of longitudinal serum samples from preclinical IBD, up to 6 years before diagnosis, have revealed the identification of a distinct glycosylation signature on antibodies (IgGs), characterized by lower galactosylation levels of the IgG fragment crystallizable (Fc) domain that remained stable until diagnosis. This IgG2 Fc glycan trait was linked to increased antimicrobial antibodies, notably anti-Saccharomyces cerevisiae (ASCA), revealing a glycome–ASCA hub in serum preceding CD development by years. Mechanistically, this agalactosylated ASCA IgG, found in the preclinical phase, activates a proinflammatory pathway by engaging innate immune cells, such as dendritic cells and natural killer cells, via FcγR-dependent mechanisms, triggering NF-κB and CARD9 signaling. This proinflammatory role of ASCA was demonstrated to be dependent on mannose glycan recognition and galactosylation levels in the IgG Fc domain. This pathogenic property was validated in vivo, as adoptive transfer of ASCA antibodies into mice increased their susceptibility to intestinal inflammation, a response that is absent in FcγR-deficient mice. This study identifies a glycosylation signature in IgGs preceding CD and highlights the glycome–ASCA pathway as central to inflammation initiation, offering a potential biomarker for CD prediction and a target for prevention.

The interplay between EDCs and inflammatory biomarkers

Juan Arrebola, Univ. of Granada

Juan Pedro Arrebola is an Associate Professor at the University of Granada and a researcher at the Biosanitary Research Institute of Granada. His career has focused on environmental epidemiology, particularly the impacts of long-term exposure to environmental chemical pollutants (e.g., plastics, pesticides, etc.) on the development of cardiometabolic conditions.

He has a special interest in biomonitoring studies to identify potential subclinical biomarkers of effect, including oxidative stress, hormonal unbalance or inflammation.

Juan P. Arrebola has been involved in several research projects and consortia at regional, national, and international levels, including high-impact initiatives such as the European HBM4EU project, PARC, the INMA (Environment and Childhood) Study, MCC-SPAIN, and the Biomedical Research Consortium of Epidemiology and Public Health.

Abstract

Endocrine-disrupting chemicals (EDCs) are ubiquitous substances that can mimic or interfere with the endocrine system, potentially contributing to endocrine-related diseases such as metabolic syndrome, hormone-related cancers, and thyroid disorders, among others. Beyond their role as endocrine disruptors, many of these chemicals have been shown to induce effects such as oxidative stress and inflammation, which extend their potential health consequences and increase the complexity of their study. Common sources of these pollutants include substances used in plastic production, pesticides, and cosmetics.

The underlying hypothesis is that chronic low-dose exposure to mixtures of these chemicals may induce persistent, low-grade damage (e.g., inflammation), with effects that become more evident over time. The results from our research group on the role of environmental chemical exposure in the development of chronic health conditions will be presented, along with their associations with subclinical markers of disease, which may serve as early indicators of chronic disease onset. Additionally, ongoing work focused on potential strategies to reduce harmful exposure to these chemicals will be discussed.

Targeting immune dysfunction in ageing

João Pedro Magalhães, University of Birmingham

João Pedro de Magalhães is graduated in Microbiology from Escola Superior de Biotecnologia in his hometown of Porto, Portugal. His first experience in a research environment was as an intern (1998-1999) in the UnIGENe research group at the Institute for Molecular and Cell Biology in Porto, where he worked on Machado-Joseph disease, a neurological disorder.

As a doctoral fellow, he pursued his dream of unravelling the mechanisms of ageing by joining the Ageing and Stress Group at the University of Namur in Belgium. With the late Olivier Toussaint as his advisor, his work from 1999 to 2004 spanned molecular mechanisms of celular senescence and responses to oxidative stress, evolutionary models of ageing, and analyses of gene networks.

Fascinated by the genome and by the opportunities its sequencing opened, he then did a postdoc from 2004 to 2008 with genomics pioneer George Church at Harvard Medical School in Boston, USA. Succintly, they developed high-throghput approaches for studying ageing, including computational tools and databases, statistical models of mortality, methods for cell-based RNAi screens, and comparative genomics methods for investigating the evolution of longevity.

In 2018, Pedro joined the University of Liverpool to establish his own group on genomic approaches to ageing. In 2022, he was recruited to the University of Birmingham to take on the post of Chair of Molecular Biogerontology. They are world-leaders in employing genomics and bioinformatics to study ageing with pioneering work in studying gene networks of ageing and in sequencing and analyzing genomes from long-lived species.

Abstract

Ageing is the major biomedical challenge of the 21st century, yet it remains largely mysterious, in part because of its intrinsic complexity. In this talk, I will present systems approaches aimed at increasing our knowledge about how genes and processes impact on ageing. In particular, ageing entails substantial changes in the immune system and a pro-inflammatory state termed inflammaging, which may be targeted therapeutically. I will present network and machine learning approaches for predicting longevity genes and compounds, which we validated experimentally.

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The microbiome-inflammation axis: truth or dare?

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Human microbiome: still a hot topic?

Alexandre Almeida, University of Cambridge

Alexandre Almeida is an MRC Career Development Fellow leading the Microbiome Function and Diversity group at the University of Cambridge. His team focuses on understanding the role that the uncultured microbiome plays in human health and disease. He obtained his PhD in Microbiology at the Institut Pasteur in Paris, studying the opportunistic pathogen group B Streptococcus.

After his PhD, he relocated to Cambridge with an EBI-Sanger Postdoctoral Fellowship to expand his research to metagenomic studies of the human gut microbiome. Using computational genomic methods, his work contributed to the discovery of thousands of uncultivated bacterial species in the human gut microbiome, more than tripling the number of gut-associated species previously known.

Abstract

Research into the human microbiome has become a major area of focus in the last few decades. New studies are published every year showing novel associations between the composition of the microorganisms that colonize our bodies with the incidence of numerous human diseases. However, translation of these promising findings into new therapeutic or diagnostic applications has been limited. In this presentation, I will go over some of the major milestones in the study of the human microbiome, cover what we know, what we don't know, and discuss how we may go beyond the current state-of-the-art to leverage this exciting new knowledge towards improving human health.

Chronic Pain: is microbiome saving your gut feeling

Joana Ferreira-Gomes, FMUP & i3S

Joana Ferreira-Gomes is an Assistant Professor at the Faculty of Medicine of the University of Porto (FMUP) and Researcher of the Integrated Program in Neurobiology of Pain at i3S – Institute for Research and Innovation in Health.

She completed her degree in Microbiology at the University's School of Biotechnology Católica Portuguesa, and the Masters in Infectious Diseases at Imperial College School of Science, Technology and Medicine, University of London, in 1999 and 2000, respectively.

In 2013, she received her PhD in Neurosciences with the thesis "Neurobiological mechanisms of pain associated with osteoarthritis" from FMUP. Then, in 2021, she graduated in Medicine from the same faculty. Currently, she focuses her research on studying the impact of the microbiome on the gut-brain axis.

Abstract

Chronic pain, a highly prevalent condition globally, has long been associated with dysfunction in both the peripheral and central nervous system. However, recent advances in microbiome research have unveiled a compelling link between gut health and pain modulation, particularly through the lens of metainflammation—a chronic, low-grade inflammatory state.

Emerging evidence shows that microbiota-derived signals, such as short-chain fatty acids (SCFAs) and lipopolysaccharides (LPS), exert a modulatory effect on the gut-brain axis, by either acting directly on sensory neurons or indirectly through the modulation of immune cell activity and inflammatory responses, thus contributing to pain sensitivity and the pathophysiology of chronic pain.

Understanding the mechanistic role of the microbiome in chronic pain pathogenesis presents an opportunity to develop novel therapeutic strategies, offering hope for better, more personalized treatments for patients suffering from chronic pain.

Fetal programming and Inflammation

Marta Selma-Royo, IDIBAPS

Marta Selma-Royo got her PhD in Biotechnology from the Polytechnic University of Valencia (UPV) in 2020. Her PhD project was conducted at the Institute of Agrochemistry and Food Technology (IATA), part of the Spanish National Research Council (CSIC), in the group of Prof. M Carmen Collado. The research was focused on the perinatal factors that can affect the maternal and child microbiota and how these could influence the child's development during the first years of life.

After this period, she worked as a postdoctoral researcher at the Centre for Integrative Biology (CIBIO) at the University of Trento (UNITN). The project was conducted at the Computational Microbiology led by Prof. Nicola Segata. This group is a pioneer in the study of how the alterations in the composition of the human microbiota can be related to prevalent diseases using a computational approach. In Dr. Segata's group, Marta opened a new line of research in the study of the microbiota, from a combined point of view based on experimental and computational analysis. Currently, Marta Selma-Royo is developing her research in the Fundació de Recerca Clínic Barcelona – Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS). There, she's focused on the characterization of the maternal microbiota and how it can influence the evolution of the pregnancy and the health of both the mother and the child. The team explores the maternal factors that can be modulated during pregnancy and affect bacterial colonization to develop clinical and/or dietary strategies that improve human health.

Abstract

Human gut microbiome (GM) is recognized as essential player in several essential physiological functions that maintain host homeostasis. Indeed, the GM has been proposed as a key element for infant development that would be involved in intestinal and immune system maturation. Growing evidence has reported associations between non-communicable diseases (NCDs) such as obesity, allergies, and other immune-related diseases and disrupting factors of microbial colonization, including C-section delivery or antibiotics. Therefore, exist a close interconnexion between the perinatal environment, neonatal microbial colonization and infant development with a potential impact on the susceptibility to these diseases later in life.

While the maternal GM is defined as the main inoculum for the bacterial seeding that initiates the neonatal colonization process, our knowledge about the maternal gut microbiota during pregnancy and its impact on foetal development is limited. Even though the specific effector pathways are not well understood, recent evidence suggests that maternal GM during pregnancy has gut-distant effects, including on gestational process.

In this context, our research aims to decipher the exogenous factors that could impact maternal GM and its effect on foetal and infant health. This presentation will introduce our work in understanding how maternal gut microbiota can be modulated by lifestyle-related factors and how these are associated with differences in infant bacterial colonization and gut epithelium and immune system maturation. Delving into the intricacies of maternal GM could be the first step for the design of new strategies targeting GM modulation impacting both women's health and neonatal programming with long-lasting consequences for the infant and future adult.

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ORAL COMMUNICATIONS

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ORAL COMMUNICATION # 1

Defining metabolic health in obesity – comparison of obesity phenotype definitions along with Calcium and Magnesium levels in obese patients undergoing bariatric surgery

Anna Plümacher[1,2]; Cláudia Camila Dias[3,4]; Bárbara Peleteiro[5,6,7,8]; Paula Freitas[9,10,11]; Inês Fortuna[9]; Eduardo Lima[9,11]; Elisabete Martins[12,13,14]; Maria João Martins[2,10]

University of Potsdam, Germany[1]; Unit of Biochemistry, Department of Biomedicine, Faculty of Medicine, University of Porto, Porto, Portugal[2]; Knowledge Management Unit, Faculty of Medicine, University of Porto, Porto, Portugal[3]; CINTESIS@RISE, Department of Community Medicine, Information and Health Decision Sciences (MEDCIDS), Faculty of Medicine, University of Porto, Porto, Portugal[4]; Centro de Epidemiologia Hospitalar, Unidade Local de Saúde São João, Porto, Portugal[5]; Departamento de Ciências da Saúde Pública e Forenses e Educação Médica, Faculdade de Medicina, Universidade do Porto, Porto, Portugal[6]; EPIUnit-Instituto de Saúde Pública, Universidade do Porto, Porto, Portugal[7]; Laboratório para a Investigação Integrativa e Translacional em Saúde Populacional (ITR), Universidade do Porto, Porto, Portugal[8]; Faculdade de Medicina, Universidade do Porto, Porto, Portugal[9]; Instituto de Investigação e Inovação em Saúde (i3S), Universidade do Porto, Porto, Portugal[10]; Integrated Responsibility Center for Obesity (CRI-O), São João Local Health Unit, Porto, Portugal[11]; Serviço de Cardiologia, ULS S. João EPE, Porto, Portugal[12]; Department of Medicine, Faculty of Medicine, University of Porto, Porto, Portugal[13]; RISE-Health, Faculty of Medicine, University of Porto, Porto, Portugal[14].

Background: There is no standardized definition for obesity phenotype characterization. Metabolic healthy obesity (MHO) refers to a subset of obese individuals with low cardiometabolic risk. Magnesium (Mg) is crucial for insulin secretion, insulin signaling, and blood pressure regulation, while calcium (Ca) may negatively affect Mg homeostasis. Aims: to compare 6 different obesity phenotype definitions and, in each one, to examine metabolic parameters along with Ca, Mg, and Ca:Mg ratio in blood from bariatric surgery patients from CRI-O (Porto, PT).

Methodology: We studied 3,316 patients [body mass index (BMI) 43±6 kg/m^2, age 43±11 y (mean±SD)] undergoing bypass, gastric band or sleeve surgery. Inclusion was based on BMI or abdominal obesity. For obesity phenotype classification, 6 definitions were used: NCEP ATP III, 2002; Karelis, 2004; Meigs, 2006; Khan, 2011; Plümacher, 2024; Schulze, 2024. Metabolic and mineral assessments were performed at baseline and 1st follow-up after surgery. IBM SPSS Statistics was used for statistical analysis (vers. 29, 2023).

Results: Baseline MHO classification ranged from 11.1% (Karelis) to 70.8% (Meigs), with high blood pressure frequently being decisive (highest at 83.1%, NCEP ATP III), among all the parameters from the 6 definitions. At follow-up, 2.5% (NCEP ATP III) to 53.9% (Schulze) of overweight or obese patients remained classified as metabolically unhealthy (MUHO). Ca:Mg ratio was significantly higher in MUHO in 5 definitions at baseline (except Karelis) and in all at follow-up. Ca was significantly higher in MUHO across all definitions at baseline and in 5 at follow-up (except NCEP ATP III). Mg was significantly higher in MHO in 4 definitions at baseline (NCEP ATP III, Meigs, Khan, Plümacher) and 3 at follow-up (Khan, Schulze, Plümacher).

Conclusions: These findings emphasize the importance of uncovering the relevance of mineral balance in metabolic health and the need for a standardized obesity phenotype characterization.

Keywords: Metabolic healthy obesity; Metabolic unhealthy obesity; Obesity phenotypes; Magnesium; Calcium.

Conflict of Interest: None Disclosed.

Funding: No funding to report.

ORAL COMMUNICATION # 2

Effect of chrysin on appetite signaling in fructose-fed rats: a proteomic approach

Henrique Santos[1]; Hugo Osório[2]; Nelson Andrade[1,3]; Fátima Martel[1,2]

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Background: The increase in the consumption of Western diets, which are rich in trans-fats and carbohydrates such as fructose, is associated with an increase in obesity, diabetes, and metabolic syndrome incidence. [1] The dietary polyphenol chrysin, belonging to the flavonoid family, has recently proved to protect against some of the Metabolic Syndrome features induced by fructose-feeding in the rat. [2] Interestingly, when chrysin and fructose were combined, a lower food ingestion and a higher fluid ingested was observed. [2] This prompted the present work, that aims to unveil whether fructose and chrysin affect appetite regulation.

Methodology: Hypothalamus of the animals engaged in the previous study from the group [2], belonging to 4 groups (Control, Chrysin, Fructose and Fructose+ Chrysin), were used for proteomics analysis by LC-MS/MS (Liquid Chromatography with tandem mass spectrometry).

Results: After LC/MS processing and data research, 8333 proteins were identified with unique and Razer peptides set to equal or higher than 2. Of the 22 proteins related to eating behavior detected in the samples, Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha isoform (PI3K), Tyrosine 3 monooxygenase, Signal transducer and activator of transcription (STAT3), as well other proteins, significantly altered in the Fructose+Chrysin group, when compared to the varius control groups.

Conclusions: This work shows that the association of Fructose and Chrysin causes significant changes in the expression of several hypothalamic proteins related to the eating behavior (enzymes (TH), ion channels (Slc24A4) and intracellular signaling molecules (Stat3 and PI3K). The involvement of these proteins on the changes in eating/drinking behavior in Fructose + Chrysin animals should be further investigated Keywords: Fructose; chrysin; proteomics; sweet taste; appetite

Conflict of Interest: None Disclosed

Funding: No funding to report

ORAL COMMUNICATION # 3

Quality of vegetarian diets and its' association with metabolic and inflammatory outcomes: preliminary results from the VeggieNutri project

Cátia Pinheiro [1,2*]; Isabella Bracchi [1,2]; Juliana Guimarães [1,2]; Joana Amaro [3,4,5]; Cláudia Camila Dias [6]; Andreia Oliveira [5,6,7]; Altin Ndrio [8]; João Tiago Guimarães [1,5,8]; João Costa Leite [2,9]; Rita Negrão [1,10]; Elisa Keating [1,10*]

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Background: Diet quality (DQ) assessment in vegetarian populations is scarce, in part due to the lack of a robust DQ Index for that purpose. In this study, we developed the VeggieNutri-Index to assess diet quality of omnivorous (OMNI), lacto-ovo-vegetarian (LOV) and vegan (VEG) healthy adults, as well as its association with metainflammation outcomes.

Methodology: 392 OMNI, LOV and VEG adults were included. Waist circumference (WC), blood pressure (BP), weight and height were measured, and body mass index (BMI) was calculated. Blood metabolic and inflammation markers were measured, and HOMA-IR was calculated. Participants answered a food frequency questionnaire. VeggieNutri-Index was developed based on nutrient recommendations from the Food and Nutrition Board [1]. Spearman correlations were conducted to test for the association between DQ and metainflammation markers.

Results: Participant's age (mean ± SD) was 36 ± 12 years. Distribution by dietary groups was: 240 (61%) OMNI, 94 (24%) LOV and 58 (15%) VEG. Median (P25; P75) DQ decreased with increasing strictness of diet (Median (P25; P75) DQ in % in OMNI, LOV and VEG: 78.4 (74.2; 80.7), 74.6 (70.1; 77.6) and 70.3 (65.3; 72.5), respectively, $p<0.001$). DQ negatively correlated with blood homocysteine in total sample ($r_s= -0.102$, $p=0.045$) and in the OMNI group ($r_s= -0.144$, $p=0.028$). In LOV group, DQ negatively correlated with WC ($r_s= -0.336$, $p = 0.001$), systolic and diastolic BP ($r_s= -0.318$, $p = 0.002$ and $r_s= -0.354$, $p=0.001$), respectively) and with C-reactive protein ($r_s= -0.210$, $p=0.044$). In VEG group, DQ negatively correlated with HOMA-IR ($r_s= -0.259$, $p=0.049$).

Conclusions: Our preliminary data suggest that plant-based diets may compromise DQ which correlated with metainflammation markers. The developed VeggieNutri-Index may be a promising tool to assess the quality of plant-based diets, while empowering health-care providers and policy makers to update dietary guidelines for these special population groups.

Keywords: Anthropometry; Diet quality; Inflammation; Metabolic outcomes; Plant-based diets.

Conflict of Interest: Authors have no conflict of interest to declare.

Funding: Cátia Pinheiro was funded by FCT/MCTES (Fundação para a Ciência e a Tecnologia and Ministry of Science, Technology, and Higher Education) under CINTESIS by a PhD scholarship (reference UI/BD/151504/2021). This research was funded by national funds through FCT, Fundação para a Ciência e a Technology, I.P., within the scope of the project "RISE-LA/P/0053/2020 and CINTESIS, R&D Unit (reference UIDB/4255/2020)".

ORAL COMMUNICATION # 4

Visceral Adipose Tissue Browning and Inflammation in Women with Endometriosis

José Pedro Abobeleira [1,2]; Ana Catarina Neto [1,2]; Jan Mauersberger [1,2]; Maria Salazar [1,2]; Maria Botelho [1,2]; Ana Sofia Fernandes [3]; Margarida Martinho [3]; Maria Paula Serrão [4,5]; Adriana Raquel Rodrigues [1,2,6]; Henrique Almeida [1,2]; Alexandra Maria Gouveia [1,2]; Delminda Neves[1,2]

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Background: Endometriosis patients commonly present low body mass index and adiposity, equating an inverse relationship between body fat and disease. Actually, altered circulating miRNAs present in endometriosis induce browning of pre-adipocytes in vitro, supporting such relationship. Thus, we hypothesize that browning and inflammation processes mediate adipose tissue (AT) dysfunction in endometriosis and proceeded to molecular characterization of such pathways in AT samples collected from endometriosis patients.

Methodology: Samples from visceral (VAT) and subcutaneous AT (SAT) were collected from surgeries for endometriosis (n = 32) or uterine myoma (n = 14; controls). Blood catecholamines were assessed by high-performance liquid chromatography and IL-6 and TGF-β levels by ELISA. Adipocyte cross-sectional areas were analyzed in H&E-stained sections using computer-assisted morphometry. Macrophage (F4/80; Galectin-3) and browning (UCP-1; PGC-1α) molecules were identified in AT using dual-labelling immunofluorescence. Expression of inflammation (IL-6; MCP-1; Galectin-3; CD206; TIMP1; TGF-β) and browning-related (UCP-1; PGC-1α; DIO2; CITED1; CIDEA; TMEM26; TBX1; PRDM16; PPAR-γ) mRNAs and proteins were assessed in AT by RT-PCR and Western blotting, respectively.

Results: Endometriosis patients presented smaller adipocyte area, especially in VAT. Serum norepinephrine levels were lower but serum IL-6 was increased in patients. UCP-1, PGC-1α, IL-6, and MCP-1 proteins were upregulated in VAT from endometriosis women and CD206 downregulated, compared to controls. No differences were found between groups in mRNA expression of IL-6, TIMP1, and TGF-β and in Galectin-3 protein levels in VAT. Levels of all studied proteins remained unchanged in SAT when comparing groups.

Conclusions: Our findings evidence browning and pro-inflammatory features in VAT of endometriosis patients, associated with a pro-catabolic state that together promote AT dysfunction and disease progression.

Keywords: Adipose tissue, Browning, Endometriosis, Inflammation.

Conflict of Interest: None

Funding: This research was supported by the Portuguese Society of Gynecology (Bolsa SPG 2020). The contract DL57/2016/CP1355/CT0009 of A.R. Rodrigues was funded by the FCT – Fundação para a Ciência e Tecnologia-Portugal.

ORAL COMMUNICATION # 5

Influence of Obesity and Adipose Tissue Distribution in the Regulation of SARS-CoV-2 Cell Entry Mediators: ACE2, TMPRSS2, ADAM17, and NRP1

Maria Salazar [1,2]; Mariana Ferreira [1]; Sandra Marisa Oliveira [3]; Francisca Saraiva [3]; Carlos Pinho [4]; Mariana Jarnalo[5]; Inês Correia-Sá [5]; Inês Falcão-Pires [3]; Adelino Leite-Moreira [3]; Delminda Neves [1,2]; Henrique Almeida [1,2]; Adriana Rodrigues [1,2,6]; Alexandra Gouveia [1,2]

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Background: Obesity impacts COVID-19 severity, driven by SARS-CoV-2, which primarily enters cells via ACE2 receptor. Other proteins, such as TMPRSS2, ADAM17 and NRP1 potentiate infection. This study aims to investigate how the expression of those molecules in adipose tissue (AT) depends on depot location and obesity status.

Methodology: AT samples were collected from non-obese individuals (BMI 19.88–29.48kg/m²) from subcutaneous abdominal superior (AS), abdominal inferior (AI), thigh(T), and visceral epiploon(E) regions. Subcutaneous AT was also obtained from patients previously obese (BMI 22–27.2kg/m², formerly 33.5–52.6kg/m²) and with obesity(BMI 30.43–35.52kg/m²). Protein and mRNA levels of ACE2, TMPRSS2, ADAM17, and NRP1 were measured by qPCR and western blot.

Results: All analyzed proteins were expressed at higher levels in visceral E compared to subcutaneous (AS, AI, and T). *ACE2* mRNA was increased in E compared to AI, whereas *NRP1* was diminished in E relative to T. *ADAM17* mRNA expression was consistent across all fat depots.

Individuals with obesity showed significantly increased protein levels for all SARS-CoV-2 entry mediators compared to controls. A positive correlation between BMI and protein levels of ACE2, TMPRSS2, and NRP1 was observed in AS and/or E depots. Conversely, *ACE2* mRNA in E decreased with increasing BMI.

After weight loss, protein expression of ACE2 and NRP1 significantly decreased, but TMPRSS2 and ADAM17 remained similar as found in the group with obesity. *ADAM17* mRNA was unexpectedly lower in both ex-obese and obese compared to controls, while *ACE2* and *NRP1* did not differ across groups.

Conclusions: Obesity and visceral AT associate with enhanced expression of proteins involved in SARS-CoV-2 entry, which may contribute to COVID-19 severity. Weight loss may mitigate this risk by reducing ACE2 and NRP1 protein levels.

Keywords: Adipose Tissue, Obesity, COVID-19

Conflict of Interest: None Disclosed

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ORAL COMMUNICATION # 6

Exploring Transthyretin's Interactions with Alzheimer's Disease Biomarkers: Levels and Stability Insights

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Background: Transthyretin (TTR) has attracted interest for its potential neuroprotective function, particularly in Alzheimer's Disease (AD). This protein interacts with amyloid-beta (Aβ) to inhibit Aβ aggregation and decrease neurotoxicity, thereby decelerating the progression of AD.

Methodology: Our study assessed TTR levels and tetrameric stability in both plasma and cerebrospinal fluid (CSF) in patients at different stages of AD, including those with mild cognitive impairment (MCI-AD, n=29) and Dementia-AD (n=37). We examined correlations between TTR parameters and several clinical, biochemical, and genetic markers.

Results: We found a significant reduction in plasma TTR levels in Dementia-AD patients compared to the MCI-AD group, with a significant gender-specific effect observed in women. CSF TTR levels remained unchanged. Stability of TTR did not differ significantly across groups, whether in plasma or CSF. In MCI-AD patients, CSF TTR levels inversely correlated with key markers of amyloid pathology and neurodegeneration, including Aβ40, p-Tau181, t-Tau, and NfL. CSF TTR instability also showed a negative correlation with the Aβ42/Aβ40 ratio and CSF Aβ42 levels, indicating a link to increased amyloid burden. In the Dementia-AD group, decreased plasma TTR levels were associated with higher GFAP levels, indicating an association with neuroinflammation. Furthermore, plasma TTR instability was associated with both CSF TTR instability and tau pathology markers (p-Tau181, t-Tau). After detecting a strong association between CSF TTR instability and CSF Aβ42, we investigated the impact of Aβ42 on TTR tetrameric stability, observing a significant reduction after 24-hour incubation.

Conclusions: Our findings indicate that TTR is involved in key processes such as Aβ clearance, neurodegeneration, and neuroinflammation across different stages of AD. The destabilization of TTR by Aβ42 may impair its protective function, underscoring the importance of TTR in the pathology of AD.

Keywords: Transthyretin; Alzheimer's Disease; Human Cohort; Stability; Neuroinflammation.

MET-CONF 24

A HOT TOPIC IN METABOLIC DYSFUNCTION

2ND CONFERENCE OF THE DOCTORAL PROGRAM

IN METABOLISM – CLINICAL AND EXPERIMENTAL

SPEED TALKS

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SPEED TALK # 1

Placental pathology of SARS-CoV-2 affected pregnancies of obese and non-obese patients

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Background: The possible impact of the combination of SARS-CoV-2 infection and maternal obesity in placental pathology has not been properly investigated. The aim of this study was to compare the placental histopathology in active SARS-CoV-2 infected obese and non-obese patients.

Methodology: This was a retrospective cohort study that included placentas prevenient from deliveries from December 2017 to July 2023. The Control group (n=17) corresponds to placentas from healthy mothers, the OB group (n=14) corresponds to placentas from pregnant women with pre-gestational obesity, the SARS group (n=19) includes placentas from healthy mothers with active SARS-CoV-2 infection, and the OB+SARS group (n=12) includes placentas from obese mothers with active SARS-CoV-2 infection.

Results: Gestational age at delivery was significantly lower in the OB+SARS group than in the SARS group. Symptomatic infection was more common, and moderate to severe symptomatology was observed only in the OB+SARS group. Regarding placental histopathology, a higher risk for occurrence of ischemic injury in the OB+SARS group than in Control, higher occurrence of subchorionic fibrin deposits in the OB+SARS group than in Control, and a lower risk of developing chorangiosis in the OB+SARS when compared to the OB group, and in the SARS group, when compared with the Control group, were observed.

Conclusions: An increased risk for development of placental lesions related to both maternal and fetal malperfusion and ischemic injury in placentas affected by SARS-CoV-2 infection, and an increased risk of occurrence of such lesions when obesity coexists with this infection was found.

Keywords: Placenta, Histology, Obesity, SARS-CoV-2, COVID-19.

Conflict of Interest: The authors disclose no conflicts of interest in this work.

Funding: This work was supported by Fundação para a Ciência e Tecnologia (FCT) [2021.09409.BD].

The Influence of Obesity and Maternal Deprivation on Inflammatory and Behavioral Parameters in Offspring During Neurodevelopment

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Background: The global obesity epidemic is linked to changes in diet and lifestyle, with studies showing that intrauterine exposures increase the risk of behavioral, cognitive, and obesity-related disorders in adulthood. Maternal care deprivation in early life also raises the likelihood of long-term behavioral problems and psychiatric disorders, such as depression. Additionally, a high-fat diet can lead to chronic peripheral inflammation, with an exacerbated release of cytokines. Thus, this study aimed to evaluate the inflammatory and behavioral parameters of mice subjected to maternal obesity and depression induced by maternal deprivation (MD).

Methodology: Sixty female Swiss mice were used, divided into two groups: Control Group (normolipidic diet) and Obese Group (high-fat diet) to induce an animal model of obesity. The protocol was based on a high-fat diet consumption over eight weeks. Subsequently, the females underwent gestation, and after the offspring were born, they were divided into four groups: Control Offspring (CO), Control Offspring + MD (CO + MD), Maternal Obesity Offspring (MOO), Maternal Obesity Offspring + MD (MOO + MD). The offspring were weaned at 21 days. At 21, 30, and 60 days, the animals were subjected to behavioral tests and subsequently euthanized, where brain structures were isolated for biochemical analyses.

Results: The results showed a compromise in locomotor activity, especially in the obesity and maternal deprivation group, as well as impairments in exploration and self-grooming at 30 days of age. Furthermore, a significant increase in interleukin-6 (IL-6) was observed in the group combining obesity and maternal deprivation, in the hippocampal region, at 30 days of age.

Conclusions: It is concluded that both obesity and maternal deprivation influence behavior and inflammatory parameters, and that the interaction of both factors in certain structures potentiates these damages.

Keywords: Obesity, Maternal Deprivation, Neurodevelopment.

Conflict of Interest: The authors declare that they have no known competing financial interests or personal relationships that could influence the work

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SPEED TALK # 3

Impact of Maternal Obesity on Microbiota-Dependent Immune Programming in Early-life

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Background: Early-life gut microbiota is modifiable by external factors such as delivery mode and maternal microbiota. It exerts a vital role in the development of the child's immunity and any disruption to its composition can impair the maturation of the immune system, causing future health issues. Considering the mother's role in early-life, as one of the main sources of microorganisms to the offspring, it is crucial to assess whether maternal health can influence the infant's gut microbiota and, thus, the immune response. Therefore, the study aims to understand the impact of maternal obesity on child's gut microbiota immunomodulation ability, from one month up to one year postpartum.

Methodology: Gut microbiota of infant stool samples was separated by a series of centrifugations and inactivated by UV radiation. The gut microbiota was used to stimulate monocyte-derived dendritic cells (DCs) and T cells, and their activation levels were evaluated by flow cytometry.

Results: The results indicate that the gut microbiota enabled DC activation, as evidenced by the increased expression of CD86 and CD40. As for the impact on the adaptative immunity, assessed by T cell activation in cocultures with DCs, it was observed that it enabled early T cell activation, through higher expression of CD69. Preliminary results showed no significant differences in the activation levels of DCs and T cells between infants of obese and lean mothers throughout time.

Conclusions: A protocol was successfully optimized for separating and inactivating infant gut microbiota and, later immune cell stimulation. The infant gut microbiota could stimulate immune cells from the innate and adaptive immune systems. However, further studies are needed to clarify if maternal obesity influences child immune priming.

Keywords: Microbiota, Dysbiosis, Obesity, Early-Life, Immunity

Conflict of Interest: None disclosed

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SPEED TALK # 4

Sulfur Amino Acid Restriction Mitigates High-Fat Diet-Induced Molecular Alterations in Cardiac Remodeling Primarily via FGF21-Independent Mechanisms

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Background: Dietary sulfur amino acid restriction (SAAR) elicits various health benefits, some mediated by fibroblast growth factor 21 (FGF21). However, research on SAAR's effects on the heart is limited and presents mixed findings. This study aimed to evaluate SAAR-induced molecular alterations in cardiac remodeling and their dependence on FGF21.

Methodology: Male C57BL/6J wild-type and FGF21 knockout mice were randomized into four dietary regimens, including normal fat and high-fat diets (HFDs) with and without SAAR, over five weeks.

Results: SAAR significantly reduced body weight and visceral adiposity while increasing serum FGF21 levels. In the heart, SAAR induced molecular metabolic alterations indicative of enhanced lipid utilization, glucose uptake, basal insulin signaling, mitochondrial biogenesis, and calcium handling. SAAR also elicited opposing effects on the cardiac gene expression of FGF21 and adiponectin. Regarding cellular stress responses, SAAR mitigated the HFD-induced increase in the cardiac expression of genes involved in oxidative stress, inflammation, and apoptosis, while upregulating antioxidative genes. Structurally, SAAR did not induce alterations indicative of cardiac hypertrophy and it counteracted the HFD-induced fibrotic gene expression.

Conclusions: Overall, most alterations induced by SAAR were FGF21-independent, except for those related to lipid utilization and glucose uptake. Altogether, SAAR promotes cardiac alterations indicative of physiological rather than pathological remodeling, primarily through FGF21-independent mechanisms.

Keywords: Sulfur amino acid restriction; high-fat diet; fibroblast growth factor 21; cardiac remodeling; metabolic health

Conflict of Interest: None Disclosed

SPEED TALK # 5

The influence of age on FGF21 dynamics and weight loss outcomes after bariatric and metabolic surgery

Ana Luísa De Sousa-Coelho [1,2,*]; Laura Veríssimo [3]; Carolina Lopes [3]; Victor Yassuda [3]; Carina Dias [1]; Joana Dias [1]; Andreia Fernandes [4], Céu Laranjo [4]; Paulo Cardoso [3,4]; Bibiana I. Ferreira [2,3]; Mónica T. Fernandes [1,2]; Tina Sanai [4]; Mercedes Sanchez [4;] João Maia-Teixeira [4]

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Background: Circulating fibroblast growth factor 21 (FGF21) is involved in suppressing inflammation across various tissues, particularly in adipose tissue. Due to its anti-inflammatory and metabolic regulatory properties, FGF21 is a potential therapeutic target for obesity and obesity-related metabolic disorders. Our goal is to investigate early changes in FGF21 levels following weight loss induced by bariatric and metabolic surgery (BMS).

Methodology: To determine serum FGF21 levels, blood was collected in fasting condition from individuals with obesity before BMS (T1), and 3 to 6 months after (T2), and analyzed through a specific enzyme-linked immunosorbent assay. Body composition was evaluated through bioimpedance analysis. Changes in FGF21, and total body weight (BW), free-fat mass (FFM), skeletal muscle mass (SkMM) and body fat mass (BFM) losses (L), were calculated.

Results: From a sample of 20 patients (mean age 49,7 years old, 80% female), mean BW was 110,5 Kg (body mass index 41,2 Kg/m^2), before BMS. As expected, all patients showed decreased BW at T2 (*p<0,001*), with total BW loss (TBWL) from 8 to 27,3%. Body composition parameters also showed significant reductions. On average, FGF21 levels significantly increased from T1 (720,4 pg/mL) to T2 (1290 pg/mL; *p=0,049*), although changes were highly variable. Interestingly, patients in a subset who showed a decrease in FGF21 after BMS were older than those whose FGF21 levels increased. Age also negatively correlated with TBWL (r -0,5350; *p=0,0151*) and BFML (r -0,5102; *p=0,0364*).

Conclusions: From this preliminary analysis, we found that FGF21 levels increased globally at an early timepoint following BMS-induced weight loss. Older patients exhibited a different response, suggesting that changes in FGF21 levels may influence the degree of weight and fat tissue loss. This could potentially reduce the intervention's benefits in reducing inflammation and improving overall metabolic health.

Keywords: Ageing; Fibroblast growth factor 21; Obesity; Bariatric and metabolic surgery; Inflammation.

Conflict of Interest: None.

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MET-CONF 24

A HOT TOPIC IN METABOLIC DYSFUNCTION

2ND CONFERENCE OF THE DOCTORAL PROGRAM IN METABOLISM – CLINICAL AND EXPERIMENTAL

POSTERS

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POSTER # 1

Adiponectin/leptin ratio in fetal blood relates to both maternal and infant cardiometabolic outcomes

Juliana Morais[1,2,3]; Débora Coutinho[1]; Ana Filipa Ferreira[1]; Joana Miranda[1,4], Inês Falcão-Pires[1] and Adelino Leite-Moreira[1,5]

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Background: Adiponectin and leptin are two adipokines involved in fetal and neonatal growth. Adiponectin-leptin ratio (AdipoQ/Lep) has been proposed as a promising biomarker of metabolic risk. In this context, this study aims to explore the association between AdipoQ/Lep quantified in fetal blood and maternal-infant cardiometabolic phenotypes.

Methodology: A total of 29 mother-neonate pairs were recruited upon admission to the obstetrics service in a tertiary center between September 2022 and April 2023. Blood and umbilical cord samples were collected in a sterile bag with CPDA-1 anticoagulant solution by the obstetric team at delivery. Adiponectin and leptin levels were measured in umbilical cord plasma by the immunoassay ELISA kit. Transthoracic echocardiography was performed on the offspring at 4±1 months after delivery.

Results: The AdipoQ/Lep ratio in the fetal blood from mothers with pregestational obesity (2.42±1.04) was lower compared to those with normal weight (4.89±1.64), p=0.007) and overweight (4.89±1.97), p=0.004)). No correlations were found between AdipoQ/Lep and pregestational weight (ρ=-0.322, p=0.088) or gestational weight gain (ρ=-0.267, p=0.162). Regarding infant outcomes, a significant association between AdipoQ/Lep ratio and weight-for-length z-score (ρ=-0.560, p=0.002) and BMI-for-age z-score at birth were found (ρ=-0.584, p<0.001). Notably, at the time of the echocardiographic evaluation, offspring mitral A-wave velocity correlated positively with AdipoQ/Lep (ρ=0.422, p=0.023), and with left ventricular isovolumetric relaxation time (ρ=0.369, p=0.049).

Conclusions: This study is the first one to describe significant associations between the AdipoQ/Lep ratio in umbilical cord plasma and maternal-infant outcomes. Although further studies are needed to confirm these findings, our results support the potential of this adipokine ratio as a promising biomarker of the offspring's cardiometabolic health.

Keywords: Adiponectin, Leptin, umbilical cord blood, cardiometabolic health

Conflict of Interest: None Disclosed

Funding: This work was supported by Bolsa de Estudo João Porto da Sociedade Portuguesa de Cardiologia, by RTP Maratona da Saúde 2017 and by national funds through FCT - Portuguese Foundation for Science and Technology, under the scope of the Cardiovascular R&D Center - UnIC (UIDB/00051/2020 and UIDP/00051/2020). Juliana Morais and Ana Filipa Ferreira (UI/BD/152306/2021 and SFRH/BD/138925/2018, respectively).

POSTER # 2

Adiponectin/leptin ratio in fetal blood relates to both maternal and infant cardiometabolic outcomes

Juliana Morais[1,2,3]; Débora Coutinho[1]; Ana Filipa Ferreira[1]; Joana Miranda[1,4], Inês Falcão-Pires[1] and Adelino Leite-Moreira[1,5]

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Corresponding author's: Juliana Morais, up201502374@up.pt

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Conclusions: This study is the first one to describe significant associations between the AdipoQ/Lep ratio in umbilical cord plasma and maternal-infant outcomes. Although further studies are needed to confirm these findings, our results support the potential of this adipokine ratio as a promising biomarker of the offspring's cardiometabolic health.

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Conflict of Interest: None Disclosed

Funding: This work was supported by Bolsa de Estudo João Porto da Sociedade Portuguesa de Cardiologia, by RTP Maratona da Saúde 2017 and by national funds through FCT - Portuguese Foundation for Science and Technology, under the scope of the Cardiovascular R&D Center - UnIC (UIDB/00051/2020 and UIDP/00051/2020). Juliana Morais and Ana Filipa Ferreira (UI/BD/152306/2021 and SFRH/BD/138925/2018, respectively).

POSTER # 3

Linking cataracts and age-related macular degeneration: are their biochemical and inflammatory profiles similar?

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Background: Age-related macular degeneration (AMD) is characterised by central vision loss, progressive macular tissue degeneration and changes in the vasculature. Cataract is also characterised by progressive blindness with blurred vision, due to lens opacity. They are two of the most common causes of vision impairment worldwide, both linked to ageing. This study aimed to identify differences in biochemical and inflammatory profiles between cataracts and AMD in Portuguese patients.

Methodology: Patients with cataracts (18) and neovascular AMD (nAMD) (21) were recruited in Unidade Local de Saúde de São João, Porto. This study considered demographic data, haemogram analysis data, inflammatory indexes and biochemical markers levels. Statistical analysis was performed using SPSS, with p-value<0.05 considered statistically significant.

Results: No statistical differences were found between the two groups, except for the age of the patients, indicating that nAMD and cataract patients share the same biochemical and inflammatory profiles. In both groups, most patients were overweight, with comparable lipidic and glycemic profiles, without signs of an inflammatory state or major metabolic alterations.

Conclusions: Both diseases are influenced by environmental factors and lifestyle and are associated with low-grade inflammation. While no major plasma alterations were found, common biochemical profiles suggest a potential link between them, despite being diseases affecting different eye layers. However, it is important to mention that a small sample was used, and patients' daily medication can explain the stable biochemical profiles.

Keywords: Age-related macular degeneration; cataracts; inflammation; biochemical

Conflict of Interest: None Disclosed.

Funding: This project was funded by SPO PhD grant 2021 and GER/AbbVie grant 2022.

Effect of Gliflozins in Combination with Metformin on Pancreatic Cancer Cell Lines

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Background: Pancreatic cancer (PC) is the ninth leading cause of cancer-related deaths worldwide. Diabetic patients have an increased risk and mortality rates for PC. Sodium-glucose co-transporter 2 (SGLT2) inhibitors and metformin (Met) are widely used anti-diabetic medications. Both Met and SGLT2 inhibitors have anticancer properties in PC, but nothing is known concerning their combined effect. So, we investigated the *in vitro* effect of SGLT2 inhibitors combined with Met.

Methodology: Two pancreatic cancer cell lines (PANC-1 and AsPC-1) and a normal fibroblast cell line (HDFa) were used. The effects of canagliflozin and dapagliflozin and/or metformin on cell proliferation (^{3}H-thymidine incorporation assay), viability (MTT assay), glucose uptake (^{3}H-deoxy-D-glucose uptake assay), cell migration (injury assay), apoptosis (annexin-V) and cell cycle (flow cytometry) were evaluated.

Results: Canagliflozin and dapagliflozin possessed cytotoxic, antiproliferative, and pro-apoptotic properties in the tested PC cell lines. In PANC-1 cells, the anti-migratory and pro-apoptotic effects were enhanced when dapagliflozin was combined with Met, and G1 cell cycle arrest was enhanced when dapagliflozin or canagliflozin was combined with Met. In AsPC-1 cells, the cytotoxic effect and the G1 cell cycle arrest were enhanced when canagliflozin and dapagliflozin, respectively, were combined with Met. Only the cytotoxic effects of SGLT2 inhibitors, but not the combination treatments, involved PI3K and JNK-dependent pathways in AsPC-1 cells.

Conclusions: In conclusion, combination treatments increased the anticancer effects in a cell type-dependent way in the two investigated cell lines. Additionally, the cytotoxic effect of SGLT2 inhibitors was dependent on the PI3K and JNK pathways in AsPC-1 cells, but Met appears to act via a distinct mechanism.

Keywords: Panc-1 and AsPC-1 pancreatic cancer cell lines; SGLT2 inhibitors; metformin; PI3K and JNK intracellular signaling pathways

Conflict of Interest: None Disclosed

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Effect of dietary carotenoids and polyphenols on pancreatic cancer cell metabolism

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Background: Pancreatic cancer (PC) is one of the most common causes of cancer-related death and one of the cancers with lowest survival rates. Metabolic switches such as the Warburg effect, glutamine addiction and lactate shuttle allow cancer cells to increase their nutrient uptake and energy production. These changes are associated with an overexpression of membrane transport proteins for these nutrients, namely GLUT1, ASCT2 and MCT1. Our aim was to determine the effect of some selected carotenoids (astaxanthin, β-carotene, crocin and fucoxanthin) and polyphenols (chrysin, genistein, kaempferol and quercetin) on nutrient uptake by two PC cell lines (AsPC-1 and PANC-1).

Methodology: The effect of carotenoids and polyphenols on glucose, glutamine and lactic acid cellular uptake was assessed by measuring 3H-deoxy-glucose (3H-DG), 3H-glutamine (3H-GLN) and 3H-lactic acid (3H-L) cellular incorporation. The effect of these compounds on transcription rates for the nutrient transporters was assessed by measuring the mRNA levels of GLUT1, ASCT2 and MCT1 by qRT-PCR. Lastly, we evaluated cell viability with the MTT assay, in the presence of nutrient transport inhibitors (BAY-876, GPNA and NPPB).

Results: Crocin and chrysin were the compounds with the most prominent effect on nutrient uptake. Namely, crocin decreased the uptake of 3H-DG and 3H-L (by 10-20%), and chrysin decreased the uptake of 3H-DG and 3H-GLN (by ±20%) in the AsPC-1 cell line. Crocin and chrysin did not change GLUT1, ASCT2 and MCT1 transcription rates. Both compounds promoted a decrease in cell viability, in a concentration-dependent manner. When combined with nutrient transport inhibitors, crocin and chrysin did not show an additional cytotoxic effect.

Conclusions: Our results show that crocin and chrysin promote a decrease in AsPC-1 viability, possibly related to an inhibitory effect on nutrient cellular uptake.

Keywords: Pancreatic cancer, Carotenoids, Polyphenols, Glucose, Glutamine, Lactic acid

Conflict of Interest: None Disclosed

Funding: No funding to report

POSTER # 6

Identification of dual-target antidiabetic mushrooms natural compounds using virtual screening

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Background: Glycogen synthase kinase-3beta (GSK-3β) inhibitors and PPARγ agonists are instrumental in combating metainflammation of type 2 diabetes. Hyperactivation of GSK-3β leads to insulin resistance and inflammation, while PPARγ regulates lipid and glycemic metabolism, and its agonists help reduce inflammation and enhance insulin sensitivity. The discovery of compounds that inhibit GSK-3β and activate PPARγ offers dual therapeutic benefits for type 2 diabetes treatment.

Methodology: A database with 414 natural compounds present in mushrooms was used. Virtual Screening analysis was performed using GOLD molecular docking software and the PLP scoring function. The experimental 3D structures used were: GSK-3β in complex with BIM (bis-(indole)maleimide pyridinophane) inhibitor (PDB: 2OW3) and PPARγ in complex with a partial agonist nTZDpa (PDB: 2Q5S). The co-crystalized inhibitors were used as control. Also, an *in silico* ADMET (Absorption, Distribution, Excretion, Metabolism, and Toxicity) analysis was performed.

Results: The virtual screening identified promising compounds with dual-target potential. The potent compounds were Cerebroside A, B, C, and D. Cerebroside D showed the highest PLP scores, with values of 107 for GSK-3β and 118 for PPARγ. Cerebroside A, B, and C had PLP scores higher than BIM and agonist nTZDpa controls with PLP score: 87 and 106. In addition, all four compounds demonstrated a satisfactory ADMET profile.

Conclusions: Of the 414 compounds analyzed, four performed as dual inhibitors of GSK-3β and PPARγ, with emphasis on Cerebroside D found in the Lentinula edodes (shiitake). Therefore, this study offers novel approaches to potentially therapeutic molecules for type 2 diabetes by integrating computational-experimental methods.

Keywords: Virtual Screening, Mushrooms and Antidiabetic Compounds

Conflict of Interest: None

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POSTER # 7

Fatty Liver Index as a Marker for Metabolic Health in Obese Patients undergoing Bariatric Surgery: Associations with Calcium and Magnesium

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Background: Fatty liver, a marker of insulin resistance (IR), is quite prevalent in metabolic syndrome, yet not included in its definition criteria. Magnesium (Mg) plays a key role in insulin secretion and signaling, blood pressure regulation, and inflammatory response. Calcium (Ca) may interfere with Mg homeostasis. Aims: to examine the relationship between the fatty liver index (FLI), obesity phenotype classification, IR/insulin sensitivity indexes (IRISI), metabolic parameters, and mineral status in bariatric surgery patients (CRI-O, Porto, PT).

Methodology: We studied 3,316 patients [body mass index (BMI) 43±6 kg/m^2, age 43±11 y (mean±SD)] undergoing bypass, gastric band or sleeve surgery. Inclusion was based on BMI or abdominal obesity. FLI (Bedogni, 2006), IRISI (Matthews, 1985; Matsuda, 1999; Simental-Mendía, 2008), and metabolic and mineral assessments were performed at baseline and post-surgery 1st follow-up. NCEP ATP III (2002) was used for obesity phenotype classification [metabolic healthy obesity (MHO) <3 abnormalities present]. IBM SPSS Statistics was used for statistical analysis (vers. 29, 2023).

Results: IR, measured by the homeostasis model assessment of insulin resistance and the triglyceride/glucose indexes, associated positively with FLI at both time points (p<0.001). Matsuda insulin sensitivity index correlated negatively with FLI at baseline (p<0.001). 41.9% of the patients were classified as MHO at baseline, 97.5% at follow-up. FLI was significantly lower in MHO patients at both time points (p<0.001). Across all patients, a) FLI correlated positively with glucose, C-reactive protein, blood pressure, Ca, and Ca:Mg ratio at both time points (p<0.05), b) the correlation between FLI and Mg was not significant at baseline but became significant at follow-up (p<0.05).

Conclusions: FLI inclusion as a criterion in metabolic syndrome definitions should be considered. Further research is needed to explore the role of mineral balance in metabolic health.

Keywords: Fatty liver; Metabolic healthy obesity; Metabolic unhealthy obesity; Magnesium; Calcium.

Conflict of Interest: None Disclosed.

Funding: No funding to report.

POSTER # 8

The role of glycometabolism in B cells producing antibodies associated with autoimmunity

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Background: Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation and deterioration of synovial tissue. One of the hallmarks that characterizes RA is the presence of circulating autoantibodies such as anti-citrullinated protein antibodies (ACPA), which can be detected years before the diagnosis. In RA patients, ACPA variable domain (VD) exhibits elevated levels of *N*-glycans, which are present on approximately 90% of circulating ACPA. Glycan binding proteins (GBP), that are expressed/secreted by diverse immune cells, have the ability to bind carbohydrates and mediate various immune processes. The variable-domain glycans (VDG)-GBP interaction may have a potential role in B cell selection and function, contributing to the breach of tolerance observed in autoimmune diseases, although this remains largely unexplored.

The aim of this project is to evaluate whether VDG, on ACPA-specific B cells, establish interactions with GBPs and, potentially, regulate the function and selection of autoreactive B cells.

Methodology: Evaluation of ACPA-specific B cell surface glycoprofile and activation was done by flow cytometry. Glycogenes expression was assessed by RT-qPCR.

Results: ACPA-specific B cells, with and without VDG, show an altered glycosylation profile, at the cell surface, and glycogenes expression. Additionally, B cells with VDG demonstrated a tendency to a more activated profile, dependent on the interaction with other immune cells.

Conclusions: In conclusion, this work provides the characterization of the glycosylation profile in ACPA-specific B cell lines, with and without VDG. And suggests a role for VDG in regulating the B cell activity and function, with potential impact in autoimmunity, a topic that needs to be further exploited.

Keywords: Autoimmunity; *N*-glycosylation; Autoantibodies; Variable-domain glycans; B cells

Conflict of Interest: None to disclose.

Funding: This work was funded by European ERC Synergy project “GlycanSwitch”.

POSTER # 9

Influence of Fat Diet-Induced Obesity on Melanoma

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Background: Melanoma is an aggressive skin cancer with a high metastatic potential. Obesity has been identified as a possible risk factor, aggravating the development and progression of melanoma. Nonetheless, in pre-clinical models, adiposity has been shown to reduce lung metastases, suggesting the existence of an 'obesity paradox' in melanoma, which is poorly understood. Herein, we aimed to investigate the impact of fat diet-induced obesity, in melanoma, using an in vivo murine model submitted to different fat diets, to clarify this paradox and the role of adiposity in melanoma progression.

Methodology: C57BL/6J mice were fed with 3 different diets: Normal Diet (ND), High Fat Diet (HFD), and IsoCaloric restriction Diet (ICD), for almost 6 months. Afterwards, B16-F10-Luc-GFP dual reporter melanoma cells were inoculated in dorsal skinfold and tail vein for the development of primary tumors and lung metastases, respectively. Tumors and metastases development were analyzed using luciferase in vivo bioluminescence imaging. Results: HFD-fed animals weighed significantly more (51.6g ± 4.1g; n=18) than the animals on the ND and ICD (34.2g ± 3.5g, n=16; 33.6g ± 4.7g, n=18, respectively) diets. Obesity had a negative impact on primary tumors, promoting their development and growth and impaired melanoma metastisation, with a greater number of metastases and tumor burden being detected in obese animals through bioluminescence imaging, contradicting the 'obesity paradox'.

Conclusions: Although these findings are not conclusive, they provide an important basis for future research into the influence of body fat on the risk and progression of melanoma. Understanding the molecular and cellular mechanisms of this relationship is crucial to confirming the existence of the 'obesity paradox' and discovering new diagnostic and prognostic markers for melanoma.

Keywords: Melanoma; Metastasis; Obesity; Obesity Paradox; B16-F10

Conflict of Interest: None Disclosed

Funding: Study supported by "Fundação para a Ciência e a Tecnologia (FCT)" under the project FATTYMESS - Fat Diet-induced Obesity in Melanoma Metastasis (DOI:10.54499/EXPL/SAU-NUT/0843/2021)

Glycosylation remodeling at the gut mucosa: a novel strategy to tackle Inflammatory Bowel Disease

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Background: Inflammatory bowel disease (IBD) is a chronic debilitating disorder of the gastrointestinal tract comprising Crohn's disease (CD) and ulcerative colitis (UC). Despite the etiology of IBD remaining unclear, it is known that glycosylation plays a key role in its immunopathogenesis. Our group has demonstrated that mucosal T cells from UC patients exhibit decreased levels of β1,6N-acetylglucosamine (GlcNAc) branched *N*-glycans, positively correlating with T cell hyperactivity and disease severity. We also showed that mice deficient in the *Mgat5* gene (encoding *N*-acetylglucosaminyltransferase (GnT)-V-mediated branched *N*-glycosylation) display increased susceptibility to severe colitis. *Mgat5*-KO mice treated with glycans displayed disease control by inhibition of Th1/Th17 responses. Hence, we aim to unravel whether glycosylation remodeling represents a new strategy to tackle IBD.

Methodology: Two complementary approaches were carried. Firstly, we developed murine intestinal organoids, derived from wild-type mice, that were characterized and glycomodulated to promote/abrogate complex *N*-glycans. We have also explored the impact of glycosylation remodeling *in vivo*, using glycoengineered mouse models that lack complex *N*-glycans in the intestinal mucosa. The impact of alterations in intestinal glycosylation was explored in both homeostatic vs inflammatory conditions.

Results: We were able to reprogram the glycosylation profile of gut organoids. We have also shown that glycosylation remodeling impacts intestinal immune populations, with mice displaying divergent susceptibility to DSS-induced colitis.

Conclusions: This work provides a new tool to study the impact of glycosylation on the gut epithelial compartment and its interaction with immune cells, pinpointing glycosylation as a key mechanism in maintaining intestinal homeostasis.

Keywords: IBD, *N*-glycans, glycosylation reprogramming, organoids

Conflict of Interest: None disclosed

Funding: ECCO Grant 2023

Bacteriophages and growth factors stabilized in microneedles as a 2 in 1 approach to diabetic foot ulcer treatment

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Background: Diabetic foot ulcers (DFUs) are chronic wounds that often become infected with bacteria, such as *Escherichia coli*. With the increase in DFUs and multidrug-resistant bacteria (MDR), novel antimicrobial and regenerative therapies are needed. Bacteriophages (phages) and recombinant epidermal growth factors (EGF) are promising therapies for DFUs, given their potential in infection control and wound regeneration. This project aimed to develop microneedles loaded with *E. coli*-specific phages and recombinant pig EGF (rpEGF), to test their efficacy in resolving infection and promoting re-epithelialization in an ex vivo wound model.

Methodology: *E. coli*-specific phages were isolated and characterized, and their individual and combined antibacterial effects were tested in vitro against *E. coli* host strains. Alginate-gelatin microneedles loaded with phages and rpEGF were produced, and their antimicrobial and regenerative activities were assessed using an ex vivo pig skin wound model.

Results: The five phages had a combined lytic activity of 90% against 21 clinical *E. coli* isolates including MDR. A phage cocktail of the five phages was more effective in reducing *E. coli* than the individual phages. However, the phage cocktail was less effective when delivered via microneedles in the ex vivo model, where bacteria formed biofilms. The combination of phage and rpEGF was compatible, as phage stability or antibacterial efficacy were not compromised. rpEGF had little impact on promoting keratinocyte migration in the ex vivo model, but it did not negatively affect skin integrity.

Conclusions: The compatibility of phages and rpEGF within the microneedle system highlights the potential for further optimization of this dual-therapy approach for treating chronic wounds infected with multidrug-resistant bacteria.

Keywords: Diabetic foot ulcer, phage, epidermal growth factor

Conflict of Interest: None Disclosed

Funding: No funding to report

Exploring the Health Benefits of Lentil Phenolics: Antioxidant and Immunomodulatory Effects

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Background: Lentils are rich in nutrients such as protein, fibre, minerals and flavonoids, with a low glycemic index that helps avoid glycemia peaks. Epidemiological data suggest potential benefits in preventing cardiovascular diseases and diabetes, yet consumption remains low. This study aims to identify the lentil variety with the highest phenolic and flavonoid content, antioxidant capacity, and anti-diabetic effects while evaluating its cytotoxicity and immunomodulatory activity.

Methodology: Four raw and cooked *Lens culinaris L*. varieties (Kermit, Green, Brown, Red) were analyzed for total phenolics, flavonoids, antioxidant, and anti-diabetic activities. Cytotoxicity and immunomodulatory effects of phenolic extracts were assessed in Caco-2 cells by quantifying inflammatory markers Interleukin(IL)-6 and IL-8 through ELISA.

Results: Kermit showed the highest phenolic and flavonoid content, antioxidant, and anti-diabetic activities, making it the best candidate for *in vitro* analyses. No cytotoxicity was observed in Caco-2 cells exposed to Kermit´s phenolic extracts tested concentrations. Additionally, IL-6 and IL-8 production significantly decreased compared to control, and the extracts showed anti-inflammatory effects in IL-1β-stimulated cells, as evidenced by reductions in IL-6 and IL-8 secretion.

Conclusions: Kermit's phenolic extracts demonstrate promising anti-inflammatory and anti-diabetic potential, highlighting lentils as valuable functional foods for chronic disease prevention.

Keywords: Antioxidant; Anti-diabetic; Flavonoids; Health benefits; Lentils.

Conflict of Interest: None disclosed.

POSTER # 12

Evaluate the influence of TTR stabilization on Aβ deposition and Neuroinflammation: Addressing the Unmet Need for Alzheimer's Treatment

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Background: Alzheimer's disease (AD) is the most common type of dementia, characterized by the presence of brain amyloid-β (Aβ) plaques. The presence of Aβ is thought to be the primary cause of microglial activation in AD. Neuroinflammation plays a fundamental role in this disease and in the acute phase the effects are beneficial. However, persistent activation of microglia and astrocytes can contribute to AD pathogenesis. Transthyretin (TTR), a protein decreased in AD patients, binds Aβ facilitating its removal from the brain. TTR instability results in its faster clearance and decreases its ability to bind Aβ, thus, TTR stabilization may be a new approach to treat AD. A recent study has shown that IDIF (Iododiflunisal), a TTR stabilizer acting as a small molecular chaperone (SMC) of the TTR/Aβ interaction, can decrease Aβ deposition in 4.5 months 5XFAD mice. Here we intend to analyse the effect of the SMC Flufenamic acid on Aβ amyloid burden and neuroinflammation. Although acting as a TTR stabilizer, Tolcapone does not enhance the TTR/Aβ interaction and will used as a negative control.

Methodology: Transgenic 5XFAD mice were used in this study. A control group was euthanised at 2.5 months (before the treatment started), the other groups, namely the other control, and animals receiving Flufenamic acid or Tolcapone since the age of 2.5 months were euthanised at 4.5 months. Half of their brains were used to analyse Aβ deposition and the microglia marker iba1, by immunohistochemistry.

Results and conclusion: We expect that Flufenamic acid treatment will result in decreased Aβ amyloid burden, while no effect is anticipated for Tolcapone. As for neuroinflammation, the results are unpredictable and might depend on the ability of Flufenamic acid to prevent, delay or remove amyloid. Future studies will examine astrocyte activation and Aβ40 and Aβ42 total levels in these animals' brains.

Keywords: Alzheimer, Transthyretin stabilization, Neuroinflammation, Flufenamic acid

Conflict of Interest: None Disclosed

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POSTER # 13

Impact of Bariatric and Metabolic Surgery on the Control of Obesity-Related Metabolic Comorbidities

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Background: Obesity is one of the most common diseases in the population entailing numerous comorbidities, namely type 2 diabetes (T2D) and dyslipidaemias (DLP). It is characterized as an increased accumulation of adipose tissue, contributing to increased systemic inflammation. Bariatric and metabolic surgery (BMS) shows the more sustained weight loss in individuals living with obesity. In a pilot study, our aim was to verify the changes in the control of T2D and DLP, early as 3 to 6 months post BMS.

Methodology: Patients who were candidates to BMS were characterized by age, sex, body weight (BW) and as living with comorbidities such as T2D, hypercholesterolemia and hypertriglyceridemia, based on the clinical information, prescribed medication, and biochemical analysis (Hb1Ac, glycemia, total cholesterol (chol), LDL-chol, HDL-chol and triglycerides). Considering variables from baseline (M0) to the follow-up at 3 to 6 months after BMS, the improvements in the control of these diseases was established. Body mass index (BMI) and frequencies were calculated.

Results: From a sample of 24 patients (78,3% female), mean age was 47 years old. At M0, body weight (BW) was 111,5 kg (BMI 41,96 Kg/m^2). Considering the clinical information, medication in use and blood tests results before surgery, we identified 66,7% with pre-diabetes and 12,5% diagnosed with T2D. Regarding DLP, 50% showed hypercholesterolemia, 12,5% hypertriglyceridemia, and 4,2% both. At 3 to 6 months post op, mean BW was 93,4 kg and BMI was 33,22 Kg/m^2. Most patients showed improvements in T2D and DLP control at this early timepoint after BMS, meaning only 12,5% were considered in the pre-diabetes range, 8,3% with hypercholesterolemia, and 4,2% with hypertriglyceridemia.

Conclusions: From this preliminary analysis, we show that surgical treatment of obesity, even in short term, contributed positively to a better glycemic and lipidemic control, which can overall contribute to decreased systemic inflammation.

Keywords: Bariatric and Metabolic Surgery, Obesity, Systemic Inflammation, Diabetes Mellitus, Dyslipidaemia

Conflict of Interest: None.

Funding: This research was funded by the Agency for Clinical Research and Biomedical Innovation (AICIB) with the support of the solidarity account “Todos Por Quem Cuida (TPQC)”, within the scope of the awarded project IMPPACTO.

POSTER # 14

Improvements in hepatic function in patients with obesity after bariatric and metabolic surgery

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Background: Obesity and metabolic dysfunction-associated fatty liver disease (MAFLD), previously referred as non-alcoholic fatty liver disease (NAFLD), are diseases whose prevalence has been increasing significantly over the last decades. These are closely related, since MAFLD is one of the most common comorbidities of obesity, having a prevalence between 50% and 90%. MAFLD is characterized by the presence of hepatic steatosis, and it can progress to more severe conditions such as steatohepatitis, fibrosis and cirrhosis. This study aimed to investigate the potential changes in hepatic enzyme levels and NAFLD risk scores in patients with obesity undergoing bariatric and metabolic surgery (BMS) in an early time-point after the procedure.

Methodology: Evaluations were performed before BMS (M0) and at follow-up 3 to 6 months after (M3/6). Besides circulating hepatic enzymes and triglycerides levels, patients' age, body mass index (BMI) and waist circumference were used to calculate NAFLD scores such as the "Fatty liver index" (FLI) and the "BAAT score".

Results: Our sample consisted of a total of 22 patients (16 female; mean age 47,18 years old). The average body weight in M0 was 114,1 kg and in M3 it decreased to 92,06 kg, consistent with a reduction in BMI from 41,65 kg/m^2 to 33,59 kg/m^2. Compared to M0, NAFLD scores decreased in the M3/6 evaluation, but still averaged above normal reference levels. Regarding specific liver enzyme levels, there was a significant decrease of gamma-glutamyl transferase (GGT), resulting in values within the normal range. By contrast, the values of aminotransferases and alkaline phosphatase showed no significant changes.

Conclusions: We found significant changes in GGT levels and in the NAFLD scores, reflecting improvements in the liver function of the patients early after BMS. Nevertheless, despite initial weight reduction, some patients may continue to face elevated MAFLD risk, requiring ongoing monitoring and more targeted interventions.

Keywords: Obesity; MAFLD; Hepatic function; NAFLD diagnosis scores

Conflict of Interest: None.

Funding: This research was funded by the Agency for Clinical Research and Biomedical Innovation (AICIB) with the support of the solidarity account "Todos Por Quem Cuida (TPQC)", within the scope of the awarded project IMPPACTO.

POSTER # 15

Antioxidant and Anticancer Activity of Natural Products from *Mentha* species

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Background: Medicinal plants have been used for centuries for their pharmacological properties, being the most ancient and widely used form of medication. This study investigated the antioxidant and anticancer potential of *Mentha pulegium* L., *Mentha piperita* L., and *Mentha aquatica* L.

Methodology: The plant extracts were obtained by subcritical water extraction at different pressures and temperatures. The antioxidant activity was tested against the radicals DPPH$^{\bullet}$, ABTS$^{\bullet+}$, $^{\bullet}$NO, and $^{\bullet}$OH. The total phenolic content was evaluated by the Folin-Ciocalteu method, and compounds were identified through HPLC-DAD. The anticancer potential was assessed by the MTT assay. The cell lines RKO (colon adenocarcinoma), SH-SY5Y (neuroblastoma), B16-F10 (melanoma), and 3T3-L1 (fibroblasts) were exposed to the plant extracts at concentrations of 100 µg/mL to 6.25 µg/mL. Viability was evaluated at 24 and 48 hours.

Results: Extracts obtained at 60 bar and 150°C demonstrated antioxidant activity and high phenolic content, with *M. aquatica* showing the best results, followed by *M. piperita* and *M. pulegium*. However, none of the extracts decreased cell viability to be considered with a potential anticancer activity. Notably, *M. pulegium* and *M. aquatica* extracts (150°C, 60 bar) promoted the proliferation of 3T3-L1 fibroblasts.

Conclusions: Even thought the extracts did not present potential anticancer activity at the tested concentrations, the proliferation of the fibroblast may be promising for properties such as tissue regeneration. The significant antioxidant activity registered, most likely associated with the compounds identified thought HPLC-DAD, is also promising and warrants further investigation.

Keywords: Mentha, subcritical water extraction, phenolic content, antioxidant potential, anticancer

Conflict of Interest: None Disclosed

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Impact of gut microbiome on functional recovery in stroke patients

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Background: Stroke is the second leading cause of death worldwide, resulting in significant neurological impairment and long-term disability, thereby imposing substantial health and economic burden (1). Emerging evidence suggests that the gut microbiome plays a crucial role in the response to stroke (2). To explore the potential link between the gut microbiome and post-stroke recovery, we conducted a longitudinal study involving 32 stroke patients assessed at two time points: stroke admission (T0) and three months later (T1).

Methodology: Clinical data, as well as faecal and blood samples, were collected. Stroke clinical measurements were evaluated using the National Institute of Health Stroke Scale (NIHSS) for stroke severity and the modified Rankin Scale (mRS) for disability. Faecal microbiome profiling was conducted using 16S rRNA gene amplicon sequencing, while nuclear magnetic resonance (NMR) was used for metabolomic profiling of plasma samples.

Results: As expected, the gut microbiome variation was strongly influenced by inter-individual differences (49%), whereas mRS (1.34%) and antibiotic history (0.87%) contributed to a smaller proportion. Interestingly, stroke patients with higher disability (increased mRS) displayed augmented *Blautia* proportions and decreased plasma metabolites, such as isoleucine and valine. The follow-up of stroke patients between T0 and T1 showed a higher prevalence of *Prevotella* and a lower prevalence of *Ruminococcus* enterotypes. Additionally, patients exhibited a higher prevalence of the dysbiotic, pro-inflammatory *Bacteroides* 2 community type during stroke events than a healthy Western cohort. No association was found between NIHSS scores at T0 and mRS scores at T1, indicating that the severity of neurological deficits did not predict functional independence.

Conclusions: Despite the small sample size and inability to assess causality, our study showed a potential link between gut dysbiosis and stroke, offering insights as potential biomarkers for improving stroke management.

Keywords: microbiome, microbiota, stroke, functional outcome, mRS

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

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POSTER # 17

Examining how Enzyme Replacement Therapy affects the invariant Natural Killer T cells in individuals with Acid Sphingomyelinase Disease

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Background: Acid sphingomyelinase deficiency (ASMD) is a rare lysosomal disease caused by SMPD1 gene mutations, leading to sphingomyelin accumulation. Sphingomyelin restrains the activation of invariant Natural Killer T cells (iNKT), crucial for immune regulation. Consequently, upon this accumulation in ASMD mice and patients, there is a decrease in iNKT cell frequency [1], which in mice can be prevented by Enzyme Replacement Therapy (ERT). ERT is currently available for the visceral form of ASMD.

Methodology: This study recruited two male Portuguese ASMD patients undergoing ERT with an escalating dosage that reached the full dose in week 14. A male patient with 67 years, asplenic, with diffuse interstitial lung disease with an important lung compromise and a male patient with 52 years with splenomegaly, lung disease and low platelet count. Clinical and immunological analyses was done before-ERT and during ERT.

Results: Both patients reached the full ERT dose at 3 months of treatment. One of the patients interrupted ERT after reaching the full dose, the 52 years old patient continued ERT and was analyzed 3 months after the maximum ERT dosage. At that time we were able to observe normalization in platelet counts and improvement in biomarkers, namely Lyso SM-509. The immunological analyses show no significant change in iNKT cells frequency or phenotype, in both patients.

Conclusions: Our current results indicate that no effects on iNKT cells are seen until maximum ERT dosage is reached, hinting at a possibly still inadequate time of enzyme to allow changes in iNKT cells, or that disease progression is already too advanced for reversal of iNKT cell defect with ERT. Importantly the patient maintained under ERT show improvement of the metabolic parameters.

While the presented results span only for 6 months post-ERT initiation, we plan to extend this research for over a year, while emphasizing the need for a larger recruitment of patients to enrich our analysis further.

Keywords: Acid sphingomyelinase deficiency, Lysosomal disease, Invariant Natural Killer T cells, Enzyme Replacement Therapy

Conflict of Interest: None Disclosed

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Exploring Cork's Antioxidant Effects: Insights into Inflammation

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Background: To evaluate the therapeutic potential of cork-based formulations by evaluating the effects of different concentrations and combinations of cork extracts on the anti-aging properties and overall efficacy of the products. This goal involves exploring diverse formulation techniques and ratios to identify the most effective composition for maximum benefits against inflammation.

Methodology: Two colorimetric methods were used in this study to measure the antioxidant capacity, ABTS and DPPH. Both of an anti-radical character.

Results: Antioxidant Capacity by DPPH Method in Microplates: The DPPH free radical capture assay showed that the cork sample has a remarkable ability to neutralize DPPH radicals, indicating a strong antioxidant activity. This result suggests that cork contains molecules capable of donating electrons or hydrogen to mitigate the action of free radicals. Antioxidant Activity by the ABTS Method in Microplates: The ABTS assay corroborated the results obtained with DPPH, showing that cork is effective in neutralizing the ABTS radical. This test reinforces the antioxidant versatility of cork, being able to act in different redox environments.

Conclusions: The high antioxidant content positions cork as a material of great interest for applications in fields such as cosmetics, nutrition, and medicine, where antioxidant activity plays a crucial role in the protection and preservation of cellular health. These findings not only highlight cork's richness in bioactive compounds but also open new avenues for its use in products aimed at preventing oxidative damage."

Keywords: Cork. Antioxidant. Inflammation. Bioactive. Antiaging.

Conflict of Interest: None Disclosed

Funding: No funding to report

POSTER # 19

Type 2 Diabetes Activates Apoptotic Signaling in Prostate Epithelium Through Oxidative Stress Mechanisms

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Background: Prostate epithelium is highly sensitive to oxidative stress. As previously described in several studies in literature, type 2 diabetes leads to a systemic inflammation that can compromise the normal function of the mentioned epithelium. Clinical and epidemiological studies also showed that the masculine population with type 2 diabetes tends to have prostate hyperplasia, but the causes for this phenomenon are still not clear. Thus, the aim of the study is to understand the impact of the diabetic environment on the prostate healthy epithelium.

Methodology: This study used a normal prostate epithelium cell line - HPEpiC. This cellular model was exposed to an in vitro simulated diabetic environment using plasma from type 2 diabetes patients. Then, a series of functional assays were then conducted on the cells post plasma addition, such as viability and death phenotype, proliferation, oxidative stress assessment, and mitochondrial function.

Results: The viability and proliferation of the cell model were reduced by more than 50% in the diabetic environment. The cell death assessment demonstrated that the population of death cells is in apoptotic phenotype. The results of oxidative stress methods demonstrated that these cells are subjected to higher stress in diabetes, also observed in the decreased mitochondrial respiratory rate.

Conclusions: These results reveal that type 2 diabetes leads prostate epithelium to become apoptosis, mainly caused by oxidative stress and mitochondrial dysfunction, which prevents the cells from having their normal activity. Thus, these results might point out that the prostate of people with diabetes becomes hyperplasic due to a reduction of normal epithelium, which allows the entrance of liquid into the internal/interstitial tissues of the prostate and leads it to grow and become more exposed to the inflammatory environment of diabetes. Also, this is the first time that this phenomenon was assessed with such biochemical characterizations, opening this study to move on and potentially achieve new insights, for example, on biomarkers to assess prostate health state in men's diabetic population.

Keywords: Apoptosis; Mitochondria; Oxidative stress; Prostate epithelium; Type 2 diabetes.

Conflict of Interest: None Disclosed

Funding: The principal investigator is funded by FCT through the grant 2022.12441.BD.

Type 2 Diabetes and Metabolic Syndrome Impacts the Oxidative Stress of Prostate Cancer Models

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Background: Prostate cancer has a diversity of risk factors, but several studies point out that type 2 diabetes and metabolic syndrome are the most concerning of them. Nevertheless, the way that each metabolic dysregulation affects prostate cancer is currently understandable to be different, mainly because they seem to have opposite effects, with metabolic syndrome enhancing tumoral features. Thus, the study aims to understand the impact of each metabolic disease on the oxidative stress levels of different prostate tumoral and non-tumoral cell lines.

Methodology: This study used a normal prostate epithelium cell line – HPEpiC, and two different prostate cancer cell lines – PC3 and LNCaP. These cellular models were exposed to an *in vitro* simulated diabetic and/or metabolic syndrome environment using plasma from patients. Then, two methods of oxidative stress assessment were used: glutathione ratio, and lipid peroxidation.

Results: In general, the results pointed to higher oxidative stress rates in metabolic syndrome-related conditions, while type 2 diabetes tended to reduce their values.

Conclusions: These results demonstrated that, even though the paradox between type 2 diabetes and prostate cancer happening, and the cells are dying, it is not caused by the effect of oxidative stress, which is according to previous results that showed that these cells are dying by necrosis (it was expected that oxidative stress leads to apoptosis and not necrosis). However, as expected, metabolic syndrome enhanced the oxidative stress, which potentiates the accumulation of mutations, and potentially the aggressiveness of the tumor. Thus, the prevention of such metabolic dysfunctions could ameliorate the prostate cancer treatment outcome.

Keywords: Metabolic syndrome; Oxidative stress; Paradox; Prostate cancer; Type 2 diabetes.

Conflict of Interest: None Disclosed

Funding: The principal investigator is funded by FCT through the grant 2022.12441.BD.

Synergistic effects of tauroursodeoxycholic acid (TUDCA) and 3-Bromopyruvate (3-BP) on pancreatic cancer cells in an adipose environment

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Background: Pancreatic cancer has increased over the past 25 years, becoming the sixth leading cause of cancer deaths worldwide. With obesity as a major risk factor, it remains a significant global health concern, highlighting the urgent need for effective new treatments. Tauroursodeoxycholic acid (TUDCA) shows potential in protecting pancreatic function by reducing endoplasmic reticulum stress, while 3-bromopyruvate (3-BP) is a promising antitumor agent. This study aims to evaluate the synergistic effects of TUDCA and 3-BP on pancreatic tumor cells in an obesity-mimicking adipose environment.

Methodology: The secretome of mature adipocytes derived from 3T3-L1 cells was used to mimic the adipose environment. The effects of 0.5µM TUDCA, 15µM 3-BP, and their combination were evaluated on pancreatic tumoral (Panc-1) and non-tumor (hTERT-HPNE) cells in an adipose environment, over 48 hours. Cell viability and migratory capacity were evaluated using the MTT and the injury assay, respectively. Statistical analysis was performed using GraphPad Prism 8.0.1.

Results: The adipose environment significantly increases the viability of non-tumor pancreatic cells ($\rho<0.0001$) after 48 hours, without notably affecting the viability of tumor cells. Additionally, adiposity increases cell migration in both cell lines ($\rho<0.0001$). In obese context, the combined treatment of TUDCA and 3-BP significantly reduces tumor cell viability ($\rho<0.01$) and migration ($\rho<0.01$), with no significant impact on nontumor cells.

Conclusions: These results demonstrate that combining TUDCA and 3-BP effectively reduces pancreatic tumor cell viability and migration in an adipose environment, highlighting its potential as a targeted therapy for pancreatic cancer, especially in the context of obesity.

Keywords: Pancreatic cancer; Obesity; Tauroursodeoxycholic acid; 3-Bromopyruvate; Synergistic antitumor strategies.

Conflict of Interest: None Disclosed Funding: The principal investigator is funded by FCT through the grant 2021.06521.BD.

MET-CONF 24

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