10TH IMIBIC YOUNG INVESTIGATORS MEETING

IMIBIC BUILDING
CONFERENCE ROOM
CÓRDOBA, 16-17 MAY, 2019

ABSTRACT BOOK

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ABSTRACT BOOK

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Programme

Day 1 (16th May)

08:00 – 08:30	**Registration and Poster display**
08:30 – 08:50	**Opening ceremony**
08:50 – 10:20	**SESSION I. Nutrition, Endocrine and metabolic diseases** **Chairs**: María de los Ángeles Gálvez Moreno and Antonio Rodríguez Ariza.
Ia. 08:50 – 09:05	Adipose tissue extracellular matrix remodeling in obesity. **Carmen Tercero Alcázar**.
Ib. 09:05 – 09:20	Novel mechanisms for pubertal control - GRK2 in GnRH neurons regulates puberty onset: Implications for metabolic and pharmacological modulation of pubertal timing. **Mª Soledad Avendaño Herrador**.
Ic. 09:20 – 09:35	Healthy dietary pattern improves microvascular endothelial function in patients with atherosclerotic coronary disease from the CORDIOPREV study. **Marta Millán Orge**.
Id. 09:35 – 09:50	Effectiveness of physical activity interventions on obese children evaluated by accelerometer: systematic review and meta-analysis. **José Manuel Jurado Castro**.
Ie. 09:50 – 10:05	Identification of molecular signature of subcutaneous adipose tissue from obese patients in response to bariatric surgery using SWATH-MS proteomic analysis. **Julia Sánchez Ceinos**.
If. 10:05 – 10:20	Diminished secretory capacity of KNDy neurons in conditions of acute energy deficiency: Implications for reproductive dysfunction in conditions of malnutrition. **Miguel Ruiz Cruz**.
10:20 – 10:50	**Coffee Break**

10:50 – 12:20 SESSION II. Cancer

Chairs: Marina Álvarez de Benito and Feliciano Priego Capote.

IIa. 10:50 – 11:05 The splicing factor SF3B1 is overexpressed in hepatocellular carcinoma and could represent a new therapeutic target. **Juan Luis López Cánovas**.

IIb. 11:05 – 11:20 Phosphorylation-dependent regulation of NOTCH1 intracellular domain by dual-specificity tyrosine-regulated kinase 2. **Rosario Morrugares Carmona**.

IIc. 11:20 – 11:35 Pladienolide B exerts anti-tumoral actions in pancreatic ductal adenocarcinoma by targeting altered spliceosome component SF3B1. **Ricardo Blázquez Encinas-Rey**.

IId. 11:35 – 11:50 Urine ghrelin O-acyltransferase (GOAT) enzyme as a useful biomarker for the diagnosis of significant prostate cancer. **Antonio Jesús Montero Hidalgo**.

IIe. 11:50 – 12:05 The different tumor budding status in colorectal cancer is associated with molecular subtypes and specific immune profiles. **Silvia Guil Luna**.

IIf. 12:05 – 12:20 The splicing factor NOVA1 is overexpressed in pancreatic neuroendocrine tumors and increases aggressiveness and malignancy features in vitro. **Sergio Pedraza Arévalo**.

12:20 – 13:50 SESSION III. Chronic and Inflammatory diseases

Chairs: María del Mar Malagón Poyato and Miguel González Andrades.

IIIa. 12:20 – 12:35 Characterization of the molecular serum profile related to the increased cardiovascular risk in Rheumatoid Arthritis patients. Modulation by biological drugs. **María Luque Tévar**.

IIIb. 12:35 – 12:50 FGF23 produces arterial stiffness through changes in vascular smooth muscle cell phenotype. **María Encarnación Rodríguez Ortiz**.

IIIc. 12:50- 13:05 Nrf2 plays a protective role against intravascular hemolysis-mediated acute kidney injury. **Cristina García Caballero**.

IIId. 13:05 – 13:20 Comparative study of characterization and determination of immunomodulatory efficacy of bone marrow-derived mesenchymal stem cells expanded with platelet lysate or fetal bovine serum supplemented medium. **Kristina Pavlovic Pavlovic**.

IIIe. 13:20 -13:35 Impact of clostridium difficile infection in patients hospitalized with ulcerative colitis. **Beatriz Gros Alcalde**.

IIIf. 13:35 – 13:50 Systemic inflammation in preterm newborn and in necrotizing enterocolitis. **Cristina Pérez Garía**.

13:50 – 15:20 Lunch

15:20 – 16:20 Poster session I
Chairs: Manolo Tena Sempere, María Dolores Fernández García and Alejandro Ibáñez Costa.

16:20 – 17:50 SESSION IV. Multidisciplinary
Chairs: María Elena Mateos González and Juan Ruano Ruiz.

IVa. 16:20- 16:35 Potential therapeutic role of Neuronostatin and the G protein-coupled receptor GPR107 in Prostate Cancer. **Prudencio Sáez Martínez**.

IVb. 16:35 – 16:50 Age-dependent effect of metabolic phenotypes on carotid atherosclerosis in patients with coronary heart disease (CORDIOPREV study). **Mª Magdalena Pérez Cardelo**.

IVc. 16:50 – 17:05 Evaluation of hepatitis E virus genotype 3 in semen and testis during the acute phase: results from humans and naturally infected wild boar. **Pedro López López**.

IVd. 17:05 – 17:20 MGRNA-Seq: A light-weight, portable and scalable RNA-Seq analysis pipeline for biomedical research. **Martín Garrido Rodríguez-Córdoba**.

IVe. 17:20 – 17:35 Presence and pathophysiological role of the truncated SST5TMD4 splicing variant of the somatostatin receptor subtype 5 in human high-grade astrocytomas. **Jesús Miguel Pérez Gómez**.

IVf. 17:35 – 17:50 Fibroblast growth factor 23 (FGF23) is regulated by nutrient availability. **Ángela Vidal Carrascosa**.

Day 2 (17th MAY)

08:30 – 09:00 **Registration and Poster display**

09:00 – 10:30 **SESSION V. Nutrition, Endocrine and metabolic disesases**
Chairs: Mariano Rodríguez Portillo and Elena Pérez Nadales.

Va. 09:00 – 09:15 Postprandial lipemia modulates alpha cell function in the prediction of type 2 diabetes development: from CORDIOPREV study. **Isabel Pozuelo Sánchez**.

Vb. 09:15 – 09:30 Impact of obesogenic extracellular cues on lipid accumulation. **Jaime David López Alcalá**.

Vc. 09:30 – 09:45 Ablation of AMP-Activated Protein Kinase (AMPK) in GnRH neurons produces reproductive and metabolic alterations: Implications for the metabolic control of reproduction. **Alexia Barroso Romero**.

Vd. 09:45 – 10:00 Effect of dietary intervention on the expression profiles of miRNAs involved in the progression and regression of atherosclerosis in patients with cardiovascular disease **Yelizaveta Krylova**.

Ve. 10:00 – 10:15 Automated method for quantitative determination of steroids in serum by SPE–LC–MS/MS. **Diego Luque** Córdoba.

Vf. 10:15 – 10:30 Lipid biomarkers of the adipose tissue in obesity-induced insulin resistance. **Alejandro Fernández Vega**.

10:30 – 11:00 **Coffee Break**

11:00 – 12:00 **Poster session II**
Chairs: Manolo Tena Sempere, María Dolores Fernández García and Alejandro Ibáñez Costa

12:00 – 13:00 **Plenary lecture. “Neurons without batteries: Chasing a cure for mitochondrial encephalopathy”. Dr. Albert Quintana. Institut de Neurociències. Universitat Autònoma de Barcelona.**

13:00 – 13:30 **Awards and Closing ceremony**

Description of the review process for selecting oral/poster presentations

Authors submitted their works through the Young Investigator abstract submission website from March 25th to April 7th. During the submission process, each author selected a specific scientific category (among the five IMIBIC Scientific Programs) and a preferred type of presentation (oral or poster).

At the deadline, a total of 105 abstracts were received. On April 8th, the Organization Committee distributed all abstracts received among 8 external reviewers during a face to face meeting without any information of authors, affiliation, etc. All reviewers were selected based on their distinguished scientific background and solid experience in evaluating research projects. The full list of the external reviewers can be found at the beginning of this book. External reviewers evaluated abstracts from April 8th to April 24th, scoring the communications between 0 and 5. ***It should be noted that the Organization Committee has not evaluated or scored any of the submitted abstracts***.

On April 25th, the Organization Committee held a new face to face meeting to distribute all abstracts evaluated into oral communications or poster presentations based on the score provided by the reviewers and the preference of selection of the participants (oral vs. poster). Thus, oral communications were divided in 5 sessions (6 communications/each), while poster presentations were distributed in 2 sessions (5 and 4 presentations were selected for the first and the second session, respectively, to be presented in front of the chairs). Considering the number of oral presentations submitted for each category, consistent with the IMIBIC Scientific Program, the Organization Committee decided to establish two sessions for *Nutrition, Endocrine and metabolic diseases, and* one session for *Cancer (Oncology and Oncohematology),* one session for *Chronic and Inflammatory diseases* and, one multidisciplinary session, which includes different communications from the five categories.

Description of the review process for award selection

In order to motivate and boost high-quality presentations, IMIBIC establishes awards to the best oral presentation within each of the 5 sessions. These awards will be selected based on the scores of the Scientific Committee, comprised by 4 scientific coordinators (2 translational and 2 clinical) and all the chairs of the sessions (13 researchers), as well as by the scores of the 8 external reviewers. The full list of members of the Scientific Committee, chairs and external reviewers can be found in this book. The Scientific Committee and Chairs will score every presentation from 0 to 5, taking into consideration the following criteria: (i) scientific quality of the work, (ii) presentation skills of the presenter, and (iii) capacity to answer the questions raised by both the audience

and moderators. The final score for each presentation will consist of the average of the score obtained by the Scientific Committee and chairs, and also the score provided by the external reviewers. The five highest scored oral presentations will compete for the Best Presentation Award of the Meeting. Presenters who were awarded in the last editions were excluded of the process.

To assess the poster presentations, three chairs of the IMIBIC/UCO will visit the 9 highest scored abstracts according to the external reviewers. They will be scored following the same criteria applied for oral presentations. The highest scored poster per session will be awarded.


ORAL COMMUNICATIONS
Abstracts

SESSION I

Nutrition, Endocrine and metabolic diseases

Ia. Adipose tissue extracellular matrix remodeling in obesity

Authors: Tercero-Alcázar C.[1], Rodríguez-Viso P.[1], López-Álcala J.[1], Molero-Murillo L.[1,2], Guzmán-Ruiz R.[1,2], Malagón MM.[1,2]
Affiliations: [1]GC-11, Department of Cell Biology, Physiology, and Immunology, IMIBIC/University of Córdoba/Reina Sofia University Hospital, Córdoba, Spain, [2]CIBER Pathophysiology of Obesity and Nutrition (CIBERobn) CB06/03/.
Scientific Program: Endocrine and metabolic diseases.
Keywords: Extracellular matrix, proteoglycans, fibrosis, adipose tissue, obesity.

Abstract:
In obesity, the expanding adipose tissue undergoes dysregulated remodelling leading to fibrosis, which appears detrimental for organ function. Fibrosis is characterized by the modification of both the amount and type of extracellular matrix (ECM) proteins. Previous proteomic studies from our group revealed increased levels of the proteoglycan, lumican, in the subcutaneous adipose tissue of insulin resistant *vs*. normoglycemic obese individuals, along with enhanced collagen deposition. However, the role of lumican in ECM architecture and its contribution to the development of metabolic disease is still unknown. Herein, we aimed at analysing the interaction between the extracellular environment and the adipocytes through the development of a three-dimensional culture system to mimic obesity-associated conditions as well as to investigate the relevance of lumican in adipocyte pathophysiology. To this end, 3T3-L1 adipocytes were cultured in collagen-I matrices, with or without lumican. The results show that lumican in 3D gels impaired 3T3-L1 cell differentiation by decreasing the expression of transcriptional regulators (C/EBP, SREBP-1, PPAR-γ), which was accompanied by increased levels of endoplasmic reticulum and oxidative stress markers, activation of apoptosis and decreased adiponectin secretion. These effects were mediated by the activation of mechanotransduction pathways driven by lumican-induced reorganization of collagen-I fibers, which resulted in nuclear translocation of the transcriptional co-activator, YAP, and increased accumulation of the nuclear envelope protein, lamin. Direct effects of lumican on integrin-activated Akt signalling were also observed. Our observations suggest that the accumulation of ECM components in the adipose tissue, such as collagen-I or lumican, modifies ECM organization, which results in the activation of downstream effector molecules leading to impaired lipid accumulation and adipokine secretion in adipocytes. These results, together with our observations demonstrating that lumican is released by adipocytes in response to hyperglycaemic/hyperinsulinemic conditions, support a role for this proteoglycan in obesity-associated metabolic disease.
Funding: MINECO/FEDER (BUF2016-76711-R; BFU2017-90578-REDT); CIBERobn (ISCIII).

Ib. Novel mechanisms for pubertal control - GRK2 in GnRH neurons regulates puberty onset: Implications for metabolic and pharmacological modulation of pubertal timing

Authors: Avendaño MS 1-4; López-Perdices C 2-4, Gaytán F 1-4, Ruiz-Pino F 1-4; Vázquez MJ 1-4; Heras V 2, 4; Romero-Ruiz A 1-4; Roa J 1-4; Pinilla L 1-4; Tena-Sempere M 1-4.
Affiliations: 1CIBER Physiopathology of Obesity and Nutrition (CIBEROBN), Instituto de Salud Carlos III, 2Maimonides Institute of Biomedical Research of Cordoba (IMIBIC), Cordoba; 3Reina Sofia University Hospital (HURS), Cordoba; and 4Department of Cell Biology, Physiology and Immunology, University of Cordoba 14004 Córdoba, Spain
Scientific Program: Nutrition, endocrine and metabolic diseases
Keywords: GRK2, Gpcr54, kisspeptin, puberty, metabolism

Abstract:
Reproduction is essential for perpetuation of species and reproductive problems are a major cause of medical consultation and treatment worldwide. Among reproductive alterations, changes in the age of puberty have been reported recently, especially in girls. Yet, the reason for this phenomenon, which may have durable adverse consequences in later health, remains unknown. The G protein-coupled receptor kinase 2, GRK2, is a ubiquitous serine/threonine protein kinase that is able to phosphorylate and desensitize several G protein coupled receptors (GPCR). Compelling, as yet limited, evidence in vitro suggested a potential role of GRK2 in mediating desensitization of Gpr54, the canonical receptor for the puberty-activating peptide, kisspeptin, which is abundantly expressed in GnRH neurons. Yet, the physiological role of GRK2 in modulating kisspeptin signaling, and hence puberty onset, remains unexplored. By a series of expression and functional analyses, we have addressed the putative function of central (hypothalamic) GRK2 in the regulation of puberty in preclinical models. Expression analyses revealed a gradual increase of GRK2 mRNA and protein levels in the hypothalamus during postnatal maturation, especially in the preoptic area (POA), where most GnRH neurons reside. Yet, a drop in GRK2 expression was also detected during the late-juvenile to pubertal transition. Pharmacological blockade of GRK2 enhanced Ca+2 responses to kisspeptin-10 (Kp-10) in Gpr54-expressing GT1-7 cells in vitro, while central inhibition of GRK2 in vivo augmented LH and FSH responses to Kp-10, and mildly advanced puberty onset. Selective ablation of GRK2 in GnRH neurons caused also the enhancement of Kp-10 responses in vivo and markedly advanced puberty onset. Moreover, central inhibition of GRK2 partially reversed the delay of puberty onset caused by postnatal undernutrition, a condition in which hypothalamic GRK2 expression was increased. Our results are the first to demonstrate that GRK2 negatively regulates kisspeptin signaling in GnRH neurons, thereby playing a relevant role in the fine tuning of pubertal timing, in normal and metabolically compromised conditions.

Ic. Healthy dietary pattern improves microvascular endothelial function in patients with atherosclerotic coronary disease from the CORDIOPREV study.

Authors: Marta Millán Orge, José D. Torres Peña, Antonio Pablo Arenas Larriva, Andrea Corina, Juan Luis Romero Cabrera, José Jiménez Torres, Cristina Hidalgo Moyano, Pablo Pérez Martínez, Javier Delgado Lista, José López Miranda.
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Scientific Program: Nutrition, Endocrine and metabolic diseases
Keywords: Endothelial function, atherosclerotic disease, diet.

Abstract:
Background and aims: Endothelial dysfunction plays an important role in the development of atherosclerotic cardiovascular disease. It is known that factors related to diet may influence vascular reactivity, however, to date, there are only a few studies showing the long-term effects of diet on endothelial function in patients with established coronary disease. Thus, our objective was to explore whether long-term consumption of a Mediterranean diet (MedDiet) rich in olive oil or a low-fat diet (LF diet) was associated with an improvement in microvascular endothelial function in patients with high cardiovascular risk from the CORDIOPREV clinical trial (NCT00924937).
Methods: Endothelial function was measured in 298 patients using laser Doppler flowmetry to calculate the hyperemia area after 4 minutes induced ischemia, before and after 6 years of intervention with a MedDiet [35% of calories from fat (22% mono- unsaturated) and 50% from carbohydrates] and LF diet [28% fat (12% monounsaturated) and 55% of calories from carbohydrates].
Results: Both, MedDiet and LF diet improves hyperemia area after 6 years compared to baseline [9570.36 ± 294.46 vs. 4909.56 ± 212.33; $p<0.001$]. However, we found no differences in hyperemia area between diets at 6 years.
Conclusions: Long-term consumption of a healthy dietary pattern, MedDiet rich in extra virgin olive oil or LF diet, improves endothelial function in patients with atherosclerotic coronary disease. These findings show the key role of the dietary recommendations, which are sometimes ignored in clinical practice and allow us to prevent cardio-metabolic complications.

Id. Effectiveness of physical activity interventions on obese children evaluated by accelerometer: systematic review and meta-analysis

Authors: José Manuel Jurado-Castro, Mercedes Gil-Campos, Hugo González-González, Francisco Jesús Llorente-Cantarer
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Scientific Program: Nutrition, Endocrine and metabolic diseases
Keywords: physical activity, obesity, children, accelerometer

Abstract:
Introduction. Despite the global recommendations on physical activity, childhood obesity it has increased, with no specific and unique recommendations for the pre-pubertal stage (6-12 years). Objective. To determine the effectiveness of physical activity interventions in obese children with 6-12 years objectively measured by accelerometry. Methodology. A search was made in 11 databases, the main ones being: MEDLINE (Pubmed), Cochrane and WOS. A combination of MeSH terms was established. Results. A total of 3336 studies were identified, with 229 of them potentially eligible based on the inclusion criteria. Finally, 10 articles were included in the meta-analysis. The meta-analysis showed improvements in BMI in children in the intervention group with respect to control (P <0.001), in addition to a significant increase in the minutes of moderate and vigorous physical activity (P <0.001). Conclusions. Interventions in obese children seem to be effective in reducing BMI, in addition to producing an increase in minutes of physical activity moderate and vigorous. Active videogames can be a useful strategy for obesity reduction, although it should be complemented with strengthening exercises and aerobic activity.

Ie. Identification of molecular signature of subcutaneous adipose tissue from obese patients in response to bariatric surgery using SWATH-MS proteomic analysis.

Authors: J. Sanchez-Ceinos1,2, C. Tercero Alcazar1, I. Ortea 3, Navarro-Ruiz MC1,2, DA. Cano4, JL. Pereira-Cunill4, PP. García-Luna4, MM. Malagón1,2, R. Guzmán-Ruiz1,2
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Scientific Program: Nutrition, Endocrine and metabolic diseases
Keywords: adipose tissue, bariatric surgery, SWATH-MS.

Abstract:
Bariatric surgery (BS) is the most effective strategy to reduce weight loss and improves metabolic status in morbidly obese patients. However, the safety, efficacy and cost-efficiency of BS may vary in relation to the initial anthropometric and metabolic status (BMI or T2D) of obese patients. It has been accepted that BS induces a significant reorganization of the adipose tissue that contributes to its beneficial effects although; the mechanisms driving these changes have not yet been fully elucidated and novel studies are necessary to define the molecular basis of the beneficial effects of BS. To this end, SWATH-MS proteomic approach was employed to analyse the response of subcutaneous adipose tissue (SAT) to surgery-induced weight loss before and after BS. Patients were stratified according to obesity diagnostic time in short- and long-standing obesity (<15 and >30 years, respectively). A total of 930 proteins were obtained in the SAT proteome of patients. SWATH analysis identified 156 statistically significant proteins after BS. Among then, 93 and 11 proteins were specifically detected in short-term and long-term obese patients, respectively. Posterior bioinformatic analyses (Panther, iPathwayGuide, IPA) identify Fatty Acid Beta-oxidation and Tricarboxylic Acid Cycle as the main biological processes modified by BS. Notably, these processes were significantly increased in short-standing obese patients; no differences were detected in long-term obesity patients. Other key factors, such as the adipogenic regulatory factor (ADIRF) increased independently of obesity evolution. In conclusion, proteomic analysis showed different molecular signatures in SAT of obese patients after BS, evidencing alternative processes involved in the beneficial effects of BS on adipose tissue, largely dependent on the duration of obesity.
Funding: JJAA/FEDER (PI-0159-2016); MINECO/FEDER (BUF2016-76711-R; BFU2015-70454-REDT); ADIPOSEQ, CIBERobn (ISCIII).

If. Diminished secretory capacity of KNDy neurons in conditions of acute energy deficiency: Implications for reproductive dysfunction in conditions of malnutrition

Authors: Miguel Ruiz-Cruz, Inmaculada Velasco, Delphine Franssen, Alexia Barroso, Leonor Pinilla, Manuel Tena-Sempere, Juan Roa
Affiliations: Instituto Maimónides de Investigación Biomédica de Cordoba (IMIBIC); Department of Cell Biology, Physiology and Immunology, University of Cordoba; Hospital Universitario Reina Sofía; and CIBER Fisiopatología de la Obesidad y Nutrición, Instituto de Salud Carlos III, 14004 Córdoba, Spain
Scientific Program: Nutrition, Endocrine and metabolic diseases
Keywords: Reproduction, kisspeptin, metabolism, fasting, DREADDs

Abstract:
Reproduction is an energy-demanding function that is regulated by the metabolic state, being inactivated in situations of energy deficit that could compromise the survival of the individual and his/her progeny. Kiss1 neurons, which produce the neuropeptides called kisspeptins, act as transducers of this metabolic information to the brain centers governing reproduction. During the last decade, special attention has been paid to the transcriptional regulation of the genes encoding kisspeptins (namely, Kiss1) and its receptor, Gpr54, in situations of metabolic stress, as fasting, obesity and diabetes. However, little attention has been paid to the existence of other types of non-transcriptional mechanisms influencing the activity of these neurons in conditions of metabolic distress. In this context, the objective of this work was to evaluate the effect of 24-hour fasting, as model for malnutrition and negative energy balance seen in clinically relevant conditions, such as anorexia or cachexia, on the secretory capacity of Kiss1 neurons located in the arcuate nucleus (ARC), also known as KNDy neurons, as evaluated by a combination of expression and functional analyses. Our results suggest the existence of an inhibitory mechanism influencing selectively the secretory capacity of these neurons in fasting conditions. This conclusion is based on the observation that LH response to the pharmacogenetic activation of KNDy neurons, using virogenetic expression and activation of DREADDs, is reduced after 24-hour fasting, despite the fact that (i) kisspeptin content in these neurons is higher; and (ii) the secretory response of LH to the central injection of Kisspeptin is enhanced in this condition. Thus, our results are the first to suggest the existence of an inhibitory mechanism specifically regulating the secretion capacity of KNDy neurons, which likely contributes to the impairment of reproductive function in conditions of malnutrition. The molecular mechanisms and eventual translational implications of this phenomenon warrant future investigation.

SESSION II

Cancer (Oncology and Oncohematology)

IIa. The splicing factor SF3B1 is overexpressed in hepatocellular carcinoma and could represent a new therapeutic target

Authors: Juan L. López-Cánovas, Mercedes del Rio-Moreno, Juan M. Jiménez-Vacas, Araceli Lara-López, Fernando López-López, Marina E. Sánchez-Frias, Manuel Rodriguez-Peralvarez, Manuel de la Mata, Justo P. Castaño, Raúl M. Luque, Manuel D. Gahete.
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Scientific Program: Cancer (Oncology and Oncohematology)
Keywords: Hepatocellular Carcinoma, Splicing, SF3B1, Pladienolide B, preclinical model.

Abstract:
Hepatocellular carcinoma (HCC) is the second cause of cancer-associated deaths and its prognosis remains poor. Therefore, it is necessary to identify new therapeutic targets. A common molecular feature in most tumoral pathologies is the alteration of the expression of splicing variants, which could be associated to the dysregulation of the splicing machinery (spliceosome and splicing factors). Since the splicing machinery could represent a potential therapeutic target and its alteration in tumoral pathologies is poorly understood, we aimed to identify components of the splicing machinery altered in HCC and with potential druggability. *In silico* analysis of four different cohorts of patients with HCC [Wurmbach Liver (75 patients), Roessler Liver (43 patients), Roessler Liver 2 (445 patients) and Mas liver (115)] revealed that the splicing factor SF3B1, whose activity can be pharmacologically modulated by available drugs (e.g. pladienolide-B), was consistently overexpressed in all cohorts studied. Therefore, we next aimed to characterize the functional and mechanistic consequences of pladienolide-B treatment in different HCC cell lines (HepG2, Hep3B and SNU-387) and xenografted tumors. The *in vitro* approaches showed a clear, dose-dependent inhibitory effect of Pladienolide-B treatment in functional parameters such as proliferation, migration, tumorspheres formation and clonogenic assays in the three cell lines used, while its effects on normal-like hepatocytes was significantly lower. This inhibitory effect was associated with the modulation of the expression of key tumoral markers (KI67, CDK2, etc). Interestingly, the combination of pladienolide-B and sorafenib seemed to exert greater *in vitro* effects than treatments alone. Finally, a single intratumor dose of pladienolide-B was sufficient to reduce *in vivo* tumor growth in Hep3B-induced xenograft tumors, an effect that was comparable to that exerted by sorafenib alone. Therefore, this study demonstrates that SF3B1 is overexpressed in HCC and its pharmacological inhibition with pladienolide-B could represent a new therapeutic strategy for patients with HCC.

Funding: ISCIII (PI17-02287, PI16-00264), Junta de Andalucía (BIO-0139) and CIBERobn.

IIb. Phosphorylation-dependent regulation of NOTCH1 intracellular domain by dual-specificity tyrosine-regulated kinase 2

Authors: Rosario Morrugares, Alejandro Correa-Sáez, Rita Moreno, Martín Garrido-Rodríguez, Eduardo Muñoz, Laureano de la Vega[4] and Marco A. Calzado
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These two authors contributed equally to this work.
Scientific Program: Cancer (Oncology and Oncohematology)
Keywords: Notch1, DYRK2, phosphorylation, cell signaling, kinase, cancer

Abstract:
NOTCH proteins constitute a receptor family with a widely conserved role in cell cycle, growing and development regulation. NOTCH1, the best-characterized member of this family, regulates the expression of key genes in cell growth and angiogenesis, playing an essential role in cancer development. When this receptor is activated, its intracellular domain (Notch1-IC) translocates to the nucleus and acts as transcription factor. Functional studies implicate NOTCH signaling essentially in all of the hallmarks of cancer, being associated with abnormal expression, high mutation rate and poor survival in several types of tumors. These observations provide a relevant rationale to propose the inhibition of Notch1-IC as a strategy for treating various types of cancer. Notch-IC activity or stability are mainly controlled by interaction with other proteins or post-translational modifications. FBW7 ubiquitin E3 ligase-mediated degradation is considered one of the most relevant and requires the previous phosphorylation at Thr-2512 residue.

In the present study, we describe for the first time a new regulation mechanism of the NOTCH1 signaling pathway mediated by Dual Specificity Tyrosine-phosphorylation-Regulated Kinase 2 (DYRK2). We prove that DYRK2 phosphorylates Notch1-IC in response to chemotherapeutic agents and facilitates its proteasomal degradation by FBW7 ubiquitin ligase. We identified that Thr-2512 phosphorylation is necessary for Notch1-IC degradation by DYRK2. Moreover, we also prove that both proteins interact and colocalize at the nucleus level. Generation of DYRK2 knockout cell lines by CRISPR/Cas9-mediated genome editing has allowed us to describe how DYRK2 regulation by chemotherapeutic agents has a relevant effect on the viability, motility and invasion capacity of cancer cells expressing NOTCH1. In summary, we show the ability of DYRK2 to regulate Notch1-IC, which represents a novel regulation mechanism of the expression and function of this transcription factor with relevant implications in tumorigenesis and cancer prevention.

IIc. Pladienolide B exerts anti-tumoral actions in pancreatic ductal adenocarcinoma by targeting altered spliceosome component SF3B1

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Scientific Program: Cancer (Oncology and Oncohematology)
Keywords: PDAC, splicing, SF3B1, Pladienolide B.

Abstract:
Pancreatic ductal adenocarcinoma (PDAC) is one of the deadliest cancers worldwide, mainly due to its late diagnosis and poor response to treatment. Thus, early diagnosis biomarkers and new treatment targets are needed to tackle this pathology. Emerging evidence indicates that dysregulated alternative splicing is a common feature of all tumors, pointing at altered splicing as a new hallmark of cancer. Actually, splicing dysregulation results in altered profiles of gene expression and often generates abnormal splice variants with oncogenic activity. In this context, there is growing interest in a spliceosome component essential for the splicing process, named SF3B1 (Splicing Factor 3B Subunit 1), in that it can be targeted by Pladienolide-B, a drug that selectively blocks its activity disrupting the splicing process. Here, we aimed to explore SF3B1 as a potential therapeutic target in PDAC. To this end, we first analyzed *SF3B1* expression in tumor vs non-tumor adjacent tissues in a set of formalin-fixed paraffin-embedded PDAC samples (n=79), as well as in two model cell lines (PDAC-derived MIAPaCa-2, and the normal-like pancreatic cell line HPDE-E6E7). Then, the effect of Pladienolide-B treatment on different tumor features was evaluated in HPDE-E6E7 and MIAPaCa-2 cells. Results revealed an overexpression of *SF3B1* in PDAC tissue compared to non-tumor adjacent tissue. Likewise, expression of *SF3B1* was higher in MIAPaCa-2 than in HPDE-E6E7 cells. Moreover, Pladienolide-B treatment decreased key tumor-related features, including cell proliferation and migration, in MIAPaCa-2 tumor cells, but not in HPDE-E6E7 cells. Interestingly, Pladienolide-B treatment also altered the pattern of alternative splicing of *BCL2*, a pivotal regulator of apoptosis, increasing the expression of its pro-apoptotic isoform (Bcl-xS). Altogether, these results reveal that *SF3B1* is altered in PDAC, and that its blockade by Pladienolide-B exerts antitumoral effects, thus suggesting its potential value as a new therapeutic avenue for PDAC.
Funding: MINECO (BFU2016-80360-R, BFU2013-43282-R, 8CO1/007176); ISCIII (FI17/00282, PI17-02287); GETNE (GETNE G1404) and CIBERobn.

IId. Urine ghrelin O-acyltransferase (GOAT) enzyme as a useful biomarker for the diagnosis of significant prostate cancer

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Scientific Program: Cancer (Oncology and Oncohematology)

Keywords: prostate cancer; non-invasive biomarker; urine; GOAT enzyme; ELISA

Abstract:

Prostate cancer (PCa) represents the most common tumor pathology among men in developed countries. However, PCa diagnosis is limited by the lack of suitable biomarkers. Indeed, the prostate-specific antigen (PSA) test, the current gold-standard for PCa diagnosis, displays low specificity and leads to numerous unnecessary biopsies. We have recently demonstrated that the plasma levels of ghrelin-O-acyl transferase (GOAT)-enzyme are higher in PCa-patients (n=183) compared to healthy-controls (n=129). In this study, we aimed to validate the potential of GOAT-enzyme as noninvasive PCa biomarker using plasma and urine samples from an ampler and more representative cohort of patients with and without PCa (n≈1000). GOAT-enzyme levels were evaluated by commercial ELISA in morning urine and plasma samples from: 1) healthy-volunteers (n=97); 2) patients with suspect of PCa but with negative biopsy (n=549); 3) patients with non-significant PCa (non-SigPCa; Gleason-Score=6; n=143); and 4) patients with significant PCa (SigPCa; Gleason-Score≥7; n=204). Circulating GOAT-levels were higher in PCa-patients compared to controls (healthy-volunteers and patients with negative biopsy) and demonstrated that urine GOAT-enzyme levels were also higher in PCa-patients compared to both control groups. Indeed, urine GOATenzyme levels were especially higher in patients with SigPCa. In fact, urine GOATenzyme levels outperformed the capacity of PSA to diagnose SigPCa, especially in patients in the grey zone (with PSA ranging 3-10ng/mL, wherein the diagnostic capacity of PSA is tremendously reduced). Since the diagnostic capacity of GOATenzyme levels was independent from all the clinical variables analyzed [e.g. PSA, age, digital rectal examination (DRE)], the use of urine GOAT-enzyme levels could improve the diagnostic potential of the current nomograms in clinical practice, which are based on multivariate model combining clinical parameters (i.e. age, DRE, etc.). Thus, our results demonstrate that urine GOAT-enzyme levels could represent a novel/useful noninvasive biomarker for PCa diagnosis, especially for patients in the grey zone of PSA.

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IIe. The different tumor budding status in colorectal cancer is associated with molecular subtypes and specific immune profiles.

Authors: Silvia Guil-Luna, Rafael Mena, Carmen Navarrete-Sirvent, Laura López-Sánchez, Jon Peñarando, Marta Toledano, Rafael Jiménez-Izquierdo, Carlos Villar, Cesar Díaz, Francisco Javier Medina-Fernández, Juan De la Haba-Rodríguez, Enrique Aranda, Antonio Rodríguez-Ariza.

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Scientific Program: Cancer (Oncology and Oncohematology)

Keywords: Patient-derived xenografts; colorectal cancer, tumor budding.

Abstract:

Tumor heterogeneity remains one of the current challenges for the success of the new targeted therapies in colorectal cancer (CRC). On the other hand, tumor budding has been found to be of prognostic significance for several cancers including CRC. Thus, preclinical platforms which faithfully reflect the complex tumor biology in this malignancy are a fundamental component of precision oncology. Here, we classified CRC tumors and their corresponding patient derived xenograft (PDX) models into the consensus molecular (CMS) subtypes by an immunohistochemistry approach. Then, we analyzed and correlated peritumoral and intratumoral budding and the immune gene expression profile for each molecular subtype in patient tumors and their PDXs. CMS subtypes and tumor budding were reliably reproduced in PDX models with characteristic immune signatures related to the molecular subtype and budding grade. High grade of tumor budding and endothelial nitric oxide synthase (eNOS) expression was intimately related with poor-prognosis CMS4 subtype. Interestingly, TLR family and immune checkpoints were highly detected in tumors with high grade of budding both in patient and PDX tumors. Our data support a link between tumor budding and immune microenvironment in CRC and confirm the high potential of PDXs as valuable models to evaluate tumor budding as a therapeutic target in different CRC molecular subtypes.

IIf. The splicing factor NOVA1 is overexpressed in pancreatic neuroendocrine tumors and increases aggressiveness and malignancy features in vitro.

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Scientific Program: Cancer (Oncology and Oncohematology)

Keywords: NOVA1, splicing, neuroendocrine tumors, aggressiveness

Abstract:

Altered alternative splicing is arising as a universal tumor feature in cancer, turning splicing and its control into an emerging, transversal cancer hallmark. Dysregulation of the splicing machinery may represent a key underlying cause for these alterations. We recently discovered aberrantly spliced variants of somatostatin receptor 5 (SST5TMD4) and ghrelin (In1-ghrelin) genes and demonstrated their link with malignancy features in pancreatic neuroendocrine tumors (PanNETs). Here, we analyze the expression of pivotal components of the splicing machinery in PanNETs and explore the role of the splicing factor NOVA1 in aggressiveness. To this end, we first measured the expression levels of 45 components of the splicing machinery in 20 PanNETs samples and 20 paired non-tumoral adjacent tissues, using a custom-made microfluidic-based qPCR array. This revealed that the expression profile of the splicing machinery is profoundly dysregulated in PanNETs, and that NOVA1 is one of the factors displaying most severe changes, which, in addition, associate with relevant clinical features. Thus, we explored the role of NOVA1 in BON-1 and QGP-1 cell-lines by measuring signaling pathways and aggressiveness features, including proliferation and growth of xenografted tumors in mice. In vitro assays demonstrated that NOVA1 overexpression increased cell proliferation; conversely, NOVA1 silencing markedly decreased cell proliferation. Interestingly, overexpression or silencing of NOVA1 led to changes in the activation-inhibition of key signaling pathways (AKT, MAPK) and in the expression of key molecular markers (CCND1, CASP3). Notably, alteration of NOVA1 in PanNETs-cells influenced their responsiveness to everolimus in terms of proliferation. Finally, NOVA1 overexpression markedly increased the growth of BON-1 xenografted tumors in nude mice. These results demonstrate that splicing machinery is altered in PanNETs, and provide compelling evidence for a role of the splicing factor NOVA1 in PanNETs aggressiveness, thus paving the way to explore its possible value as a biomarker and therapeutic target in PanNETs.

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SESSION III

Chronic and Inflammatory diseases

IIIa. Characterization of the molecular serum profile related to the increased cardiovascular risk in Rheumatoid Arthritis patients. Modulation by biological drugs.

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Scientific Program: Chronic and Inflammatory diseases.

Keywords: Rheumatoid Arthritis, Cardiovascular Risk, Biological drugs, microRNAs, NETosis, inflammatory molecules.

Abstract:

Background/Purpose**:** 1- To characterize the serum molecular profile associated to the increased cardiovascular (CV) risk present in Rheumatoid Arthritis (RA) patients. 2- To evaluate the *in vivo* and *in vitro* effects of biological drugs on the reestablishment of this altered molecular profile. Methods: Serum samples of 280 RA patients and 100 healthy donors (HD) were studied. miRNnomes were identified using next-generation sequencing miRNA assay. Inflammatory and oxidative stress biomolecules and NETosis-derived products were quantified, and the CV-Risk Score was calculated following EULAR recommendations. Carotid intima-media thickness (CIMT) was evaluated as early atherosclerosis marker. *In vivo* effects of biological drugs [Infliximab (IFX, anti-TNFa), Tocilizumab (TCZ, anti-IL6R) and Rituximab (RTX, anti-CD20)] were evaluated before and after 6 months of therapy. RA patients' serum with high and low CV-risk scores were added to HUVECs and leukocytes subsets purified from HD -either in the presence or in the absence of biological drugs-, and activity profiles were evaluated. Results: 104 circulating miRNAs were found altered in RA patients. Functional classification (IPA) established their involvement in inflammatory response, immunological and hematological diseases. Circulating biomolecules related to inflammation, NETosis, oxidative stress and miRNAs were found coordinately altered in RA patients' serum. Hard clustering analysis differentiated 3 clusters representing different CV-risk profile groups. *In vivo* treatments with IFX, TCZ and RTX reduced disease activity and induced the re-establishment of normal levels in altered biomolecules. Mechanistic *in vitro* studies showed increased pro-inflammatory profiles of leukocytes subsets and HUVECSs after treatment with serum from high CV-risk score-RA patients, which were reversed by biological drugs. Conclusion: 1. Specific mediators of inflammation, oxidative damage and NETosis, along with the miRNAs modulating their expression, coordinately contribute to a higher CV-risk score in RA patients. 2. Biological drugs restore the normal levels of these altered biomolecules, reducing the CV risk in RA patients.

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IIIb. FGF23 produces arterial stiffness through changes in vascular smooth muscle cell phenotype

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Scientific Program: Chronic and inflammatory diseases

Keywords: FGF23, c-terminal FGF23, VSMC, arterial stiffness, peripheral pulse pressure, pulse wave velocity, miR-221, chronic kidney disease.

Abstract:

Vascular smooth muscle cells (VSMC) contribute to the maintenance of blood vessel structure. VSMC exhibit two clearly differentiated functional phenotypes, contractile and synthetic. It is unknown what stimuli promote this phenotypic transition or whether the imbalance in the transition from a contractile to a synthetic phenotype could be involved in pathological processes leading to vascular abnormalities. In patients with chronic kidney disease (CKD), high levels of c-terminal fibroblast growth factor 23 (FGF23) are associated with mortality and cardiovascular disease. The present study was conducted to evaluate whether high levels of FGF23 are involved in the phenotypic transition of VSMC, thus contributing to subsequent arterial stiffness.

High levels of FGF23 promoted VSMC transition from a contractile to a synthetic phenotype. These effects were mediated by FGFR1 and Ras/MAPK signaling activation. Inhibition of both pathways enhanced contractile phenotype of VSMC. FGF23 also reduced the levels of the pro-contractile microRNAs miR-221 and miR-222. miR-221 transfection recovered the contractile phenotype of VSMC decreased by FGF23. In experimental animal studies, exogenous infusion of FGF23 promoted the synthetic phenotype of VSMC and decreased plasma levels of miR-221. Finally, in patients at early stages of CKD and metabolic syndrome, there was a significant correlation between FGF23, pulse wave velocity, peripheral and central pulse pressure. Similarly, in these patients, the highest levels of FGF23 inversely correlated with plasma levels of miR-221 and miR-222.

In conclusion, high levels of FGF23 were associated with the phenotypic transition of contractile to synthetic VSMC and in patients at early stages of CKD with increased arterial stiffness.

IIIc. Nrf2 plays a protective role against intravascular hemolysis-mediated acute kidney injury

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Scientific Program: Chronic and Inflammatory diseases.

Keywords: Intravascular hemolysis, acute kidney injury (AKI), hemoglobin (Hb), Nuclear factor erythroid-2-related factor 2 (Nrf2).

Abstract:

Intravascular hemolysis is a common characteristic of surgical procedures and several diseases. Massive intravascular hemolysis induces renal toxicity, leading to acute kidney injury (AKI). Erythrocyte destruction leads to the release of hemoglobin (Hb) and heme-derived products to plasma, which are then reabsorbed by the proximal tubular epithelium. Renal cell exposure to Hb and metabolites promotes cell death and oxidative stress. Nuclear factor erythroid-2-related factor 2 (Nrf2) is a transcription factor that drives the expression of genes involved in cellular defense against oxidative stress. We investigated the role of Nrf2 in intravascular hemolysis and whether Nrf2 activation protected against Hb/heme-mediated renal damage *in vivo* and *in vitro*. We observed renal Nrf2 activation in human hemolysis and in an experimental model of intravascular hemolysis promoted by phenylhydrazine intraperitoneal injection. Hb and heme induced Nrf2 transcriptional activity in AREc32 cells and induced Nrf2 mRNA expression, Nrf2 nuclear translocation and reduced the intracellular levels of the Nrf2 repressor Keap-1 in murine tubular cells. In wild-type mice, Hb/heme-released from intravascular hemolysis promoted AKI, resulting in decreased renal function, enhanced expression of tubular injury markers, oxidative and endoplasmic reticulum stress and cell death. These features were more severe in Nrf2-deficient mice, which showed decreased expression of Nrf2-related antioxidant enzymes,

including HO-1 and ferritin. Nrf2 activation with sulforaphane protected against Hb-toxicity in mice and cultured tubular epithelial cells, ameliorating renal function, kidney injury and reducing cell stress and death. Nrf2 genotype or sulforaphane treatment did not influence the severity of hemolysis. In conclusion, our study identifies Nrf2 as a key molecule protecting against renal damage associated to hemolysis and opens novel therapeutic approaches to prevent renal damage in patients with severe hemolytic crisis. These findings provide new insights into novel aspects of Hb-mediated renal toxicity and may have important therapeutic implications for intravascular hemolysis related diseases.

IIId. Comparative study of characterization and determination of immunomodulatory efficacy of bone marrow-derived mesenchymal stem cells expanded with platelet lysate or fetal bovine serum supplemented medium.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: *Mesenchymal stem cells; Human platelet lysate; Fetal bovine serum; Cell therapy; Immunomodulatory effect.*

Abstract:
INTRODUCTION:
Bone marrow-derived mesenchymal stem cells (BM-MSCs) represent an ideal tool for many cell-based therapies. *In vitro* expansion of these cells includes fetal bovine serum (FBS) as enrichment of the culture media, however, due to its xenogeneic compounds its use for clinical purposes is being discouraged. Human platelet lysate (PL) represents an efficient alternative to FBS for clinical-scale expansion of BM-MSCs.
AIM:
In this study we characterized BM-MSCs expanded in medium with FBS and two types of PL, in order to evaluate the effect upon BM-MSCs immunomodulatory activity, proliferation, secretion of paracrine factors and apoptosis. Additionally, we have evaluated cells function and phenotype under the different culture conditions.
METHODS:
BM-MSCs were isolated from bone marrow derived of healthy donors and expanded up to passage two in culture mediums enriched with FBS or LP from two different manufacturing protocols. Cell phenotype and function were analyzed by flow cytometry and adipogenic/osteogenic differentiation. Proliferation rates and cell morphology were performed by flow cytometry, and immunomodulatory effects were analyzed by co-cultivating BM-MSCs with peripheral blood mononuclear cells. Finally, we evaluated paracrine factors secretion by ELISA analysis and evaluated apoptosis levels with an Annexin V assay.
RESULTS:
We proved that the different culture conditions did not modify BM-MSCs function, phenotype and immunomodulatory effects. In addition, even after executing their immunomodulatory activity, these cells characteristics did not significant change.
CONCLUSION:
BM-MSCs expanded in the different conditions presented similar tendencies in proliferation, phenotype, differentiation and immunomodulatory capacities. Both PL proved to be able to supply BM-MSCs expansion.

IIIe. Impact of clostridium difficile infection in patients hospitalized with ulcerative colitis

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Scientific Program: Chronic and inflammatory diseases
Keywords: Ulcerative colitis, inflammatory bowel diseases, Clostridium DifficileKeywords: Hepatocellular Carcinoma, Splicing, SF3B1, Pladienolide B, preclinical model.

Abstract:
Background: Clostridium diffile (CD) infection is increasing in general population and, especially, in patients with inflammatory bowel diseases (IBD). Patients with ulcerative colitis (UC) and CD infection during a flare can present a higher morbidity and mortality.
Objectives: A) To evaluate the proportion of CD infection in patients hospitalized with UC. B) To compare the rates of colectomy and mortality in UC admitted with and without CD infection. C) To analize the association between the infection and worse results according to readmissions, need of treatment escalation and hospital stay. D) To describe predictive factors associated with worse evolution in patients with CD infection.
Methods: Cases and controls retrospective study. We included hospitalized UC patients with a flare in our hospital from 2000 to 2018. Variables related to hospital stay, adverse events, need of colectomy in the first year and mortality were collected. We analyzed the data with SPSS using Chi-squate test, Kruskal wallis and multivariant analysis to identify factors of worse evolution.
Results: We analyzed 235 UC patients. 62.1% male, mean age 43.6 years (SD 12). 72% presented extensive colitis and 22% left coliits. 7.7% had perianal disease and 8.7% extraintestinal manifestations. Endoscopic activity was 75.8% Mayo score 3 and 23% Mayo score 2. 15.9% of the patients had complications during their hospitalization related to their disease: 37.8% had toxic megacolon, 11% perforation and 11.2 % needed surgery.
28 patients (12.2%) had CD infection, among them 23.5% suffered recurrence infection of CD during follow-up. The presence of CD infection was statistically significant related to a higher rate of readmission (48.1% vs 23%, p= 0.007) and higher rates of colectomy during the first year from the admission (13% vs 2.9%, p=0.05). No differences were found between both groups of patients regarding the development of complications related to their IBD, need for treatment intensification and early and late mortality. No predictors of poor evolution were identified in the multivariant analysis.
Conclusions: CD infection is prevalent in hospitalized UC patients, with high rates of recurrence. This infection is associated with higher rates of readmission and greater need of colectomy during the first year.

IIIf. Systemic inflammation in preterm newborn and in necrotizing enterocolitis

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Scientific Program: Infectious and Immunological diseases. Organ transplantation.

Keywords: Newborns, necrotizing enterocolitis, cytokines, systemic inflammatory status.

Abstract:

Introducction: Necrotizing enterocolitis (NEC) is derived from an excessive inflammation in the newborn bowel in preterm newborns, and it seems to be associated to a systemic inflammatory status that has been poorly characterized.

Materials and Methods: It is a descriptive, analytical, observational case-control study. Three groups were established: Neonates born ≥37 weeks of gestational age (GA), at term (T group), neonates born before 37 weeks of GA, preterm (PT group), and a group of NEC patients (NEC group). Multiplexed immunoassays were used to determine the concentrations of and hepatocyte growth factor (HGF), IL-1β, IL-6, IL-8, MCP-1, nerve growth factor, TNF, leptin, adiponectin, PAI-1 and resistin in plasma samples.

Results: In NEC, most cytokines/markers assayed in plasma were higher than in T infants, except HGF, MCP-1, adiponectin, resistin and PAI-1. So, ratio leptin/adiponectin was decreased in NEC patients. Plasma levels of IL-1β, IL-8 and HGF were also increased in PT infants compared with the T group. PT children additionally exhibited decreased adiponectin and leptin. A moderate correlation between resistin and PAI-1 levels, as well as those with other systemic inflammatory markers were found, especially with TNF-α. In addition, PAI-1 showed a positive correlation with systemic IL-1β and IL-8 concentrations.

Conclusion: PT neonates present mild systemic inflammation. The lower leptin levels in PT and in NEC patients, could be related with lower body weight in these groups compared with T. Adiponectin is considered to exert anti-inflammatory action, but these results indicate that this adipokine seems to be not implicated in NEC, so other mechanisms should be involved.

SESSION IV

Multidisciplinary

IVa. Potential therapeutic role of Neuronostatin and the G protein-coupled receptor GPR107 in Prostate Cancer

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Scientific Program: Cancer (Oncology and Oncohematology).

Keywords: Somatostatin-System, Neuronostatin, GPR107, Prostate Cancer, Therapeutic Tool.

Abstract:

Somatostatin (SST)-system is a hormonal-pleiotropic-system involved in the regulation of multiple pathophysiological functions. Specifically, certain components of the SST-system are dysregulated in several endocrine-related cancers, wherein these alterations seem to influence their development/progression. However, the presence and role of neuronostatin (NST) and its putative receptor GPR107, two members of this system, have not been fully explored in cancer. Consequently, we investigated the role of NST/GPR107-system in prostate cancer (PCa), one of the most diagnosed tumors among men worldwide, whose most aggressive phenotype [Castration-Resistant-PCa (CRPC)] remains lethal nowadays. Functional parameters (cell-proliferation/migration) were analysed in response to NST-treatment and GPR107-silencing in different PCa-cell-lines [androgen-dependent (AD) LNCaP and androgen-independent (AI) 22Rv1 and PC-3; which are models of hormone-sensitive and CRPC, respectively], and in normal prostate (NP) cells (RWPE-1 cell-line and primary-cell-cultures). Moreover, western-blotting, qPCR and microfluidic-based-qPCR-array were used. NST-treatment significantly inhibited proliferation/migration rate only in AI-PCa-cells. Mechanistically, the antitumor capacity of NST was associated with a reduction in GPR107-expression, and a significant down-regulation of key-genes involved in proliferation/migration/PCa-aggressiveness (i.e. *MKI67/CDK6/ MMP9/PRPF40A/sst5TMD4/AR-v7/ln1-ghrelin/EZH2/MYC*) and with the modulation of important oncogenic-signalling-pathways (ERK/AKT/JNK). Remarkably, these antitumor effects exerted by NST on AI-PCa-cells were blunted after GPR107-silencing, suggesting that the antitumor actions of NST in PCa-cells might be mediated via GPR107. Indeed, we found that GPR107 was significantly overexpressed in AI-PCa-cells compared to RWPE-1-cells, as well as in a cohort of PCa-samples compared to healthy-adjacent-tissues (n=85) and in two *in silico* cohorts (Grasso/Varambally). Finally, GPR107-silencing in AI-PCa-cells induced a significant decrease in proliferation/migration rate and evoked a similar dysregulation in the expression pattern of genes previously found in response to NST-treatment (i.e. downregulation of *sst5TMD4/AR-v7/ln1-ghrelin/MKI67*). Altogether, our results demonstrate that NST-treatment reduces PCa-aggressiveness in CRPC-cells via GPR107 and through the alteration of different key molecular-signalling-pathways, suggesting that NST/GPR107-system might be considered as a novel therapeutic tool for CRPC.

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IVb. Age-dependent effect of metabolic phenotypes on carotid atherosclerosis in patients with coronary heart disease (CORDIOPREV study)

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Scientific Program: Nutrition, Endocrine and metabolic diseases
Keywords: Carotid atherosclerosis, metabolic phenotypes, healthy obese, cardiovascular risk factors

Abstract:
Background: The relation between obesity and an increased risk of future cardiovascular events appears to be more closely linked to certain clinical or metabolic phenotypes than to obesity itself. Aging is also associated with a high risk of cardiovascular disease. Our aim was to establish whether aging influenced the metabolic phenotypes regarding to cardiovascular risk, evaluated by changes in the intima media thickness-common carotid (IMT-CC), in coronary heart disease (CHD) patients.
Methods: In this cross-sectional study, 1002 CHD patients, from the CORDIOPREV study, were studied at entry. We determined their metabolic phenotypes, classified them according to age, and performed carotid ultrasound assessment to obtain their IMT-CC values. Carotid atherosclerosis was considered to exist if IMT-CC>0.7 mm.
Results: Age determined a higher IMT-CC, regardless of the metabolic phenotype (all p<0.05). Metabolically healthy non-obese (MHNO) patients aged<60 showed a lesser prevalence for carotid atherosclerotic disease than metabolically sick non-obese (MSNO) and obese (MSO) phenotypes, while MHNO patients aged≥60 only showed less prevalence for the disease than the MSO phenotypes. In the total population, carotid atherosclerosis seems to be associated with age, sex, impaired fasting glucose (IFG), hypertension and high sensitivity C-reactive protein (hsCRP). However, in patients aged<60, carotid atherosclerosis is associated with sex and IFG and in the age≥60 group, with hypertension and hsCRP.
Conclusion: Our results suggest that CHD patients aged≥60 years lose their metabolic flexibility compared to patients aged<60 years. Thus, MHO patients aged≥60 years show the same risk of suffering carotid atherosclerosis as those with metabolic disease (MSNO and MSO). However, MHO patients aged <60 years have a lower risk of carotid atherosclerosis than MSO but with an intermediate risk compared to MHNO and MSNO. This fact indicates the need to reduce those parameters related to obesity in patients with CHD before entering old age.

IVc. Evaluation of hepatitis E virus genotype 3 in semen and testis during the acute phase: results from humans and naturally infected wild boar.

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Scientific Program: Infectious and Immunological diseases. Organ transplantation.
Keywords: Hepatitis E; sperm; wild boar; sexual transmission; genotype 3.

Abstract:
Background and objective: The efficiency of sexually transmitted hepatitis E virus (HEV) infection is unknown. Our objective was to evaluate the presence of HEV in semen and testicles in individuals with acute genotype 3 HEV infection.
Methods: We included in the study two populations. Firstly, 12 male humans with a diagnosis of acute HEV infection. In these patients, blood and semen samples were collected on the same day or within 7 days of receiving a diagnosis of acute HEV infection. Secondly, we included 66 male wild boar. In these animals, postmortem blood and fresh tissue samples including testicles, liver and hepatic lymph nodes were collected. In blood and sperm, presence of HEV was evaluated by RT-PCR. Presence of HEV in tissues was evaluated by RT-PCR and immunohistochemistry (IHC).
Results: Two patients of the 12 HEV diagnosed males agreed to be enrolled in the study and semen samples were collected. HEV-RNA was detected in serum but not in semen in any of them. Of 66 male wild boar included in the study, two (3%) showed detectable HEV RNA in serum. One wild boar showed detectable viral load in all the sampled tissues, while the other animal showed negative results in all of them. The IHC analysis showed consistent results with the molecular analysis. Histopathological examination did not reveal any remarkable pathological change.
Conclusions: Our study shows evidence of the presence of HEV genotype 3 in wild boar testes. After histological evaluation, this presence was not associated with tissue damage.

IVd. MGRNA-Seq: A light-weight, portable and scalable RNA-Seq analysis pipeline for biomedical research

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Bioinformatics, Next Generation Sequencing, RNA-Seq, Transcriptomics.

Abstract:
The use of next generation sequencing (NGS) for the study of the transcriptome is now ten years old. Despite RNA-Seq can now be considered an established methodology, nowadays there is gap between the power of the method and its applicability, mainly due to the bioinformatic knowledge needed for the analysis of the raw output. Apart from the needed computational resources, there is a wide range of available software and tools that address different aspects of the analysis of RNA-Seq data, making the selection and tuning of a pipeline even harder in laboratories lacking bioinformaticians. In the present study, we have developed a light-weight, portable and scalable analysis pipeline for RNA-Seq data that cover the whole process from the raw data to the visualization of the results. We prepared a group of scripts in bash and R that apply a selection of open-source software to sequentially perform the following steps: (1) Quality trimming and filtering of reads, (2) alignment or pseudo-alignment to a reference genome or transcriptome, (3) summarization into counts per gene, (4) differential expression analysis, (5) differential signaling activity analysis and (6) gene set enrichment analysis. In addition, we included specific scripts for the quality control and result visualization in every step. We also translated the pipeline to the Workflow Description Language (WDL) and dockerized all the necessary software to run the pipeline into a container. Additionally, we measured the resources employed by the pipeline by applying it on different datasets of organisms commonly used in biomedical research. In summary, we present a pre-configured and portable analysis pipeline that can be directly deployed and executed on a computer or cluster, making this process available to everyone, with or without bioinformatic experience.

IVe. Presence and pathophysiological role of the truncated SST5TMD4 splicing variant of the somatostatin receptor subtype 5 in human high-grade astrocytomas.

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Scientific Program: Cancer (Oncology and Oncohematology)

Keywords: glioblastoma multiforme, aberrant splicing, SST5TMD4, high-grade astrocytomas

Abstract:

Gliomas are the most common malignant brain tumors in humans, characterised by rapid growth and invasion. According to the World Health Organization (WHO) classification, astrocytomas, the major type of gliomas, are graded from I to IV, being III and IV considered as high-grade/aggressive tumors. Specifically, grade IV astrocytomas, known as glioblastomas multiforme (GBM), are the most frequent, malignant and invasive subtype. To date, the current standard treatment of human GBM consists of surgery followed by radiotherapy and/or chemotherapy. However, the average period of survival is still only around 14 months after the first intervention. Therefore, there is a clear need for the identification of novel diagnostic/prognostic tools and therapeutic strategies to manage and treat this devastating pathology. In this context, the truncated SST5TMD4 variant, produced by aberrant alternative splicing of the *SSTR5* gene, is overexpressed and associated with increased aggressiveness in several endocrine-related tumours (e.g. pituitary/breast/prostate tumors, etc.). Therefore, the main objective of this study was to carry out a comprehensive analysis of the expression of SST5TMD4 and pathophysiological role in high-grade astrocytomas by using human primary cell cultures and GBM cell lines (U87 and U118) as experimental models. Our results revealed that SST5TMD4 variant was significantly overexpressed in human astrocytomas tissues (grade III-IV; n=34) compared to healthy-control brain tissues (n=16). Remarkably, overexpression of SST5TMD4 variant (with a specific plasmid) increased cellular proliferation, migration and tumorspheres formation whereas SST5TMD4 silencing (by specific siRNAs) decreased these functional parameters. Our data also indicate that the modulation of the expression of SST5TMD4 variant in GBM cells altered key signaling pathways associated with tumor aggressiveness. Taken together, our results demonstrate that SST5TMD4 is overexpressed in astrocytoma, which is associated to enhanced aggressiveness, supporting its potential utility as tool to develop new molecular biomarkers and drug therapies for these devastating tumors.

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IVf. Fibroblast growth factor 23 (FGF23) is regulated by nutrient availability

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Scientific Program: Nutrición, enfermedades endocrinas y metabólicas.
Keywords: FGF23, glucose, phosphorus, mTOR

Abstract:
Bone not only suffers the consequences of altered glucose metabolism but is also actively involved in the regulation of energy metabolism (Kanazawa I. Endocr. J. 2017, 64:1043-1053). Fibroblast growth factor 23 (FGF23) is a hormone secreted by osteoblasts in response to increased phosphate (P) load to facilitate phosphaturia and to decrease calcitriol production (Vervloet M. Nature Rev. Nephrol. 2019, 55:109-120). Previous epidemiological studies have suggested that FGF23 might be regulated by energy intake (DiGiuseppe R et al. PLoS ONE 2015, 10:e0133580). Moreover, experimental work has shown that feeding high calorie diets to rodents consistently increases plasma and bone FGF23 (Raya AI et al. Sci. Rep. 2016, 6:36881).

The aim of this work was to study the effect of nutrient availability on FGF23 production by bone cells. Rat osteoblast-like cells (UMR106) were cultured in Dulbecco's modified Eagle's medium with either high glucose (HG, 4.5 g/L) or low glucose (LG, 1 g/L) up to 90% confluence. Cells were cultured in normal P (NP, 1 mM) and high P (HP, 4 mM). Experiments were also conducted by adding rapamycin (Rap, 10 nM) to the HG medium. mRNA FGF23/Tbp was measured by RT-PCR. Values for the study groups were: HG-NP, 1.02±0,09a; HG-HP, 1.66±0,18b; LG-NP, 0.59±0,03c; LG-HP, 0.50±0,02c; HG-NP-Rap, 0.45±0,03c. Groups with different letters are statistically different ($p<0.05$).

FGF23 was regulated not only by P but also by nutrient availability. Cells incubated with HG consistently expressed more FGF23 than cells incubated with LG. Moreover, HP did not stimulate FGF23 under LG conditions. In addition, inhibition of the mTOR pathway by rapamycin reduced FGF23 expression in cells incubated in HG to levels comparable to cells incubated in LG. It remains to be elucidated whether the regulation of FGF23 by nutrient availability is related to a (presently) unknown role of FGF23 in energy metabolism. In any case, high concentrations of FGF23 are associated with cardiovascular morbidity and mortality (Scialla JJ et al. J. Am. Soc. Nephrol. 2014, 25:349-360); thus, reducing energy intake may have further advantages on cardiovascular health related to the decrease in FGF23.

SESSION V

Nutrition, Endocrine and metabolic disesases

Va. Postprandial lipemia modulates alpha cell function in the prediction of type 2 diabetes development: from CORDIOPREV study.

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Scientific Program: Nutrition, Endocrine and metabolic
Keywords: diabetes, alpha cell, glucagon, disease prediction, CORDIOPREV.

Abstract:
*Objective***:** Our objective was to study the factors underlying the alpha cell dysfunction, evaluated by postprandial levels of glucagon, in the progression of type 2 diabetes (T2DM) after an intervention with two healthy diets.Indeed, we evaluate whether postprandial levels of glucagon may be considered as a predictive factor of T2DM development in coronary heart disease patients from CORDIOPREV study.
Materials and methods: We included all patients (n=462) from the CORDIOPREV study without T2DM at the beginning of the study. To evaluate whether the lipemia postprandial could induces the alpha cell dysfunction, we categorized our population by tertiles (ascending order) of the area under the curve (AUC) of triglycerides (TG) and we determined the postprandial levels of glucagon. Indeed, patients were categorized by tertiles of AUC of glucagon levels after an oral glucose overload at baseline:tertile 1 (LOW group), tertile 2 (INTERMEDIATE group) and tertile 3 (HIGH group). Patients were randomized to consume either a Mediterranean or a low-fat diet. We performed a COX regression analysis to determine the T2DM risk according to AUC of glucagon groups after a median follow-up of 60 months.
*Results:*We found that patients with higher TG levels also presented higher postprandial levels of glucagon at baseline and after 2 years of dietary intervention (P=0.009). Moreover, we observed higher T2DM risk (HR: 2.59; 95% CI 1.52-4.42) in patients with higher AUC of glucagoncompared with LOW group. Indeed, these patients showed elevated insulin levels (P=0.008) and lower sensitivity to insulin in adipose tissue (P=0.047) than LOW group.
Conclusions: Our results point out that postprandial lipemia, characterized by elevated triglycerides concentration, induces pancreatic alpha cell dysfunction in patients with cardiovascular disease. Indeed, our data support that higher postprandial levels of glucagon might be considered as a useful tool to evaluate the risk of T2DM development.

Vb. Impact of obesogenic extracellular cues on lipid accumulation

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: Adipocytes, Obesity, Fibrosis, Extracellular matrix, Rab34

Abstract:
In obesity, adipocytes accumulate lipids above normal levels in their lipid droplets (LDs), thus leading to adipocyte dysfunction. Other pathogenic mechanisms that impair normal adipocyte functioning in obesity include fibrosis. However, it is unknown whether obesogenic extracellular matrix (ECM) signals alter normal communication between the intracellular organelles implicated in lipid management in adipocytes, endoplasmic reticulum (ER), LDs, and peroxisomes. Herein, 3T3-L1 cells were differentiated in a fibrotic matrix containing collagen I and increasing concentrations of the proteoglycan, lumican, which enhances ECM stiffness. Our studies show that, under these conditions, 3T3-L1 cells exhibited ER fragmentation, a type of cell stress that hindered LD and peroxisome budding from the ER. Moreover, lumican diminished the transport of the LD-associated small GTPase, Rab34, to the LD surface. This protein was identified in ER exit sites (ERES), which constitute protein and lipid transfer bridges between ER and LDs, suggesting a functional role for this protein in ER-LD contacts. Indeed, Rab34 overexpression increased LD size in 3T3-L1 adipocytes. Studies in human preadipocytes showed the same traffic pathway for Rab34 to LDs (ERES route), while in mature adipocytes the ER-Golgi intermediate compartment (ERGIC) was the preferred route. Notably, adipose tissue samples from obese mice and patients showed deregulated Rab34 expression in response to diet- and/or genetic-induced obesity and changes in insulin sensitivity. Altogether, our results suggest that ER-fragmentation triggered by fibrosis impairs ER-LDs and ER-peroxisomes interactions thus limiting the biogenesis and/or growth of these organelles. In the case of LDs, this may be due to a defective traffic of LD protein coat components, such as Rab34, through ER-LD contact sites at specific ER subdomains (ERGIC/ERES). In this context, Rab34 could represent a valuable biomarker for the design of anti-obesity therapies.
Funding: MINECO/FEDER (BFU2016-76711-R; BFU2017-90578-REDT); CIBERobn (ISCIII).

Vc. Ablation of AMP-Activated Protein Kinase (AMPK) in GnRH neurons produces reproductive and metabolic alterations: Implications for the metabolic control of reproduction

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Scientific Program: Nutrition, Endocrine and metabolic diseases
Keywords: Energy balance, puberty, AMPK, GnRH

Abstract:
Reproduction depends on body energy and metabolic status. GnRH neurons, the final output pathway of the brain controlling reproduction, integrate and transmit metabolic information to the reproductive axis. Yet, the molecular mechanisms involved in such phenomenon remain largely unfolded. AMP-activated protein kinase (AMPK) is a cellular sensor that becomes activated in conditions of energy deficit, such as anorexia or cachexia. Nonetheless, the physiological contribution of AMPK signaling in GnRH neurons to the metabolic control of reproduction is unknown. We report herein the characterization of the first mouse line, named GAMKO, with conditional ablation of α1-AMPK in GnRH neurons. GAMKO females displayed earlier puberty onset and enhanced LH (as surrogate marker of GnRH) responses to the NKB agonist, senktide, in adulthood, as well as to kisspeptin-10 at the prepubertal and adult stage. Adult GAMKO females showed also partial resilience to the inhibitory effects of negative energy balance on reproduction. Thus, GAMKO females submitted to chronic subnutrition showed a faster recovery of estrus cyclicity after re-feeding and did not respond to fasting with the consequent physiological drop of LH level and the change in the pattern of LH pulsatility. This effect was dependent on estradiol, since no changes in basal LH levels or pulsatility were detected in ovariectomized GAMKO mice subjected to fasting or subnutrition. Notably, GAMKO females showed also alterations in body composition, with increased fat mass, and modest changes in insulin and glucose tolerance. In sum, our data document a physiological role of AMPK signaling in GnRH neurons in the metabolic control of the reproductive axis, as conduit of at least part of the inhibitory actions of energy deficit. In addition, our results disclose a putative function of AMPK specifically in GnRH neurons in the control of body composition and glucose homeostasis, whose pathophysiological relevance warrants further investigation.

Vd. Effect of dietary intervention on the expression profiles of miRNAs involved in the progression and regression of atherosclerosis in patients with cardiovascular disease

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Scientific Program: Nutrition, Endocrine and metabolic diseases
Keywords: carotid intima-media thickness, microRNAs, atherosclerosis, diet, epigenetics

Abstract:
Background: Cardiovascular diseases are the primary cause of death worldwide. The common base of these diseases is atherosclerosis, a process characterized by the thickening of the carotid intima-media (cIMT). Previous studies demonstrate that miRNAs regulate biological and pathological processes, and can be regulated by diet. Our aim was to study the effect of dietary intervention on the expression of miRNAs associated with atherogenesis in patients with cardiovascular disease.
Materials and Methods: The present study included 240 patients from the CORDIOPREV study: 120 with the most extreme progression of cIMT after 5 years of low fat or Mediterranean dietary intervention (n= 55 and 62, respectively), and 120 with the most extreme regression of cIMT after 5 years of both diets (n= 51 and 68, respectively). cIMT was measured bilaterally with high-resolution Doppler echography. Expression of 28 miRNAs from peripheral blood mononuclear cells at baseline and year 5 was measured through the OpenArray platform. Statistical analyses of two-way ANOVA and PCA were performed to evaluate the differences between diets and groups.
Results: The expression of miR-221 and miR-92a was significantly lower in patients who showed cIMT regression as compared to progression after intervention of low fat diet ($p = 0.027$ and 0.032, respectively). The expression of miR-365 was significantly lower in patients who showed cIMT progression after intervention with Mediterranean versus low fat diet ($p = 0.016$). The PCA analysis showed that miR-221, miR-126 and miR-92a have a significant capacity for differentiation between groups (progression and regression cIMT) in patients who followed a low fat dietary model.
Conclusion: Changes in the expression of miRNAs involved in the progression or regression of atherosclerosis are regulated by diet in patients with cardiovascular disease. The expression profiles of miRNAs could be used as biomarkers to differentiate between groups of patients who follow specific dietary habits.

Ve. Automated method for quantitative determination of steroids in serum by SPE–LC–MS/MS

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Scientific Program: Nutrition, Endocrine and metabolic diseases
Keywords: Steroids, LC–MS/MS, Serum, SPE, MRM, Sample preparation.

Abstract:
Steroids are biologically active lipids synthesized from cholesterol. The process, known as steroidogenesis, generates different metabolite families with varied biological functions. Among them, androgens and estrogens are related with development of masculine and feminine characteristics, muscle mass, libido, spermatogenesis and regulation of female reproductive system. Progestogens, with special emphasis on progesterone, control the embryogenesis, pregnancy and menstrual cycle. Glucocorticoids and mineralocorticoids possess a role for regulation of metabolic activity, immunological functions and sodium reabsorption. Deregulation of these processes can be induced by an abnormal level of these metabolites that are found at low concentrations in biological samples in normal conditions. In this research, an automated analytical method based on solid phase extraction on-line coupled to liquid chromatography with tandem mass spectrometry detection (SPE–LC–MS/MS) was developed for quantitative determination of 16 steroids (4 progestogens, 2 estrogens, 4 androgens, 5 glucocorticoids and 1 mineralocorticoid) in serum. On-line SPE was performed by using miniaturized cartridges (10 mm length x 2 mm inner diameter) to enhance the retention/elution efficiency of steroids. This arrangement allows to reach quantitation limit at pg mL-1 levels in serum (pregnenolone 5 pg mL-1, progesterone 2 pg mL-1, 17α-hydroxypregnenolone 100 pg mL-1, 17α-hydroxyprogesterone 500 pg mL-1, estrone 1 pg mL-1, estradiol 1 pg mL-1, androstenedione 2 pg mL-1, DHEA 50 pg mL-1, DHT 5 pg mL-1, testosterone 5 pg mL-1, 11-deoxycortisol 2 pg mL-1, 21-hydroxyprogesterone 50 pg mL-1, corticosterone 2 pg mL-1, cortisone 2 pg mL-1, cortisol 200 pg mL-1 and aldosterone 5 pg mL-1) by direct injection of 100 µL serum. The precision of the method, estimated as between-days variability, was below 25% for all steroids. For this reason, the method is especially suited for implementation in clinical studies demanding for high-throughput analysis.

Vf. Lipid biomarkers of the adipose tissue in obesity-induced insulin resistance

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Scientific Program: Nutrition, Endocrine and metabolic diseases

Keywords: Metabolic disorders, Obesity, MALDI-Imaging, Sphingolipids, Ether-phospholipids.

Abstract:

Obesity is associated with increased risk for insulin resistance (IR), type 2 diabetes (T2D), cardiovascular disease and cancer. Adipocyte hypertrophy in obesity involves enhanced accumulation of triglycerides and other neutral lipids in lipid droplets as well as changes in membrane lipids. In fact, sphingolipids and ether-phospholipids have emerged as key players and potential biomarkers in metabolic disorders, although their biogenesis and turnover in adipocytes remain unclear. Herein, we developed a novel MALDI-Imaging approach coupled to liquid chromatography (LC-MS/MS) to analyze the composition and spatial distribution of lipids in histological sections of AT from obese subjects with different degrees of insulin sensitivity. MALDI-IMS experiments allowed the identification of 8000 ions corresponding to different lipid species in the three groups of subjects investigated: with normoglycaemia (NG), IR or T2D. ANOVA analysis revealed 2405 significantly different ions ($p<0.01$) among groups. PLS-DA models based on lipidomic data discriminated diabetic vs non-diabetic obese subjects and revealed a significant signature of 14 downregulated and 1 upregulated ranked ions (Top15) of T2D vs NG, which were subsequently identified as sphingomyelins and eter-phospholipids, among other phospholipids, by combining MALDI-IMS and LC-MS/MS data. Hence, we investigated the enzymes involved in the biosynthesis of these lipids during adipogenesis as well as upon exposure of 3T3-L1 adipocytes to high glucose and high insulin concentrations (HGHI) and TNFα, as models of hyperglycemia/insulinemia and inflammation, respectively. These studies revelead that both sphingolipid synthesis and ether-phospholipid biogenesis were greatly impaired upon exposure to TNFa and, to a lesser extent, to HGHI, which is largely in accordance with our lipidomic data. Altogether, our results suggest that insulin resistance in obesity is associated with the dysregulation of the lipid profile of adipocytes and further support the contribution of hyperglycemia/hyperinsulinemia and the inflammatory environment to the development of metabolic disease in obesity.

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POSTER
Abstracts

POSTER SESSION I

Cancer (Oncology and Oncohematology)

P1. Frequency of whole breast irradiation (WBRT) after intraoperative radiotherapy (IORT)

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Scientific Program: Cancer (Oncology and Oncohematology)
Keywords: Cancer, breast, radiotherapy, intraoperative, photons, boost

Abstract:
Assessing the physical parental abuse as a criminogenic factor in adolescents deprived of liberty, is the main object of study, for which it was carried out in the City of Guayaquil, Province of Ecuador from October 2018 - March 2019, with the purpose of associating causes, addressing the phenomenon as a special public health problem that affects the child and adolescent population of Ecuador, which requires a greater knowledge of the ways in which it manifests itself in different contexts, as well as its causes and consequences, since the prevalence of child maltreatment behavior is found in 33% of the population, where by means of a non-experimental study of descriptive type of cross-section or of prevalence under the method of observation of cases it was determined that 57 young people, of the total of 179 sanctioned with the socio-educational measure of deprivation of liberty were victims of physical abuse in their childhood from actions executed by his father, mother or guardian. Because of this, it is concluded that child maltreatment is a social phenomenon that threatens the health of the child and adolescent population, creating risk conditions that may compromise their adult life, for which epidemiological surveillance systems should be created that can be used to address causes and consequences of physical abuse, from the perspective of Public Health, in order to prevent delinquent behavior, considering that such violent actions are directly related to the commission of crime by adolescents, a social phenomenon that undermines the foundations of the constitutional State of Rights and Justice.

P2. 3D-MALDI-Imaging Analysis Of Human Colon Cancer Xenograft In Murine Models To Monitor Oxaliplatin/5- Fluorouracil Treatment Efficiency

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Scientific Program: Cancer (Oncology and Oncohematology)

Keywords: Maldi Imaging, Proteomics, Xenografts, FFPE, 3D-MSI

Abstract:
Xenografts are a very useful way to monitor the efectiveness, effects and performance of different oncological treatments in model organisms. Xenografts that are used in immunocompromised mice are of special interest for research groups that focus their work on the mechanisms of cancer action or in the search for new oncologic biomarkers in such a way that they can modelize new treatments behaviours. In this work, xenografts builded from human colon cancer, were transplanted to immunocompromised mice and were underwent three types of treatment with increasing concentrations of oxaliplatin and 5-FU. Thereafter, a 3D-Maldi Imaging (3D-MSI) analysis was carried out to monitor the behaviour and efectiveness of these treatments. To achieve this, serialized sections were made from FFPE samples from each treatment. After this, an in situ digestion was obtained for each slide. Subsequently, matrix was deposited over the slides and the samples were scanned in Maldi TOF / TOF. Peptide profiles corresponding to each condition were analyzed using dedicated scripts and packages in the R environment. The results obtained shown the correct grouping of the samples from the same group (treatment) by means of PLSDA. We were able to see how the most extreme conditions (higher and lower concentration) resemble their profiles more than initially expected, being the intermediate concentration the most different to control group. Afterwards, significative m/z were represented in such a way that an image can be obtained representing their distribution in each section of the conditions analyzed. Finally, the coregistration and subsequent 3D reconstruction of the top 10 m/z from the peptide profiles obtained was done by using free software and scripts developed in the IMIBIC Proteomics Unit. Our next goal is to carry out more sophisticated experiments that allow the development and advancement of the search for new biomarkers through the use of use of 3D-MSI.

P3. Dry sweat as sample for metabolomics analysis

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Scientific Program: Cancer (Oncology and Oncohematology)
Keywords: Dry sweat, fresh sweat, metabolomics, sampling, mass spectrometry, lung cancer

Abstract:

Sweat is gaining popularity in clinical metabolomics as this biofluid is non-invasively sampled and its composition is modified by several pathologies. In fact, human sweat has been recently used in metabolomic studies to discriminate between lung cancer patients and risk factor individuals. There is a lack of standardized strategies for collection of human sweat. Most studies have been carried out with fresh sweat collected after stimulation. A promising and simple alternative is sampling dry sweat by a solid support impregnated with a suited solvent. This research was aimed at comparing the metabolomics coverage provided by dry sweat collected by two solid supports (gauzes and filter papers) impregnated with different solvents. The dissolved dry sweat was analyzed by a dual approach: GC–MS and LC–MS/MS. Among the tested sampling strategies, filter paper impregnated with 1:1 (v/v) ethanoλ–phosphate buffer resulted the combination providing the highest metabolomics coverage (tentative identification of 175 compounds). Dry and fresh sweat were compared by using pools from the same individuals to evaluate compositional differences. Families of metabolites such as carnitines, sphingolipids and N-acyl-amino acids, among others, were exclusively identified in dry sweat. Comparison of both samples allowed concluding that dry sweat is better for analysis of low polar metabolites and fresh sweat is more suited for polar compounds. As most of the identified metabolites are involved in key biochemical pathways, this study opens interesting possibilities to the use of dry sweat as a source of metabolite markers for specific disorders such as cancer. In fact, N-acetyl-amino acids such as acetylhistidine had been previously found in urine from prostate cancer patients at high-significantly lower concentration than in healthy individuals. In conclusion, sampling of dry sweat could provide a standardized approach for collection of this biofluid, thus overcoming the variability limitations of fresh sweat.

P4. Development of a system to monitor DNA methylation-induced gene silencing in human cells

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Scientific Program: Cancer (Oncology and Oncohematology)
Keywords: Epigenetics; DNA methylation; Gene silencing; 5-Aza-2'-deoxycytidine; Trichostatin A; 5-meC-DNA-glycosylase (ROS1).

Abstract:
Epigenetic processes involve changes in chromatin organization and the establishment of specific patterns of gene expression. Epigenetic marks include post-translational modifications of histones, which produce activation or repression states, and DNA methylation (5-meC), a stable but reversible modification involved in transcriptional gene silencing. Aberrant DNA methylation is a hallmark of many common cancers.

The aim of this work is to develop an experimental system to study the mechanisms by which DNA methylation causes gene silencing in human cells. To this end, HEK293 cells were transfected with an *in vitro* methylated EGFP reporter using as a control the corresponding non-methylated gene. Gene reactivation was analyzed by using several epigenetic modifiers: (1) 5-Aza-2'-deoxycytidine (5-Aza-dC), (2) Trichostatin A (TSA) and (3) ROS1, a plant 5-meC-DNA-glycosylase.

Results show that methylation of the reporter gene promotes gene silencing in a time-dependent manner, suggesting that repression occurs indirectly through recruitment of transcriptional repressors and/or chromatin remodeling factors. Reactivation of the methylated gene was observed after treatment with the histone deacetylase inhibitor TSA, indicating that the transfected plasmid adopts a nucleosomal-like structure upon entry in the nucleus. On the other hand, treatment with the DNA methyltransferase inhibitor 5-Aza-dC also induced gene reactivation. Finally, gene silencing was also partially reversed by expression of the of plant DNA demethylase ROS1, indicating that this enzyme may become an useful tool to modulate gene expression. Altogether, these results indicate that the experimental system developed in this work may be used to study the molecular mechanisms involved in methylation-induced gene silencing.

P5. CE-MS based urinary biomarkers to distinguish non-significant from significant prostate cáncer

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Scientific Program: Cáncer (Oncología y Oncohematología)
Keywords: Significant Prostate Cancer, urinary peptide markers, Risk stratification

Abstract:
Background: Prostate cancer is progressing slowly when present in low risk forms but can be lethal when progresses to metastatic disease. A non-invasive test that can detect significant prostate cancer is needed to guide patient management.
Methods: Capillary electrophoresis/ mass spectrometry has been employed to identify urinary peptides that may accurately detect significant prostate cancer. Urine samples from 823 patients with PSA (<15ng/ml) were collected prior to biopsy. A case-control comparison was performed in a training set of 543 patients (nSig=98; nnon-Sig=445) and a validation set of 280 patients (nSig=48, nnon-Sig=232). 19 significant peptides were subsequently combined by a support vector machine algorithm.
Results: Independent validation of the 19-biomarker model in the 280 patients resulted in a 90% sensitivity and 59% specificity, with an AUC of 0.81, outperforming PSA (AUC: 0.58) and the ERSPC-3/4 risk calculator (AUC: 0.69) in the validation set.
Conclusions: This multi-parametric model holds promise to improve the current diagnosis of significant prostate cancer. This test as a guide to biopsy could help decreasing the number of biopsies and guide intervention. Nevertheless, further prospective validation in an external clinical cohort is required to assess the exact performance characteristics.

P6. The splicing factor SF3B1 as a novel diagnostic, prognostic biomarker and effective therapeutic target for prostate cancer

Authors: Juan M. Jimenez-Vacas, Vicente Herrero-Aguayo, Enrique Gómez-Gómez, Antonio J. Montero-Hidalgo, Antonio J. León-González, Prudencio Sáez-Martínez, Ana Martínez-López, Rafael Sánchez-Sánchez, Teresa González-Serrano, Daniel J. López-Ruiz, María J. Requena-Tapia, Justo P. Castaño, Manuel D. Gahete, Raúl M. Luque

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Scientific Program: Cáncer (Oncología y Oncohematología)

Keywords: Prostate Cancer, SF3B1, Spliceosome, Pladienolide-B, AR-v7, Prognosis

Abstract:

Prostate cancer (PCa) is one of the most common cancers types among men. Development and progression of PCa is associated to aberrant expression of oncogenic splicing variants (e.g. AR-v7, In1-ghrelin), suggesting that dysregulation of the splicing process might represent a potential actionable target for PCa. However, the role of the machinery involved in the control of splicing process, named spliceosome, remains still unknown in PCa. Therefore, we aimed to explore the role of SF3B1, one of the main functional components of spliceosome, in PCa. To this end, the expression levels (mRNA and protein) of SF3B1 were analyzed in samples from different cohorts of PCa patients [clinically-localized (n=84), highly-aggressive PCa (n=42) and TCGA dataset (n=497)]. Functional and mechanistic assays in response to pladienolide-B, a pharmacological blocker of SF3B1 function, were performed in non-tumor and tumor-derived prostate cells. Our results showed that SF3B1 was overexpressed in PCa tissues and its levels were associated to clinically and molecularly relevant PCa aggressive features (e.g. Gleason score, presence of metastasis, AR-v7 expression, etc.). Moreover, the inhibition of SF3B1 activity by pladienolide-B treatment modulated functional aggressiveness parameters (i.e. reduced proliferation, migration and tumorspheres-formation and increased apoptosis) in PCa cell lines, irrespective of AR-v7 expression, and reduced viability of primary PCa cells. Antitumor actions of pladienolide-B involved: 1) Inhibition of PI3K/AKT and JNK signaling pathways, 2) modulation of tumor markers and splicing variants (e.g. reduced expression of AR-v7, In1-ghrelin, etc.), and 3) regulation of key components of mRNA homeostasis-associated machineries (e.g. spliceosome, SMG-1–Upf1–eRF1–eRF3 (SURF) complex, exon-junction complex, etc.). Altogether, our results demonstrate that SF3B1 was overexpressed and associated to malignant features in PCa, and that its pharmacological blockade reduced PCa aggressiveness, suggesting that SF3B1 could represent a novel diagnostic/prognostic biomarker and a therapeutic target in PCa.

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P7. Comparative anticancer effect of hydroxytyrosol and its semisynthetic derivatives in prostate cancer cells

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Scientific Program: Cáncer (Oncología y Oncohematología).

Keywords: Hydroxytyrosol, prostate cancer, extra virgin olive oil

Abstract:

The use of extra virgin olive oil (EVOO) as the main source of fat in the Mediterranean-diet has been related to its positive effects on human health. Specifically, hydroxytyrosol (HT), one of the major phenolic compounds of EVOO, exerts a protective role against cancer. In fact, there is a growing interest in the development of new forms of HT to improve its bioavailability/pharmacological-activities. However, the effect of HT and its derivatives is still poorly studied in prostate cancer (PCa). Therefore, the aim of this study was to assess and compare in vitro the anticancer effect of HT and five semisynthetic-derivatives, including alkyl ethers, esters, and nitro-derivatives, in both non-malignant (RWPE-1) and cancerous (22Rv1/PC3) prostate cell-lines. To this end, the potential antitumor effects and mechanism of actions of the different compounds were evaluated using proliferation/migration-assays and real-time qPCR, respectively. The antiproliferative effect of HT and two of its derivatives, hydroxytyrosyl acetate (HT-Ac) and ethyl hydroxytyrosyl ether (HT-Et), was significantly higher in tumor PC3 cells [IC50±SEM for: HT (28.9±2.2μM), HT-Ac (23.4±3.2μM) and HT-Et (20.3±3.1μM)] than in normal RWPE-1 cells (IC50, 40-50μM range), whereas the nitro-derivatives were more cytotoxic in the non-malignant cells. Therefore, HT, HT-Ac and HT-Et were selected for further experiments. The antiproliferative effect of 30μM HT-Ac and 10μM HT-Et was significantly higher than HT in PC3 cells. Moreover, treatment with HT, HT-Ac and HT-Et significantly reduced cell migration in RWPE-1 and PC3 cells. Finally, the anticancer activity of these compounds was associated with a modulation of the expression of key-genes involved in PCa-aggressiveness (i.e. MKi67/MMP9/MYC). Altogether, our data demonstrate that the lipophilic derivatives HT-Ac and HT-Et, not only maintained the anticancer effect of the parent compound HT against PCa cells, but also improved its cytotoxic effect at selected concentrations, suggesting these derivatives might be considered as a novel therapeutic tool in PCa.

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P8. Effectiveness of thoracoscopic talc pleurodeseis in malignant pleural effusion

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Scientific Program: Cancer (Oncology and Oncohematology)
Keywords: Pleural effusion, chemical pleurodesis, lung, pleura

Abstract:

INTRODUCTION **-**Malignant pleural effusion is caused by tumors elsewhere in the body (e.g., lung and breast cancer) that metastasize to the visceral and/or parietal pleura. The obliteration of the pleural cavity with chemical pleurodesis by local instillation of sclerosing substances is the treatment of choice when the lung is completely re-expanded

OBJECTIVE -Analysis of effectiveness of thoracoscopic talc pleurodesis realized in our center and to stratify the results according to the origin of the primary tumor causing the pleural effusion.

We carried out a retrospective study of patients submitted to thoracoscopic talc pleurodesis due to malignant pleural effusion, from 2008 to 2015 (n = 105). We calculated the pleural efussion free interval (PEFI) for each patient and after that, we stratified the results according to the origin of the primary tumor causing the malignant pleural effusion.

RESULTS - We obtained a mean pleural efussion free interval (PEFI) of 51,6 months, (CI 95% 41,5 - 61,7 months). After the stratification, we obtained a PEFI of 42,3 months when the primary tumor causing the pleural effusion was a breast carcinoma, 12,7 moths for mesotheliomas, 11 months for ovarian carcinomas, 10 months when it was a lung carcinoma, 6 months for abdominal carcinoma and 5,1 month for renal neoplasms.

CONCLUSION **-** There were no significant differences between the origin of the primary tumor causing the pleural effusion and the pleural effusion free interval (PEFI) ($p > 0,05$), however, it seems that the thoracoscopic talc pleurodesis is more effective when it is used for the management of malignant pleural effusions caused by breast carcinomas, and it is poorly effective when the primary tumor causing is a renal carcinoma. It is probably because some renal carcinomas segregate fibrinolytic enzymes than can break the adherences created with the pleurodesis.

P9. DEMETER plant DNA demethylase expression in human cancer cells leads to H1.0 histone reactivation

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Scientific Program: Cancer (Oncology and Oncohematology)
Keywords: Epigenetics, DNA demethylase, DME, cancer, H1.0.

Abstract:
Methylation of cytosine in carbon 5 of the pyrimidine ring (5-meC) is a stable, but reversible, epigenetic mark that promotes transcriptional gene silencing. An alteration in DNA methylation patterns can lead to the appearance of human diseases, including cancer. Methylation levels are controlled and modified by demethylation mechanisms that are not yet completely understood in human cells, but have been well characterized in plants. The research group where this work has been carried out has previously identified a plant demethylase (DME) that releases 5-meC through a mechanism analogous to base excision repair.
Histone H1.0 is an isoform of histone 1, which interacts with the DNA integrated in the nucleosomes, allowing a greater compaction of the chromatin. Recently, an epigenetic mechanism that generates intratumoral heterogeneity and involves the H1.0 histone has been described. Specifically, reversible silencing by histone H1.0 methylation has been shown to affect the differentiation status of cancer cells and their ability for self-renewal.
In this work, it has been determined whether DME expression in colon cancer cells (DLD-1) can initiate an active DNA demethylation process, by modifying the methylation status of the CpG island corresponding to H1F0 promoter (CGI) and the adjacent region (CGI shore). It has been described that the H1F0 CGI shore contains a regulatory region controlling H1F0 expression, which undergoes methylation in cancer.
Results obtained indicate that expression of DME in DLD-1 leads to demethylation in H1FO, associated to an increase in expression, both at RNA and protein levels. This work describes a process that restores H1.0 levels, necessary to reduce the population of autoproliferative cells, which are responsible for the maintenance and growth of the tumor.

P10. Variables associated with positive target prostate biopsy guided by co-registration US-MRI

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Abstract:
Objective: To assess which clinical, analytical and imaging variables are associated with a higher probability of founding prostate cancer and significant prostate cancer in target prostate biopsy guided by co-registration US-MRI.
Material and method: A cohort of patients who underwent mpRM prior to prostate biopsy with co-registration of US-MR images was selected. In case of suspicious lesion (PIRADSv.2≥3) the patient underwent guided biopsy plus standard biopsy according to clinical practice. All MRIs were reviewed by an experienced radiologist, reclassifying their risk category. A minimum of two cores per lesion was taken, with a minimum of 1 core per 3 mm of lesion length.
Significant cancer was considered in case of a target lesion diagnosed of Gleason ≥7 and / or ≥ 5mm. A descriptive analysis was performed and in order to assess the association of each variable with the probability of diagnosing PCa or Sig PCa in the target biopsy.
Results: A total of 270 patients were evaluated. The median age was 65 years and the PSA was 6.7 ng / ml. 167 patients were diagnosed with PCa (62%). Up to 12.2% of MRI were reclassified to PIRADS <3. The target lesion was positive for PCa in 136 patients (50%) and was significant in 124 patients (45%). The multivariate analysis showed that a suspicious lesion (PIRADS ≥4), higher PSA levels, higher age, the lesion localization (anterior versus transitional gland), the fact of having no previous biopsy or being under active surveillance versus patients with a previous negative biopsy and a lower prostate volume were associated with a positive target biopsy for PCa or Sig PCa ($p<0.05$). Among these factors, the PIRADS suspicion and the location in the anterior stromal area were the variables with the strongest association with a positive biopsy (OR ≥ 5).
Conclusion: There are numerous pre-biopsy variables that are associated with a higher probability of resulting in a positive target biopsy for PCa and Sig PCa.

POSTER SESSION I

Chronic and Inflammatory diseases

P11. Muscle-skeletal disorders in musicians in training in relation to physical inactivity

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: musicians, musculoskeletal disorders, physical activity, health

Abstract:
During the last years more and more professionals and students of music present different disorders of the motor apparatus. Various studies show that 50-90% of musicians suffer different disorders throughout their careers. The chosen theme allows to know how to carry out a habitual practice of physical activity to prevent injuries of the musculoskeletal type. For this, different characteristics of the individuals of the study that are related to physical activity, health and musculoskeletal disorders will be known.
Objective: To evaluate the incidence of musculoskeletal injuries in these students according to the type of instrument and the physical activity they perform.
Method: Descriptive study. The subjects to study are students of the level of Middle Grade of the Music Conservatory "Maestro Chicano Muñoz" of Lucena (Córdoba) in different musical specialties. The level of physical activity will be determined through a self-administered questionnaire.
Results: 66.66% of the subjects in the sample stated that they carried out some sports activity on a regular basis. But only 36% perform a warm-up prior to instrumental practice. 88.88% say they have discomfort and / or pain in the back. And the risk of physical loading due to repetitive movements is high.
Conclusions: A high percentage of musicians in training report that they have had an injury that prevents them from carrying out instrumental practice successfully. And the previous warm-up and the realization of regular physical activity is not a habit among musicians.

P12. Parental physical abuse as a criminogenic factorin private adolescents of freedom

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Parental physical abuse, criminogenic factors, adolescents deprived of their liberty.

Abstract:
Assessing the physical parental abuse as a criminogenic factor in adolescents deprived of liberty, is the main object of study, for which it was carried out in the City of Guayaquil, Province of Ecuador from October 2018 - March 2019, with the purpose of associating causes, addressing the phenomenon as a special public health problem that affects the child and adolescent population of Ecuador, which requires a greater knowledge of the ways in which it manifests itself in different contexts, as well as its causes and consequences, since the prevalence of child maltreatment behavior is found in 33% of the population, where by means of a non-experimental study of descriptive type of cross-section or of prevalence under the method of observation of cases it was determined that 57 young people, of the total of 179 sanctioned with the socio-educational measure of deprivation of liberty were victims of physical abuse in their childhood from actions executed by his father, mother or guardian. Because of this, it is concluded that child maltreatment is a social phenomenon that threatens the health of the child and adolescent population, creating risk conditions that may compromise their adult life, for which epidemiological surveillance systems should be created that can be used to address causes and consequences of physical abuse, from the perspective of Public Health, in order to prevent delinquent behavior, considering that such violent actions are directly related to the commission of crime by adolescents, a social phenomenon that undermines the foundations of the constitutional State of Rights and Justice.

P13. Discovery of proteomic markers of response to anti-TNF drugs in Crohn's disease

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Anti-TNF, Crohn's disease, SWATH

Abstract:
Background: Anti-TNF biologics have improved notably the management of Crohn's disease (CD). However, 25-40% of patients treated with these drugs lose response long-term. In addition, these treatments are expensive and not without risk of adverse events.
Therefore, it is essential to identify reliable markers that will select those patients who can benefit of anti-TNF drugs, improving efficacy and safety.
Methods: 54 CD patients, were stratified according to clinical response: a) Non-primary response (NPR) at 12 weeks of treatment; b) loss of response (LR) and c) sustained clinical response (SCR), at 12 months of treatment. Plasma samples from 20 patients were collected previously to anti-TNF treatment, depleted from most abundant proteins and analysed by a SWATH differential proteomics approach. An ad-hoc spectral library was built from shotgun proteomics runs using a top 65 data-dependent acquisition method. For SWATH analysis, a 60 variable windows method was used. A Triple TOF mass spectrometer (Sciex) coupled to nanoHPLC was used for all mass spectrometry analysis. Functional pathways were analysed by DAVID Bioinformatics Resources 6.7.
Results: 77.3% patients showed SCR, 4.5% NPR and 18.2 % LR. 300 plasma proteins were quantified in all samples. As potential biomarkers of primary response we have identified 18 proteins up-regulated ($p \leq 0.009$ and fold change ≥ 2.4), related to hemostasis and metabolism of carbohydrates. 17 of these proteins are regulated by acetylation. In addition, four proteins were potential biomarkers of loss of response ($p \leq 0.05$ and fold change from 0.5 - 1.4). Two of them related to lipids metabolism.
Conclusion: Early need for anti-TNF and increased blood leucocytes count, probably related to a more severe disease, are associated with NPR. Overweight is associated with secondary loss of response to anti-TNF. In addition, hemostasis, metabolism of carbohydrates and lipids may be involved in the response to anti-TNF in CD.

P14. Transcriptomic and proteomic profiling analysis of human keratinocytes exposed to cannabidiol

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Scientific Program: Chronic and Inflammatory diseases
Keywords: Cannabidiol, Epidermis, Skin diseases, MafB, Nrf2

Abstract:
The epidermis is the outer layer of the human skin which main function is to act as an interface between the host and the environment. Among the different cells found in this epithelium, the keratinocytes have a major role as the constructor bricks of this layer. Cannabidiol (CBD) is a major non-psychotropic phytocannabinoid that attracted a great attention for its therapeutic potential against different pathologies including skin diseases. To characterize at the molecular level the effects of CBD, primary human keratinocytes were treated with CBD during 24 h. Following RNA and protein extraction, the transcriptome and proteome changes were analyzed using mRNA-Seq and SWATH-MS, respectively.
The functional analysis revealed that the CBD upregulated the expression of downstream genes and proteins such as KRT16, THBD and ADAM17, which are regulated by MafB, a transcription factor that plays a key role on keratinocyte differentiation. On the other hand, several components of the extra cellular matrix as collagens and integrins were repressed suggesting an effect of the CBD over the extracellular matrix organizational components. In addition, the transcriptomic changes analyzed using the gene set enrichment analysis revealed an upregulation of the Nrf2 pathway reflected in the induction of HMOX, SQSTM1 (p62) and GCLC genes. CBD activation of the Nrf2 pathway was mediated by nuclear export and degradation of Bach1 by the proteasome. *In vivo* studies confirmed that topical CBD induced the expression of Nrf2- and MafB-dependent genes and induced keratinocytes differentiation.
In summary, our study can set the basis for the use of topical CBD for the treatment of skin diseases including atopic dermatitis, epidermolysis bullosa or psoriasis.

P15. Liver dysfunction associated with rheumatoid arthritis. Effects of anti-citrullinated protein antibodies

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: rheumatoid arthritis, liver,

Abstract:
Background: Liver damage in rheumatoid arthritis (RA) is most common in the form of asymptomatic abnormal liver biopsies. Inflammation, oxidative stress, apoptosis and loss of lipid droplets are involved in the hepatic fibrogenesis.
Objectives: 1) To analyze the impact of RA in the liver function and 2) To evaluate the direct effect of anti-citrullinated protein antibodies (ACPAs) in the liver fibrosis.
Methods: Human study: 300 RA patients and 100 healthy donors (HD) were included. Liver function was analyzed. In vitro model: Hep G2 cells were treated with IgG-ACPAs isolated from RA patients. Mouse model: 15 CB57J/BL mice were used in Collagen Induced Arthritis(CIA)-modelling. Liver samples were collected. Activation of intracellular pathways related to fibrogenesis and molecules involved in lipid metabolism, insulin resistance, oxidative stress and inflammation were analyzed in both models.
Results: Within the normal range, the percentage of RA patients with altered levels of hepatic enzymes and albumin was significantly increased. Moreover, these levels were associated with ACPAs and inflammatory markers. IgG-ACPAs induced the expression of inflammatory and oxidative stress markers and decreased genes involved in insulin signal and lipid accumulation in Hep G2 cells. The phosphorylation of intracellular pathways involved in fibrogenesis was modulated by Ig-ACPAs. The induction of arthritis in mice elevated inflammatory cytokines and markers of macrophages presence. Phosphorylation of ERK and mTOR was increased in the liver of CIA mice.
Conclusions:
1) RA patients displayed a subclinical alteration of the hepatic enzymes associated with levels of inflammatory markers and autoimmunity, suggesting that RA might be associated with an abnormal liver function.
2) ACPAs may induce alterations in hepatic cells stimulating processes closely involved in fibrogenesis.
3) In mice, the generation of arthritis induced inflammation, reduced genes involved in lipid accumulation and modulated intracellular pathways related to fibrogenesis.
Funding: ISCIII (CP15/00158 and PI17/01316) co-funded with FEDER.

POSTER SESSION I

Infectious diseases, immunological and organ transplantation

P.16 WILD-TYPE klebsiella pneumoniae contains a persister subpopulation causing heteroresistance to carbapenems and some other BETA-LACTAMS.

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Scientific Program: Infectious and Immunological diseases. Organ transplantation
Keywords: Klebsiella pneumonaie, heteroresistance, betalactams.

Abstract:
Background: Heteroresistance (HR) can be related to the selection of resistant mutants (stable increment of the minimum-inhibitory-concentration, MIC), or the presence of persisters (can survive the lethal action of antibiotics without a MIC change). HR has been more often studied in multiresistant organisms. Here, we have evaluated if Klebsiella pneumoniae strains resistant only to aminopenicillins (wild-type; Wt-Kpn) express HR to antibiotics of clinical interest.
Materials/methods: Eight Wt-Kpn strains isolated from clinical samples of different patients have been evaluated. HR to 16 antibiotics was tested by disk diffusion, using inocula prepared with bacteria grown for 4h, 24h, 48h, 3 and 5 days on blood agar and Tryptic soy broth. HR was defined when colonies appered inside the inhibition zones; up to 10 of those colonies were cultured in antibiotic-free medium and tested again by disk diffusion to classify them as stable mutants [decreased (>5mm) inhibtion zone] or persisters (<5mm of the inhibition zone). A population-analysis-profile (PAP) was performed with imipenem and meropenem for 6 of the tested isolates.
Results: The 8 isolates corresponded to ST29, ST34, ST875, ST1825, ST2436, ST1628, ST 3477 and ST 3478. HR to carbapenems, mecillinam (PBP2 inhibitor), ceftazidime, cefepime, amoxicillin/clavulanic-acid and ceftazidime/avibactam was detected when using inocula of bacteria grown in solid medium for 48h-3d-5d. With bacteria from liquid medium or from solid medium (4-24h), HR was only observed with imipenem and ceftazidime. HR to imipenem and meropenem was documented in the 6 studied strains by PAP, with colonies (always persisters) growing up to 32-64xMIC (imipenem) and 1-8xMIC (meropenem). HR was never detected with aztreonam (PBP3 inhibitor), cefotaxime, ceftriaxone, amikacin, gentamicin and ciprofloxacin.
Conclusions: Wt-Kpn can generate a subpopulation of persisters to carbapenems, most of cephalosporins and mecillinam, but not to aztreonam, cefotaxime/ceftriaxone, aminoglycosides or ciprofloxacin. Detection of those persisters depends on the bacteria incubation time and the type of culture medium. Differences in beta-lactams behavior suggests that PBPs (but not SHV-1/11) may have relevant role in HR due to the emergence of persistes.

P17. HIV infected patients are not at higher risk for Hepatitis E Virus infection: A systematic review and meta-analysis

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Scientific Program: Infectious and Immunological diseases. Organ transplantation.
Keywords: HEV; HIV; risk factor; meta-analysis.

Abstract:
Background and objective: Hepatitis E virus (HEV) infection is the most common cause of acute hepatitis in the world. It is not well established whether people infected with the human immunodeficiency virus (HIV) are more susceptible to infection with HEV than people not infected with HIV. Many studies have evaluated this relationship, although none are conclusive. The aim of this systematic review and meta-analysis was to assess whether patients with HIV infection constitute a risk group for HEV infection.
Design: A systematic review and meta-analysis was performed in line with PRISMA.
Methods: Publication comparing HEV seroprevalences among HIV infected and uninfected populations. The analysis was matched by sex, age and geographical area, and compared patients who live with HIV and HIV-negative individuals.
Results**:** The OR for patients with HIV was 0.87 (95% CI: 0.74-1.03) in the fixed effects meta-analysis and 0.88 (95% CI: 0.70-1.11) in random effects, with I^2=47%.
Conclusions: This study did not show that HIV infection was a risk factor for HEV infection when compared with those who are HIV-negative.

P18. Impact of preformed non-c1q-binding donor-specific anti-hla antibodidies on early outcome kidney transplantation

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Scientific Program: Infectious and Immunological diseases. Organ transplantation
Keywords: C1q-binding ability, donor-specific anti-HLA antibodies, kidney allograft outcome, IgG1-4 subclasses, single antigen beads assay.

Abstract:
Background. The high sensitivity of solid phase assays to detect anti-HLA antibodies has raised the number of unacceptable mismatches of an increasingly proportion of HLA-sensitized patients, whose access to transplantation is almost impossible. Currently, beyond the presence of anti-HLA antibodies directed against donor HLA-antigens (DSA), some functional properties are being examined in an attempt to improve transplant allocation, maintaining similar success ratios. Hence, the aim of this study was to evaluate the early allograft outcome of a cohort of 12 single-kidney transplanted patients with preformed DSA without the ability to bind C1q.
Material and Methods. All transplants were ABO group compatible and were performed with a negative T+B complement-dependent cytotoxicity crossmatch result. Patients' serum was analyzed before and after transplantation to detect anti-HLA antibodies, their ability to bind C1q and their IgG1-4 subclass profile. Kidney function was evaluated (serum creatinine, glomerular filtration and proteinuria) and allograft survival was compared using the log-rank test. Rejection episodes were identified according to Banff criteria. Twelve matched single-kidney transplanted patients without preformed DSA were selected as a control group.
Results. After transplantation, DSA profile remained invariable regarding the C1q-binding ability and the IgG subclass composition, or even became negative. Allograft survival up to 30 months was not significantly different regarding the control group (p=0.148). We neither found significant differences in kidney function at any point throughout the follow-up time. Among the study cohort, 6 (50%) patients underwent biopsy. Histopathological findings suggested T-cell mediated rejection in 4 of them, with doubtful humoral component and minimum Cd4 deposition (<10%). Only 1 patient (8.3%) was diagnosed of antibody-mediated rejection and lost kidney allograft after 442 days.
Conclusions. Kidney transplantation with preformed non-C1q-binding DSA may be successfully performed. This procedure could be a feasible strategy to expand transplantation possibilities of highly-sensitized patients.

P19. Study of CMV-specific cellular immunity kinetics in renal transplant patients after receiving thymoglobulin induction therapy.

Authors: Aurora Páez-Vega, Sara Cantisán, Cristian Rodelo-Haad, Jorge Valle-Arroyo, Ana Salinas, Alberto Rodríguez-Benot, Marisa Agüera, Julian Torre-Cisneros on behalf of the INMUNOTIM study group.
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Scientific Program: Infectious and Immunological diseases. Organ transplantation
Keywords: Cytomegalovirus, renal transplant, QuantiFERON-CMV assay, T-cell response.

Abstract:
INTRODUCTION: Monitoring cytomegalovirus-specific cell-mediated immunity (CMV-CMI) in renal transplant recipients can aid in identifying patients at lower risk of CMV replication posttransplant. However, the effect of thymoglobulin induction on the recovery of CMV-specific CD8+ T-cell immunity is uncertain.
OBJECTIVE: To study the recovery of CMV-CMI in renal transplant patients after receiving thymoglobulin.
METHOD: Multicenter prospective study. CMV-seropositive renal transplant recipients with pretransplant CMV-CMI receiving thymoglobulin induction were enrolled. CMI-CMV was determined at pretransplant and at +30, +45, +60 y +90 days posttransplant. The QuantiFERON-CMV (QF) assay (Qiagen) was used to analyze CMV-CMI. A result was considered "QF Reactive" when the IFNG ≥ 0.2 IU/mL.
RESULTS: A total of 60 patients were enrolled, of which 58.3% (35/60) showed CMV-CMI at day +30, 66.7% at day +45, 73.3% at day +60 and 85% at day +90 after transplantation. We analyzed the association between pretransplant IFNG levels and the dynamics of immunity recovery. We found that patients with a pretransplant concentration of IFNG > 13 IU/mL recovered CMV-CMI more rapidly than those who had < 13 IU/mL of IFNG. Thus, 77.8% of patients with IFNG > 13 had recovered CMV-CMI at day +30 posttransplant compared to only 46.7% of patients with IFNG < 13 (p = 0.016). No association was found between thymoglobulin dose (higher or lower than median value of 375 mg/ml) and CMV-CMI recovery.
CONCLUSION: The speed of immunity recovery after transplantation is associated with the magnitude of pretransplant CMV-CMI, since the higher the IFNG concentration before transplantation, the sooner patients recover specific immunity. The thymoglobulin dose is not related to CMV-CMI kinetics.

P20. Aortic valve infiltrating pro-inflammatory cells in aortic stenosis patients

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Scientific Program: Infectious diseases, immunological and organ transplantation
Keywords: Aortic Stenosis, Cardiovascular disease, inflammation, immunopathology.

Abstract:
Aortic valve stenosis (AS) is a frequent cardiac disease in the elderly and is characterized by valvular calcification, fibrosis and inflammation, however its pathogenesis is not well known. AS has been traditionally considered a passive chronic degenerative process due to the accumulation of damage with age. Nevertheless, recent studies suggest that AS is similar to atherosclerosis, being an active inflammatory process. Particularly, it has been suggested that several immune cell types, present in the valve infiltrate, might contribute to its degeneration and to the progression towards stenosis. However, the valve inflammatory infiltrate has not been well characterized in any study regarding AS. Up to date there is no other treatment for the valve stenosis other than the replacement of the valve itself. Therefore, the characterization of the cells implicated in the inflammatory processes of the valvular stenosis is of outmost importance in order to develop new therapies for AS patients.
Here we present, for the first time, a protocol for the phenotypic characterization of aortic valve infiltrating cell populations in AS patients.

P21. Analysis of the humoral/cellular immune response discordance in healthy volunteers using two lymphocyte stimulation assays: QuantiFERON-CMV vs FASCIA

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Scientific Program: Infectious and Immunological diseases. Organ transplantation.
Keywords: Cytomegalovirus, QuantiFERON-CMV assay, FASCIA assay, humoral/cellular discordance, CMV-specific T-cell response.

Abstract:
Rationale: Around 25% of the individuals lack CMV-specific cellular immunity (CMI-CMV) when it is measured by QuantiFERON-CMV assay (QF) and, hence, they show humoral/cellular discordance. QF assay quantifies the interferon-gamma (IFNG) released by CD8+ T cells after stimulation with HLA-restricted CMV epitopes. The discordance might be related to the inability of certain individuals to recognize the stimulus of QF assay.
Objective: To analyse the association between the humoral/cellular discordance and the type of stimulus, comparing QF with FASCIA assay, which measures the blasts formation using CMV lysate as stimulus.
Methods: This cross-sectional study was carried out with CMV-seropositive healthy volunteers from The Blood Transfusion Center and Tissue of Cordoba. A single blood sample was taken of each donor and both QF (HLA-restricted peptide) and FASCIA (CMV Lysate) assays were performed.
Results: A total of 70 CMV-seropositive healthy donors were recruited. Of them, 15.7% (11/70) showed humoral/cellular discordance using QF assay. We found that blast formation with CMV lysate was lower in discordant (D+QF-) than in non-discordant donors (D+QF+) (217.0 cells/µL vs; p=0.087). The proliferation of CD4+ and CD8+ T cells tended to be lower in D+QF- than in D+QF+ donors (181.0 cells/µL vs 311.0 cells/µL; p=0.093 for CD4+ and 6.0 cells/µL vs 15.0 cells/µL; p=0.139 for CD8+). We further compared the titer of IgG anti-CMV in both groups and we observed that the median was significantly lower in discordant D+QF- than in D+QF+ donors (56.6 U/mL vs 105.0 U/mL; p<0.001)
Conclusion: Our results show that discordant D+QF- individuals have a lower proliferation capacity and lower level of IgG anti-CMV than D+QF+ donors, suggesting that the humoral/cellular discordance is not related to the type of stimulus in QF assay.

P22. New methodologies for preventing exposure to biological agents in the labs

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Scientific Program: Infectious and Immunological diseases.
Keywords: Biological agents, e-learning, new technologies, medical informatics.

Abstract:
The exposure to biological and chemical agents in laboratory is warning problem for the workers. In laboratories focused on samples, the most problem is the exposure to biological agents that can produce different sides effects especially health issues. In this sense, the practice and experience of workers play an important role in preventing accidents and correctly following the protocols for post-exposure. Based on the previous state, the practice in laboratories is essential for the learning process and correct performance. Furthermore, the rapid development of new communication technologies has allowed to improve the training by using online or in distance technologies such as virtual laboratories. The objective of this research is to present and demonstrate the importance of this technologies for workers in contact with biological agents. This research presents three online technologies based on HTML5 and MSyQL in order to improve the learning process of the employees from workers of the lab, nurses that obtained the samples and students. The first platform is called Forsan (http://www.uco.es/investiga/grupos/LVRiesgosLaborales/formacion-sanitaria/animaciones), in which are included different tools to inform and form students. The second platform is named Psam (http://www.uco.es/psam/rpsindice.php) focused on forming health professionals that may in contact with the origin of biological agents. Finally, the last platform is called Bioslab (http://www.uco.es/RiesgosLaborales/sanitario/), which is focused on prevention on the laboratories. Additionally, these virtual platforms were evaluated by different health professionals and laboratories' labs (N=27) defined these technologies as "good" and "useful" and given a 5.6 punctuation out of 7 in scale of resourcefulness. In conclusion, these technologies provide a methodology of improve for any worker or student and has been highly valuated by the users.

POSTER SESSION I

Active aging and fragility

P23. Influence of motivation on academic performance in secondary education and training cycles: Latino-American setting

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Scientific Program: Active ageing and fragility
Keywords: academic performance, motivation, training cycles, secondary education

Abstract:
Objectives: The objective of this study is to know and analyze the existing scientific production on the influence of motivation in the academic performance of the students of the Training Cycles and secondary education. Method: A limited systematic search was conducted in the Dialnet database. Period 2001-2018.The search was carried out with the following terms: academic performance & motivation, academic performance & training cycles, academic performance & secondary education. The studies were selected according to the following inclusion criteria: scientific studies that presented as variables the motivation and academic performance of the students belonging to the Training Cycles and secondary education. Results: 9 articles met the inclusion criteria. Emotional regulation, intrinsic motivation, no motivation and academic performance in secondary education students showed significant relationships. Likewise, the influence of motivational profiles (of learning, achievements and social value) on academic performance is different according to the study subject. Demographic variables such as sex refer differences between boys and girls in all the applied motivational scales and strategies, except in learning and elaboration goals. However, by controlling the effect of previous performance, it was possible to verify that some of these differences disappeared. On the other hand, some studies report that the use of a teaching methodology based on cooperative learning affects academic performance, but no improvements are observed at the students' motivational level. However, the use of ICT increases the academic performance of students by increasing the motivation of students to perform activities in digital support, but without growth of improvement in learning. With regard to the students who attend the training cycles only refers to the need for monitoring and specialized training related to motivations and learning strategies. Conclusion: In the analyzed studies, there is some controversy between levels of motivation and performance. No variations have been detected in the performance due to the motivation in secondary education and training cycles in the Latino-American setting. Therefore, it is necessary to carry out more studies about this topic.

P24. Biological aging is associated with the severity of the atherosclerosis process: CORDIOPREV study

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Scientific Program: Active ageing and fragility
Keywords: aging, arteriosclerosis, telomere length, cardiovascular disease

Abstract:
Introduction: There is an association between cardiovascular disease and accelerate biological aging. Leukocyte telomere length (LTL) is a biomarker of cellular senescence and short LTL are related to cardiovascular events. However, the association between LTL and the severity of the arteriosclerosis process remains unclear in patients with established cardiovascular disease.
Hypothesis: We aimed to investigate the relationship between LTL and carotid intima-media thickness (cIMT) and with the number of atherosclerotic plaques in patients with coronary heart disease (CHD).
Methods: This study was conducted within the framework of CORDIOPREV study (NCT00924937), in which 1002 patients with CHD were included. Blood samples were collected after 12-hour overnight fast for biochemical analysis. DNA was isolated from peripheral blood samples using "Salting Out" method and LTL was measured by real time PCR. cIMT and the presence of atherosclerotic plaques were assessed by ultrasound in both carotid arteries.
Results: We observed an inverse correlation between cIMT and LTL (r2=-0.100; p= 0.002). Patients were classified according to tertiles (T) of LTL. Those subjects in the T1 (shortest) presented higher cIMT (0.73 ± 0.007) compared with those in the T3 (largest) (0.70 ± 0.008) (P=0.03). Moreover, those patients with only one plaque showed longer LTL (1.32 ± 0.42) than those with 2 (1.25 ± 0.05) or with 3 or more plaques (1.16 ± 0.058) (p=0.039). Furthermore, systemic inflammation, measured by C-reactive protein was also inversely related with LTL (r2=-0.091; p= 0.005).
Conclusion: Our findings suggest a strong relationship between biological aging and the severity of the atherosclerotic process in patients with cardiovascular disease. Consequently, these findings emphasize the clinical need to identify subgroups of patients who must be treated more aggressively.

P25. Impact of vaginismus in the delivery process: a systematic review.

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Scientific Program: Active ageing and fragility.
Research Group: GA-02. Comprehensive Nursing Care. Multidisciplinary Perspective.
Keywords: Delivery or Birth; Vaginal birth; Vaginismus; Women.

Abstract:
Introduction: Genito-pelvic pain disorder (DSM-5) or vaginismus is considered a sexual dysfunction that is characterized by a fear to the penetration pain causing tension in the pelvic floor muscles that causes difficulty and pain in sexual intercourse or in gynecological explorations(Rabinowitz et al. 2017). The prevalence of this sexual disorder ranges from 6 to 68%, depending on the country (Achour et al. 2019). Cultural myths related to sexuality, traumatic sexual experiences, sexual abuse, restrictive sex education, anxiety problems, traumatic experiences in the genital area at an early age such as bladder catheterization, etc., influence it (Pacik et al. 2017).On the other hand, genitor -pelvic pain disorder or vaginismus affects the sexual and reproductive health of women;in this way, they are higher rates of infertility problems and at couple level.
Objective: To know how genitor -pelvic pain-disorder influences the delivery process.
Methodology: Systematic review. An electronic search was carried out during the first weeks of April 2019, using the following databases: MEDLINE, OVID SP and Web of Science. The keywords used were: birth or delivery, vaginal birth, vaginismus.The search strategy was limited to articles published between 2008 and 2019. All kind of design studies were included if participants were pregnant women with vaginismus.
RESULTS: Five articlesmettheinclusioncriteria. Two cross-sectional studies,a case report, a case-control study and a qualitative study.In the includedstudies, the vaginismus drove toan increase in the number of caesareans by maternal decision.
CONCLUSIONS: In the present review, it seems that a problem, vaginismus, go directly to another one, caesareans. So, the responsibility of the health professionals, that attend pregnant women in the delivery process,is a big one. They must be trained in the assessment of the pregnant women to treat the problem before the delivery to avoid the caesarean.

P26. Modulation of mitochondrial metabolism markers by calorie restriction and CYB5R3 overexpression in transgenic mice

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Scientific Program: Active ageing and fragility
Keywords: Cytochrome b5 reductase, caloric restriction, mitochondrial metabolism, longevity and skeletal muscle.

Abstract:
Nowadays, there is great interest in identifying enzymes which promote healthy aging and even allow to increase longevity. One of such enzymes is NADH-cytochrome b5 reductase-3 (NADH:ferricytochrome b5 oxidoreductase, EC1.6.2.2, CYB5R3), which has been documented to increase longevity and improve mitochondrial function in transgenic mice. CYB5R3 catalyzes electron transfer from NADH to cytochrome b5 and also to alternative electron acceptors as plasma membrane coenzyme Q or several exogenous compounds. Calorie restriction (CR) – a reduction of nutrient intake without reaching malnutrition - is the best defined non-genetic or pharmacological intervention that improves a plethora of parameters related to healthy aging and may also increase of longevity, at least under several circumstances. Since it has been shown that CR increases CYB5R3 levels in some tissues as liver, we are interested in elucidating how CYB5R3 overexpression and CR modulate longevity. Specifically, in this work we have focused our efforts towards the study of markers related to mitochondrial metabolism (mitochondrial complexes, mitochondrial dynamics and biogenesis, and mitophagy). We used wild-type and CYB5R3 transgenic mice that were fed during 3 months with standard chow and then transferred to a diet based on AIN93M formulation, that was provided either ad libitum or under 40% CR. Duration of the intervention was 4 months. Our studies were performed on hindlimb skeletal muscle, as a model of a postmitotic tissue which plays a relevant role in aging. We observed that CYB5R3 was significantly overexpressed in skeletal muscle of transgenic mice, but their levels were not altered by CR. Overexpression of CYB5R3 and CR produced changes of several parameters indicative of greater respiratory metabolism and enhanced mitochondrial biogenesis in skeletal muscle, but their effects did not seem to be additive.

P27. NADH-cytochrome b5 reductase-3 (CYB5R3) overexpression interferes partially with the metabolic adaptation to calorie restriction in liver mitochondria from CYB5R3-transgenic mice.

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Scientific Program: Active ageing and fragility
Keywords: Mfn2, CYB5R3, aging

Abstract:
Calorie restriction (CR) delays aging and increases lifespan in numerous organisms. Beneficial effects of CR on longevity are mainly due to an improvement in mitochondrial function. Under conditions of bioenergetic demand or CR, triglycerides are broken forming glycerol and fatty acids passing to the mitochondria to form ATP through β-oxidation pathway. Mfn2 is a GTPase of the outer mitochondrial membrane with a prominent role in fusion, and is also present in mitochondrial-associated membranes, playing a role in establishing inter-organellar bridges between mitochondria and the endoplasmic reticulum (ER). By allowing this physical interaction, Mfn2 facilitates transportation of phospholipids for their subsequent mitochondrial processing. NADH-cytochrome b5 reductase-3 (CYB5R3) is a flavoprotein necessary for the elongation and desaturation of fatty acids, which seems to be an excellent candidate as a novel effector for the regulation of metabolism, mainly at mitochondrial level. The aim of our work was to determine the impact of CR and CYB5R3 overexpression on several biomarkers of mitochondrial metabolism in liver tissue. The increase in Mfn2 levels observed in our samples under CR condition could be related to the facilitation of contacts between ER and mitochondria, which would result in an improvement in the processing of fatty deposits. However, when we studied the effects of the transgene under CR conditions, it was found that the levels of Mfn2 were decreased, which could be due to enhanced carbohydrate metabolism in CYB5R3 transgenic mice, as we have reported previously. An increase of fatty acid β-oxidation in response to CR can also influence the activity and abundance of mitochondrial complex subunits. Levels of complex III were increased by CR in both wild type and transgenic mice, which could facilitate electron flow through the mitochondrial chain. Our results support the notion that CYB5R3 overexpression might partially mitigate some of the metabolic adaptations to CR.

P28. Sexual dimorphism of mitochondrial metabolism markers in skeletal muscle for transgenic mice overexpressing NADH-cytochrome b5 reductase-3

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Scientific Program: Active ageing and fragility.
Keywords: CYB5R3, sexual dimorphism, skeletal muscle

Abstract:
Existing data on differential susceptibility to diseases or different effect of drugs in men and women demonstrates the existence of sexual dimorphism, which is not only related to biological differences (sex) but is also influenced by social characteristics (gender), which must be taken into account when designing research approaches. Differences between males and females have been also shown for model organisms, which can affect a multitude of processes related, for instance, to cardiovascular health, liver diseases or cancer risk. Including both sexes in the design of the studies is thus important to gain a greater relevance from a biomedical point of view. Studies focused on the identification of new enzymes with the ability to modulate aging are beginning to gain importance. Previous studies developed in our group have been focused on NADH-cytochrome b5 reductase-3 (CYB5R3) as a new pro-longevity gene. We documented that mice overexpressing CYB5R3 showed greater longevity and enhanced protection against aging-associated diseases.
The main objective of our work was to study sexual dimorphism in the levels of mitochondrial complexes and markers of mitochondrial dynamics and biogenesis in skeletal muscle of CYB5R3 transgenic and control mice of the C57BL/6 strain at three months of age. Skeletal muscle was chosen as a model of postmitotic tissue whose metabolic alterations may have a great impact in defining the rate of aging. The obtained results support that CYB5R3 overexpression enhances mitochondrial-dependent processes in both sexes, being this effect more remarkable in males than in females. Our results reinforce the importance of considering both sexes in studies with transgenic animals.

P29 Preliminary study for the validation of the NEAT-e Questionnaire to measure environmental awareness in nursing

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Scientific Program: Active ageing and fragility
Keywords: Validation; Questionnaire; Awareness; Environment; Nursing

Abstract

Introduction: The NEAT questionnaire (Nurses' Enviromenmental Awareness Tool) measures the level of environmental awareness in the nursing staff. It consists of three scales: "Nurse Awareness Scales" (NAS) of 11 items, "Nurse Professional Ecological Behaviors Scales" (NPEB) of 9 items and "Personal Ecological Behaviors Scales" (PEB) of the 11 items. This has been translated and adapted the Spanish (NEAT-e).

Objective: To validate the NEAT-e questionnaire as a measuring instrument of nurses' enviromenmental awareness.

Method: The sample of the pilot project consisted of 40 nurses, auxiliary nursing care technicians and nursing students of both categories of Andalusian Health Service. For the validation process, the author of the original questionnaire gave us her authorization and is approved by the Bioethic Committee of Andalusia.

The study was carried out from June 2018 to March 2019. Several methods were used for the validation: Reliability (internal consistency) was checked by Cronbach's Alpha and the construct validity by means of a factorial analysis. The analysis was made with Microsoft Excel 2010 and BM SPSS Statistics version 22.0.

Results: The internal consistency of the questionnaire was very high (Cronbach's Alpha = 0.909). The analysis the construct validity by de Factorial Analysis was lower (0.455-0.597), perhaps due to the high number of items (62) and the low sample size (40).

Conclusion: The NEAT-e questionnaire has shown internal consistency, while the construct validity analysis invites a deeper analysis to study the possibility of adjustments.

POSTER SESSION I

Nutrition, endocrine and metabolic diseases

P30. Diet composition influences kidney function preservation in CYB5R3 over-expression mice model under calorie restriction.

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Scientific Program: Nutrition, endocrine and metabolic diseases.
Keywords: Calorie Restriction; CYB5R3; Dietary intervention; Autophagy; Kidney; Mice

Abstract:
Antiaging research continues to raise interest among the general public as well as the scientific and medical communities. Calorie restriction has been repeatedly shown as one of the most robust means to improve health and survival in model organisms. However, the mechanism underneath the beneficial effects of calorie restriction remains poorly understood. The intracellular ratio of pyrimidine nucleotides (NAD+/NADH) has been proposed to be at the center stage of the anti-aging biochemical changes occurring in CR model organisms. In fact, NAD+/NADH ratio influences the activity of many proteins, including the sirtuins, which have been related as mediators of healthspan and lifespan improvement by CR. CYB5R3 is one of the enzymes that are upregulated under CR condition and affects the NAD+/NADH ratio. CYB5R3 overexpression in a transgenic mouse model has shown to mimic, to some extent, the effects of CR. In this study, we put CYB5R3-overexpressing mice under CR and analyzed the putative synergic effect of the genotype and dietary conditions under two different types of diet: chow and purified diet. We focused our analysis on kidney tissue since anti-aging strategies especially target high energy demanding tissues. Quantitative electron microscopy techniques and protein expression markers were used to analyze autophagic processes. Declining in autophagy turnover was found in the animals under a purified diet. These results indicate that diet affects renal function preservation, imposing a stronger phenotype than CR or CYB5R3 overexpression.

P31. Women's Health Promotion in the Workplace – A Systematic Review

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Scientific Program: Other - Occupational Health, occupational epidemiology and sustainability
Keywords: occupational health, women's health, total worker health

Abstract:
The present study analyzes the effectivity of interventions to promote women's health in the workplace. A systematic review has been done using Medline and SCOPUS databases. The inclusion criteria were: health promotion's intervention programs in the workplace specifically for women. Exclusion criteria: studies not written in Spanish or English; health promotion's intervention programs not specifics for women. A total of 2206 articles were found, of with 498 (22,6%) were health promotion programs in the workplace, and only 13 (2,6%) met the inclusion criteria. The results show two lines of intervention:
Breastfeeding promotion in the workplace (15,4%). Workplaces where women had less support to continue with breastfeeding after maternal leave had more probability of leaving exclusive breastfeeding before 6 months after giving birth.
Physical activity and other healthy lifestyles (84,6%). Preventing sedentarism, improve fat body mass, reduce cardiovascular risk and relieve premenstrual symptoms were the interventions studied.
In conclusion, few health promotion programs are specific for women (2,6%) and the most part of them focused only in physical activity. There are still some areas in women's health that need to be studied, being necessary to implement politics that incentive these interventions in the workplace.

P32. Relevance of pre-mRNA-splicing factor 8 (PRP8) on adipogenesis and obesity-related metabolic disease

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: PRP8, splicing, adipogenesis, obesity-related metabolic disease.

Abstract:
Obesity is accompanied by metabolic disorders, including insulin resistance (IR), and type 2 diabetes (T2D). Adipose tissue dysfunction is related to metabolic syndrome in obesity. Particularly, T2D obese individuals exhibit impaired adipogenesis, the process that allows the differentiation of preadipocytes into mature adipocytes. However, the signaling pathways and molecular mechanisms behind this pathogenic process are not completely understood. In a previous proteomic study, we identified several splicing markers to be downregulated in subcutaneous preadipocytes from obese individuals with IR/T2D as compared to those with normoglycemia. Among them, we chose an essential component of the spliceosome, PRP8, as a model molecule for further studies since the relevance of splicing in adipogenesis has not been established yet. Thus, we employed the cell line of human preadipocytes, SGBS, and examined PRP8 expression during adipogenesis as well as the response of SGBS preadipocytes upon PRP8 silencing by siRNA, using confocal microscopy, and biochemical and functional assays. Our results revealed a peak in PRP8 expression at early stages of differentiation, suggesting a role in adipogenesis. Confocal microscopy after Oil Red-O staining showed that PRP8-silenced cells exhibited altered lipid accumulation capacity together with abnormal lipid droplet storage, as well as lower expression levels of classical adipocyte markers (Adiponectin, FABP4/aP2). These morphological observations were accompanied by altered expression profiles of the splice variants of major adipogenic transcription factors (PPARG, SREBP-1), and proteins implicated in lipid droplet biogenesis and growth (Seipin/ Bscl2, Cideb, Cidec/Fsp27). Our studies also supported a role for PRP8 on lipolysis/lipogenesis (FAS, PLIN) as well as in the induction of endoplasmic reticulum stress and in the regulation of insulin signaling. In conclusion, our data indicate that mis-splicing induced by PRP8 silencing may be responsible for defective adipogenesis and adipocyte dysfunction observed in obesity-associated metabolic disease.
Funding: MINECO/FEDER (BUF2016-76711-R; BFU2017-90578-REDT); FIS/FEDER (PIE14_00005); JJAA (JJAA/FEDER PI-0159-2016); CIBERobn (ISCIII).

P33. Type 2 diabetes remission by consumption of low-fat and Mediterranean diets: from CORDIOPREV study.

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Scientific Program: Nutrition, Endocrine and metabolic diseases
Keywords: type 2 diabetes, remission, dietary intervention, CORDIOPREV

Abstract:
Aim: To evaluate the remission of newly diagnosed type 2 diabetes after the consumption of two healthy diets and without pretension of significant body weight loss during 5 years of follow-up in coronary heart disease patients from CORDIOPREV study. Indeed, we aimed to study the factors underlying T2DM remission such as beta cell functionality and insulin resistance.
Methods: We included 190 patients from the CORDIOPREV study diabetes diagnosis and were not receiving glucose-lowering treatment at the beginning of the study: 73 patients who reverted from T2DM after the dietary intervention without the use of diabetes medication to lower blood glucose levels (Responders) and 110 patients who did no respond to the dietary intervention at the end of the follow-up period (non-Responders) according to the American Diabetes Association criteria. Patients were randomized to consume either a Mediterranean or a low-fat diet. We measured glucose, insulin, glucagon, GLP-1 and free fatty acids plasma levels in the OGTT performed at baseline and after a median follow-up of 60 months. Also, we analyzed beta cell functionality and insulin resistance index.
Results: We found that Responders patients improved the glucose homeostasis, increased sensitivity to insulin in adipose tissue, lower hepatic insulin resistance and had better beta-cell functionality as compared with non-Responders patients ($p<0.05$) after the dietary intervention without a clinically significant loss of body weight.
Conclusion: Our study suggests that the remission of type 2 diabetes mellitus is possible by intervention in the lifestyle through the consumption of healthy diets such as Mediterranean or low-fat diet.

P34. Effect of fatty acids from the diet on the regulation of miR-365 and its relationship with the development of atherosclerosis in patients with cardiovascular disease.

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Scientific Program: Nutrition, Endocrine and Metabolic Diseases.
Keywords: Cardiovascular Disease, Atherosclerosis, miRNAs, Nutritional Epigenetics, Mediterranean Diet, Carotid Intima-Media Thickness (cIMT).

Abstract:
Background: Cardiovascular diseases are the leading cause of death worldwide. The common basis of these diseases is atherosclerosis, characterized by thickening of the carotid intima-media (cIMT). The quality of fatty acids from the diet has been related with risk of atherosclerosis development. Moreover, previous studies have demonstrated the role of miRNAs in mechanisms related to atherosclerosis. Our objective was to study the effect of fatty acids on the expression of miR-365 and its relationship with the development of atherosclerosis in patients with cardiovascular disease.
Materials and Methods: In the present study were included 240 patients from the CORDIOPREV study: 120 with the most extreme progression of cIMT after 5 years of low fat or Mediterranean dietary intervention (n= 55 and 62, respectively), and 120 patients with the most extreme regression of cIMT after 5 years of both diets (n= 51 and 68, respectively). cIMT was measured bilaterally with high-resolution B-mode Doppler echography. Intracellular levels of miR-365 from peripheral blood mononuclear cells at baseline and year 5 were determined through the OpenArray platform. Statistical analyses of one-way ANOVA and repeated measurements were performed.
Results: Our results show that the expression of miR-365 increased after the consumption of low fat diet in patients who showed an increase in cIMT after 5 years of follow-up ($p = 0.001$). In contrast, the expression of miR-365 increased after the intake of a Mediterranean diet in patients who showed a decrease in cIMT ($p <0.001$). Finally, the high intake of MUFA and low intake of PUFA increased the expression of miR-365 after the follow-up period in patients who showed a decrease in cIMT ($p= 0.022$; $p=0.018$, respectively).
Conclusion: The quality of fatty acids from the diet could be regulating the expression of miRNAs such as miR-365 that modulate atherosclerosis-related mechanisms in patients with cardiovascular disease.

P35. Role of Rab18 in intracellular organelle interactions in the obese adipocyte

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Scientific Program: Nutrition, Endocrine and metabolic.
Keywords: Obesity, Rab18, Lipid droplets, Endoplasmic reticulum, Peroxisomes

Abstract:
Obesity is caused by an over-intake of fatty acids, which accumulate into lipid droplets (LDs) in the adipocytes, the functional units of the adipose tissue (AT). When adipocyte storage limit is reached, dysfunctional adipocytes alter the secretion pattern of extracellular matrix (ECM) components leading to AT fibrosis. Moreover, AT inflammation is tightly linked to insulin resistance (IR), a major risk factor for the development of type II diabetes (T2D). Herein, we hypothesized that these pathological conditions might modify the interaction between organelles involved in lipid biosynthesis and metabolism, i.e., endoplasmic reticulum (ER), LDs, and peroxisomes, by altering the localization of a small GTPase that mediates these interactions, Rab18. Thus, 3T3-L1 adipocytes were differentiated in 3D (fibrosis model) and 2D (inflammation and IR model) cultures and processed for confocal microscopy studies. Our results showed ER fragmentation in fibrosis as well as changes in Rab18 content in ER subdomains connecting with LDs and peroxisomes. Specifically, Rab18 remained in the ER, rather than in LDs, in response to fibrotic conditions. Furthermore, Rab18 silencing increased the number of ER-peroxisome contacts, wherein greater signal overlap was observed. We also analyzed Rab18 traffic to immature LDs in subcutaneous and omental preadipocytes from obese patients during differentiation. We found that the ER-Golgi intermediate compartment (ERGIC) pathway was the preferred traffic route for this GTPase to reach the LD surface. Finally, we assessed Rab18 content in fat samples from normoglycemic (NG), IR and T2D obese subjects. These studies showed that IR women exhibited lower Rab18 levels than NG and T2D women, while no differences were found between men. Taken together, our results suggest a role for Rab18 in the formation and maintenance of ER-LD and ER-peroxisome links, which are likely altered in obesity-associated metabolic disease.
Funding: MINECO/FEDER (BFU2016-76711-R; BFU2017-90578-REDT); CIBERobn (ISCIII).

P36. Relationship between food and work at shifts of health personnel

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Scientific Program: Nutrition, Endocrine and metabolic.
Keywords: Health professionals, eating, rotating shift and overweight and stress

Abstract:
The interest regarding food and side effects produce by the excessive eating is growing among the population. This interest is both caused commercial campaigns and protentional health campaigns. In this sense, the health campaigns rarely stablish a relationship between nutrition and work in health professionals. The health personnel with rational shifts stands out as a risky population. It has been previously stablished how the rotational shifts interfere with the circadian cycles, leading to health issues for the employees with these shifts. These workers sometimes experiment higher level of stress than those who have fixed shifts.
In this current study, the main objective is to determine the relationship between the different shifts of health professionals and their diet; as well as investigate the relationship of work shifts with overweight and anxiety-stress.
A descriptive observational design was carried out with a descriptive exploratory survey to obtain information about nutrition, work situation and anxiety-stress level in health professionals in different centers.
A sample of n = 42 was obtained with a participation of 59.5% women and 40.5% men. The shift that appeared most was Rotary (47.6%), followed by 24 hours (19%). With respect to the BMI, 52.4% of the sample were in normal weight and 45.3% were overweight and obese. The 69% of the sample practice sports with a frequency of 2-3 days per week and the smoking habit is 26.2%. In sleep hygiene 47.6% sleep 6-7h daily and 26.2% 7-8h. The majority of staff (76.2%) consider that they have a high-average workload.
As conclusions, it is emphasized that the lack of sleep results in an alteration in circadian rhythm and an increase in BMI, with the probability of the appearance of Metabolic Syndrome and other pathologies. Nonetheless, healthy lifestyle habits are increasingly present in this group.

POSTER SESSION II

Cancer (Oncology and Oncohematology)

P37. Splicing machinery as a novel source of diagnostic and therapeutic targets in hepatocellular carcinoma

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Scientific Program: Cancer (Oncology and Oncohematology)
Keywords: Hepatocellular carcinoma, spliceosome, splicing factors, gene silencing, cell lines.

Abstract:
Hepatocellular carcinoma (HCC) represents 90% of cases of primary liver cancers, is the second cause of cancer-associated deaths, exhibits a survival rate of 17% at 5 years, and its incidence is increasing. However, there is a lack of appropriate diagnostic and prognostic biomarkers as well as therapeutic targets. A common characteristic of most cancers is the appearance of alterations in the splicing machinery (splicing factors and spliceosome components), which can lead to the generation of aberrant splicing variants involved in tumour development and progression. For this reason, the objective of the present work was the identification of splicing factors or spliceosome components with potential implication in the development and/or progression of HCC, by in silico analysis of ample HCC cohorts [Wurmbach (75 patients), Roessler (43 patients), Roessler 2 (445 patients) and Chen (197)], as well as the characterization of the role of the altered factors in the progression of HCC cell lines with different aggressive profile (HepG2, Hep3b and SNU-387). In this first approach, we analysed in silico the expression of 43 of the splicing machinery components with potential relevance in the development and/or progression of cancer. The results revealed that the expression of more than 50% of the splicing factors and spliceosome components analysed were consistently altered in HCC samples compared to normal liver in all the cohorts analysed (e.g. TRA2A, SND1, TCERG1, U2AF2, CELF1). Furthermore, the in vitro silencing in the HCC cell lines (by specific siRNAs) of certain overexpressed factors (e.g. TRA2A, SND1) induced a clear reduction of aggressiveness (proliferation, migration, tumorspheres formation, etc.), through the modulation of oncogenic splicing variants. Therefore, this study demonstrates that multiple components of the splicing machinery are dysregulated in HCC samples, wherein some of these factors could play a crucial role modulating the development/progression of this highly aggressive cancer pathology.
Funding: ISCIII (PI17-02287, PI16-00264), Junta de Andalucía (BIO-0139) and CIBERobn.

P38. Analysis of the expression of somatostatin receptors and its association with clinical and histopathological factors in patients with squamous cell carcinoma of the oral cavity

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Scientific Program: Cancer (Oncology and Oncohematology)
Keywords: Oral cavity, cancer, somatostatin, splicing

Abstract:
Somatostatin-analogues (SSAs), which bind to somatostatin-receptors (SST1-5), are frequently used to treat multiple tumor/cancer-pathologies. In this context, the hypermethylation of SSTs has been described in squamous cell carcinomas (SCC) of the head and neck. However, to date there are no studies describing the presence of SSTs in tumors of the oral cavity and its association with risk factors and histopathological factors of poor prognosis. Therefore, our objective was to analyze the expression patterns of SST-subtypes in tumors of the oral cavity and, to determine their associations with certain clinical/histopathological-factors in the process of tumor progression and clinical prognosis. A prospective observational case-control study was designed in patients diagnosed with primary oral cavity SCC. Tumor tissues and healthy-tissue (adjacent mucosa) were obtained from the same patient (n=41). mRNA was extracted and retro-transcribed, and expression levels of SST-subtypes was evaluated using a microfluidic qPCR-based array. Clinical variables from the patients (age, gender, risk factor, prognosis histopathological data, etc.) were obtained. The results showed an overexpression of some SST-subtypes in the tumor tissue of patients with SCC of the oral cavity compared to the adjacent tissue. Expression of SST2 was negatively correlated with the degree of cervical lymph node involvement. SST1, SST3 and SST5 expression showed a correlation with the degree of tumor invasive front. SST1, SST2, SST3 expression presented a positive correlation with the degree of peritumoral inflammatory infiltrate, SST4 expression with the lymphovascular infiltrate and SST5 expression with perineural infiltration. Altogether, our results reveal that SSTs expression is clearly dysregulated in SCC of the oral cavity and that these changes might be associated with relevant clinical/pathological features of aggressiveness, which invite to explore in the future the potential therapeutic role of SSAs for the treatment of patients with these tumors.
Funding: ISCIII (PI16-00264), Junta de Andalucía (BIO-0139) and CIBERobn.

POSTER SESSION II

Chronic and Inflammatory Diseases

P39. Cardiometabolic risk factors in Rheumatoid Arthritis. Modulation by TNFa and IL6R inhibitors.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Rheumatoid arthritis, cardiovascular risk factors, biological therapies.

Abstract:
Background: Increased prevalence of metabolic alterations has been observed in Rheumatoid arthritis (RA) which significantly contribute to the cardiovascular risk burden. Numerous studies suggest that cardiometabolic risk is mediated through adipocytokines. However, this relationship is not completely defined in RA.
Objective: To evaluate the relationship among cardiometabolic risk factors and the levels of adipocytokines and autoantibodies in RA patients and the effects of anti-TNF-a and anti-IL6 therapies on the cardiometabolic alterations.
Methods: 1.- A cross-sectional study including 100 RA patients and 50 age-matched healthy donors was carried out. Parameters related to the cardiometabolic risk (SCORE, ApoB/ApoA, atherogenic index and carotid intima media thickness (CIMT)) were analyzed. Serum levels of adipocytokines were evaluated. 2.-A prospective study in 30 RA patients before and after 3 months of anti-TNFa or anti-IL6R was performed.
Results: RA patients had elevated serum levels of leptin/adiponectin ratio, visfatin, resistin and inflammatory markers. Our cohort of RA patients displayed increased rates of cardiometabolic risk factors. The alteration in serum adipocytokines were closely related to the autoimmunity, disease activity and inflammation. Of note, visfatin and C3 complement levels were determinant for insulin resistance (IR), high levels of SCORE, increased parameters of CVD risk defined by ApoB/ApoA ratio and pathologic CIMT. Both biological therapies reduced clinical inflammatory markers and disease activity after the treatment. Anti-TNF-a therapy modulated the adipocytokine profile, reducing serum levels of IL-6, IL-1b, resistin and visfatin, decreasing IR. After treatment with anti-IL6R, serum levels of C3 complement, IL-1b and resistin were reduced.
Conclusions: 1) Altered adipocytokine profile is closely related to the increased cardiometabolic risk factors associated with autoimmunity and systemic inflammation in RA. 2) Anti-TNF-a and anti-IL6R therapies, administered for 3 months, could have beneficial effects in the reduction of cardiometabolic risk factors in RA.
Funding: ISCIII (PI18/00837, CP15/00158, PI17/01316 and RIER RD16/0012/0015) co-funded with FEDER.

P40. Incidence of fractures and associated risk factors during the drug holidays period with bisphosphonates

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Keywords: Osteoporosis, fractures, bisphosphonates

Abstract:
Biphophosnates are the most widely used treatment for osteoporosis. The optimal treatment duration, however, remains unclear. The occurrence of adverse effects, such as osteonecrosis of the jaw (ONJ) and atypical femoral fractures (AFF), has raised the issue of bisphosphonate discontinuation (“”drug holiday””) after a certain treatment period. The objectives were to assess the incidence of fractures in patients during the drug holidays period with bisphosphonates, as well as to determine the risk factors are associated to it.
Methods: Analytical, observational, longitudinal, and ambispective study of a cohort of patients with postmenopausal osteoporosis or men over 50 years of age treated with oral bisphosphonates (at least for 5 years) or intravenous (at least for 3 years) and who had been at least for one year in a drug holidays period, from 01/01/2012 to 12/31/17. Patients treated with corticosteroids and/or with diseases with effects on bone metabolism were excluded. Statystical analysis included a descriptive study of the variables to assess the association between the incidence of fractures and various risk factors, as well as univariate and multivariate Cox regression analysis. Results: 128 patients with osteoporosis were studied, of wich 19 (14.7%) suffered an osteoporotic fracture during the follow-up. Bivariate analysis showed in the group of patients with fractures a higher proportion of smoking patients (p = 0.004), osteopening treatment (p = 0.005) and a femoral neck t score lower at the beginning of the drug holidays period -2.07 (0.68) vs - 1.58 (0.63), p = 0.008.
In addition, there was a higher proportion of patients with fracture with moderate risk before the start of the drug holidays period (p = 0.007). The fracture survival curves were lower in patients older than 75 years (p = 0.04). When applying the same treatment, for each year increase, the risk of fracture was increased by 6% (p = 0.04), while, for the same age, this risk was increased 4.33 times in patients who were treated with Risedronate versus those with Alendronate (p = 0.05).
The multiple regression analysis showed that vertebral fracture was independently associated with Tabaco (HR 4,28 p=0,047).
Conclusion: Based on our results, it would be useful to follow closely those patients during drugs holidays period who are smokers, older than 75 years, with osteopening treatment, who present a low femoral neck tscore and / or have been previously treated with Risedronate.

P41. Potential therapeutic of senile aortic stenosis and clinical and economic implications

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: estenosis aórtica TAVI (transcatheter aortic valve implantation) tratamiento percutáneo complicaciones supervivencia.

Abstract:
INTRODUCTION: Severe aortic stenosis is a valvular disease more prevalent from the age of 65. It has become a health problem by increasing life expectancy. Quality of life limited since it involves symptoms such as dyspnea, angina and syncope with episodes of heart failure that can result in the hospitalization. The standard treatment has been the conventional valve replacement surgery but since a few years ago there is percutaneous treatment for those patients with high morbidity and mortality for conventional surgery.
MATERIAL AND METHOD: Prospective descriptive cohort study with two groups equal to or greater than 70 years with primary diagnosis of severe aortic stenosis between the years 2010 and 2011:
Surgery group: 60 patients (35♂, 25 ♀), average age: 76.1 years. Time tracking 46.3 months.
Group TAVI Corevalve: 66 patients (20♂, 46♀),average age: 79.9 years. Time tracking 51.2 months.
We would like to know:
Minor and major complications.
Total stay during the entry of the procedure.
Survival and mortality during follow-up.
Analysis the entry procedure (GRDs) costs.
ANALYSIS AND RESULTS: The analysis:
-Heart surgery valve replacement (n: 60)
-Percutaneous treatment (TAVI CoreValve) (n: 66)
We have collected 29 variables with a time tracking between 4 and 5 years.
Significant differences between gender (more males in the surgical group, p<0.01), age (percutaneous group has older, p<0.01) and ischemic heart disease prior (percutaneous group have higher incidence, p<0,05).
Hospital stay (ICU): no significant differences.
More complications in the way of access of the Corevalve and definitive pacemaker (p<0,01).
Survival: no significant difference between surgery and TAVI (p=0,280).
CONCLUSIONS: TAVI: more complications in path and greater need for definitive pacemaker.
No significant differences with respect to survival.
Significant differences with regard to hospital stay on the ground and the (largest group TAVI) total.

P42. Curcumin reduces renal damage associated to rhabdomyolysis by decreasing ferroptosis-mediated cell death

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Scientific Program: Chronic and Inflammatory diseases.

Keywords: curcumin, rhabdomyolysis, acute kidney injury, ferroptosis, myoglobin

Abstract:

Acute kidney injury is a common complication of rhabdomyolysis. A better understanding of this syndrome may be useful to identify novel therapeutic targets since there is no specific treatment so far. Ferroptosis is an iron-dependent form of regulated nonapoptotic cell death that is involved in renal injury. In this study, we investigated whether ferroptosis is associated with rhabdomyolysis-mediated renal damage and we studied the therapeutic effect of curcumin, a powerful antioxidant with renoprotective properties. Induction of rhabdomyolysis in mice increased serum creatinine levels, endothelial damage, inflammatory chemokines and cytokines expression, alteration of redox balance (increased lipid peroxidation and decreased antioxidant defenses) and tubular cell death. Treatment with curcumin initiated before or after rhabdomyolysis induction ameliorated all these pathological and molecular alterations. Although apoptosis or RIPK3-mediated necroptosis were activated in rhabdomyolysis, our results suggest a key role of ferroptosis. Thus, treatment with ferrostatin-1, a ferroptosis inhibitor, improved renal function in glycerol-injected mice, whereas no beneficial effects were observed with the pan-caspase inhibitor zVAD or in RIPK3-deficient mice. In cultured renal tubular cells, myoglobin (Mb) induced ferroptosis sensitive cell-death that was also inhibited by curcumin. Mechanistic in vitro studies showed that curcumin reduced Mb-mediated inflammation and oxidative stress by inhibiting the TLR4/NF-κB axis and activating the cytoprotective enzyme HO-1. Our findings are the first to demonstrate the involvement of ferroptosis in rhabdomyolysis-associated renal damage, and its sensitivity to curcumin treatment. Therefore, curcumin may be a potential therapeutic approach for patients with this syndrome.

P43. A three-arms randomised controlled prospective trial for the promotion of emotional component of subjective wellbeing and cardiovascular management self-efficacy in cardiac patients.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Emotional component of subjective wellbeing, Cardiovascular management self-efficacy, Cardiovascular disease, Mindfulness and Positive strengthening

Abstract:
Introduction: The promotion of wellbeing and health is a priority in the preventive guidelines for cardiovascular diseases. Thus, the aim of this study is to analyze the effectiveness of two types of psychological brief interventions -mindfulness, and positive strengthening programs- for the promotion on the emotional component of subjective wellbeing and cardiovascular management self-efficacy of cardiac patients. Method: 105 participants, with cardiovascular disease, were randomly assigned to the control group –treatment as usual- or to one of the two experimental groups according to the type of brief intervention. Procedure of this three-arms randomised controlled prospective trial followed the phases of recruitment, pre-evaluation, brief on-site intervention, two-weeks training through mobile device text messages to WhatsApp, maintenance activity and follow-up. The variables analyzed were positive and negative affect, positivity, anxiety-depression, and management self-efficacy -for chronic and cardiovascular disease. Results: For both intervention groups 32 of 35 participants completed the full program –that included training, maintenance and follow-up-, while for treatment as usual group, 29 completed all. Repeated measures design and Posthoc analyses showed that mindfulness and positive strengthening groups had across time a positive effect on the emotional states -positive and negative affect- and management self-efficacy for chronic disease in comparison with TAU group. Once the positivity and anxiety-depression were included as covariates, positivity and depression showed effect on positive affect and management self-efficacy for chronic disease, whereas that anxiety on negative affect, for both intervention groups regarding the TAU group. Discussion: The results indicate that both psychological brief interventions could be valuable to improve the emotional component of subjective wellbeing, increasing positive affect and reducing the negative effect, and management self-efficacy for chronic disease using mHealth format.

P44. 4 Years follow-up of a cohort of patients with rheumatoid arthritis in sustained clinical remission and optimization of biological therapy.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Rheumatoid Arthritis, biological therapy, optimization

Abstract:
BACKGROUND AND OBJECTIVES: Once sustained Clinical Remission (CR) is achieved under treatment with biological therapies, the most efficient strategy is optimization. Finding the lowest effective dose could minimize the risk of adverse effects and improve the cost-effectiveness of Rheumatoid Arthritis (RA) treatment.
Our objectives are 1) to proof that optimization in patients with RA and sustained CR under biological treatment maintains the proportion of patients with DAS28≤2,6 after 4 years, 2) to assess the maintenance of the effectivenes of the optimization at 4 years and 3) to analyze the time until relapse.
METHODS: Open observational prospective study that included 70 patients with RA (CREATE registry) with CR at least for 6 months, under treatment with tapered dose of biological therapy. Effectiveness was assessed with DAS28≤2,6.
Statistical analysis included: descriptive study of variables and a 95% CI, Student t-test for independent samples, repeated measures and mixed ANOVA, and Sidak adjustment. Log-rank test was used to compare time until relapse according to the biological therapy.
RESULTS: After 4 years, 27,7% (95%CI:16,82%-38,58%) of patients maintained CR with the optimized dose, with a DAS28 2,15 (0,81). Through the first year, the percentage of relapses was 15,71%, in the second year, 7,35% and 4,61% relapsed during the third year.
The median time of optimization strategy until relapse was 13,83 (3,18) months (95%CI:7,6-20,06). No significative differences were found at comparing the survival curves of the optimized patients until relapse for 4 years according to the biological therapy (TNFi vs no TNFi) (log-rank test: 0,865, p:0,352).
CONCLUSIONS: At the end of the study, most of the patients maintained DAS28 levels of LDA and half of them reached CR, including those who had turned back to the initial dose. In view of this, optimization strategy in real clinical practice is posible and effective in patients with persistently controlled RA

P45. Characterization of δ9-tetrahydrocannabinolic acid as a dual pparγ/ cb1 ligand. Implications in rheumatoid arthritis

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Δ9-THCA, PPARγ, CB1 and arthritis. CYB5R3, sexual dimorphism, skeletal muscle

Abstract:
Medicinal cannabis and purified cannabinoids have garnered worldwide attention since millions of patients can benefit from its medical properties. Remarkably, Δ9-THCA, the natural precursor of Δ9-THC, is an underexplored non-psychotropic phytocannabinoid that shows potent PPARγ agonistic activity. PPARγ is able to regulate lipid turnover and metabolism and also mediates potent anti-inflammatory activities. Herein, we have investigated the role of Δ9-THCA on PPARγ signaling and its ability to modulate classic cannabinoid receptors (CB1 and CB2), including evaluation of its efficacy in murine collagen-induced arthritis (CIA).
Both Δ9-THCA and Rosiglitazone bind to the canonical binding site in the PPARγ ligand-binding pocket but differentially regulate PPARγ co-regulator binding, transactivation and target gene expression. We found that Δ9-THCA induced osteoblastogenesis measured by Alizarin staining and by mRNA of markers specific for osteoblasts. Our data also demonstrated that Δ9-THCA binds to CB1 and CB2. Interestingly, we have evidence that Δ9-THCA works as a positive allosteric CB1 modulator. In vivo experiments showed that Δ9-THCA greatly prevent collage type II-induced arthritis in DBA/1 mice. The arthritis clinical score in Δ9-THCA-treated group was significantly less than that of CIA group. Paw inflammation and weight loss in CIA mice were also alleviated by Δ9-THCA treatment. Immunochemistry analysis showed that Δ9-THCA prevented the infiltration of inflammatory cells, synovium hyperplasia and cartilage loss in comparison to the untreated CIA group. Furthermore, the administration of Δ9-THCA significantly inhibited the expression of inflammatory genes on knee joints. The efficacy of Δ9-THCA in CIA was greatly prevented by either SR141716A (CB1 antagonist) or T0070907 (PPARγ antagonist). Finally, proteomic SWATH mass spectrometry analysis of plasmatic biomarkers demonstrated that Δ9-THCA is mediating its activity mainly through PPARγ and CB1 pathways.
In conclusion, our studies document the anti-inflammatory and osteoblastogenesis activities of Δ9-THCA highlighting its potential for the treatment of chronic inflammatory diseases such as Rheumatoid Arthritis.

P46. Molecular mechanisms underlying the renal and cardiovascular diseases in systemic lupus erythematosus. Effects of statin treatment.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Systemic Lupus Erythematosus, Transcriptomics, Monocytes, Thrombosis, renal disease, Atherosclerosis.

Abstract:
Objectives: 1. To characterize the molecular profile of monocytes from systemic lupus erythematosus (SLE) patients in relation to the pathophysiology of the disease. 2. To evaluate the role of anti-dsDNA-Abs in the regulation of these processes. 3. To investigate effects Fluvastatin treatment.
Methods: Monocytes from 81 SLE patients and 40 healthy donors (HDs) were purified by negative immunomagnetic selection. Gene expression microarrays were performed (Agilent G4112F) and functional categorization of altered genes was accomplished through IPA software. Selected genes were validated in the whole SLE/HD cohorts by RT-PCR. Serum inflammatory and oxidative profiles were evaluated by multiplex assay and specific commercial kits, respectively, and phosphorylation status of intracellular proteins was analyzed by PathScan. Clinical significance of the parameters analyzed was explored by correlation/association studies. Finally, mechanistic studies were developed to typify specific anti-dsDNA-Abs effects. Besides, the effects of in vitro Fluvastatin treatment on leukocytes were assessed.
Results: Microarray identified 553 altered genes in SLE monocytes. Relevant biofunctions/ disorders on which were involved included inflammatory, immunological, cardiovascular, neurological, renal, and reproductive disease. Associations of these genes with the anti-dsDNA-Abs positivity, early atherosclerosis and nephropathy, along with correlations with disease activity (SLEDAI) and levels of serum inflammatory and oxidative markers were demonstrated. In vitro studies established the specific modulation of several genes by anti-dsDNA, accompanied by the increase of prothrombotic/proinflammatory mediators, apoptosis induction and phosphorylation of intracellular proteins. Besides, treatment of HDs-monocytes with SLE patients' serum after Fluvastatin supplementation prevented the altered proinflammatory gene profile induced by serum from those patients before treatment.
Conclusions: 1. Gene expression profiles allowed the identification of relevant genes and pathways altered in monocytes of SLE patients and associated with the pathogenesis of the disease. 2. Anti-dsDNA antibodies control key biological processes and factors related to the pathophysiology in SLE, which are prevented by Fluvastatin treatment.
Funding: ISCIII (PI18/00837 and RIER RD16/0012/0015)-cofounded with FEDER.

P47. Molecular characterization of the atherothrombotic pathology in Antifosfolipid Syndrome.

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Keywords: Thrombosis/Antifosfolipid Syndrome/Monocytes

Abstract:
In this study we propose a triple approach to molecularly characterize the atherothrombotic pathology of Antiphospholipid Syndrome (APS): delineate their mRNA/microRNA monocyte transcriptomes; evaluate the role of antiphospholipid antibodies (aPL); and identify secreted microRNAs acting as mediators of thrombosis development.

Gene expression microarray (Agilent G4112F) and nCounter microRNA array (Nanostring) were performed on RNA isolated from purified monocytes of 40 APS patients and 40 healthy donors (HD). microRNA-mRNA interaction networks showing inverse correlated expression were identified (IPA). Gene and microRNAs integrating networks were validated (RT-PCR) in APS and non-autoimmune thrombotic cohorts. In parallel, circulating microRNAs profile in APS was branded by array and common deregulated miRNAs between monocytes and plasma were identified. HD monocytes were treated in vitro with purified aPLs and altered gene/microRNA expression promoted in monocytes and plasma was evaluated.

Microarray identified 518 altered genes in APS monocytes involved in hematological and cardiovascular function and inflammatory response, among others. Gene alterations were validated in the whole cohorts, demonstrated to be divergent of the gene profile in non-autoimmune thrombotic patients, and associated to thrombotic recurrences and early atherosclerosis. microRNA profiling also showed altered expression on APS monocytes, 19 of them inversely-correlated with 54 CVD-related target genes. Genes/microRNAs networks were associated with occurrence of thrombotic events, obstetric complications and presence of atheroma plaques. In vitro studies demonstrated the specific modulation of several genes/microRNAs by aPLs. Furthermore, those aPLs promoted the release of several miRNAs, simultaneously altered in plasma and monocytes, and related to thrombosis and atherosclerosis development.

This study provides evidence supporting the presence in monocytes of functional networks of genes and microRNAs involved in the pathophysiology of APS patients, which are primarily modulated by aPLs. Interestingly, aPLs induce the release by monocytes of specific microRNAs that might act as messengers in the bloodstream to propagate their deleterious effects

P48. Comparison of adherence to the Mediterranean diet among UCLM and UCO students.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: mediterranean diet, university, adherence, nutrition.

Abstract:
Background: The Mediterranean diet (MD) is one of the healthiest dietary models, being traditional of the Mediterranean countries. In the period of the university, habits are learned that, in their majority, are maintained.
Objective: To evaluate the differences regarding the adherence to the MD between the universities students of Castilla-La Mancha (UCLM) and Córdoba (UCO).
Methods: Observational descriptive study. Subjects and scope of study: students of UCO and UCLM. Sample: 457 students, 167 (UCO) and 290 (UCLM), average age 20.93% (DE 3.283). Instrument: Test of adherence to MD kidmed (Serra-Majem et al., 2004). Report from the Research Ethics Committee of Córdoba. Information and Informed Consent Form. Data analysis: χ^2 test with qualitative data, analysis of variance with quantitative. A $p<0.05$ was considered.
Results: There are more students with low adherence to MD in the UCLM (17%). 37.7% of university students of the UCLM have a high adherence to MD, in the UCO 35.8%. 84.5% of university students of the UCO have breakfast, those of the UCO 82.6%. 82% of UCO students eat cereals or derivatives (p=0.017) compared to UCLM (72.1%). All students of the UCO use olive oil, UCLM 96.6% (p=0.015). 78.3% of university students of the UCLM eat dairy products, compared to 72.9% of UCO. With regard to industrial bakery, the consumption by the UCLM stands out (36.9%), UCO (22.9%). 41.3% of the UCO intake of 2 yogurts and/or cheese per day, in the UCLM, 32.1%.
Conclusions: The use of olive oil in the UCO stands out, as well as a profile of university students who eat mainly cereals or by-products, and consume yogurts or cheese every day. On the other hand students of UCLM breakfast dairy and industrial pastries, cookies or cupcakes. The students of the UCO consume more “fast food” than UCLM.

P49. Maintenance therapy for pauci-immune crescentic glomerulonephritis with mycophenolate mofetil.

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Scientific Program: Chronic and Inflammatory diseases.

Abstract:
INTRODUCTION: Standard induction therapy with corticosteroids (CS) and cyclophosphamide (CYC) followed by azathioprine for manteinance has been shown satisfactory results in pauci-immune crescentic glomerulonephritis (PEGN). Mycophenolate mofetil (MF) has been introduced for the treatment of PEGN in the last years because of its immunosuppressive efficacy combined with a lower toxicity profile. In this study, we retrospectively analyse the results of the introduction of MF for maintenance in our center.
METHODS: This is a retrospective observational study including all patients diagnosed of PEGN from 2000-2018 treated with MF in monotherapy or associated with prednisone as a maintenance treatment during the follow-up. Information regarding demographics , disease and treatment (dose, outcome, adverse effects and duration) were analyzed.
RESULTS: We reported 70 patients diagnosed for PEGN. Standard induction therapy with CS and CYC was received in 60 patients (85%). 28 patients (40%) started replacement therapy during the first 6 months after the diagnosis. The remaining 42 patients (60%) were followed by an outpatient Nephrology checkup. 3 patients (8%) received maintenance therapy with MF and 24 patients (58%) received MF combined with CS. The mean treatment time was 2.3 years. The mean MF dose was 1 gr/daily. 2 patients had a relapse during the follow-up, those patients responded to increased immunosuppressive treatment. An improvement in serum creatinine levels in the follow-up was observed, creatinine on the onset was 2.8 mg/dl vs 2.1 mg/dl (p = 0.02) at the end of the follow-up.The proteinuria remained stable.There were no side effects that required withdrawal or reduction of MF therapy.
CONCLUSIONS: Our study shows that Mycophenolate is an effective and well-tolerated maintenance therapy in pauci-immune crescentic glomerulonephritis.

P50. EFFECTIVENESS OF LUNG BIOPSY FOR FIBROSING INTERSTITIAL LUNG DISEASE

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Scientific Program: Chronic and Inflammatory diseases.

Abstract:
INTRODUCTION: Fibrosis interstitial Lung Disease encompasses a large and heterogeneous group of parenchymal lung disorders, which overlap in their clinical presentations and radiological patterns.
Definitive diagnoses is done by histological examination of lung parenchyma, that can be obtained by a surgical lung biopsy or by bronchoscopic techniques.
Classic treatment is based on corticoids and inmunosuppression, eventhoug new drugs, such as nintedanib and pirfenidone ara starting to show their efficacy. When medical treatment doesn´t control the disease progression, lung transplant can be indicates.
OBJECTIVE: To analyze the effectiveness of surgical lung biopsy(open Vs Video assisted, VATS) for the interstitial fibrosis lung disease.
PATIENTS AND METHODS: Restrospective study from 85 patients that underwent a surgical lung biopsy in our Unit from 2011 to 2018. Demographic aspects, type of surgical technique, pathological aspects, mobility, mortality and its diagnostic effectiveness was studied.
RESULTS: 19 open biopsies where performed by open surgery and 66 where done by VATS surgery. A final diagnostic was achieved in 72 cases. The median hospitalization for VATS was 2 days and 5 days for open surgery. Both median drain removement was performed on the first day after surgery. All of our surgeries reached diagnostic in 80 % of the cases.
CONCLUSIONS: In our experience, surgical lung biopsy offers a high diagnostic efectiveness for fibrotic luna disease. There are no different between different surgical techniques, open surgery or videoassisted procedures. Video-asisted surgery is associated with less morbidity and decreases hospital stay.

POSTER SESSION II

Infectious diseases, immunological and organ transplantation

P51. Hepatitis E virus in captive nonhuman primates in zoos in Spain

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Scientific Program: Infectious and Immunological diseases
Keywords: Hepatitis E, Nonhuman primates, Spain, Zoonotic.

Abstract:
Hepatitis E virus (HEV) is an emerging zoonotic pathogen that has been detected in different animal species. A survey study was carried out to assess HEV infection in nonhuman primates (NHPs) housed in zoos in Spain. Anti-HEV antibodies were detected in eight of the 181 NHPs tested (4.4%; 95%CI: 1.4-7.4). At least one seropositive animal was detected in five of the 33 species sampled (15.2%). This is the first report of seropositivity in black-and-white ruffed lemurs (Varecia variegata), common chimpanzees (Pan troglodytes) and Barbary macaques (Macaca sylvanus). Anti-HEV antibodies were found in six of the eight zoos included in the study (75.0%). Seroconversion was detected in one chimpanzee, which confirms HEV circulation in one zoo between 2015 and 2016. Seropositivity was significantly higher in hominids than in other NHP families. HEV RNA was not detected in any of the serum samples tested. The results indicate susceptibility of NHPs to HEV infection. Further studies are required to elucidate the role of these species in the epidemiology of HEV.

P52. Aortic valve infiltrating pro-inflammatory cells in aortic stenosis patients

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Scientific Program: Infectious and Immunological diseases.
Keywords: Aortic Stenosis, Cardiovascular disease, inflammation, immunopathology.

Abstract:
Aortic valve stenosis (AS) is a frequent cardiac disease in the elderly and is characterized by valvular calcification, fibrosis and inflammation, however its pathogenesis is not well known. AS has been traditionally considered a passive chronic degenerative process due to the accumulation of damage with age. Nevertheless, recent studies suggest that AS is similar to atherosclerosis, being an active inflammatory process. Particularly, it has been suggested that several immune cell types, present in the valve infiltrate, might contribute to its degeneration and to the progression towards stenosis. However, the valve inflammatory infiltrate has not been well characterized in any study regarding AS. Up to date there is no other treatment for the valve stenosis other than the replacement of the valve itself. Therefore, the characterization of the cells implicated in the inflammatory processes of the valvular stenosis is of outmost importance in order to develop new therapies for AS patients.
Here we present, for the first time, a protocol for the phenotypic characterization of aortic valve infiltrating cell populations in AS patients.

P53. Determining factors of the hemodynamics and dysfunction of the criopreserved homografts implanted from ross surgery

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Scientific Program: Infectious and Immunological diseases. Organ transplantation

Keywords: Ross procedure, Aortic valve, Homograft, Pulmonary stenosis, Echocardiography, survival, Valves.

Abstract:

The use of the Ross procedure in adults is currently controversial, as a replacement of the aortic valve with the patient's own pulmonary valve (autograft) and the pulmonary valve with homograft. This procedure is performed only in a few centers with experience. While there are few echocardiographic studies on the appearance of homograft dysfunction.

The main objective is to know the most prevalent hemodynamic factors in the dysfunction and/or degeneration of cryopreserved pulmonary homografts implanted in Ross surgery.

It is about an observational, descriptive, retrospective and unicentric study, from Clinical Management Unit of Cardiovascular Surgery of the Reina Sofía University Hospital (HURS), Córdoba, Spain. Corresponding to a series of patients operated on for Ross surgery during the period from 1997 to 2017 inclusive. Among the variables of the study, five groups stand out: the preoperative baseline characteristics of the patient, the characteristics of the homograft, the perioperative and postoperative characteristics, as well as the echocardiographic and functional follow-up (at one year, at 2-5 years and after the last revision). The data will be collected by consulting the clinic history of the old and computerized medical records of each patient. A descriptive analysis will be carried out, using the mean and standard deviation, as well as absolute and relative frequency. Regarding the comparison of two independent arithmetic means, the pertinent tests will be used for each case: Student's t test or Mann-Whitney U test, ANOVA test, or the Kruskall-Wallis test, chi-square test, applying the exact test of Fisher. Likewise, a multivariate analysis will be carried out using a binary logistic regression that is raw and adjusted for possible confounding variables. As limitations, we would have the characteristics of an observational study. The project has been approved by the Provincial Ethics Committee.

P54. Impact of Antimicrobial Stewardship Programme on carbapenemics in the survival of bacteremia and pneumonia due to Pseudomonas aeruginosa and Enterobacteria producing Extended-Spectrum β-Lactamases (ESBLS) in a tertiary hospital: a before-and-after interventional study.

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Scientific Program: Infectious and Immunological diseases.
Keywords: Imipenem, Meropenem, Antimicrobial Stewardship, sentinel events, Pseudomonas aeruginosa, Enterobacteria ESBLS.

Abstract:
Background: The treatment of infections caused by multiresistant gram-negative bacteria is a growing challenge in many hospitals. To combat this problem, the development of Antimicrobial Stewardship Programmes (ASP), consisting of specialists in antimicrobial use from different units coordinated by infectious diseases specialists, is recommended.
Purpose: The aim was to assess the impact of ASP on the survival of bacteremia and pneumonia (nosocomial and ventilator-associated) due to Pseudomonas aeruginosa and Enterobacteria producing ESBLs in a tertiary university hospital
Material and methods: A quasi-experimental study was designed before (March 2013–February 2014) and during the intervention(March 2014–February 2016).Patients with sentinel events (bacteremia and pneumonia due to Pseudomonas aeruginosa and Enterobacteria producing ESBLs)were identified and analysed through the microbiology computer system(micro-dynamic), digital medical record (Diraya) and clinical documentation service. The results were presented using percentages for qualitative variables (p values were determined using Chi-square or Fischer test).Statistical tests were carried out at the 5%significance level. Data was performed in SPSS.
Results: The results show that there were no significant differences in survival between both periods at 14 days after the diagnosis of sentinel events: Bacteremia and pneumonia due to Pseudomonas aeruginosa (72.2% vs 87.5%, p=0.258) and (17.2% vs 14.3%, p=1.0),respectively; and bacteriemia and pneumonia due to Enterobacteria producing ESBLs (17.2% vs 11.1%, p=0.508) and (30% vs 25.9%, p=1.0), respectively. In addition, there were no significant differences in survival at 30 days after the diagnosis of the sentinel events: Bacteremia and pneumonia due to Pseudomonas aeruginosa (33.3% vs 25%, p=0.538) and (27.6% vs 28.6%, p=0.930), respectively; and bacteremia and pneumonia due to Enterobacteria producing ESBLs (34.5% vs 20.6%, p=0.154) and (40% vs 29.6%, p=0.696), respectively. Therefore, there was no more mortality during the intervention period in which the use of carbapenems was optimized
Conclusion: Sentinel events survival rates did not decrease because of the intervention, so ASP has proven to be a safe tool for antimicrobial optimization.

P55. Colonization by KPC-producing Klebsiella pneumoniae (KPC-Kp): validation of two quantification methods for monitorization of KPC-Kp carriage load in a prospective cohort of colonized patients.

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Scientific Program: Infectious and Immunological diseases.
Keywords: Klebsiella pneumoniae carbapenemase (KPC)-type enzymes, bacterial load, carbapenem-resistant Enterobacteriaceae (CRE).

Abstract:
Background: The spread of Klebsiella pneumoniae carbapenemase (KPC)-type enzymes has led to the emergence of carbapenem-resistant Enterobacteriaceae (CRE), mostly K. pneumoniae, as important nosocomial pathogens. Asymptomatic, intestinal colonization with carbapenem-resistant Enterobacteriaceae (CRE) is a known risk factor for subsequent CRE infection and mortality. We hypothesized that this association may be partly explained by the degree of gut colonization (bacterial load) and aimed to develop a quantitative molecular method to test this hypothesis.
Materials/methods: Observational, prospective cohort study, 1-year follow-up, with monthly monitoring of KPC-Kp load. The bacterial load was determined by two methods [1]: a culture-based method (CFU of KPC-producing K. pneumoniae relative to total aerobic bacteria [KPC-Kp/TAB]) versus a qPCR method to calculate copy number of blaKPC gene relative to 16S rRNA gene (blaKPC/16S rRNA). Correlation and agreement between methods evaluated by Spearman's rank coefficient (ρ) and Kendall's coefficient of concordance. ROC-based criteria and Youden index to establish an optimal cut-point for dichotomization of carrier state and estimation of specificity, sensitivity, validity index, PPV and NPV of molecular relative to culture-based method.
Results: A total of 113 rectal swabs from 34 KPC-Kp colonized patients were analyzed. The two methods showed a high correlation (ρ=0.838, p <0.001). The area under the ROC curve (AUC) was 0.834, with an optimal cut-point value of 0.003% copies blaKPC/16S rRNA for the molecular method,

resulting in 75.3% sensitivity, 87.5%, specificity and a Youden Index of 0.63. Validity index was 77.9%, with a PPV of 95.7% and a NPV of 48.8%. Clinical concordance was low (W=0.17), but significant (p<0.001). This may reflect the differential sensitivities and inherent limitations of both methods for determination of KPC-producing K. pneumoniae load, particularly the differences in measuring units (CFU versus blaKPC gene copy numbers).

Conclusions: There was a strong correlation between the two KPC-Kp carriage load quantification methods. Diagnostic accuracy of the molecular relative to the bacteriological method was high, which allows shortening of the quantification time.

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POSTER SESSION II

Active aging and fragility

P56. Nursing overload and critical care patient safety relationship

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Scientific Program: Active aging and fragility
Keywords: Nursing workload, ICU, safety, quality and nursing care

Abstract:
Objectives: Background: During the last decade, progressively appeared a change within the nursing critical care culture, giving more importance to patient's safety and establishing quality care improvement as the main outcome. Consequently, it has been necessary to increase nursing interventions and therefore nursing workload.
Outcome: The main outcome is to determine if nursing overload is related to patients' safety. The secondary outcome is to identify the relationship between nursing workload and mortality or the apparition of adverse events.
Method: Systematic review. Electronic searches were carried out in the following databases: PubMed, Embase and Web of Science. The search strategy was: "intensive care nursing", workload and "patient safety". The search was performed between 30/03/2019 and 01/04/2019. We included clinical trials and observational studies published in the last ten years. The review protocol was register at PROSPERO (ID: 130676).
Results: 417 studies were identified (162 Web of Science, 150 Embase, 105 PubMed), after removing 138 duplicates, we reviewed 279 studies by title and abstract, choosing 42 articles to be read at full text. Finally, we agreed to include 9 papers in this review. The articles selected showed the relationship between nursing workload and mortality, increment of the length of stay and the apparition of adverse events, the main adverse events described were Ventilator acquired pneumonia, pressure ulcers and nosocomial infections.
Conclusion: There is an association between nursing workload and patient safety, evidenced by an increment of mortality and adverse event on adults hospitalized in critical care units.

P57. Measuring pain in cognitively impaired people: systematic review

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Scientific Program: Active ageing and fragility
Keywords: cognitive dysfunction, pain measurement, self-reports, observational scales

Abstract:
Introduction: Pain on third age people is a problem yet to be resolved, especially for those with cognitive impairment. It is not uncommon for cognitively impaired patients to receive less analgesic prescriptions than those who are not impaired: the main reason for said undertreatment is the difficulty for health professionals to assess and measure pain on this population.
Objective: Identifying and getting to know the existing scientific production regarding scales to valuate pain in patients with dementia.
Methodology: Systematic review following the PRISMA modified criteria. We queried the main health science databases: ProQuest, PubMed, Scopus and Cochrane. The search was carried out between April and September 2018, using the following keywords: "Cognitive dysfunction" AND "Pain measurement". The research articles included in the review were observational studies published within the last five years in English, Spanish or Portuguese.
Results: Self-reports are considered the most trustworthy measure to evaluate the existence and intensity of pain in patients with mild-to-moderate cognitive impairment. However, when the person has a reduced abstract reasoning capability, the use of this kind of scales is complex because these reports might not be comprehensible by the subjects. As an alternative, observational scales can be used in cases when the patient has a severe cognitive impairment and disability to communicate. There are multiple observational scales, one of them being PAINAD: the most useful one due to the use of simple vocabulary and its short extension.
Conclusions: Choosing the right scale to use is determined by the level of impairment presented by the patient, and including any of them is recommended as part of the pain assessment protocol.

P58. Social support in the European Health Survey in Spain of 2014

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Scientific Program: Active ageing and fragility
Keyword: Aged; Social support; Nursing care; Caregivers

Abstract:
Introduction: Considerable growth in the number of people over 65 and over, and levels of dependency, leads to study the social support available for this sector of the population. Social support, seen from a broad perspective, is the combination of human and material resources available in order to overcome a certain crisis. Arias-Astray and Barron-Lopez (2008) indicates that social support includes all emotional, informational and material aid' transactions received from informal, intimate networks, other groups and the global community.
Objective: To know social support received by elderly people of 65 years old in Spain.
Methodology: Observational descriptive study. The object of study has been the records about people residing in Spain aged 65 or over, obtained from the analysis of the European Health Survey in Spain (EESE) of 2014. Descriptive analysis of sociodemographic variables, and variables related to social support has been carried out.
Results: A total of 6520 records of people aged 65 and over were analyzed. Both men and women studied have people to help them in case of problems. Significant differences were found between social support and civil status ($p<0,001$). Elderly without partner find it more difficult to get help in case of serious problems; on the contrary, married people find help more easily with other people.
Conclusions: It can be concluded that elderly in Spain have social support. Since social support can act as a protective factor against problems such as loneliness, stress and depression, it seems necessary to expand studies along these lines.

P59. Tranexamic acid in trauma patients in emergency department: systematic review and meta-analysis

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Scientific Program: Active ageing and fragility
Keywords: Tranexamic acid, trauma, emergency

Abstract:
Introduction: Tranexamic acid is a synthetic analog of lysine that inhibits fibrinolysis by blocking the binding of plasminogen to fibrin. It is part of the group of anti-hemorrhagic drugs, prevents and treats blood loss. Aim: To analyze the effect of tranexamic acid in trauma patients treated in the emergency department. Methods: A systematic review was developed in the databases: Medline, Embase, Cochrane, Web of Science and Clinical Trials; including clinical trials involving patients with severe trauma with age greater than or equal to 16 years, whose intervention was the administration of tranexamic acid in the emergency department in the first 8 hours after the trauma. Results: We selected 4 clinical trials with a total of 20697 patients. A decrease in mortality was detected [OR 0.89 (95% CI 0.83-0.96); p = 0.004; I2 = 0%] and better functional status (Glasgow Outcome Scale) [OR 0.60 (95% CI 0.39-0.94); p = 0.02; I2 = 0%] in patients with severe trauma after administration of tranexamic acid. On the contrary, a longer stay in the Intensive Care Unit was found [MD 2.55 (95% CI 0.04-5.06); p = 0.05; I2 = 0%]. Conclusion: the results obtained seem to be in line with the fact that the administration of tranexamic acid decreases the mortality and improves the functional status in patients with severe trauma assisted in the emergency department; however, the stay in the Intensive Care Unit of the patients thus treated is longer.

P60. Predictors of functional recovery after hip fracture in elderly patients

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Scientific Program: Active ageing and fragility
Research Group: GC-05 - Systemic Autoimmune and Chronic Inflammatory Diseases of the Musculoskeletal System and Connective Tissue
Keywords: functional recovery, hip fracture and elderly

Abstract:
Introduction: Osteoporotic fractures of the proximal femur hereafter referred to as hip fractures, and the subsequent functional dependency of the patients after surgery, present a global challenge to healthcare systems and for patients and their families.
Objetive: In this study, we describe and analyze the factors associated with functional prognosis after hip fracture in elderly patients.
Methods: We searched MEDLINE and the Cochrane Central Register of Controlled trials, using the core search terms 'hip fracture', 'functional recovery', 'prognostic factors', 'functionality', 'sociological factors', 'healing', 'elderly' and 'older adults'. The search strategies for the systematic review were: 'functional recovery AND predictors AND hip fracture' and 'hip fracture AND prognostic factors AND healing'. The search strategy was limited to articles published between 2001 and 2019. Review and all observational study were included if participants were adults (> 65 years) and analyzed predictive factors of functionality after hip fracture surgery. The Grades of Recommendation, Assessment, Development and Evaluation approach were used to evaluate the quality of the evidence.
Results: Thirty-two studies were eligible for full review. Six articles were eliminated due to low level of evidence. Among the remaining there was a moderate level of evidence (Ia, IIb, III). Only seven studies developed predictors of functional recovery after hip fracture. In these studies, patients were followed up between three and fourteen months. Good cognitive status predicted a good recovery in five of the studies, have less comorbidities and age predicted a good recovery in three of them, living in a private home before the fracture, ambulation before fracture and family status in two of them.
Conclusion: Our systematic review revealed that age, good cognitive status, living in a private home before fracture; ambulation before fracture, less comorbidities, and family status were key predictors of better functional postoperative recovery of hip fracture in elderly patients.
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P61. Systematic review of qualitative studies about the decision-making on the location of care of the elderly: Preliminary results

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Scientific Program: Active ageing and fragility
Keywords: Decision-making, Aged, Location of care

Abstract:
Objective: To synthesize the evidence with qualitative methodology in order to achieve a deep understanding of how decisions are made on the location of care of the elderly.
Design/Methodology: A systematic review of qualitative studies was used. It was conducted in six databases: Web of Science, PubMed, Scopus, CINAHL Complete, PsycINFO and SciELO Citation Index. This review was registered in PROSPERO (registration number: CRD42018084826), and the review protocol was published in BMJ Open1.
To carry out this preliminary analysis, the Journal Citation Reports of 2017(JCR) has been consulted through the Web of Science2.The calculations of the dates have been made taking into account the end date of the search strategy (29 November 2017).
Preliminary results: Of the 46 articles finally included, 71.7% have been published between 2008-2017, and 8.7% between 2016-2017. Being the article with the oldest publication date of the year 1987.
The 65.2% of articles was published in journals indexed in JCR, distributing in Q1 (8.7%), Q2 (28.3%), Q3 (23.9%) and Q4(4,3%). The Journal of Aging Studies is the most common indexed journal.
Regarding the classification categories of these journals, we find that the most common is NURSING (Social Science Edition:SSCI), followed by GERONTOLOGY(Social Science Edition:SSCI) and NURSING(Science Edition:-SCIE).
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POSTER SESSION II

Nutrition, endocrine and metabolic diseases

P62. Influence of the time of evolution of type 2 diabetes mellitus on the degree of impairment renal function and carotid atherosclerosis: role of advanced glycation end products.

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Scientific program: Nutrition, Endocrine and metabolic disease.
Keywords: chronic kidney disease, diabetes mellitus, urine albumin, carotid atherosclerosis, cardiovascular disease, advanced glycation end products.

Abstract:
Background. Type 2 Diabetes mellitus (DM2) is the main cause of chronic kidney disease with an increased incidence of cardiovascular disease (CVD) and systemic complications. The determination of the thickness of the carotid intima-media (GIMc) is considered a surrogated marker of CVD. Our objective was to determine if the time of evolution of DM2 in patients with coronary heart disease (CHD) influences renal function, the degree of carotid atherosclerosis and the concentration of advanced glycation end products (AGEs).
Methodology. 540 CHD patients with DM2 were selected at the beginning of the CORDIOPREV study. They were classified according to the time of evolution of DM2: long-standing DM2 patients (n = 350) and recent DM2 diagnosis (n = 190). Renal function, evaluated by glomerular filtration rate and albuminuria, the degree of carotid atherosclerosis (GIMc), serum levels of AGEs, and other anthropometric and biochemical parameters were determined.
Results. Our data show that those long-standing DM2 patients had a greater impairment in renal function, with a lower glomerular filtration rate and higher albuminuria, compared with patients with recently diagnosed DM2. We didn´t find significant differences in GIMc between both groups. Regarding AGE levels, patients with recently diagnosed DM2 presented lower levels of these glycotoxins compared to long-standing DM2 patients.
Conclusion. Our results indicate that long-standing DM2 patients have a higher cardiovascular risk (greater deterioration of renal function, higher serum levels of AGEs and a tendency to present greater carotid atherosclerosis) than patients with recently diagnosed DM2. These results are of great interest since renal complications derived from diabetes lead to an increase cardiovascular morbidity and mortality, so the study of possible mechanisms that lead to this situation, such as the elevation of AGE concentrations, could predict the evolution of DM2 and the final development of CVD.

P.63 Massive determination of polar lipids in biological samples by LC–MS/MS

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Scientific Program: Nutrition, Endocrine and metabolic diseases
Keywords: lipidomics, metabolomics, biofluids, LC—MS/MS

Abstract

Lipids are involved in numerous biological functions and have been widely associated to the development of several pathologies such as cardiovascular diseases or type-2 diabetes. For this reason, the development of methods with high capability for detection of lipids in biological samples is required. Discrimination of lipids in polar (mainly glycerophospholipids, sphingolipids and saccharolipids) and non-polar (glycerolipids, sterol lipids and fatty acyls) fractions is frequently used in clinical analysis since polar and non-polar lipids require different procedures for sample preparation, chromatographic separation and mass spectrometry detection. Several methods have been used for determination of polar lipids, with predominance of those based on LC–MS/MS due to their high ionization capability. The main problems in the determination of polar lipids are the chemical diversity, the isomeric character and the wide concentration range at which they can be detected.

In this research, the objective was to develop a method for massive qualitative/quantitative determination of polar lipids in biological samples. For this purpose, a LC–MS/MS strategy was designed by combination of acquisition methods with a triple quadrupole mass analyzer. The strategy was carried out in two steps: a) A first step for detection of lipids by monitoring selective fragmentation patterns representative of each lipid family; and b) a second step for confirmation of lipid species by detection and identification of product ions associated with the fatty acids that are conjugated. This approach allowed detecting 490 polar lipids pertaining to the following families: ceramides, sphingomyelins and sphingoid bases, lysoglycerophospholipids with different polar groups, glycerophosphatidylcholines, glycerophosphatidylethanolamines, glycerophosphatidic acids, glycerophosphatidylglycerols, glycerophosphatidylinositols, glycerophosphatidylserines and plasmalogens (O-alkyls and O-alkenyls families). The method has been applied to a cohort formed by 384 individuals in order to obtain a qualitative and quantitative distribution of polar lipids in plasma.

P64. Prediction of presurgical treatment in Cushing's disease according to clinical data and molecular profile

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Scientific Program: Nutrition, Endocrine and metabolic diseases
Keywords: Cushing's disease; hypercortisolism; presurgical treatment; clinical data; molecular profile

Abstract:
Introduction. The duration of hypercortisolism in Cushing's disease (CD) appears to be inversely related to the reversibility of complications, which in turn increase mortality. This makes it necessary to identify medical therapies capable of normalizing cortisol overproduction before transsphenoidal surgery. The aim of this study was to determine if the clinical data of patients with CD before surgery allow predicting the presence and/or abundance of somatostatin (ssts) and dopamine (DRs) receptors at the corticotrophic adenoma, in order to start a more effective and personalized presurgical medical treatment.
Patients and methods. Retrospective study performed through review of clinical histories and molecular profile analysis of corticotrophic tumors. We included all patients diagnosed with CD (2005-2014) treated with transsphenoidal surgery, and whose tumor sample was analyzed in the Department of Cell Biology, Physiology and Immunology of the University From Córdoba. The correlation study was performed using Spearman's Rho.
Results. 9 women with CD and molecular profile analysis of corticotrophic tumor. Age 47.33 ± 12 years. A positive correlation was observed between tumor size at diagnosis and levels of receptor expression sst2 [rho= 0,731 (p=0,04)], sst3 [rho= 0,735 (p=0,038)], DR2 [rho= 0,821 (p=0,023)], DR4 [rho= 0,946 (p=0,000)] y DR5 [rho= 0,900 (p=0,037)]. In addition, there was a marked inverse correlation between ACTH levels at diagnosis and the sst5 receptor [rho= -0,767 (p=0,016)].
CONCLUSIONS. Tumor size at the diagnosis of CD seems to show a direct correlation with the levels of expression of sst2 and DR2 receptors, suggesting that in patients with CD with macroadenoma in the initial study, preoperative treatment with somatostatin analogs and/or dopamine may be helpful. In addition, the inverse correlation between ACTH levels at diagnosis and sst5 expression questions whether the specific analogues of this receptor would be useful in the presurgical treatment of CD.

P65. Molecular Diagnosis in Reproductive Medicine: In search of a specific signature of circulating miRNAs for the stratification of polycystic ovary syndrome.

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Scientific Program: Nutrition, Endocrine and metabolic diseases

Keywords: miRNAs, biomarker, PCOS

Abstract:

Small, non-coding RNAs (or miRNAs) are key regulators of multiple cellular functions, which are endowed with important pathophysiological implications. In addition, miRNAs are detected in plasma, with as yet unknown physiological functions. In any event, circulating miRNAs have been proposed also as putative biomarkers for a wide spectrum of pathologies, including cardiovascular, metabolic and some reproductive diseases.

Polycystic ovary syndrome (PCOS) is a highly prevalent, but largely heterogenous endocrine disorder, characterized by ovulatory dysfunction, hyperandrogenism and/or cystic ovaries, in need of improved diagnostic and therapeutic options. PCOS is frequently associated to metabolic disorders, such as obesity and insulin resistance. To a large extent, heterogeneity of presentation of the syndrome is at the basis of the difficulties of its diagnosis and management in the clinical setting. Accordingly, a substantial fraction of affected women remain undiagnosed up to relatively late stages of the disease.

To provide molecular tools for better stratification of PCOS patients, we present here our unbiased search of changes in circulating miRNAs in a cohort of 181 women, with or without PCOS (as defined by Rotterdam criteria), further stratified depending on the presence or not of obesity (BMI>30). High-throughput miRNA analysis using n-Counter technology were performed in plasma samples from a representative subset of women from each group (N=6/group), and data were subjected to correlation and principal component analysis.

The main results of this work are: (i) we have optimized highly efficient selection of house-keeping miRNAs for plasma analyses, (ii) we have defined a selection of miRNAs that stratifies precisely case vs. control samples and (iii) we have confirmed by qPCR in the whole cohort (n=181) the most relevant targets obtained after n-Counter analysis.

While final validation of results is still ongoing, we believe our molecular studies will help to set an integral diagnostic system based on miRNA determination in blood samples that would permit better diagnosis (even at asymptomatic stages) and improved stratification of women suffering PCOS.

P66. Autism spectrum disorder (asd) with and without mental regression is associated with changes in the fecal microbiota

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Scientific Program: Nutrition, Endocrine and metabolic diseases.

Keywords: Autism Spectrum Disorder; children; intestinal microbiota; nutrients.

Abstract:

New microbiome sequencing technologies provide novel information about the potential interactions among intestinal microorganisms and the host in some neuropathologies as autism spectrum disorders (ASD). The microbiota–gut–brain axis is an emerging aspect in the generation of autistic behaviors. The aim of this study was to evaluate the fecal metagenomic profiles in children with ASD and compare them with healthy participants. This comparison allows us to ascertain how mental regression could influence the intestinal microbiota profile. For this reason, a subclassification in children with ASD by mental regression (AMR) and no mental regression (ANMR) phenotype was performed. The present report was a descriptive observational study. Forty-eight children aged 2–6 years with ASD were included: 30 with ANMR and 18 with AMR. In addition, a control group of 57 normally developing children was selected and matched to the ASD group by sex and age. Fecal samples were analyzed with a metagenomic approach using a next-generation sequencing platform. Several differences between children with ASD, compared with the healthy group, were detected. Namely, Actinobacteria and Proteobacteria at phylum level, as well as, Actinobacteria, Bacilli, Erysipelotrichi, and Gammaproteobacteria at class level were found at higher proportions in children with ASD. Additionally, Proteobacteria levels showed to be augmented exclusively in AMR children. Preliminary results, using a principal component analysis, showed differential patterns in children with ASD, ANMR and AMR, compared to healthy group, both for intestinal microbiota and food patterns. In this study, we report, higher levels of Actinobacteria, Proteobacteria and Bacilli, aside from Erysipelotrichi,

and Gammaproteobacteria in children with ASD compared to healthy group. Furthermore, AMR children exhibited higher levels of Proteobacteria. Further analysis using these preliminary results and mixing metagenomic and other "omic" technologies are needed in larger cohorts of children with ASD to confirm these intestinal microbiota changes.

P67. Postprandial lipemia precedes type 2 diabetes development: from the CORDIOPREV study.

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Scientific Program: Nutrition, Endocrine and metabolic diseases
Keywords: diabetes, postprandial lipemia, free fatty acids, CORDIOPREV.

Abstract:
Objective: Our objective was to evaluate whether postprandial lipemia is associated with the incidence of type 2 diabetes mellitus (T2DM) in patients with coronary disease from the CORDIOPREV study.
Materials and methods: This study included 462 patients from the CORDIOPREV study without T2DM at baseline. Patients were categorized depending on the area under the curve (AUC) of free fatty acids (FFA) by tertiles (ascending order) measured after standard oral glucose tolerance test (OGTT) at baseline: tertile 1 (LOW group), tertile 2 (INTERMEDIATE group) and tertile 3 (HIGH group). Patients were randomized to consume either a Mediterranean or a low-fat diet. We performed a COX regression analysis to determine the T2DM risk according to the AUC of FFA groups after a median follow-up of 60 months. Further, we evaluated insulin resistance and beta-cell function.
Results: We found that patients with high level of FFA presented lower insulin sensitivity, lower beta-cell function and higher hepatic insulin resistance compared with LOW group (all, $p<0.05$). Moreover, we observed higher T2DM risk in patients with higher AUC of FFA (HR: 4.04; 95% CI 2.24-7.28) and in intermediate AUC of FFA patients (HR: 2.45; 95% CI 1.34-4.48) compared with LOW group.
Conclusion: Our study suggests that higher postprandial level of free fatty acids lead to a lipotoxicity effect which could be associated with insulin resistance and lower beta-cell function. In addition, our results support that postprandial lipemia could be used as a predictive tool to assess the risk of T2DM development.

P68. Comparison of anthropometric indices for predicting the risk of metabolic syndrome.

Authors: Elena Raya Cano.
Scientific Program: Nutrition, Endocrine and metabolic

Abstract:
Metabolic syndrome (MetS) is a multifactorial pathophysiological state that encompasses a series of risk factors such as: abdominal obesity, insulin resistance, hypertension (HBP), atherogenic dyslipidemia (low HDL cholesterol and increased triglycerides (TG), endothelial dysfunction and a proinflammatory systemic state. The importance of metabolic syndrome (MetS) lies in its close association with the high risk of cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM).

MetS has become an epidemic worldwide, the result of a high prevalence of obesity and a sedentary lifestyle. For this reason, an early detection of MetS in a susceptible population is essential, which prevents the progression of these risk factors. Recently, a non-invasive method of early detection based on the measurement of WHtR and blood pressure has been presented. In addition, numerous studies have shown the association of MetS with indicators of abdominal adiposity, highlighting the predictive capacity of these indices

The objective of the present study is to determine the predictive capacity of the anthropometric indexes on the MetS, classifying them into two groups, on the one hand the classical anthropometric indexes; body mass index (BMI), waist circunference (WC), waist to hip ratio (WHR), waist to height ratio (WHtR), and percentage of body fat (%BF), and on the other hand the indices proposed in recent years; a body roundness index (BRI), body adiposity index (BAI), a body shape index (ABSI), abdominal volumen index (VAI), conicity index (CI).

A cross-sectional study on 636 workers, 204 are women and 432 men. Among them, 59 have metabolic syndrome.

Currently, we are analyzing the data collected to obtein results and conclusions.

P69. The fat composition dietary and homocistein levels modulating the interaction between polymorphysm clock gen and lunch time: cordiprev study

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Scientific Program: Nutrition, Endocrine and metabolic diseases
Keywords: chronobiology, clock gen, lunch time, fat composition dietary, homocysteine

Abstract:
Introduction: Currently the circadian rhythm has been implicated with a lot of interactions of our organism. A wild variety of ambiental factors like our life habits (dietary composition and timing of food intake) or genetical factors could affect the circadian rhythm and bring on the metabolic diseases.
Objective: Analyse if the variability in gen CLOCK interacts with lunch time modulating by the fat composition of the diet and the incidence of cardiovascular risk factors in coronary patients.
Material and methods: Data was obtained through questionnaire about biorhythm of 100 patients of CORDIOPREV study (NCT00924937), classifying about earlier eaters (<15:00 hours) and late eaters (>15:00 hours). Furthermore, through a dietary questionnaire it was obtained the daily consumption of fatty acids and differents food groups. They were determined in these patients the lipids profile, C reactive protein level and homocysteine. Finally, it was done the genotyping of several polymorphism (rs1801260, rs4864548, rs934945 y rs2305160) of gen CLOCK.
Results: There was a significative interaction between the rs4864548 polymorphism of gen CLOCK and the lunch time, indicating the carriers of minority allele A who took lunch after 15:00 h, a decrease in the consumption of omega-3 in the diet (p-interaction = 0,04), at expense of a lower consumption of nuts (p-interaction = 0,04); and exhibiting these patients higher homocysteine plasmatic level than homozygous for the majority allele G. In the other parameters analysed (lipid profile, C reactive protein and consumption of the rest of fatty acids) no significant differences were found.
Conclusion: These results could suggest the interaction, modulated by the consumption of fat in the diet and homocysteine level, between lunch time and the variants of gen CLOCK, in coronary patients.

P70. Differential abundance proteomics reveals growth hormone replacement therapy reverses serum protein changes in children with growth hormone deficiency

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Scientific Program: Nutrition, Endocrine and metabolic diseases
Keywords: growth hormone (GH), GH deficiency (GHD), GHD treatment, proteomics, biomarkers, SWATH

Abstract:
Background: Growth hormone (GH) deficiency (GHD) produces delayed growth and short stature, but also affects bone health, cardiovascular function, metabolic profile, and therefore quality of life. Early GH replacement treatment during childhood improves clinical outcomes in these patients, although no markers related to GH therapy have been reported to date. However, studies in adult GHD patients and in short-stature children have suggested that GH therapy influences lipoprotein metabolism. In this study, we apply quantitative proteomics to assess serum protein abundance changes in GHD children after GH treatment, and we compare the profile obtained with the protein changes observed previously for the same patients before treatment.
Methods: Serum from 15 prepuberal patients with GHD was collected before and after six-month GH treatment. Samples were subjected to high-abundance protein depletion, protein precipitation and trypsin digestion. Abundance changes in serum proteins were analyzed using a variable SWATH DIA differential proteomics approach. A Triple-TOF 5600+ Q-TOF (Sciex), coupled to nano-LC, was used for all MS analysis. An ad-hoc peptide library was previously built from the samples using a top 65 DDA LC-MS/MS.
Results: Quantitative data was obtained for 273 serum proteins in all analyzed samples. A total of 39 proteins presented abundance changes (Wilcoxon p-val<0.05) after six-month GH treatment (16 up-regulated and 23 down-regulated). Thirty out of these 39 proteins had been previously described as changing in GHD children as an effect of the disease. Specifically, the apolipoprotein group, clearly down-regulated in GHD children, was now found up-regulated as a consequence of GH treatment.
Conclusion: Six-month GH replacement treatment reversed serum protein changes produced by GHD, and corrected alterations in lipoprotein metabolism in GHD children.

P71. miR-223-3p: Type 2 Diabetes Predictive Marker by Regulation of Adipose Tissue Function

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Scientific Program: Nutrition, Endocrine and metabolic diseases

Keywords: miR-223-3p, adipose tissue, metabolic disease

Abstract:

Adipose tissue constitutes an important source of circulating microRNAs (miRNAs), which can regulate gene expression within cells or act as adipokines on distant tissues. A recent study of patients with high risk of metabolic syndrome development, participating in the CORDIOPREV clinical trial (NCT00624637), indicated that miR-223-3p plasma levels represent a potential prediction marker for type 2 diabetes (T2D), since this miRNA is reduced in CORDIOPREV patients that developed T2D (Incident-T2D) in comparison with those that did not (Non-T2D) after a follow-up of 24 months. Moreover, miR-223-3p plasma levels positively correlated with adipose tissue dysfunction index. Exposure of 3T3-L1 adipocytes to sera from Incident-T2D individuals evoked an inflammatory response as compared to cells treated with sera from Non-T2D individuals. miR-223-3p expression levels in human and murine adipocyte cell lines (SGBS/3T3-L1) was maximal at the end of the differentiation process, whereas miR-223-3p was mainly secreted by cells at initial stages of differentiation. Notably, exposure of adipocytes to TNFα to induce insulin-resistance resulted in the up-regulation of miR-223-3p expression, which was retained inside the cells due to TNFα-induced blockade of exosome sorting and release. These results led us to characterize the effect of miR-223-3p overexpression in (pre)adipocytes. In-silico research of potential miR-223-3p targets revealed that this miRNA could play a role in insulin signaling and vesicular traffic, specifically, in glucose transporter 4 (GLUT-4) traffic. We confirmed a negative role of miR-223-3p on both GLUT-4 translocation to the plasma membrane and glucose uptake through insulin dependent and independent pathways, in both preadipocytes and mature adipocytes, that finally altered their lipid storage capacity. In all, our studies suggest that miR-223-3p plays an important role in adipose tissue function, mainly by regulating glucose metabolism, that can be impaired under inflammatory conditions, thus contributing to the development of T2D.

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P72. A microbiota-based predictive model for type 2 diabetes development: from the CORDIOPREV study.

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Scientific Program: Nutrition, Endocrine and metabolic diseases
Keywords: gut microbiota; type 2 diabetes; predictive model; coronary heart disease; CORDIOPREV.

Abstract:
Objective: Recent studies have shown that Type 2 Diabetes Mellitus (T2DM) patients have an altered gut microbiota composition, although it is unknown if these alterations precede the development of T2DM. We aimed to evaluate whether gut microbiota composition, added to clinical biomarkers would have the potential to improve the prediction of new incident cases of T2DM in patients with Coronary Heart Disease (CHD).
Methods: We included in this study all patients from the CORDIOPREV study without T2DM at baseline (n=462). Of these, 107 patients developed T2DM according to the American Diabetes Association (ADA) diagnosis criteria after a median follow-up of 60 months, whereas 355 patients remained free of this disease during this period. The baseline gut microbiota composition was analyzed by 16S rRNA gene on the Illumina MiSeq platform. Predictive models were built by random forest algorithm and the performance was evaluated by ROC analysis.
Results: We found a differential baseline gut microbiota profile between patients who developed T2DM and those who remained free of the disease. The addition of baseline microbiome to clinical variables increased the area under the curve (AUC) from 0,632 to 0,946. Further, we built a microbiome-based risk score, and we found a higher T2DM development risk for patients with a high-risk score as compared to patients with a low-risk score (HR:3.22, 95%CI: 1.56-6.66). This higher T2DM development risk was associated with a lower DI (p=0.048) and a higher HIRI (p=0.046).
Conclusion: Our results support a potential role of gut microbiota as a predictive biomarker and as a pathogenic factor in T2DM development.

P73. Obesogenic environments linking fibrosis and metabolic disease

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Scientific Program: Endocrine and metabolic diseases.
Keywords: Adipose tissue, extracellular matrix components, obesity, obesogenic environment, fibrosis.

Abstract:
Adipose tissue (AT) cells are surrounded by extracellular matrix (ECM) proteins whose composition and remodeling are of crucial importance for adipocyte function. ECM is a highly dynamic structure composed by multiple molecules produced by AT cells, including collagens, adhesion proteins and proteoglycans. During obesity, AT expansion is linked to the developed of fibrosis, which is defined as an excessive accumulation of ECM components. This can result from an imbalance between excess synthesis of fibrillary components, such as collagens I, III and VI, and an impaired degradation of these proteins. Moreover, the proteoglycan, lumican, which is dysregulated in obesity (our proteomic results), is involved in collagen fibrillogenesis, suggesting a role for lumican in the developed of fibrosis. Therefore, the aim of this work was to analyse the regulation of ECM production both during adipocyte differentiation and in response to different obesogenic environments, including hyperglycemia/hyperinsulinemia [by exposure to high glucose and high insulin (HGHI) concentrations], inflammation (TNFα) and adipocyte hypertrophy with or without insulin resistance (exposure to oleate or palmitate, respectively) in 3T3-L1 cells. Our RT-qPCR results showed alterations in the expression profile of Collagen I, III and VI in preadipocytes in response to all the obesogenic conditions tested. In addition, western blotting studies revealed that lumican is produced by adipocytes in response to hyperglycaemic/hyperinsulinemic conditions. In all, we describe the obesity-associated changes occurring in the adipose tissue ECM and the obesogenic insults leading to the development of pathogenic fibrosis that alter the interplay between adipocytes and their microenvironment.
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P.74 DPP4 effect and its inhibition by vildagliptin on osteogenic and adipogenic Differentiation of human mesenchymal stem cells

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Scientific Program: Active ageing and fragility.
Keywords: DPP4, DPP4 inhibitor, vildagliptin, mesenchymal stem cells, osteogenesis, adipogenesis

Abstract :
Dipeptidyl peptidase4 (DPP4) is a ubiquitous exopeptidase and occurs as a cell membrane bound protein as well as in a soluble, extracellular form. DPP4 cleaves chemokines, neuropeptides, and peptide hormones and regulates several physiological processes. The increase of DPP4 in plasma is associated with diabetes and osteoporosis. DPP4 plays a major role in glucose metabolism. It is responsible for the degradation of incretins (GLP-1 and GIP). In bone, DPP4 acts on proteins involved in bone formation such as IGF-1, SDF1, NPY and PYY. DPP-4 Inhibitors (Gliptins) increases GLP-1 and GIP levels, which inhibit glucagon release, increases insulin secretion, decreases gastric emptying, and decreases blood glucose levels in diabetic subjects. Bone mass loss associated with diabetes decreases with Gliptins. During the adipogenesis, DPP4i favors fat droplets accumulation. Mesenchymal stem cells (MSC) are precursors of adipocytes and osteoblasts. Aging and diabetes potentiated MSC differentiation through the adipogenic lineage at the expense of the osteoblastic phenotype, which favors bone loss and osteoporosis.
Aim: To study the DPP4 effect on human MSC differentiation into osteoblasts and adipocytes.
MSC cultures were induced to differentiate into osteoblasts and adipocytes in presence or absence of 200, 400 or 800 ng/ml of DPP4, in combination or not with 100 nM of the vildagliptin. Expression of osteogenic and adipogenic genes were analyzed, as well as the mineralization in osteoblasts and fat droplets formation in adipocytes through alizarin-red and oil-red O stains, respectively. DPP4 on adipogenesis did not exert significant changes. However, on osteoblastogenesis, higher concentrations of DPP4 decreased mineralization, which was reversed by vildagliptin. The results suggest that, in diabetes, DPP4 increase can negatively affect bone formation and promote bone loss. This effect may be partly prevented by use of gliptins. Therefore, these drugs, in addition to improving blood glucose levels, can exert a positive effect on bone mass.

P75. The Translational-back-translation of the Berlin questionnaire

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Abstract:
Introduction / Aim: To describe the transcultural adaptation phase of the Berlin questionnaire, as a first step of the validation process is this questionnaire for the diagnosis of sleep apnea hypopnea syndrome (SAHS) for the Spanish population.
Materials and Methods: The translation-back-translation methodology for transcultural adaptation of questionnaires for use in health research proposed by WHO has been used.
A direct and inverse translation has been made, followed by a synthesis and cultural adaptation through qualitative methodology. A Spanish translator with command of the original language of the instrument (English) will perform the direct translation of the questionnaire from English into Spanish. Next, a second translator, blind to the original questionnaire, native English and fluent in Spanish, will perform the reverse translation or backtranslation.
Each translator will assess for each question of the questionnaire the difficulty he had in finding a conceptually equivalent expression between both languages (0 to 10). A panel of experts will be constituted by the members of the research team, who will classify the items according to the difficulty that the first two translators had in finding a conceptually equivalent expression. The correlation between their scores will be analyzed using Pearson's linear correlation coefficient. It will be considered necessary to carry out a new translation and back translation of the items of high difficulty.
Results: Of the10 items, 8 were equivalent and only 2 had minor modifications, which did not affect the meaning of the question.
Conclusions: The cultural adaptation to the Spanish context was successful since the translation-back-translation process produced a version similar to the original one

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