1ª edição - Jornadas do Programa Doutoral em Metabolismo – Clínica e Experimentação

4 de novembro de 2022

BOCK OF ABSTRACTS

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Índice

1. Introdução ao tema das jornadas

A Comissão Científica da 1ª Edição das Jornadas do Programa Doutoral em Metabolismo – Clínica e Experimentação (PDMCE) apresenta neste documento os vários resumos das sessões protagonizadas pelos oradores convidados, assim como os resumos selecionados para comunicação oral ou apresentação em formato poster.

As Jornadas do PDMCE vêm suceder o Simpósio de Metabolismo que tem vindo a ser organizado pelo Departamento de Biomedicina da Faculdade de Medicina da Universidade do Porto (FMUP). Um evento que tem sido um sucesso ao longo dos anos.

As Jornadas do PDMCE focam o seu programa na área da **obesidade** e **diabetes** e pretende chegar a vários profissionais de saúde, entre os quais, médicos, enfermeiros, nutricionistas, entre outros, assim como investigadores das referidas áreas. O evento decorrerá essencialmente de forma presencial no **Auditório do Centro de Investigação Médico da FMUP** no dia **04 de novembro de 2022**, uma vez que a componente física é fundamental para uma aprendizagem prática e fraterna de troca de experiências.

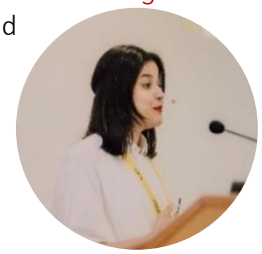
Para mais informação: https://jornadaspdmce.med.up.pt/

2. Resumo dos Oradores Convidados

2.1. Into Diabesity

Diabesity in numbers – where are we and where to go? - Helena Trigueiro[1]

[1] Ulster University, Northern Ireland



Obesity and diabetes are two very prevalent diseases currently affecting around 650 million and 537 million adults, respectively. What can be done about this? Helena Trigueiro promises to unveil the current public policies on the table and how we, clinicians and/or researchers, can play an active role in the fight against these diseases.

New biomarkers for diagnosis of diabesity - João Sérgio Neves[1]

[1] Department of Endocrinology, Diabetes and Metabolism | Centro Hospitalar Universitário de São João | Faculty of Medicine of University of Porto

Obesity and diabetes are two diseases with a marked burden in western societies and with a very rapid growth worldwide. Despite their classic definition as different entities, diabetes (particularly type 2 diabetes) and obesity are deeply interconnected. Approaches to diagnosis, monitoring and treatment that recognize the interlink between obesity and diabetes have greater probabilities to be successful in addressing these complex conditions. In that context, the field of research on obesity and diabetes and the clinical approach to both diseases is moving towards considering them as a continuum. New biomarkers to diagnosis diabesity are a growing field of research. We can classify these biomarkers as markers of fat tissue dysfunction, markers of glycemic and metabolic dysfunction and markers of risk of pathophysiological severity and progression of diabesity. In this session, an overview of new biomarkers for diabesity diagnosis will be presented, with a focus on the most promising markers.

Mitochondria – The missing link in diabesity - Edoardo Bertero[1]

[1]Department of Internal Medicine, University of Genova, Genova, Italy – Cardiovascular Disease Unit, IRCCS Ospedale Policlinico San Martino – Italian IRCCS Cardiology Network, Genova, Italy

Doctor Edoardo Bertero will provide an overview of the function of mitochondria in energy metabolism in diabetes with an emphasis on metabolic anomalies, mitochondrial malfunction, and storage illnesses related to diabesity.

2.2. Diabesity-related diseases

Type 3 Diabetes - Paula Moreira

Cristina Carvalho[1,2,3], Sónia C. Correia[1,2,3], Susana Cardoso[1,2,3], **Paula I. Moreira**[1,2,4]

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Alzheimer's disease (AD) is the most common form of dementia worldwide. AD is considered a "silent killer" since the disruption of brain integrity and function and consequent neuronal demise precede the clinical manifestations of the disease by decades. AD can be divided into different types based on age of onset and genetic predisposition. Sporadic AD accounts for over 95% of cases and begins after the age of 65 years and familial AD is rare and usually manifests in younger individuals. Despite the limited knowledge regarding the initial trigger(s) of sporadic AD, the progress in basic and clinical research during the last decades suggests that faulty brain insulin action and energy metabolism contribute to the onset and progression of the disease. Since these alterations are similar to those occurring in type 2 diabetes (T2D), the term "type 3 diabetes" has been proposed for AD. In fact, strong evidence demonstrates that T2D is a major risk factor for sporadic AD. Studies from our laboratory demonstrate that animal models of AD and T2D share several brain anomalies and the induction of brain insulin resistance causes AD-like pathological features in rats. More, the antidiabetic drug liraglutide ameliorated oxidative/nitrosative stress, inflammation and amyloid pathology in a mouse model of AD.

MAFLD – Naomi Lange[1]

[1]Inselspital – Universitätsspital Bern, Switzerland

Metabolic-dysfunction-associated fatty liver disease (MAFLD), defined as presence of steatosis in ≥5% of hepatocytes with underlying metabolic conditions, is the most common liver disease worldwide with around 25% of the adult European population affected. In individuals with diabetes type 2 (T2DM) prevalence is as high as 70%. T2DM and obesity are main risk factors associated with more severe forms of MAFLD, such as steatohepatitis (prevalence in T2DM: 30-40%), and significant fibrosis/cirrhosis (prevalence in T2DM: 12-20%). Other risk factors include genetic variants (e.g. PNPLA3 rs738409), lifestyle factors (e.g. alcohol consumption) and demographic parameters (e.g. age).

Many risk factors for MAFLD exhibit strong sex differences. NAFLD overall prevalence is higher in men, but risk for advanced fibrosis increases sharply after onset of menopause in women. This is due to postmenopausal metabolic dysfunction (e.g. increase in visceral obesity), as well as loss of direct antifibrotic effects of estrogen.

Non-invasive diagnosis of MAFLD is based on steatosis in ultrasound or controlled-attenuation parameter and fibrosis staging (e.g. blood-based FIB-4 score). Lifestyle measures are the first-line treatment. Weight loss of 5-10% of bodyweight in obese (3-5% in lean) individuals improves steatosis

and inflammation, and possibly fibrosis. Currently, no pharmacological treatment is approved for the treatment of MAFLD in Europe or the USA. GLP-1 agonists show promising results regarding steatohepatitis resolution but not fibrosis regression.

Depression and anxiety – **Margarida Figueiredo Braga**[1]

[1]Centro Hospitalar Universitário de São João; Faculty of Medicine, University of Porto; i3S – Institute of Research and Innovation in Health

Doctor Margarida Figueiredo Braga is conducting her research in pathophysiologic and psychological mechanisms of depressive disorders namely the cross talk between endocrine, neurotransmitter and immune dysfunction. This presentation about anxiety and depression associated with diabesity, provides a discussion of how obesity and diabetes are related to mental health.

2.3. New therapies – issues and questions

Fecal transplant and probiotics – **Diogo Pestana**[1]

[1]Nova Medical School | Faculdade de Ciências Médicas, Universidade NOVA de Lisboa

There is a strong relationship between environmental factors and the development of disease. Doctor Diogo Pestana is committed to the development of new microbiome-based therapies for disorders associated with diabesity in which dysbiosis may be involved. He will bring us a discussion about the benefits and disadvantages of a fecal transplant and the use of probiotics.

Diabetic foot treatment by hyperbaric approach – **Daniela Martins-Mendes**[1]

[1]Hospital Fernando Pessoa, Portugal; i3S – Institute of Research and Innovation in Health, University of Porto

Diabetic foot is one of the most common diabetes complications and is associated with significant morbidity and mortality. The potential benefits of hyperbaric oxygen therapy (HBO) in diabetic patients with a foot ulcer will be discussed by Doctor Daniela Martins-Mendes.

Industry in Diabesity: latest trends – **Jorge Caria**[1]

1 Diretor Médico, Novo Nordisk Portugal

In the vast majority of cases of Obesity and Type 2 Diabetes, a chronic pattern of behavior is observed in which the person with obesity ingests much more calories than those consumed. Thus, the focus of the clinical development of new drugs has focused on achieving a potent appetite suppression, by modulating the neurohormonal signaling pathways that regulate it. Two large

phase 3 clinical trials already published in the New England Journal of Medicine, with drugs analogous to these hormones, showed a reduction in body weight of 15 to 21%, after one year of treatment at the maximum dose, in people with obesity and without type 2 diabetes. Many other molecules are in clinical development, and it is expected that by the end of this decade, average body weight loss of between 25% and 30% will be achieved. It is therefore important to discuss how Health Systems should adapt to take full advantage of these new technologies in the fight against the biggest pandemic of the 21st century. What is the physician's role in the treatment of obesity? When (not) to start pharmacological treatment? For how long? What is the future role of nutritionists in nutritional re-education? What is the role of digital health in the fight against Obesity?

3. Resumos selecionados para Comunicação Oral

3.1. CO01 – Inês Vasconcelos

Urocortin-2 and its effects in an animal model of metabolic syndrome

Inês Vasconcelos[1]*, Rui Adão[1], Glória Conceição[1], Daniela Miranda-Silva[1], Pedro Vaz-Salvador[1], Joana Santos-Gomes[1], Beatriz Rego[1], Inês Falcão-Pires[1], Adelino F. Leite-Moreira[1], Carmen Brás-Silva[1,2]

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Background: Hypertension, diabetes mellitus and obesity, commonly referred to as metabolic syndrome, frequently coexist and are associated with greater risk of cardiovascular diseases. Urocortin 2 (Ucn2) is a cardioprotective peptide belonging to the corticotrophin releasing hormone (CRH) family that has been found to be anorexigenic and display beneficial effects in glucose homeostasis. This study aimed to evaluate Ucn2's effect in glucose homeostasis in an animal model of metabolic syndrome.

Methodology: 18-week-old male ZSF1-Lean (n=26) and ZSF1-Obese (n=28) rats randomly received either UCN2 (15 µg/kg/day, subcutaneously) or vehicle (0.9% NaCl), for 12 weeks. During the treatment period, oral glucose tolerance and insulin resistance were performed. Following the treatment period, the animals were euthanized and samples were collected for histological analysis.

Results: ZSF1-Obese animals showed both poorer insulin resistance and glucose tolerance while also displaying strikingly increased fasting blood glucose. UCN2 therapy significantly attenuated animals' fasting blood glucose, however, no improvement was found in insulin sensitivity or glucose tolerance. Morphometric analysis revealed markedly increased liver weight in Obese animals that was found to be decreased in animals that were subjected to treatment. In histological analysis, fatty infiltration of the liver was found to be notably elevated in ZSF1-Obese rats and was greatly reduced with UCN2 treatment, although not reaching statistical significance.

Conclusions: UCN2 treatment displayed a beneficial effect in Obese animals' hepatic steatosis and, although it showed a beneficial effect on animals' fasting blood glucose, it did not reverse insulin resistance and glucose intolerance. The concentration of UCN2 administered might have been insufficient to reveal marked metabolic effects and requires further investigation.

Key words: Urocortin; ZSF1; Obesity; Metabolic syndrome

3.2. CO02 – Ana Luísa de Sousa Coelho

Reversal of diabesity after bariatric surgery

Paulo Cardoso[1,2]; Mercedes Sanchez[2]; João Maia-Teixeira[2]; Ana Luísa De Sousa-Coelho[3,4,5]*

Faculdade de Medicina e Ciências Biomédicas, Universidade do Algarve, Faro [1]; Centro Hospitalar Universitário do Algarve (CHUA), Faro [2]; Escola Superior de Saúde, Universidade do Algarve, Faro [3]; Algarve Biomedical Center Research Institute (ABC-RI), Faro [4]; Algarve Biomedical Center (ABC), Faro [5]; *alcoelho@ualg.pt

Background: Obesity is associated with increased risk of type 2 diabetes (T2D), and when both diseases coexist, the term diabesity is used. Bariatric surgery (BS) is indicated to reverse obesity and

may foster the remission of T2D. The main goal of this study was to evaluate the reversal rate of diabesity in obese diabetic patients submitted to BS.

Methodology: A retrospective cohort study included patients submitted to BS in one single center, with either a previous diagnosis of diabetes, antidiabetic medication in use, and/or glycated hemoglobin (HbA1c) above 6.5 % before surgery (m0). The reversal of obesity was considered when patients achieved a body mass index (BMI) ≤ 30 Kg/m2. Full remission of T2D was considered when patients showed a level of HbA1c < 6.5 % without the use of any kind antidiabetic drugs, at one year after BS.

Results: Out of a sample of 387 patients who performed BS during a 7 years period, a total of 78 patients was included (83.3% female; mean age=51.5 years old). One month after surgery (m1), mean % of excess body weight loss (EBWL) was 26.1+±1.3 %. Indeed, only 3.8% of the patients achieved obesity remission at the first month (m1). Twelve months after BS (m12), mean % EBWL was 77.6±18.1% (sample=65 patients). Consequently, the reversal of obesity was observed in 52.6% of the patients at m12. Full remission of T2D was achieved in 52.6% at m12 (n=54). When splitting those accomplishing full remission of T2D (DR, n=40) at m12 from those who did not (NDR, n=13), we found the DR group showed 79.3±18.8% EBWL vs. 70.9+-16.8% EBWL in NDR group. Conversely, from those achieving reversal of obesity (ObR, n=41) at m12, 68.3% also achieved remission of T2D, while only 50% did in those who did not fully reversed obesity (NObR, n=24).

Conclusions: Full reversal of diabesity was achieved in some, but not in all patients after BS. The remission of both obesity and T2D might depend on different factors such as age, T2D duration and basal BMI.

Key words: bariatric surgery; obesity; type 2 diabetes; diabesity; remission

3.3. CO03 – Bárbara Mota

High Caloric diets in the middle-age: the effects on cognition, anxiety, astrogliosis, and GABAergic system

Bárbara Mota[1, 2, 3*]; Carla Bettencourt[1]; Sandra Marques[1,5,6]; Pedro Pereira[1, 2, 4]; Daniela Silva[1,2]; M. Dulce Madeira[1, 2, 4]; Nuno Mateus[3]; Armando Cardoso[1, 2, 4**]

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Background: High caloric diets are becoming predominant and it is known that affect the brain and seem to be even more deleterious in the middle-age, with metabolic consequences and a decline in cognition. However, more studies are necessary to understand the effects of these dietson the brain. This work aims to better understand the alterations induced by two different high caloric diets, high fat (HF) and high fat-high sugar (HFHS) in the hippocampus, a region importantfor cognition, and to comprehend the possible mechanisms that may underlie the alterations induced by these diets, focusing on astrogliosis and GABAergic system.

Methodology: 18-month-old male Wistar rats were randomly divided into 3 groups: Control, HF, and HFHS. After 12 weeks of diet, they were submitted to the behavioral tests: Morris water maze; open-field, elevated plus-maze, and novel object recognition. After that animals were euthanized and processed for immunohistochemistry for neuropeptide Y (NPY) and glial fibrillary acidic protein (GFAP).
Results: HFHS animals have impaired spatial learning and working memory and increased anxiety-like behavior, associated with decreased levels and density of small GFAP-IR neurons onCA1-CA3 and hilus regions of the hippocampus, and a decrease in the density of NPY-IR neuronsin hilus. HF animals also show impaired working memory but with a decreased anxiety-like behavior, associated with increased levels and density of small GFAP-IR neurons on CA1-CA3 and hilus regions.
Conclusions: The consumption of HF or HFHS diets in old rats increased the astrogliosis in the hippocampus which may justify, at least partially, the impairment of spatial learning and working memory. Beyond that, the HFHS diet also impacted the GABAergic system by decreasing the density of NPY-IR neurons on dentate hilus, which may justify the higher impact on the behavior of HFHS compared with the HF diet.

Keywords: middle-age; high-caloric diets; hippocampus; learning and memory; astrogliosis

3.4. CO04 – Inês Castela

Adiponectin/leptin ratio is related with adipose tissue dysfunction and insulin resistance in adults with obesity

Inês Castela[1,2,3*], Juliana Morais[3,4], Inês Barreiros-Mota[1,2], Marta P. Silvestre[1,3], Cláudia Marques[1,3], Catarina Rodrigues[1,2], Shámila Ismael[1,2,3], João R. Araújo[1,3], Miguel Ângelo-Dias[1,2], Catarina Martins[1,2], Luís Miguel Borrego[1,2,5], Rosário Monteiro[3,6,7], Sílvia Ribeiro Coutinho[8,9], Conceição Calhau[1,3], Cátia Martins[8,10,11], Ana Faria[1,2,3], Diogo Pestana[1,3], Diana Teixeira[1,2,3]

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Background: Adipose tissue dysfunction may lead to alterations in adipokine secretion profile, namely adiponectin and leptin, supporting an environment conducive to insulin resistance. Despite its association with insulin signalling is well-accepted, the relative contribution of adipose tissue dysfunction in explaining peripheral insulin resistance remains controversial. This study aimed to

investigate the feasibility of the adiponectin/leptin ratio (AdipoQ/Lep) as an adipose tissue biomarker in adults with obesity, without diabetes.

Methodology: Data were collected from a clinical trial conducted in adults with obesity [mean body mass index: 35.4 ± 3.7 kg/m^2] (NCT02169778). Plasma adipokines were measured through multiplex bead-based flow cytometric immunoassays. A forward stepwise multiple linear regression model was used to explore the relationship between the AdipoQ/Lep and HOMA-IR.

Results: A lower AdipoQ/Lep was correlated with a higher body mass index, body fat mass, waist-to-height ratio, and plasma resistin. Multiple linear regression analysis revealed that 48.6% of HOMA-IR variance was explained by variations in triacylglycerols, AdipoQ/Lep, and waist-to-hip ratio ($P < 0.001$), being AdipoQ/Lep the strongest independent predictor (Beta = -0.449, $P < 0.001$).

Conclusions: These results suggest that different characteristics associated with adiposity (i.e., total amount, distribution, and function of adipose tissue) may be behind the variance of HOMA-IR in the context of obesity, rather than a single component. Early identification of individuals at higher risk of developing metabolic complications through adipose tissue dysfunction assessment and the staging of obesity and its transient phenotypes can contribute to improve the therapeutic decision-making.

Key words: adiponectin/leptin ratio; adipose tissue function; insulin resistance; metabolic dysfunction; obesity

3.5. CO05 – Mário Fontes

Systemic inflammatory and metabolic profile in exudative age-related macular degeneration

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Background: Age-related macular degeneration (AMD) is a worldwide leading cause of severe, irreversible vision impairment. However, its exact pathophysiology is yet relatively poorly understood. The aim of this study is to evaluate the systemic inflammatory and metabolic profile in exudative AMD.

Methodology: Patients with a recent diagnosis of exudative AMD, ≥ 65 years-old, without other relevant inflammatory, infectious, or neoplastic diseases were recruited. Patients diagnosed with senile cataract, without signs of AMD, and fulfilling the remaining criteria were recruited as controls. Peripheral venous blood was collected for analysis of hemogram, C-reactive protein (C-RP), erythrocyte sedimentation rate (ESR), cholesterol, triglycerides, glucose, hemoglobin A1C (HbA1C), NLR (neutrophil-to-lymphocyte ratio), MHR (Monocyte-to-HDL-cholesterol ratio), PLR (platelet-to-lymphocyte ratio) and SII (systemic immune-inflammation index).

Results: 21 cases and 18 controls were included. While no differences were found in sex distribution between groups, AMD patients were older than the controls (82 vs 74 years-old, p<0.001). A higher platelet count and PLR were found in AMD patients (258.65 vs 213.00 *10^6/L, p=0.030; 147.89 vs 110.68, p=0.013, respectively). No significant differences were observed when comparing RDW, WBC, C-RP, ESR, NLR, MHR and SII between groups. Concerning the metabolic profile, higher levels of total and LDL-cholesterol were identified in AMD patients (190.65 vs 162.12 mg/dL, p=0.024; 107.75 vs 80.59 mg/dL, p=0.013). HDL-cholesterol, triglycerides, glucose and HbA1c levels did not differ between groups.

Conclusions: In this study, we found a significant increase in platelet count, PLR, total and LDL-cholesterol levels in patients with exudative AMD. A systemic metabolic and inflammatory derangement can be, at least partially, responsible for the development of AMD and its progression to the exudative form.
Key words: AMD; Inflammation; Metabolism

4. Resumos selecionados para apresentação de Poster

4.1. P01 – Elisabete Teixeira

Alterations of voltage-gated potassium channel: a new player in the carcinogenesis of familial and sporadic follicular cell-derived thyroid tumors?

Elisabete Teixeira[1,2]; Hugo Prazeres[1]; Paula Soares[1,2*]

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Background: By Next Generation Sequencing, in a family with hereditary non-medullary thyroid carcinoma, our team identified a new potentially pathogenic germline mutation (p.Gly106Arg) in the KCNB2 gene, a voltage-gated potassium channel (vgKCN). This mutation was present in family members affected by the disease, being absent in healthy family members and in control individuals of the general population. Mutations in vgKCN were shown to impact protein function. Since potassium efflux by the cell is a necessary condition for cellular homeostasis, the disruption of a vgKCN can impact the function of other ion channels and result in cancer. Mice studies showed that KCNE2 disruption indirectly impairs sodium-iodide symporter (NIS) function, and therefore iodide uptake by the cell, resulting in hypothyroidism or goiter.

Hypothesis: We hypothesized that by indirect effect on NIS function, vgKCN mutations may increase predisposition to thyroid cancer and maybe explain why some patients do not respond to radioiodine (RAI) therapy.

Methodology: Copy-number variation of 59 genes is being analysed in tumours from 18 patients by NGS. Using Nthy-ori 3-1 cells, CRISPR-RNP techniques are being initiated to obtain KCNB2 knockout cells and KCNB2 p.Gly106Arg mutated cells followed by functional studies to fully understand how the mutation may influence carcinogenesis both in familial and in sporadic thyroid cancer forms. The capability of the altered cells to import radioactive iodine will be analysed as will be the possibility of using KCN modulators to enhance RAI uptake. Lastly, studies in zebrafish will be conducted following the same methodology.

Conclusions: If our hypothesis is verified, it can enable us to identify subsets of patients that do not respond to RAI. This may introduce vgKCNs as good pharmacological targets in thyroid cancer therapy.

Key words: voltage-gated potassium channels; hereditary cancer; germline mutation; sporadic cancer; molecular oncology.

4.2. P02 – Carla Luís

Bilateral breast cancer & body mass index

Carla Luís[1,2,3]*, Rute Fernandes[4], Deolinda Sousa Pereira[4], João Firmino-Machado[5,6,7], Pilar Baylina[2,3,8], Rúben Fernandes[2,9], Raquel Soares[1,2,3]

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Background: Breast cancer (BC) and obesity are two closely associated pathologies with increasing incidence and mortality rates (1,2). Women with unilateral BC have a higher risk of developing bilateral breast cancer (BBC) (3) and BBC incidence varies between 1.4% and 11.8% (3). A retrospective cohort study, from DOC database, observed a significant association between obesity and BBC disclosing that overweight women are more likely to develop BBC while obese women are less likely (*unpublished data*) compared to normal-weight women. To better address the implications of obesity in BBC, we performed a statistical analysis of extracted BBC information from the DOC database.
Methodology: Statistical analysis included binomial analysis for population proportions and Pearson's chi-squared test for BMI analysis. Normal distribution for age was checked applied Kruskal-Wallis test. Cox regression was used for Overall Survival (OS). Statistical significance was set at p-value<0.05. In age at diagnosis was considered the first diagnosis. Metachronous BBC was consider with one year interval. Most advanced stage and differentiation grade were considered for analysis.
Results: From a total of 2279 cases with BC included in the DOC database, 42 cases presented BBC (1.8%). In the first assessment with a binomial test, we observed significant increase in cases of synchronous BBC (p-value<0.001), and increased women with BBC with the same histological type (p-value=0.044) and the same molecular subtype (p<0.001), alias, molecular subtype was the same for all included patients.
BMI statistical analysis revealed that obese women were diagnosed later (p-value=0.230). BBC cases associated with family history were increased (p-value=0.228). All obese women presented grade 3 for differentiation grade (p-value=0.017). Overweight women presented better outcomes for OS.
Conclusions: We observed interesting findings in results stratified by BMI, from which we highlight OS, overweight patients have better OS with lower tumour stages and lower differentiation grades.
Key words: Breast Cancer; Bilateral Breast Cancer; Obesity; BMI

4.3. P03 – Marco G. Alves

Human spermatozoa release insulin in a glucose-dependent manner

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Background: Insulin is an essential regulator of spermatogenesis, acting directly on the differentiation of spermatogonia or indirectly via metabolic modulation of both Sertoli and Leydig cells. In addition, insulin is suggested to play a significant role in human spermatozoa capacitation, though, the mechanisms remain unknown. This study aimed to determine if human spermatozoa produce and

whether they express PC1/3 and PC2, which are enzymes responsible for proinsulin cleavage. Additionally, we further studied the effects of different glucose stimuli in these mechanims.

Methodology: Seminal samples of normozoospermic men (n = 15) were submitted to a density gradient and two fractions were separated according to their motility (high vs low). The mRNA and protein expression of insulin, PC1/3 and PC2 mRNA were determined, and their localization revealed by immunofluorescence. Insulin in spermatozoa extracts was quantified by HPLC. High motility spermatozoa were incubated in a BWW medium with increasing glucose concentrations (0, 5.5, 11, and 22 mM). After 6 h, secreted insulin was quantified by ELISA.
Results: We were able to identify the expression of insulin, PC1/3, and PC2 mRNA, as well as the corresponding proteins. Insulin mRNA and protein expression were found to be increased in highly motile spermatozoa. The release of insulin into the media was found to be glucose concentration-dependent. Human spermatozoa produce relatively modest amounts of insulin (in the pg/mL range), implying an autocrine or paracrine function.
Conclusions: This study showed that human spermatozoa express PC1/3 and PC2, enzymes that cleave proinsulin, and that insulin is released by human spermatozoa in a glucose concentration-dependent manner. The study of insulin signaling opens the path to a better knowledge of the bioenergetics of human spermatozoa and the development of innovative therapeutics.
Keywords: Glucose; Insulin; Sperm Bioenergetics; Spermatozoa

4.4. P04 – Catarina Isabel dos Santos Rodrigues

Is the phenylalanine-restricted diet a risk factor for overweight in patients with phenylketonuria? A Systematic Review and Meta-Analysis

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Background: Although it is commonly stated that a Phe-restricted diet is associated with overweight in patients with PKU, it is unclear if this perception is supported by scientific evidence. This work aimed to determine if patients on a Phe-restricted diet are at a higher risk of overweight compared to healthy individuals.

Methodology: A literature search was carried out on PubMed, Cochrane Library and Embase databases. Inclusion criteria were studies that included: 1) patients with PKU on a Phe-restricted diet, followed up by a PKU centre; 2) non-PKU controls; 3) anthropometric measures or prevalence of overweight. Studies were randomized controlled trials (RCTs), non-RCTs or observational studies. Risk

of bias of individual studies was assessed using the *Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies*, and quality of the evidence using the *NutriGrade*.

Results: From 829 articles identified, 15 were included in the systematic review and 12 in the meta-analysis. BMI was similar between patients with PKU and non-PKU controls (SMD=0.12 [−0.04, 0.28], p=0.14; I^2 =27%, p=0.18). However, a subgroup of patients with classical PKU had a significantly higher BMI than non-PKU controls (SMD=0.24 [0.04, 0.45], p=0.02; I^2=31%, p=0.17). The subgroup of studies assessed as having a high risk of bias found a significantly higher BMI in patients with PKU (SMD=0.20 [0.03, 0.37], p=0.02; I^2=1%, p=0.42). This highlights the fragility of the evidence supporting the idea that a Phe-restricted diet promotes overweight and indicates the need for studies with improved methodology.

Conclusions: There is no evidence to support the concept of Phe-restricted diet as a risk factor for the development of overweight. Given the increasing prevalence of overweight in the general population, patients with PKU need lifelong follow-up, with personalised nutritional counselling, that should aim to prevent overweight.

Key words: Overweight; Phenylalanine; Phenylketonuria

4.5. P05 – Sofia Martinho Dimitri Pinheiro

Influence of diabetes in response to ultrasound-guided pulley release treatment for trigger finger

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Background: Diabetes has an important role in the development of several musculoskeletal disorders, such as stenosing flexor tenosynovitis of the finger (SfTf). The etiopathophysiology of SfTf in diabetic patients is associated with both chronic hyperglycemia, increased amounts of visceral adiposity and chronic inflammation. Recently, multiple image-guided interventional radiology musculoskeletal treatment options have been developed, such as ultrasound-guided percutaneous pulley release for trigger finger. We aim to summarize recent research providing insight into the etiological mechanisms through which diabetes contributes towards collagen disfunction and accumulation, resulting in the development of SfTf , as well as how diabetes influences response to interventional radiology treatment of this disorder.

Methodology: Review of existing literature on etiopathophysiology of SfTf in diabetic patients and how diabetes influences response to ultrasound-guided treatment in SfTf.

Results: Chronic hyperglycemia stimulates the creation of cross-links between collagen molecules, impairing degradation and resulting in the build-up of excessive collagen deposits in the cartilage, ligaments, tendon sheaths and tendons. Increased adipocytes in diabetic patients secrete proteins and cytocines such as TNF-α, IL-6 and IL-13 which result in overproduction of pro-inflammatory factors, destruction of normal tissue architecture and fibrosis. Both hyperglycemia and adipocytes inhibit efferocytosis, limiting natural resolution.

Conclusions: Diabetes can negatively influence outcomes in SfTf patients and may impact the decision of which specific procedure technique should be employed. Further studies are necessary to define how diabetes influences response to ultrasound-guided realease of the A1 pulley in SfTf, as well as the extent to which control of blood sugar levels can contribute towards the personalization and optimization of patient follow up.

Key words: collagen; diabetes; interventional radiology; trigger finger; ultrasound

4.6. P06 – Manuela Meireles

Postprandial glycemia after a high-rich carbohydrate meal: a randomized cross-over clinical trial on olive leaf tea effect

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Background: Infusions of olive leaves have been used in traditional herbal medicine as a way to treat and prevent many diseases, including diabetes. Olive leaves are naturally rich in oleuropein, and previous studies have shown the potential of oleuropein in mitigating diabetes and diabetes complications in vitro and in vivo. This study aimed to investigate the effect of natural olive leaves tea on postprandial glycemia in healthy volunteers, when ingested with a high-carbohydrate meal comparing with a placebo tea. The hypothesis present was that olive leaf tea would improve glycemic control and modulate postprandial glycaemia.

Methodology: Thirteen healthy adults participated in a double-blinded, randomized, placebo-controlled, and cross-over design trial. Participants ingested a test meal composed of 2 slices of wheat bread (110g) and 50g of apricot peach with olive leaf tea (OLT) or two slices of wheat bread (110g) and 50 g of apricot peach with 250 ml of placebo tea (CON) in two different moments, and after a wash-out period. Capillary blood glucose was measured at times 0, 15, 30, 60, 90 and 120 min after ingestion of each test meal.

Results: At baseline, there were no significant differences between capillary plasma glucoses measured before the CON or OLT interventions. Consumption of OLT resulted in a delay in peak time (48,5 $\pm$ 4,2 min vs 35,7 $\pm$ 4,0 min, p=0,03) and a significant increase in glucose area under the curve compared to placebo (14502,7 $\pm$ 640,8 vs 13633,3 $\pm$ 869,4, p= 0.03). No significant differences ($p<0.05$) between conditions at individual time points were denoted.

Conclusions: Olive leaf tea did not ameliorate a glycemic curve induced by carbohydrate rich meal ingestion, however OLT delay on glycemic peak should be further explored. Also, future studies should account for chronic consumption in order to provide a better understanding on glycemic regulation over time.

Key words: Olive leaf tea; postprandial glycemia; diabetes.

Trial registration: ClinicalTrials.gov NCT05397509

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4.7. P07 – Alexandra Aveiro

The influence of adipocytes' secretome and immune response on bacterial growth

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Background: Obesity and antimicrobial resistance are considered a threat to global public health. The state of obesity entails an imbalance in the production of proinflammatory and anti-inflammatory factors that contributes to infections' susceptibility. *Klebsiella pneumonae* is part of the ESKAPE being one of the most virulent and antibiotic resistant bacterial pathogens, with high prevalence in hospital and community-acquired bacterial infections. Bacteria's alarming ability to gain resistance has raised concerning obstacles in antimicrobial therapies in patients with chronic inflammation, such as obese individuals.

This study aimed to understand the influence of an inflammatory obesity-mimicking environment in the growth of *Klebsiella pneumonae* strains with different antibiotic resistance.

Methodology: The secretome of the cell lines Raw 264.7 (macrophages) and 3T3-L1 (adipocytes) were collected to serve as conditioned media for bacterial growth. Antibiotic-resistant *Klebsiella pneumonae* strains (ATCC, carbapenem-resistance (CR), extended-spectrum beta-lactamase (ESBL) and CR/ESBL) were exposed to a variety of conditioned media (DMEM, DMEM with 10% and 50% adipocyte secretome (SA), macrophage secretome (SM), and macrophage secretome previously conditioned with 10% and 50% SA). Bacteria growth curves assessment was performed by absorbance measurement in a kinetic mode for a period of 5 days.

Results: Results showed that for ATCC strain the different mediums didn't provide distinct growth conditions between them. However, when different resistance signatures were considered, the growth profile showed distinct differences. The CR strain showed higher population in the mediums with SM, regardless the percentage of SA, while the ESBL strain presented higher population in the mediums with SA without SM. Interestingly, for 50% SA, having SM in the medium or not showed no difference. For the strain with both resistances (CR/ESBL), results were similar to the CR strain.

Conclusions: Overall, results showed that the resistance to carbapenems is a greater risk factor than resistance to extended spectrum cephalosporins in a SM environment.

Key words: Obesity; Antimicrobial Resistance; Secretome; Macrophages

4.8. P08 – Sofia João dos Santos Nogueira

Early consumption of a high-sugar diet induces metabolic dysfunction and intestinal inflammation via alterationsof TLR signaling

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Background: The intestinal immune system plays a pivotal role in the modulation of glucose homeostasis and, its deregulation has been implicated in the pathogenesis of metabolic disorders. It remains poorly understood the long-lasting metabolic effects of sugar beverages intake in younger age and, less is known, about how diet affects the intestinal inflammatory signaling pathways. Thus, we evaluated the metabolic and intestinal homeostasis disruption and activation of immune responses induced by early consumption of sugar beverages in rat.

Methodology: Male Wistar rats (n=18), at postnatal day 21–23 were submitted to one of two diets for 14 weeks: Control diet (C), fed with standard diet and water ad libitum; high-sugar diet (HS), feed with standard diet and with free access to30% sucrose solution. Metabolic parameters were evaluated in adulthood: body weight, visceral adiposity, and fasting blood glucose. Duodenal tissue samples were processed for histological analysis. Gene expression of nuclear factor-kappa B (NF-Kb), Toll-like receptors (TLR2; TLR4) and inducible nitric oxide (iNOS) were performed in jejunal and colonic samples. Statistical analyses were performed with JASP 0.16.1.0.

Results: HS fed rats had higher levels of glucose levels ($p < 0.01$) and adiposity ($p < 0.05$), but no differences in the total body weight at the end of dietary intervention were observed. Histological changes were observed in duodenal villi from HS-fed rats and showed a tendency to had higher number of goblet cells per villus. In addition, HS induced an increase in the jejunal mRNA expression of TLR2 ($p<.05$), NF-κB ($p<.01$) and a decrease of iNOS ($p<.001$). In the colon, no changes on inflammatory regulators were detected.

Conclusions: HS intake disrupted metabolic function with an upregulation of NF-κB/TLR2 signaling pathway only in small intestine. It supports the idea that dietary factors during critical early-life periods can shape immunity programming and alter metabolic regulation, leading to obesity.

Key words: High-sugar diet; young rat model; metabolic dysfunction; intestinal inflammation.

4.9. P09 – Patrícia Braga

The impact of insulin resistance on metabolic and mitochondrial performance of human kidney cells

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Background: Diabetic nephropathy (DN) and insulin resistance (IR) in kidney cells are considered the main causes of end-stage renal failure. Additionally, Hyperglycemia (HG) and increased Fatty Acids (FA) are observed in patients with type 2 diabetes mellitus, where lipid accumulation has been correlated to IR. No studies demonstrate the contribution of mild to severe HG and IR itself in the onset and progression of DN. Thus, we aimed to explore the effect of mild and severe HG (5, 11, 22 mM of glucose) with or without induced IR in cellular metabolism, and in mitochondrial quality control in a human immortalized kidney cell line (HK-2).

Methodology: HK-2 were cultured in increasing concentrations of glucose, with or without Palmitic Acid (PA) for 24 hours. IR in HK-2 was induced with PA and cellular cytotoxicity was evaluated. The effect of HG and IR in the consumption/production of metabolites was analyzed. Additionally, in vivo mitochondria function was assessed, as well as mitochondrial complex I (CI) and II activities and mitochondrial membrane potential. We also evaluated FA oxidation and lipid accumulation.

Results: PA was able to induce IR and altered the metabolic fingerprint in HK-2 secretome since Glucose, Glutamine, Lactate, Pyruvate, Alanine and Glutamate concentration increased in comparison to the same conditions without PA-induced IR, where gluconeogenic amino acids played a key role to supply energy. It was also observed that FA was not the preferential carbon source for HK-2 cells, resulting in its accumulation. Mitochondrial parameters of HK-2 cells are increased in mild HG condition, but rapidly decrease when cultured in high HG, being this effect more pronounced with IR. Furthermore, in those conditions there was a decrease in CI activity of electron transport chain and an increase in mitochondrial membrane Potential.

Conclusions: Bioenergetic profile of HK-2 is negatively impacted by HG and IR, suggesting that changes in metabolism mediated by progression from mild to severe HG and IR has a key role in DN.

Key words: Diabetic nephropathy; hyperglycemia; Insulin Resistance; Lipid accumulation; Mitochondrial Bioenergetics and Metabolic reprogramming.

4.10. P10 – Sofia Martinho Dimitri Pinheiro

Ultrasound-guided hydrodistension for adhesive capsulitis: the effect of diabetes on treatment outcomes

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Background: The impact of diabetes on the development of adhesive capsulitis (AC), as well as the effect on ultrasound (US)-guided glenohumeral hydrodistension treatment outcomes remains unclear. In this study, we aim to identify predictors of US-guided hydrodistension outcomes, as well as comparing the treatment efficiency in diabetic and non-diabetic patients.
Methodology: A total of 135 patients with AC who underwent US-guided hydrodistension were prospectively included. Demographics and factors linked to chronic inflammation and diabetes were recorded. Patients were followed-up for 6 months. Functionality and pain were evaluated with the Disabilities of the Arm, Shoulder and Hand (DASH) and the Visual Analogue Scale (VAS) score. Statistical analysis was performed with Mann-Whitney U test, linear, and binary logistic regression.
Results: Diabetes was identified in 25/135 patients (18.5%). Diabetic patients had worse DASH and VAS score at presentation ($P < 0.0001$) and presented with a higher grade of AC ($P < 0.0001$) and lower range of motion ($P < 0.01$) compared to non-diabetics. Higher DASH ($P = 0.025$) and VAS scores ($P = 0.039$) at presentation were linked to worse functionality at 6 months. Presence and duration of diabetes, and the number of hydrodistension repeats, correlated with worse VAS and DASH scores at 6 months. The number of procedure repeats was the only independent predictor of complete pain resolution at 6 months (OR 0.418, P = 003).
Conclusions: Diabetes is associates with more severe AC symptoms at presentation and worse US-guided hydrodistension treatment outcomes. In patients with resistant AC, repeating the intervention is independently linked to worse outcomes for at least 6 months post-intervention.
Key words: adhesive capsulitis; collagen; diabetes; interventional radiology; ultrasound.

4.11. P11 – Lídia Cristina Alves da Rocha

The role of nurse macrophages and erythroblastic islands in acute myeloid leukemia

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Background: Acute myeloid leukemia (AML) is a heterogenous blood cancer associated with a poor prognosis. AML patients often present with severe anemia at diagnosis. However, the mechanism for anemia in AML remains unclear. Erythrocytes originate through the process of erythropoiesis, which includes the differentiation of erythroblasts within a niche, called erythroblastic island (EBI). EBI comprises a central macrophage (nurse cell), which is surrounded by developing erythroblasts. The present study aims to explore how erythropoiesis is affected and erythroblasts lost in AML.
Methodology: Experiments were performed using the well-established MLL AF9 AML mouse model, which recapitulates a particular subtype of human AML. Hematopoietic progenitor cells, erythroid populations and nurse cells were evaluated by flow cytometry during the progression of AML. Native EBIs were quantified by imaging flow cytometry. Additionally, nurse cells were characterized in primary human patient samples.
Results: Quantitative analysis showed that erythroblastic subpopulations were significantly reduced in the AML bone marrow. Indeed, more differentiated erythroblasts were lost at very early AML

infiltration levels. In contrast, megakaryocyte-erythrocyte progenitors, were lost only at high infiltration rates. A reduction in the proliferation of erythroblasts that develop within the EBI niche was observed. Consistently, native EBIs and nurse cells were largely lost in AML. The loss of nurse cells was also confirmed in human AML samples.

Conclusions: This study revealed that in AML there is a disruption of an important niche for the development of erythropoiesis – the EBI, which induces a loss of erythroblasts. Future studies are needed to explore the mechanism underlying the loss of EBI function and of nurse cells in AML, which will have important implications in the management of patients with anemia.

Key words: Acute myeloid leukemia; erythropoiesis; erythroblastic island; erythroblasts; nurse cells

4.12. P12 – Cátia Ramos

The impact of aberrant glycosylation in gastric cancer cells aggressiveness and metabolism

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Background: De novo synthesis of aberrant glycans by gastric cancer (GC) cells is associated with patients' poor survival. Our group demonstrated that these glycans could enhance cancer cell aggressiveness in vitro and in vivo by activating key signalling pathways. In addition, we were pioneer in detecting these glycans in GC extracellular vesicles (EVs). In this study we aimed to explore the impact of aberrant glycans in GC cell behaviour. In addition, the impact of EVs carrying these glycans in reprogramming the phenotypic behaviour of recipient cells was also evaluated.

Methodology: We studied the migration capacity (wound-healing assay) and metabolic activity (seahorse) of GC cells displaying different aberrant glycosylation. Furthermore, we isolated EVs from the same models by ultracentrifugation and characterized by transmission electron microscopy (TEM), nanoparticle tracking analysis (NTA) and western blot (WB). The migration capacity of GC cells treated with EVs carrying aberrant glycans was also evaluated.

Results: The presence of aberrant glycans induced alterations in the migration capacity and metabolic activity of GC cells. Furthermore, GC cells displaying tumor-associated glycans secreted larger amounts of EVs and an enrichment of the aberrant glycans were observed in EVs when compared to the parental cells. Interestingly, we observed that EVs carrying aberrant glycans were able to induce increased migration in different GC recipient cell lines, in contrast to control EVs.

Conclusions: We have demonstrated that aberrant glycosylation induces alterations in the biological behaviour and activity of GC cells. Furthermore, those alterations could be transferred to recipient cells by GC EVs. We will further explore the capacity of EVs in reprograming recipient cells' behaviour and metabolism in vitro and using animal models.

Key words: Gastric Cancer; Glycosylation; Extracellular Vesicles; Metabolism; Migration.

4.13. P13 – Anna Carolina Cortez-Ribeiro

Olive oil consumption and maternal-fetal outcomes: a systematic review of the evidence

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Background: Nutrition plays a significant role during pregnancy. The risk of maternal-fetal complications decreases with a balanced eating pattern. For instance, the Mediterranean diet is correlated with improved health status and reduced risk of gestational diabetes, preeclampsia, hypertension, and pre-term birth. Olive oil is an essential component of this dietary pattern. Thus, the aim of this study was to systematically review the evidence between olive oil consumption and the risk of adverse maternal-fetal outcomes.

Methodology: The study was guided by the PICO protocol and the following research question: "How does olive oil consumption/supplementation affect maternal-fetal outcomes compared to non/low-consumption in pregnant women?". We searched the Web of Science, Scopus, PubMed, and Biblioteca Virtual em Saúde electronic databases (October and November 2021). The keywords used were pregnancy, olive oil, and pregnancy outcomes. The review included all the available studies in English and Portuguese. Exclusion criteria were as follows: (i) unrelated to olive oil consumption, (ii) other outcomes, and (iii) animal studies.

Results: Nine articles, six experimental and three observational were included. In maternal outcome studies (n=6), a higher olive oil consumption was associated with a lower prevalence of gestational diabetes mellitus, preeclampsia, and cardiovascular disease. In fetal outcome studies (n=8), olive oil consumption was associated with a lower risk for small- or large-for-gestational-age infants.

Conclusions: Consumption of olive oil confers protective effects on pregnancy outcomes. However, further studies are needed, specifically designed for the impact of olive oil consumption on maternal-fetal outcomes.

Key words: olive oil; maternal-fetal outcomes; pregnancy; review.

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4.14. P14 – Ana Sousa

Tryptophan, kynurenine pathway and kidney function in heart failure patients with and without Diabetes Mellitus

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Background: Tryptophan (TRP) and kynurenine pathway has been related to cardiovascular disease progression and insulin resistance. We assessed downstream TRP metabolites of the kynurenine

pathway and renal function parameters in heart failure (HF) patients. We, also, evaluated potential effect modifications according to their diagnoses of diabetes mellitus (DM).

Methodology: The pilot study enrolled 22 HF patients with ejection fraction ≤ 40%, which were stratified: diabetic (DM) and non-diabetic (NonDM) groups. Patients were recruited from the Centro Hospitalar do Tâmega e Sousa, EPE. Urinary TRP and its metabolites (KYN, kynurenine; KA, kynurenic acid) were measured with a liquid chromatography with ultraviolet and fluorescence detection (our previous published method). Urinary creatinine and serum urea and creatinine levels were measured with a Prestige 24i automated analyzer and, the estimated glomerular filtration rate (mL/min/1.73m²) was calculated. Statistical analyses were conducted using JASP 0.16.1.0.

Results: Higher urinary TRP and metabolites levels (mmol/mol Cr) were measured in HF compared to controls (p<.05). KYN levels tend to be higher in DM than NonDM. DM patients had a higher KYN/TRP ratio (p<.05), while KA/KYN ratio tend to be lower (p=.08) compared to NonDM patients. Serum urea levels (mg/dL) were higher in DM[(mean±SD) 71±24; p<.05] than in NonDM (46±14). DM patients had a lower eGFR [(Min-Max; 50th percentile); 59-80; 73] than NonDM (p<.001). In DM patients, positive correlation was found between KYN/TRP ratio and eGFR (rho=0.75; p<.05) and negative correlation between KYN/TRP ratio and KA/KYN ratio (rho=-0.76; p<.05). In NonDM patients, only a negative correlation was found between KYN/TRP and KA/KYN (rho=-0.77; p<.01).

Conclusions: We found an abnormal kynurenine pathway of tryptophan catabolism in HF patients, which was correlated with mild loss of kidney function, but only in those who had diabetic heart disease.

Key words: Heart failure; Diabetes Mellitus; Tryptophan metabolites; Kynurenine pathway; Kidney function.

4.15. P15 – Filipe Miguel Pinto Morais

Impact of exercise training on cardiac metabolic remodelling in a pulmonary arterial hypertension animal model

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Background: Exercise training (ExT) has been widely recognized for its cardiovascular benefits in several pathophysiological conditions. Still, the molecular mechanisms associated with its utilization as a therapeutic approach for pulmonary arterial hypertension (PAH) remain poorly understood. Thus,

this study aims to increase the comprehension of the cardioprotective effects of ExT in PAH, focusing on the metabolic alterations induced by ExT in the right ventricle (RV).

Methodology: The monocrotaline (MCT)-induced PAH animal model was used and male Wistar rats were submitted to two weeks of treadmill exercise training (5 days/week, 60 min/day, 25m/min), two weeks after disease establishment. Subsequently, hemodynamic evaluation was performed and at the end of the experiments, the animals were euthanized by exsanguination and the RV, left ventricle, lungs, right tibia and gastrocnemius were collected, weighted/measured, and stored for biochemical analysis.

Results: ExT rats showed an improved RV diastolic function despite the presence of cardiac overload. At a molecular level, an increase in glucose uptake to cardiomyocytes through glucose transporter type 4 (GLUT4) and an increase in lactate dehydrogenase (LDH) activity were observed. Exercise did not reverse the decrease of fatty acid oxidation verified in MCT-induced PAH but increased the levels of the transcription factors PGC-1α and PPAR-γ. Two weeks of exercise did not modulate the changes in amino acids metabolism associated with PAH.

Conclusions: Our study shows that two weeks of continuous aerobic exercise of moderate intensity, performed in a late stage of the disease, counteracts RV cardiac dysfunction and modulates the metabolic remodelling secondary to MCT-induced PAH.

Key words: pulmonary arterial hypertension; glucose metabolism; right ventricle; treadmill exercise.

4.16. P16 – Isabella Coraini Bracchi

Essential trace elements status in Portuguese pregnant women and their association with neonatal outcomes: a prospective study from the IoMum cohort

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Background: Inadequate levels of essential trace elements (ETEs) have been associated with poor neonatal outcomes. The aim of the present study was to characterize urinary levels of ETEs in Portuguese pregnant women and their association with neonatal anthropometry.

Methodology: This prospective study was conducted at Porto and Lisbon regions, from April 2018 to December 2021. Pregnant women were invited to participate at the routine 1st trimester ultrasound scan when they provided a random spot urine sample and sociodemographic data. Clinical data were

provided by clinical records. Exclusion criteria were: twin pregnancy, gestational age at recruitment < 10 or ≥ 14 weeks, non-delivery of urine samples and not signing the informed consent. Cobalt (Co), Copper (Cu), Manganese (Mn), Molybdenum (Mo) and Zinc (Zn) urinary levels were measured by inductively coupled plasma-mass spectrometry.

Results: The study sample included 614 pregnant women. The mean ± SD age at recruitment was 33 ± 5 years and the median (P25-P75) gestational age at recruitment was 12 (12-12) weeks. The overall median (P25-P75) ETEs urinary concentrations were, in µg/L: Co, 0.31 (0.12-0.53); Cu, 11.20 (6.89-18.21); Mn, 1.70 (0.74-3.09); Mo, 38.54 (21.57-62.35); and Zn, 255.67 (145.86-455.75). Mn urinary levels above the 50th percentile (> 1.70 µg/L) were associated with increased risk of small for gestational age (SGA) birth weight (crude OR [95%CI] = 2.811 [1.155-6.841]; p = 0.023). Additionally, lower maternal Zn urinary levels were associated with an increased risk of SGA birth head circumference (crude OR [95%CI] = 2.525 [1.015-6.232]; p = 0.046).

Conclusions: Given the association between birth weight small for gestational age and long-term dysmetabolism outcomes, our results suggest that Mn excessive exposure during pregnancy could associate with fetal programming of dysmetabolism.

Key words: Essential trace elements; pregnancy; neonatal outcomes.

4.17. P17 – Sofia Reis Brandão

Cardiac metabolic adaptation after doxorubicin and mitoxantrone on adult mice

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Background: The number of cancer survivors has increased considerably in the last decades and, therefore, the comorbidities that develop after therapy have been gaining more attention. Doxorubicin (DOX) and mitoxantrone (MTX) are chemotherapeutic agents widely used in cancer. Both drugs present similar clinical cardiac toxic effects; however, the molecular mechanisms underlying their cardiotoxicity are not completed elucidated. Thus, our work aimed to study the molecular effects of DOX and MTX on the heart of adult mice focusing mainly on metabolic adaption.

Methodology: Male CD-1 mice received biweekly intraperitoneal injections within three weeks (a total of 6 injections): control mice received saline solution, while DOX- and MTX-treated mice received a total cumulative dose of 18 mg/kg and 6 mg/kg, respectively. These doses are pharmacological

relevant and clinically similar. Mice were euthanized one week after the last injection for collection of heart, where proteins, acylcarnitines and amino acids content was assessed through Western blot and tandem mass spectrometry.

Results: Both DOX and MTX decreased AMP-activated protein kinase (AMPK) and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) content and decreased free carnitine (C0) and increased acetylcarnitine (C2) concentration, highlighting decreased glycolysis and increased fatty acids oxidation. In addition, DOX decreased phosphofructokinase (PFKM) and electron transfer flavoprotein-ubiquinone oxidoreductase (ETFDH) content, and the concentration of several amino acids, pointing to a bigger impact on glycolysis, oxidative metabolism, and amino acids turnover.

Conclusions: DOX and MTX affect cardiac remodeling differently being that DOX modulated energetic metabolism more severely than MTX. Therefore, more studies comparing the two drugs will improve the insights on their cardiotoxic molecular mechanisms and propose more adequate treatments.

Key words: cardiotoxicity; anticancer agents; molecular mechanisms; heart metabolism.

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4.18. P18 – Alexandra Moreira-Pais

The impact of lifelong exercise on age-induced skeletal muscle wasting

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Background: Aging is accompanied by skeletal muscle atrophy and exercise (EX) seems to be a promising tool to decelerate its progression. The aim of this study was to characterize the early skeletal muscle metabolic adaptations that occur with aging in rats and how lifelong aerobic EX can mitigate those adaptations.

Methodology: Male Wistar rats were divided into 4 groups: sedentary and sacrificed at 35 (SED1) or 61 (SED2) weeks and exercised age-match (EX1, EX2). EX1 and EX2 animals started a treadmill EX program at 6 weeks old for 23 or 50 weeks, respectively (5 days/week 60 min/day; treadmill speed was set for 70% of the maximal speed capacity). Morphometric evaluation of *soleus* (SOL) and

gastrocnemius (GAS) was performed and integrated with anthropometric data. Metabolism markers were evaluated by immunoblotting or spectrophotometrically.

Results: Body weight increased with aging and decreased with EX. Aging decreased the GAS and SOL mass-to-body weight ratios, indicating muscle wasting. EX increased these ratios, which was accompanied by increased fibrosis (higher in SOL). GAS fibers CSA increased in EX2 animals, suggesting muscle hypertrophy. The GAS from SED2 and EX2 animals had greater heterogeneity in fibers CSA, a histological hallmark of muscle aging. With aging occurred a decrease in citrate synthase activity only in the SOL (higher number of type I fibers), indicating lower mitochondrial density. PFKM levels increased with aging in GAS, suggesting a higher reliance on glycolysis. No differences were found in ATP synthase β, ETF dehydrogenase or PGC1α levels, revealing that aging/EX did not affect GAS metabolic phenotype. AMPK activation was triggered in SED2 animals, possibly contributing to muscle wasting, and blunted in EX2 animals.

Conclusions: Lifelong EX counteracted the aging-induced muscle wasting, though without involving metabolic remodeling. AMPK activation during EX seems to be blunted in older animals.

Key words: Aging; exercise; muscle wasting.