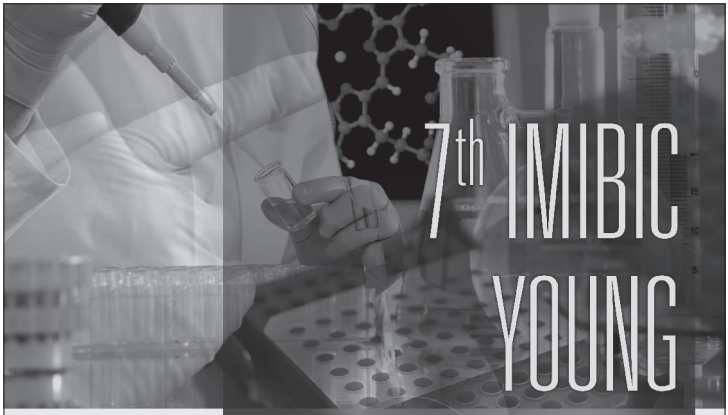
7th IMIBIC YOUNG INVESTIGATORS MEETING

ABSTRACT BOOK

IMIBIC BUILDING
CONFERENCE ROOM
CÓRDOBA, 10-11 MAY, 2016



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Acknowledgements
We thank the External Reviewers and the members of the Scientific Committee for their kind collaboration. We greatly acknowledge the Colegio de Médicos de Córdoba for its support and commitment to promote research among residents.

7th IMIBIC YOUNG INVESTIGATORS MEETING PROGRAMME

Day 1 (10th May)	
9:00-9:30	**Opening ceremony. Registration and Poster display**
9:30-10:45	**SESSION I. Cancer (Oncology and Oncohematology)**
I.a 9:30-9:45	Endothelial nitric oxide synthase in colorectal cancer: a potential new therapeutic target in stem cell-like poor-prognosis subtype. **Jon Peñarando Sáez**
I.b 9:45-10:00	Potential therapeutic treatment of Biguanides (Metformin, buformin and phenformin) for pituitary adenomas. **Mª Carmen Vázquez Borrego**
I.c 10:00-10:15	Key proteins regulation of the DNA Damage Response Pathway CHK2 and CDC25A in the context of carcinogenesis. **Maribel Lara Chica**
I.d 10:15-10:30	HIPECT4. Multicentric randomized controlled trial about the influence of HIPEC in localy advanced colorrectal cancer in abscense of carcinomatosis. A protocol study. **Rubén García Martín**
I.e 10:30-10:45	Protein expression of FGFR3, PI3K, AKT, p21Waf1/Cip1 and Cyclin D1 and D3 in patients with T1 bladder cancer: clinical implications and prognostic significance. **Álvaro Sánchez González**
10:45-11:15	**Coffee Break. Poster Showcase**
11:15-12:45	**SESSION II. Chronic and Inflammatory diseases**
II.a 11:15-11:30	Neuroligin deficient mutants of C. elegans overexpress comt-4: a crosspoint between dopamine and serotonin pathways. **Ángel Rodríguez Ramos**
II.b 11:30-11:45	Potential impact of in vivo Ubiquinol supplementation in the prevention of atherothrombosis in Antiphospholipid Syndrome Patients. Preliminary results of a clinical trial. **Iván Arias de la Rosa**
II.c 11:45-12:00	Assessment of Fatigue in Spondyloarthritis and Its Association with Disease Activity. **Clementina López-Medina**
II.d 12:00-12:15	Measuring anxiety regulation strategies: development and preliminary validation of an instrument. **Rosario Castillo Mayén**
II.e 12:15-12:30	TNFalpha-Damaged-HUVECs Microparticles modify Endothelial Progenitor Cell functional activity. **Carlos Luna Ruiz**

II.f 12:30-12:45	AP-1 inhibition by SR11302 protects human hepatoma HEPG2 cells form bile acids inducded apoptosis by restoring the NOS-3 expression. **Sandra González Rubio**
13:00-14:00	**Plenary lecture. Dr. Sergi Castellví-Bel IDIBAPS, Barcelona**
14:00-15:30	**Lunch**
15:30-16:00	**Poster Showcase**
16:00-17:00	**SESSION III. Infectious and Immunological diseases. Organ transplantation.**
III.a 16:00-16:15	Impact of colistin therapy on mortality of multidrug-resistant and colistin-sensitive acinetobacter baumannii bacteremia in critically ill patients. **Tania Amat Serna**
III.b 16:15-16:30	Hepatitis E infection in wild boar as a potential route of transmission to humans: Results of the HepEboar Study. **Salvador Barea Chacón**
III.c 16:30-16:45	Risk of tuberculosis after lung transplantation: the value of pretransplant chest computed tomography and the impact of mTOR inhibitors and azathioprine use. **Emilio Guirao Arrabal**
III.d 16:45-17:00	Effect of hypoxic preconditioning on mesenchymal stem cells functionality of patients with chronic limb ischemia. **Luis Miguel Paco Meza**
17:00-17:30	**Poster Showcase**
17:30-19:00	**SESSION IV. Nutrition, Endocrine and metabolic diseases**
IV.a 17:30-17:45	Rab34 is a novel regulator of lipid accumulation in adipocytes. **Andrés Trávez García**
IV.b 17:45-18:00	Magnesium supplementation improves outcomes but impairs bone mineralization in a rat model of Chronic Kidney Disease-Vascular Calcification. **Juan Miguel Díaz Tocados**
IV.c 18:00-18:15	Regulation of endothelial function is modified by two healthy diets in patients with established cardiovascular disease. **José David Torres Peña**
IV.d 18:15-18:30	Identification of a novel kisspeptin pathway in glial cells: A new contributing circuit for kisspeptin-driven control of puberty?. **Encarnación Torres Jiménez**
IV.e 18:30-18:45	Does the conten of dietary calcium modifies the urinary excretion of phosphate?. **Maria Dolores Salmerón Rodríguez**

IV.f 18:45-19:00	Adipokines directly modulate the function of different pituitary cell types in primates (Papio anubis and Macaca fascicularis) through common and distinct intracellular signaling pathways. **André Sarmento Cabral**
Day 2 (11th May)	
9:00-10:30	**SESSION V. Nutrition, Endocrine and metabolic diseases**
V.a 9:00-9:15	Chronic consumption of a healthy diet improves postprandial lipemia response and insulin resistance in diabetic patients from the CORDIOPREV study. **Beatriz Gómez Marín**
V.b 9:15-9:30	Changes in the splicing machinery as a tool to predict the development of type-2 diabetes in high-risk patients. **Mercedes del Río Moreno**
V.c 9:30-9:45	Relationship between intake and urinary phosphate excretion in patients with chronic kidney disease (CKD). **Mª Victoria Pendón**
V.d 9:45-10:00	Factors influencing telomere length and cardiovascular disease. From the Cordio-Prev Study. **Cristina Hidalgo Moyano**
V.e 10:00-10:15	Changes in gut microbiota according to the progresion of metabolic syndrome. **Sonia García-Carpintero Fernández- Pacheco**
V.f 10:15-10:3	Hypothalamic GRK2, via GPR54, modulates puberty onset. **Marisol Avendaño Herrador**
10:30-11:00	**Coffee Break**
11:00-11:30	**Poster Showcase**
11:30-13:00	**SESSION VI. Cancer (Oncology and Oncohematology). Active ageing an fragility.**
VI.a 11:30-11:45	Differential sensitivity of prostate cancer cells to galiellalactone. A proteomic approach. **Víctor García González**
VI.b 11:45-12:00	Functional role of somatostatin receptor subtype 1 (sst1) in prostate cancer: an in vitro approach. **Sergio Pedraza Arévalo**
VI.c 12:00-12:15	Recent advances in human sweat metabolomics for lung cancer screening. **Mónica Calderón Santiago**

VI.d 12:15-12:30	Assessment of RIFLE and AKIN criteria to define acute renal dysfunction for HIPEC procedures for ovarian and non ovarian peritoneal malignances. **Juan Manuel Cabrera Bermón**
VI.e 12:30-12:45	The truncated somatostatin receptor, sst5TMD4, is overexpressed in prostate cancer, where it increases malignant features by altering key signaling pathways and tumor suppressors/oncogenes. **Juan Manuel Jiménez Vacas**
VI.f 12:45-13:00	Age related pharamethers can be improved by a mediterranean diet supplemented in hydroxytyrosol. **Andreea Corina Baba**
13:00-13:30	**Awards and Closing ceremony**

ORAL COMMUNICATIONS
Abstracts

SESSION I

Cancer
(Oncology and Oncohematology)

I.a Endothelial nitric oxide synthase in colorectal cancer: a potential new therapeutic target in stem cell-like poor-prognosis subtype.

Authors: *Peñarando J, Mena R, López-Sánchez LM, Villar C, Sánchez R, Centeno M, Jiménez-Arranz A, Gómez-Barbadillo J, Díaz C, De la Haba-Rodríguez JR, Aranda E, Myant K, Rodríguez-Ariza A.*

Group: GC6 New therapies in cancer.

Nitric oxide (NO) has been highlighted as an important factor in tumor processes. Although the inducible nitric oxide synthase (iNOS) form has received most of the attention, recent literature indicates that endothelial form (eNOS) can also modulate different tumor processes including angiogenesis, invasion, and metastasis. However, the role of eNOS in cancer stem cell (CSC) biology is almost unknown. We have previously shown, through NO depletion, that NO exerts autocrine and/or paracrine effects on stem-related signaling pathways which are essential for the generation and maintenance of CSC subpopulation in human colorectal cancer cell lines and in a xenograft model. Here, we show that NO removal with the NO scavenger c-PTIO decreased the proliferation of intestinal Apcfl/fl organoids from VIL-CRE-ERT2-APCfl/fl mouse model and this effect was higher than in WT organoids. Besides, NO scavenging decreased the expression of stem cell markers such as Lgr5, Troy, Vav3 and Slc14a1 in intestinal Apcfl/fl organoids. eNOS was overexpressed in intestinal Apcfl/fl organoids and Apcfl/fl tissue, where the immunostaining was found in both the epithelial and non-epithelial compartments of intestinal crypts. Furthermore, using a non-toxic probe for the detection of NO in living tissues, we found a higher production of NO in Apcfl/fl crypts. We also classified 40 human colorectal tumors in different molecular subtypes using different genetic signatures and found high eNOS expression at RNA and protein level in the stem cell-like subtype, which is characterized by poor prognosis and survival. We also found a high expression of eNOS in advanced (T4) and poorly differentiated human tumors. Finally, chemoresistant (5-FU+oxaliplatin) human cancer cell lines (Hct116 and DLD1) generated in our laboratory showed eNOS overexpression compared with parental sensitive tumor cells. Thus, our data show that eNOS is a new and unexpected potential new target in poor-prognosis stem cell-like colorectal tumors. Funded by PI13-00553.

I.b Potential therapeutic treatment of Biguanides (Metformin, buformin and phenformin) for pituitary adenomas.

Authors: *Mª Carmen Vázquez-Borrego, Antonio C. Fuentes-Fayos, Alejandro Ibáñez-Costa, Eva Venegas-Moreno, Alfonso Soto-Moreno, Mª Ángeles Gálvez, Justo P. Castaño, Raúl M. Luque.*

Group: GC8 Hormones and cancer.

Pituitary adenomas (PA) comprise a commonly underestimated pathology in terms of incidence and associated morbimortality. Somatostatin- and dopamine-analogs constitute the main medical treatment for PA. However, an appreciable subset of patients are resistant or poorly responsive to these drugs, and hence, the search for new therapies to control tumor growth and/or hormone secretion is crucial. Biguanides such as metformin (MF; commonly used to treat type-2 diabetes), buformin (BF) and phenformin (PF) have been shown to exert antitumor actions in different tumor types (e.g. colon and breast cancer), but their actions in PA cells have not been fully reported. The aim of this study was to determine the effect of these biguanides on key functional parameters (i.e. cell viability, hormone secretion, calcium-signaling) in human PA cell cultures [corticotropinomas, somatotropinomas and non-functioning PA (NFPAs)] and PA cell-lines (GH3 and AtT-20). Expression profile of receptors for somatostatin (ssts) and dopamine (DRs) showed typical profiles for each pathologies (corticotropinomas: sst5>sst2>sst1; somatotropinomas: $sst5^{3}sst2$; NFPAs: $sst3^{3}sst2$; DR2 was the most abundant DR in all these PAs). Interestingly, MF moderately, albeit consistently reduced cell viability in PA cells and cell-lines, while treatment with PF and BF reduced cell viability more noticeably, with the effect of PF very particularly intense in corticotropinomas. These effects might involve a calcium-dependent mechanism, since treatment with these biguanides clearly altered the kinetics of cytosolic free calcium. Finally, MF and BF showed a non-significant trend to reduce ACTH secretion in corticotropinomas, whereas, in primary pituitary cell culture of two primate species, MF and PF significantly decreased ACTH and GH release. Taken together, our results reveal a clear inhibitory effect of biguanides on PA cell viability and pituitary hormone release in vitro, and given their demonstrated clinical safety suggest a potential therapeutic role of these compounds for the treatment of patients with PAs.

I.c Key proteins regulation of the DNA Damage Response Pathway CHK2 and CDC25A in the context of carcinogenesis.

Authors: *Maribel Lara-Chica, Carmen García-Limones, Carla Jiménez Jiménez, Moisés Pérez, Rosario Morrugares, Eduardo Muñoz, Marco A. Calzado.*

Group: GC4 Inflammation and cancer.

The DNA Damage Response (DDR) pathway assures the proper cell division when the genome is damaged, so that only those cells whose DNA had been repaired proliferate. CHK2 (checkpoint kinase 2) and Cdc25A (Cell division cycle 25A) are important downstream proteins, constituting the main DDR mediators of the G1/S and G2/M transitions. Given their relevant role as regulators of cell cycle progression, we focus on the regulation of these proteins in cancer processes. In this report we first demonstrate how SIAH2, an E3 ubiquitin ligase, interacts with CHK2 and mediates its ubiquitination and proteasomal degradation. In response to DNA damage, interaction between both proteins is disrupted, thus avoiding CHK2 degradation and promoting its stabilization. This regulation triggers consequences on cell cycle progression, as cellular arrest induced by DNA damage is reverted by SIAH2 expression through the control of CHK2 levels. Under hypoxic conditions CHK2 levels are decreased in parallel to SIAH2 induction. Similarly, we provide evidence suggesting that resistance to apoptosis induced by genotoxic agents in cells subjected to hypoxia could be partly explained by the mutual regulation between both proteins. We also describe that Cdc25A expression levels are down-regulated by a novel Cdc25A-kinase, facilitating its proteasomal degradation. The expression study of both proteins in lung cancer cells reveals an important inverse correlation, which occurs specially in a cellular model system of bronchial epithelial cell squamous differentiation. Taken together, these results indicate that SIAH2 regulates CHK2 basal turnover, with important consequences on cell cycle control and on the ability of hypoxia to alter DNA damage-response pathway in cancer cells. Likewise, our findings show Cdc25A-kinase as a new regulator of Cdc25A in lung cancer. These data certainly help to improve our knowledge of the tumorigenic process and could open a road to the development of new therapeutic strategies against cancer.

I.d HIPECT4. Multicentric randomized controlled trial about the influence of HIPEC in localy advanced colorrectal cancer in abscense of carcinomatosis. A protocol study.

Authors: *García Martín, R., Arjona-Sánchez A., Rufián Peña, S., Casado Adam, A., Sánchez Hidalgo, JM., Muñoz Casares, FC., Díaz López, CA., Torres Tordera, EM, Briceño-Delgado J.*

Groups: Others.

Colorectal cancer is one of the most important cause of death in our country and in the world. His prognosis worsens dramatically if it is associated with peritoneal carcinomatosis. The new combined surgical treatments with chemotherapy have managed to increase the survival rate, even in advanced stages. Cytoreductive surgery in adition with HIPEC (Hipertermic Intraperitoneal Chemotherapy) in peritoneal carcinomatosis from diverse origins, has increase survival and disease-free period. It is thought that the use of HIPEC in the absence of carcinomatosis can decrease the rate of locoregional recurrence as well as could increase survival without an increment in morbidity and mortality. MATERIAL AND METHODS: An open, multicenter, randomized trial to evaluate the adjuvant effect of intraperitoneal hyperthermic chemotherapy with mitomycin C associated with surgery versus surgery alone in locally advanced colorectal carcinoma (T4 Nx M0). We will study a population about 200 patients, divided in two groups, experimental and control, randomized with a computer system. In experimental group, the treatment includes cytoreductive surgery, target organs resection and HIPEC, versus cytoreductive surgery and target organs resection in control arm. RESULTS: As primary endpoint, locoregional control (LC) and rate of locoregional disease control (LC %) at 12 months 3 years. Secondary variables will be: morbidity peri and postoperative (CTCAE clasification), and perioperative mortality, to 30 and 90 days post-intervention. Overall survival (OS) in months, and survival rate (%OS 12 m, 3 years). Disease-free survival (DFS) rate in months and disease-free period (% DFS at 12 m, 3 years). As security variables, incidence and severity of adverse events (AE). CONCLUSIONS: We want to show that cytoreductive surgery associated with HIPEC in the absence of carcinomatosis in colorectal cancer, reduces recurrence rates and increases patient survival without increasing the morbidity.

I.e Protein expression of FGFR3, PI3K, AKT, p21Waf1/Cip1 and Cyclin D1 and D3 in patients with T1 bladder cancer: clinical implications and prognostic significance.

Authors: *Sánchez-González, Álvaro. Blanca-Pedregosa, Ana M. Carrasco-Valiente, Julia. Ruiz-García, Jesús M. Gómez-Gómez, E. López-Beltrán, Antonio. Requena-Tapia, M José.*

Group: GA7 Urology and sexual medicine.

Objective: To determine the differential protein expression of FGFR3, PI3K (PI3Kp110α, PI3KClassIII, PI3Kp85 subunits), AKT, p21Waf1/Cip1 and Cyclin D1 and D3 in T1 bladder cancer versus. normal tissue and study its possible role as markers of early recurrence. Material and methods: A total of 40 patients with T1 bladder cancer who underwent a transurethral resection and 12 cases of adjacent normal tissue (control group) were included in our study. The protein expression levels were evaluated by Western blot method and the means and percentages were compared using Students t and Chi-square tests. Survival analysis was performed using the Kaplan-Meier and log-rank tests. Result: We detected an increase of protein expression levels of FGFR3, PI3Kp110α, PI3KClassIII, Cyclin D1, D3 and p21Waf1/Cip1 in tumor tissue versus. normal tissue. Nevertheless, these differences were not significant for PI3Kp85 and AKT. We observed statistically significant correlations between PI3Kp110α, PI3Kp85 and AKT protein levels and early recurrence (p=0.010, p=0.027 and p=0.027 respectively), PI3KClassIII (p=0,019), PI3Kp85 (p=0,027) and Cyclin D3 (p=0.001) with tumor type (primary vs. recurrent), FGFR3 (p=0.014) with tumor size and PI3Kp110α (p=0.034) with the multifocality. Survival analysis pointed to PI3Kp110α (p=0,024), PI3Kp85 (p=0,013) and AKT (p=0,001) as markers of early recurrence free survival. Conclusions: An increase of protein expression levels were observed in bladder tumor tissue, likewise protein over-expression of PI3Kp110α , PI3Kp85 and AKT is associated with an increased of early recurrence free survival in patiens with T1 bladder tumors.

SESSION II

Chronic and Inflammatory diseases

II.a Neuroligin deficient mutants of C. elegans overexpress comt-4: a crosspoint between dopamine and serotonin pathways.

Authors: Ángel Rodríguez Ramos, María del Mar Gámez Del Estal, Montse Porta de la Riva, Julián Cerón and Manuel Ruiz Rubio.

Group: GC20 Genetics and behavioural diseases.

Neuroligins, neuronal membrane adhesion molecules, have been involved in neuro-psychiatric and neuro-developmental disorders. Neuroligins interact with its partners neurexins and other specific proteins in the synaptic cleft. The gene nlg-1 of Caenorhabditis elegans codes NLG-1, an ortholog of human neuroligins. NLG-1 modulates dopaminergic and serotoninergic pathways which control the locomotory rate of the nematode. When well fed animals are transferred to a plate with bacteria they reduce the locomotory rate. This behavior, which depends on dopamine, is known as basal slowing response (BSR). Alternatively food deprived animals, when moved to a plate with food (bacterial lawn) further decrease their locomotory rate. This behavior, known as enhanced slowing response (ESR), is serotonin dependent. C. elegans mutants deficient in nlg-1 are deficient in BSR, ESR and other locomotory behaviors such as gentle touch response or sinusoidal pattern of locomotion. Here we report that nlg-1-deficient mutants of C. elegans overexpress comt-4 which encodes for COMT-4, an enzyme that has been predicted to have a catechol-O-methyltransferase activity involved in dopamine catabolism. comt-4 knockdown of nlg-1-deficient mutants recovered the wild type phenotypes of BSR, ESR, gentle touch response and sinusoidal pattern of locomotion. On the other hand nrx-1-deficient mutants only showed deficiency in the ESR and had a wild type expression of comt-4. Based on these results, we propose a model of how the neuroligin could modulate the locomotory rate. The understanding of the molecular mechanism by which neuroligin-neurexin deficiency could alter some behaviors in C. elegans could help to explain the etiology of some neurological disorders which are still unknown.

II.b Potential impact of in vivo Ubiquinol supplementation in the prevention of atherothrombosis in Antiphospholipid Syndrome Patients. Preliminary results of a clinical trial.

Authors: *Iván Arias-de la Rosa, Carlos Perez-Sanchez, Maria Ángeles Aguirre Zamorano, Francisco Velasco, Patricia Ruiz-Limon, Nuria Barbarroja, Yolanda Jiménez Gómez, Maria Carmen Abalos-Aguilera, Pedro Segui, Eduardo Collantes-Estevez, Lucia Fernandez-del Rio, Jose Antonio Gonzalez-Reyes, Jose Manuel Villalba, Ma Jose Cuadrado and Chary Lopez-Pedrera.*

Group: GC5 Systemic and chronic inflammatory autoimmune diseases of the locomotor system and connective tissue.

Background/Purpose: To investigate the beneficial effects of in vivo ubiquinol (Q, reduced form of CoQ10) supplementation on athero-thrombosis prevention in APS patients. Methods: This study was conducted on 32 APS patients randomized to receive either Q (200 mg/day) or placebo for one month. Studies were performed in plasma and purified leukocytes subsets. Plasma Q levels, various prothrombotic/proinflammatory and oxidative stress markers were evaluated. miRNAs expression in monocytes was determined using Nanostring miRNA arrays. Ultrastructural evaluation of mitochondria in monocytes was performed by electron microscopy. Endothelial activity analysis was performed by Laser-Doppler. Carotid intima media thickness (CIMT) was measured as an atherosclerosis marker. Results: Q treatment improved endothelial function in APS patients and decreased tissue factor (TF), IKK and IL8 protein levels in monocytes. Several proinflammatory mediators were further reduced in monocytes and neutrophils. Comparing to controls, 57 miRNAs were found significantly altered in APS patients. Among them, 26 were reversed by Q treatment. Functional classification of those miRNAs showed a preponderance of target mRNAs involved in free radical scavenging, inflammatory response, cardiovascular disease, and reproductive system disease. Q supplementation reduced both the levels of peroxides and the percentage of monocytes with altered mitochondrial membrane potential. Q treatment also increased the mitochondrial size in monocytes. Ten out of 14 patients showing atheromatous plaques had also suffered thrombotic events. These pathologic processes were linked to a poorer endothelial function. Q effects were particularly relevant in those APS patients with pathologic CIMT and thrombotic recurrences, showing a better response to Q treatment with improved endothelial function. Conclusion: Q supplementation significantly improved endothelial function, and reduced mitochondrial dysfunction, oxidative stress and the expression of prothrombotic/proinflammatory proteins. Underlying epigenetic mechanisms seem to be involved. Our results support the potential impact of Q in the prevention of atherothrombosis in APS patients. Supported by: CTS-7940, PI12/01511, KANEKA.

II.c Assessment of Fatigue in Spondyloarthritis and Its Association with Disease Activity.

Authors: *Clementina López-Medina, Ruxandra Elena Schiotis, Pilar Font-Ugalde, Maria Carmen Castro-Villegas, Jerusalem Calvo-Gutiérrez, Rafaela Ortega-Castro, Rocío Jiménez-Gasco, Alejandro Escudero-Contreras, and Eduardo Collantes-Estévez.*

Group: GC5 Systemic and chronic inflammatory autoimmune diseases of the locomotor system and connective tissue.

Objective. To evaluate fatigue in patients with spondyloarthritis (SpA) and to define its association with disease-related factors and patients' features. Methods. A cross-sectional multicenter study which includes 2251 patients with SpA selected from the national Spondyloarthropathies Registry (the Spanish Society of Rheumatology; REGISPONSER) Spanish cohort. The primary outcome was the assessment of fatigue performed with the first item of the Bath Ankylosing Spondyloarthritis Disease Activity Index followed by the study of its relation with different factors organized into 4 groups: sociodemographics, emotional, disease-related, and disease activity. Univariate logistic regressions, multivariate logistic regression, and multiple linear regressions were performed to relate fatigue with the studied covariates. Results. Mean fatigue score in all patients with SpA was 4.3 ± 2.9, with statistically significant differences between different SpA types. In univariate logistic regressions, significant differences were seen for many variables included in the 4 groups. Multivariate logistic regression showed that high fatigue score was related with sex (female), emotional component, the Ankylosing Spondylitis Quality of Life score, stiffness, and high levels of 2 visual analog scale items (vertebral pain in the last week and patient's global assessment of disease activity). The multivariate linear regression showed that fatigue was mainly explained by disease-related factors and disease activity (54.1%), but sex and emotional status may also be involved in 13.5% of the variance. Conclusion. Fatigue is associated with disease-related factors and mostly with SpA activity. However, the emotional component and sex may contribute to the onset of fatigue.

II.d Measuring anxiety regulation strategies: development and preliminary validation of an instrument.

Authors: *Rosario Castillo-Mayén, Carmen Tabernero, Tamara Gutiérrez-Domingo, Esther Cuadrado, Bárbara Luque-Salas & Alicia Arenas.*

Group: Others.

This study presents the development and preliminary validation of a self-report measure that assesses anxiety regulation strategies. The item generation process considered a wide range of strategies that individuals may engage with to manage their anxiety. One-hundred and seventy participants fulfilled the initial 25-items measure. After exploratory and confirmatory factor analyses, results supported the existence of a three-factor solution. Each factor represented a different type of strategy, namely: cognitive (e.g., writing), passive (e.g., watching TV), and physical activity (e.g., going to the gym). Reliability analysis showed adequate internal consistence of the final 21-items scale and of each factor. Correlational analyses showed initial support for both concurrent and divergent validity, which along with previous results indicated good psychometric properties of the scale. Moreover, results revealed the preferred tendency of individuals to deal with anxiety, as well as some gender differences in the use of different strategies to regulate anxiety feelings. Additional analyses pointed to the relationship of these strategies with positive and negative affect and with the perception of self-efficacy to regulate negative emotions in general. According to the process model of emotion regulation, this measure could be useful for assessing what individuals do to modulate their response when experiencing anxiety, and, thus, for guiding successful psychological interventions. Concerning the biomedical field, applications of this instrument and associated results might be especially relevant for patients whose medical condition is closely related to an adequate emotional regulation. This is the case of, for example, patients with cardiovascular disease, wherein the appearance, prognosis and recovery from this illness importantly depend on the individuals' psychological skills to modulate their emotions.

II.e TNFalpha-Damaged-HUVECs Microparticles modify Endothelial Progenitor Cell functional activity.

Authors: *Carlos Luna, Andrés Carmona, Matilde Alique, Julia Carracedo, Rafael Ramirez.*

Group: GC7 Nephrology. Cell damage in chronic inflammation.

Endothelial progenitor cells (EPCs) have an important role in the maintenance of vascular integrity and homeostasis. While there are many studies that explain EPCs mechanisms action, there are few studies that demonstrate how they interact with other emerging physiological elements such as Endothelial Microparticles (EMPs). EMPs are membranous structures with a size between 100-1000nm that act as molecular information transporter in biological systems and are known as an important elements in develop different pathologies; moreover a lot of works explains that are novel biomarkers. To elucidate these interactions, we proposed an in vitro model of endothelial damage mediated by TNF-alpha, in which damaged EMPs and EPCs are in contact to assess EPCs functional effects. We have observed that damaged EMPs can modulate several EPCs classic factors as colony forming units (CFUs), contribution to repair a physically damaged endothelium (wound healing), binding to mature endothelium, and co-adjuvants to the formation of new vessels in vitro (angiogenesis). All of these in a dose-dependent manner. Damaged EMPs at a concentration of 103 MPs/ml have an activating effect of these capabilities, while at concentrations of 105 MPs/ml these effects are attenuated or reduced. This in vitro model helps explain that in diseases where there is an imbalance between these two elements (EPCs and damaged EMPs), the key cellular elements in the regeneration and maintenance of vascular homeostasis (EPCs) are not fully functional, and could explain, at least in part, endothelial dysfunction associated in various pathologies.

II.f AP-1 inhibition by SR11302 protects human hepatoma HEPG2 cells form bile acids inducded apoptosis by restoring the NOS-3 expression.

Authors: *Sandra González-Rubio, Gustavo Ferrín, Clara I Linares, Patricia Aguilar-Melero, Manuel L Rodríguez-Perálvarez, José Luis Montero-Álvarez, Manuel de la Mata.*

Group: GC2 Oxidative and nitrosative stress in acute and chronic liver disease.

Background: The harmful effect of bile acids accumulation during cholestasis is associated with oxidative stress and endothelial nitric oxide synthase (NOS-3) expression decrease in liver cells. We investigated the relationship between these two biological events and the role of transcription factor (TF) AP-1 in the NOS-3 expression regulation during experimental cholestasis in HepG2 cells. Methods: Glycochenodeoxycholic acid (GCDCA, 0.5mM) was administered 48h after cell culture. The SOD mimetic compound MnTBAP (1mg/mL) and the mitochondria-targeted antioxidant MitoQ (1μM) were tested as antioxidant molecules. Curcumin, Quercetin, SR11302 and L-NAME were administered at 4μM, 20μM, 50μM and 5mM, respectively. Oxidative stress was measured using probes DHE, DCF and ADHP. Mitochondrial respiratory activity was assayed spectrophotometrically. Cell death was analysed by measuring the caspase-3 activity and LDH release. Gene expression was measured by qRT-PCR. AP-1 promoter binding was identified by chromatin immunoprecipitation (ChIP) assay. Protein expression was performed by western blot. Promoter activity was assessed by the luciferase activity assay. NOS activity was determined by nitrite+nitrate accumulation in the extracellular medium. Growth capacity was assessed by the trypan blue exclusion test. Results: Cytotoxic response to GCDCA was characterized by oxidative stress, respiratory complex II+III activity decrease and cell death. GCDCA induced the expression and activation of TFs cJun and cFos, and caused a higher binding capability of these at position -666 of the NOS-3 promoter (pNOS-3). This was related to pNOS-3 activity decrease and a consequent reduced expression and activity of NOS-3 protein. In GCDCA-treated cells, antioxidants reduced activation of cJun/cFos and caused pNOS-3 activity recovery, NOS-3 expression/activity increase and cell survival. Similarly, the specific inhibition of AP-1 by SR11302 reverted the GCDCA cytotoxic effect. Moreover, the NOS inhibitor L-NAME abolished the protective effect of the retinoid. Conclusions: AP-1 as transcriptional repressor of NOS-3 expression provides a new potential therapeutic target during cholestatic diseases.

SESSION III

Infectious and Immunological diseases. Organ transplantation

III.a Impact of colistin therapy on mortality of multidrug-resistant and colistin-sensitive acinetobacter baumannii bacteremia in critically ill patients.

Authors: *Tania Amat, Antonio Gutiérrez-Pizarraya, José Garnacho-Montero, Isabel Machuca, Irene Gracia-Ahufinger, Elena-Pérez-Nadales, Alvaro Torre-Giménez, Jose Miguel Cisneros, Julián Torre-Cisneros.*

Group: GC3 Infectious diseases.

Background: Multidrug-resistant Acinetobacter baumannii (MDR-Ab) has emerged as a common cause of severe sepsis in critically ill patients. Colistin is the treatment of choice for MDR-Ab. The impact on mortality of empirical therapy with colistin and combined targeted therapy with tigecycline or vancomycin is unknown. To investigate the efficacy of the empirical use of colistin and combined targeted therapy with colistin and tigecycline or vancomycin in the treatment of colistin-sensitive MDR-Ab bacteremia in critically ill patients. Material/methods: Multicenter retrospective cohort study. Involving two hospitals belonging to the Spanish Network for Research in Infectious Diseases (REIPI). Critical patients with monomicrobial bloodstream infections (BSI) due to MDR-Ab (113 patients) were studied in which specific criteria were applied for the analysis of Colistin empirical therapy (CET) or tigecycline-based or vancomycin-based (plus colistin) combined targeted therapy (CTT). Multivariate analyses were performed using logistic regression to control for confounding. All-cause 14- and 30-day mortality (crude). Results: 14-day and 30-day mortality rates were 13% and 54% for CET, 21% and 50% for tigecycline-based CTT and 4% and 31% for vancomycin-based CTT, respectively. The adjusted OR (95% CI) for 14-day mortality was 1.15 (0.33-4.03) for CET, 1.28 (0.32-5.17) for tigecycline-based CTT and 0.19 (0.02-2.35) for vancomycin-based CTT. The adjusted OR (95% CI) for 30-day mortality was 2.29 (0.95-5.51) for CET, 6.56 (0.66-65.22) for tigecycline-based CTT and 5.52 (0.51-59.72) for vancomycin-based CTT. Conclusions: CET and tigecycline-based or vancomycin-based CTT with colistin do not decrease 30- and 14-day crude mortality of BSI due to MDR-Ab in critical patients.

III.b Hepatitis E infection in wild boar as a potential route of transmission to humans: Results of the HepEboar Study.

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Group: GC3 Infectious diseases.

Background: The hepatitis E virus (HEV) is an RNA virus that causes acute hepatitis in humans. In the Infectious Diseases unit of the Hospital Reina Sofía de Córdoba, a case was found in which the consumption of infected wild boar meat caused acute HEV infection in several members of a family. Because of the potential for zoonotic transmission of HEV infection through the consumption of infected animal meat, the objective of this study was to evaluate the prevalence of HEV in wild boar (sus scrofa) in Cordoba. Material and Methods: Wild boar from a hunting reserve in Cordoba were sampled during October 2015 and February 2016. An intracardiac blood sample was collected from the selected animals at each hunting reserve. Serum samples were preserved in RNAlater and stored at -80 °C until analysis. HEV RNA was extracted using the QIAamp Viral RNA Mini Kit (Qiagen, Germany). For the detection of HEV RNA, in-house real-time PCR was performed, using the QIAGEN OneStep RT-PCR Kit. HEV infection was defined as the presence of HEV RNA in serum. A descriptive analysis was carried out. Results: The study population consisted of one hundred and forty-two wild boar, belonging to 12 hunting areas. Sixty-four were male and seventy-eight were female. According to age group, 11.9% were juveniles, 19.7% were sub-adults, and 68.4% were adults. HEV RNA infection was found in 22.5% of wild boar (32/142) and in 58.3% of the hunting zones (7/12). There was a prevalence of HEV infection was higher among males than females (31.7% vs. 15.4%; p=0.023). No differences were found according to the age of the animals. Conclusion: Our study shows a high prevalence of HEV infection in wild boar. This implies that contact with or consumption of infected animals could be a significant route of HEV transmission to humans.

III.c Risk of tuberculosis after lung transplantation: the value of pretransplant chest computed tomography and the impact of mTOR inhibitors and azathioprine use.

Authors: *Emilio Guirao-Arrabal, Francisco Santos, Javier Redel-Montero, José Manuel Vaquero, Sara Cantisán, Elisa Vidal, Álvaro Torre-Giménez, Antonio Rivero, Julián Torre-Cisneros.*

Group: GC3 Infectious diseases.

Background. It is necessary to determine the incidence and risk factors for tuberculosis (TB), as well as strategies to assess and treat latent tuberculosis infection (LTBI) in lung transplant recipients. Methods. A retrospective cohort study of 398 lung transplant recipients was performed. Episodes of TB were studied and the incidence rate was calculated. Logistic regression analysis was used to analyze specific variables as potential risk factors for TB. Results. Median follow-up was 558 days (range 1-6636). Six cases (1.5%) of TB were documented in 398 transplant patients. The incidence density of TB was 406.3 cases/100000 patients-year (95% CI, 164.7-845), which is higher than in the general population (13.10 cases/100000 persons-year). All cases occurred in the period 1993-2006, when the tuberculin skin test (TST) and treatment of LTBI in positive TST patients were not protocolized. Pretransplant computed tomography (CT) showed residual lesions in 50% of patients who developed TB, although the TST was negative and the chest radiograph was inconclusive. Multivariate analysis identified the presence of residual lesions in the pretransplant chest CT (OR 11.5, 95% CI 1.9-69.1, p=0.008), use of azathioprine (OR 10.6, 95% CI 1.1-99.1, p=0.038) and use of everolimus (OR 6.7, 95% CI 1.1-39.8, p=0.036) as independent risk factors for TB. Conclusions. Residual lesions in the pretransplant chest CTs and the use of azathioprine and mTOR inhibitors are associated with the risk of TB.

III.d Effect of hypoxic preconditioning on mesenchymal stem cells functionality of patients with chronic limb ischemia.

Authors: *Paco-Meza LM; Romero M; Nogueras S; Carmona MD; Jiménez R; Martín V; Suela J; Cañadillas S-Herrera C.*

Group: GC14 Cell therapy.

Background: Mesenchymal stem cell (MSCs) transplantation was proved to induce therapeutic angiogenesis in patients with chronic limb ischemia (CLI). MSC are usually cultured under normoxic conditions corresponding to atmospheric oxygen (21%). Nevertheless, physiological oxygen tension in the bone marrow is lower (<7%). Our previous results in MSC from healthy donors demonstrated a hypoxia effect on migration capacity and paracrine activity. The aim of this study is to evaluate the effects of hypoxic preconditioning (3%O2) on the functionality of MSCs isolated from chronic limb isquemia patients (MSC-CLI). Methods: In vitro, MSCs-CLI were pre-conditioned under hypoxic conditions (3% O2) for 72 hours and compared to MSC-CLI cultured under normoxic conditions (21% O2). MSCs-CLI phenotype was determined by flow cytometry. Proliferation capacity and differentiation potential towards mesoderm were also analyzed. MSCs-CLI migration was induced by endothelial growth-factor (VEGF) and (SDF-1) as quimio-attractants .Growth-factors secretion (VEGF and IL-6,) was quantified by ELISA. Angiogenic capacity was analyzed using an edothelial tube formation assay. Moreover, hypoxia-induced gene expression profile was determined by microarray analysis. Results: Hypoxic pre-conditioning did not alter either the phenotype or differentiation potential of MSCs-CLI. In addition, MSCs-CLI proliferation rate was not modified by low oxygen tension. MSCs-CLI from hypoxia and normoxia groups were able to differentiate to mesodermal lineage. SDF-1 and VEGF induced migration, increased under hypoxic conditions vs normoxic conditions but not in a significant manner. Secretion analysis by ELISA showed greater values of VEGF, IL-6, in hypoxic pre-conditioned MSCs-CLI, although this increment was not statistically significant. Angiogenic capacity was significantly higher in hypoxic group. Microarray analysis revealed that 76 genes modified their expression levels (> 2 fold change) under hypoxic conditions. Conclusions: Our results demonstrate that hypoxic preconditioning enhances MSC-CLI angiogenic capacity. This fact could improve cell therapy efficacy, but further studies are still needed to elucidate the mechanisms involved.

SESSION IV

Nutrition, Endocrine and metabolic diseases

IV.a Rab34 is a novel regulator of lipid accumulation in adipocytes.

Authors: *Trávez A., López-Alcalá J., Sánchez-Ceinos J., Rabanal-Ruiz Y., Guzman-Ruiz R., Garcia-Navarro S., Gracia-Navarro F., Vázquez-Martínez R., and Malagón M.M.*

Group: GC11 Metabolism and adipocyte differentiation. Metabolic syndrome.

Rab proteins represent the largest family in the ras-like small GTPase superfamily and regulate major trafficking events in the cells. One member of this family, Rab34, has been characterized as a component of the Golgi apparatus mediating intra-Golgi transport. Recently, we carried out a proteomic analysis of the fat storage organelles, the lipid droplets (LDs), from control vs. insulin-stimulated 3T3-L1 adipocytes, which enabled the identification of Rab34 as a novel LD-associated protein and led us to characterize it in adipocytes. We observed that Rab34 protein content increased during adipocyte differentiation. Interestingly, Rab34 also underwent a shift in localization during adipogenesis, from a Golgi distribution at early stages of differentiation, residing thereafter transiently in the ER-Golgi intermediate compartment (ERGIC), to finally locate at the LD surface in differentiated adipocytes. Time-lapse video-microscopy of 3T3-L1 cells exposed to oleic acid and insulin revealed that Rab34 surrounds LDs as soon as the fatty acid is taken up by adipocytes, thus suggesting a role for this protein in lipid uptake and/or storage. In line with this, overexpression of Rab34 increased intracellular lipid accumulation in both non-differentiated and differentiated 3T3-L1 cells. Notably, Rab34 silencing reduced the lipolytic activity and the protein content of the lipid lipase, HSL, in 3T3-L1 cells. To get further insights on Rab34 function, we examined the interactome of this GTPase in non-differentiated and differentiated 3T3-L1 cells. Among the Rab34 interactors there are components of the retrograde Golgi-to-ER transport system, the cytoskeleton chaperonin, TCP1 ring complex, structural proteins and proteins involved in fatty acid synthesis (i.e, de novo lipogenesis). All together these data suggest that Rab34 association to LDs is a hallmark of adipocyte differentiation and support a role for this protein both in fatty acid synthesis and lipid hydrolysis. Funding: MINECO/FEDER (BFU2013-44229-R), J. Andalucía/FEDER (PI-0200/2013), and CIBERobn (ISCIII), Spain.

IV.b Magnesium supplementation improves outcomes but impairs bone mineralization in a rat model of Chronic Kidney Disease-Vascular Calcification.

Authors: *Díaz-Tocados JM, Peralta A, Rodríguez-Ortiz ME, Herencia C, Martínez-Moreno JM, Montes de Oca A, Vergara N, Carvalho CG, Frazão JM, Almadén Y, Rodríguez M, Muñoz-Castañeda JR.*

Group: GC7 Nephrology. Cell damage in chronic inflammation.

INTRODUCTION: In Chronic Kidney Disease (CKD) patients, magnesium-containing phosphate binders are commonly used in order to maintain mineral parameters. We previously demonstrated that high magnesium levels directly inhibit Parathyroid Hormone (PTH) releasing and prevent hyperphosphatemia and vascular calcification in a rat model of CKD. However, the effect of magnesium on bone is poorly understood. OBJECTIVE: To investigate whether magnesium diet supplementation, in addition to its phosphate binder properties, has or not significant effects on bone homeostasis. METHODS: To test the effect of magnesium on bone we developed a murine model of CKD-vascular calcification. Rats underwent 5/6 nephrectomy, received vitamin D overdose (80ng/kg) intraperitoneally every other day and were fed a high phosphate-normal magnesium diet (P1.2%-Mg0.1%), a high phosphate-high magnesium diet (P1.2%-Mg0.6%) or a normal phosphate-normal magnesium diet (P0.6%-Mg0.1%). Sham rats underwent simulated surgery and fed a standard chow diet. Bone mineralization was assessed by double-calcein labeling at days 9 and 2 before sacrifice. After two weeks, 24 hours urine was collected, animals were euthanized and plasma samples, aortas and femurs were obtained. RESULTS: As expected, serum creatinine increased in uremic animals and P1.2%-Mg0.1% rats developed hyperphosphatemia and vascular calcification, that it was prevented in both P1.2%-Mg0.6% and P0.6%-Mg0.1% groups. PTH levels in P1.2%-Mg0.6% and P0.6%-Mg0.1% rats were lower than those observed in the P1.2%-Mg0.1% group, consistent with a reduced number of osteoclasts observed in undecalcified distal femur samples. Interestingly, the number of osteoblasts were higher in the P1.2%-Mg0.6% group as compared with P0.6%-Mg0.1%, leading to higher bone volume, similar to sham rats. Nevertheless osteoid accumulation and defective mineralization was also observed in P1.2%-Mg0.6% femurs, suggesting that high magnesium may impair hydroxyapatite crystals formation. CONCLUSION: Our results demonstrate that magnesium supplementation decreases bone reabsorption and increases osteoblast number and bone formation in CKD while mineralization is impaired.

IV.c Regulation of endothelial function is modified by two healthy diets in patients with established cardiovascular disease.

Authors: *José David Torres-Peña, Juan Francisco Alcalá-Díaz, Francisco Gómez-Delgado, Franscisco Fuentes-Jimenez, Andreea Corina, Vanessa Navarro-Martos, Pablo Pérez-Martínez, José López-Miranda.*

Group: GC9 Nutrigenomics and Metabolic Syndrome.

OBJECTIVES: determine if consumption of a healthy dietary pattern (Mediterranean diet rich in olive oil (MedDiet) or Low-fat) is associated with improvement of endothelial function in patients with established cardiovascular disease. MATERIALS AND METHODS: 1002 patients were randomized to consume a MedDiet (34% fat, 22% monounsaturated) or AHA type diet, low in fat and high in complex carbohydrates (28% fat, 12% monoinsturada). At baseline and after one year of dietary intervention endothelial function was analyzed by laser doppler fluxometry. RESULTS: Consumption of both diets induced improvement in endothelial function compared to baseline . Thus ,the consumption of MedDiet improved endothelial function: basal flow (143.63 ± 3.51 vs. 89.21 ± 4.8 ; p = 0.001), peak flow (318.45 ± 6,14 vs. 219, 41 ± 9.02; p = 0.001) and hyperemia area (5709.41 ± 325.9 vs. 4282.28 ±174.89, p = 0.001). Likewise, the low-fat diet also improved basal flow (140.81 ± 5.43 vs. 86.16 ± 3.2; p = 0.001), peak flow (305.90 ± 8.72 vs. 234, 77 ± 12.4; p = 0.001) and hyperemia area (5490.48 ± 4426.31 ± 283.19 vs. 192.05; p = 0.001). CONCLUSIONS: Our data suggest that long-term consumption of a healthy diettary pattern is associated with improvement of endothelial function in high cardiovascular risk patients. Future research in this area will enable us to move towards a personalized nutrition and apply different nutrition models according to different risk subgroups.

IV.d Identification of a novel kisspeptin pathway in glial cells: A new contributing circuit for kisspeptin-driven control of puberty?

Authors: Torres-Jiménez E, Chowen J, Roa J, Pinilla L, Colledge WH, Romero-Ruiz, A, Tena-Sempere M.

Group: GC10 Hormonal regulation of energy balance, puberty and reproduction.

Puberty is a key developmental phenomenon with durable consequences along the lifespan; recent reports suggest that alterations in the timing of puberty might be linked to a variety of adverse health outcomes and increased all-cause mortality. Puberty is controlled by complex networks of regulatory signals that modulate GnRH neurosecretion. Kisspeptins, the products of Kiss1 neurons, acting via their receptor, Gpr54, in GnRH neurons, are master regulators of puberty. In addition, glial cells are known to play important roles in the control of GnRH neurosecretion. However, the potential role of glial cells in mediating of kisspeptin actions remains unexplored. We present herein evidence for a putative kisspeptin-signaling pathway in glial cells that might play a role in the central control of puberty. Proteomic analyses revealed an up-regulation of GFAP protein (a glial cell marker) levels in the hypothalamus of Kiss1 null (KO) mice following icv injection of kisspeptin-10 (Kp-10). Glial responses to Kp-10 administration in Kiss1 KO mice were confirmed by qPCR and Western blot analyses in the hypothalamic preoptic area. In support of a tenable Gpr54-mediated pathway in glial cells, qPCR analyses demonstrated expression of Gpr54 in primary cultures of rodent astrocytes, in which Kp-10 stimulation caused phosphorylation of the canonical elements of the intracellular kisspeptin-signaling pathway, ERK/MAPK and Akt. To obtain further evidence for the role of such pathway in the control of puberty, we have generated a novel mouse line with selective deletion of Gpr54 in glial cells, by heterozygous crossing of Gpr54-loxP and GFAP-Cre lines. Initial analyses suggest a delay in the timing of puberty in GFAP-Gpr54 null mice. Further studies are in progress in order to validate these initial observations and to provide conclusive evidence for a role of this novel kisspeptin-glial signaling pathway in the control of GnRH neuro-secretion and puberty onset.

IV.e Does the conten of dietary calcium modifies the urinary excretion of phosphate?

Authors: *Maria Dolores Salmerón Rodríguez, María Victoria Pendón Ruiz de Mier, Rafael Santamaría Olmo, Noemí Vergara Segura, Erena Ruiz Mora, María Dolores López Zamorano, Juan Muñoz Castañeda, Pedro Aljama García, Mariano Rodríguez Portillo*

Group: GC13 Calcium metabolism. Vascular calcification.

Introduction: Hyperphosphatemia is associated with cardiovascular risk. It is not known if a high intake of phosphate with the consequent phosphaturia has adverse effects even in the absence of hyperphosphatemia. It is not well established if phosphaturia reflects with precision the oral intake of phosphate and, presumably the intestinal absorption of phosphate could be modified by the content of calcium in the diet. Objective: To evaluate the correlation between phosphate and calcium intake with urinary excretion of phosphate. Methods: Cross-sectional study in a homogeneous group of 50 patients with metabolic syndrome and mild chronic kidney disease (CKD II-III). We analyzed demographic, clinical and analytical variables (Blood and urine collection for 24 hours) as well as a dietary survey in the three days prior to obtaining biological samples. Results: The results obtained from the analysis of the study population were: mean age, 61 ± 9 years; male, 76%; hypertension, 100%; diabetes, 52%; dyslipidemia, 82%; body mass index, 32.3 ± 4.1; hyperuricemia, 60% and smokers, 16%. The calculated amount of phosphate intake was 887 ± 277 mg while the calculated amount of calcium intake was 590 ± 254mg. The value of the intake calcium is clearly below the recommended values (1000-1200mg / day). There was significant correlation between intake of phosphate and phosphate plasma levels (r^2 = 0.31, p = 0.03) but no correlation was found between phosphate intake and urinary excretion of phosphate in a 24 hours urine collection (p = 0.6). It was observed that the content of calcium in the diet correlated with calciuria (r^2 = 0.51, p = 0.015) but not with the urinary excretion of phosphorus (p = 0.9). Conclusion: No significant relationship was observed between phosphate intake and excretion of phosphate. However, there was correlation between calcium intake and urinary calcium excretion.

IV.f Adipokines directly modulate the function of different pituitary cell types in primates (Papio anubis and Macaca fascicularis) through common and distinct intracellular signaling pathways.

Authors: *André Sarmento-Cabral, Lisa C. Halliday, Maria M Malagon, Rhonda D. Kineman, Justo Pastor Castaño, Raul M. Luque.*

Group: GC8 Hormones and cancer.

Adipose tissue represents a true endocrine organ that dynamically secretes multiple hormones referred to as adipokines that regulate key physiological processes. Adipokines and their receptors are also expressed and regulated in the pituitary suggesting that locally-produced adipokines, as well as those derived from adipose tissue, might comprise a relevant regulatory circuit to modulate pituitary function. However, direct pituitary actions of different adipokines remain controversial. Here, primary pituitary cell cultures from two-normal nonhuman primates species (Papio anubis and Macaca fascicularis) were used as model-systems to determine the direct impact of key adipokines (leptin, resistin, and adiponectin; 4h-incubation) on pituitary cell-function. Both leptin (10ng/ml) and resistin (0.1nM) stimulated GH release, a response that was blocked by somatostatin. Conversely, adiponectin (10nM) decreased basal GH release, and was also able to inhibit GHRH-, but not ghrelin-stimulated GH secretion. We found that these adipokines activate both common (AC/PKA and PI3K) and distinct (PLC/PKC, intra-/extra-cellular calcium, MAPK or mTOR) signaling-pathways to exert their effects on GH secretion. Of note, these adipokines not only regulated somatotrope function but also controlled other pituitary cell types. Specifically: 1) Leptin stimulated PRL/ACTH/FSH but not LH/TSH release; 2) adiponectin stimulated PRL, inhibited ACTH and did not alter LH/FSH/TSH release; and 3) resistin increased ACTH release and did not alter PRL/LH/FSH/TSH secretion, all these effects being mediated through activation of specific signaling-cascades. Moreover, treatment with these three adipokines directly regulated the expression of key receptors/transcription-factors known to control the function of all pituitary cells (e.g. Pit-1, GHRH-R, ghrelin-R, somatostatin-Rs, dopamine-Rs, CRH-R, Kiss1-R, GnRH-R, insulin-R and/or IGFI-R). Altogether, these results show that adipokines can directly modulate the function of different pituitary cell-types in primates, by regulating hormone-release through common and distinct intracellular-signaling pathways, as well as by regulating the expression of receptors and/or transcription factors important in the normal function of these cell-types.

SESSION V

Nutrition, Endocrine and metabolic diseases

V.a Chronic consumption of a healthy diet improves postprandial lipemia response and insulin resistance in diabetic patients from the CORDIOPREV study.

Authors: *Beatriz Gómez-Marín, José David Torres-Peña, Ana Isabel Pérez-Caballero, Francisco Fuentes-Jiménez, Francisco Gómez-Delgado, Javier Delgado-Lista, Pablo Pérez-Martínez, José López-Miranda.*

Group: GC9 Nutrigenomics and Metabolic Syndrome.

OBJECTIVE: to explore whether the chronic consumption of two healthy dietary intervention (Mediterranean diet (MD), rich in olive oil (35-38% of calories as fat, 22% monounsaturated fatty acids (MUFA)) versus a low fat diet (LFD) (<30% of calories as fat, 12% MUFA)) improves postprandial lipemic response and insulin resistance in diabetic patients. MATERIALS AND METHODS: 254 diabetic patients from the CORDIOPREV study clinical trial (NCT00924937) underwent an oral fat load test meal (FLT), at baseline and three years of follow-up, with 0.7 g fat/kg body weight (12% satured fatty acids (SFA), 10% polyunsaturated fatty acids (PUFA), MUFA 43%, 10% protein and 25% carbohydrates). Serial blood test analyzing lipid fractions were drawn at 0, 1, 2, 3 and 4 hours during postprandial state. Postprandial TG levels at any point of lipemia > 220 mg/dL were considered altered (Curr Vasc Pharmacol 2011; 9 (3): 258-70). HOMA-IR as a marker of insulin resistance index determined. RESULTS: After both interventions we observed a reduced area under the curve (AUC) of TG ($p < 0.001$) and a decrease in the percentage of patients who had altered lipemia at some point (50.4% vs 47.2% ($p<0.05$)). The MD induced a more favorable profile than the LFD, with a greater decrease in the AUC of TG ($p=0.003$). Besides, a lower HOMA-IR ($p < 0.05$) index was observed after ingestion of both models of diet. CONCLUSIONS: Chronic consumption of a healthy dietary pattern (Mediterranean diet rich in olive oil or low fat diet) improve the postprandial lipemia response in diabetic patients suggesting an improvement in metabolic flexibility. Our findings confirm the importance of the diet as mesure to reduce the cardiometabolic risk attributed to exaggerated postprandial lipemia.

V.b Changes in the splicing machinery as a tool to predict the development of type-2 diabetes in high-risk patients.

Authors: *Mercedes del Río-Moreno, Manuel D. Gahete, Sergio Pedraza-Arévalo, Antonio Camargo, Javier Delgado-Lista, Francisco Gracia-Navarro, Francisco Pérez-Jiménez, José López-Miranda, Raúl M. Luque, Justo P. Castaño.*

Group: GC4 Inflammation and cancer.

Prevalence of metabolic syndrome (MetS) and type-2 Diabetes (T2D) is growing dramatically worldwide. Loss of phenotypic flexibility, i.e. the difficulty to cope with different stressors to maintain metabolic homeostasis, contributes critically to the development of MetS/T2DM. Thus, it is essential to identify the key modifiers of phenotypic plasticity that define an individual's susceptibility to develop T2DM. In this scenario, emerging evidence indicates that, under adverse metabolic conditions, the splicing machinery is markedly dysregulated in many tissues. We hypothesized that such a dysregulation could contribute to loss of phenotypic flexibility, and, as gene expression pattern in PBMCs commonly reflects disease-characteristic expression patterns, we reasoned that changes in spliceosome components of PBMCs might serve as biosensor/early indicators of MetS/T2D. To test this notion, expression of selected components of the major (n=13) and minor spliceosome (n=4), and associated splicing factors (n=28) was evaluated in PBMCs from 40 patients, who were initially non-T2D but in high-risk to develop T2D, and had suffered a prior cardiovascular event (CORDIOPREV study). Actually, during the 3-year follow-up, 20 individuals developed T2D and 20 did not (controls). PBMCs were isolated from basal and 4-h post-prandial blood, at the inclusion in the study and after 3-years. Results revealed that initial expression of relevant splicing factors and spliceosome components was altered in PBMCs from individuals who subsequently developed T2D. However, the most remarkable changes were observed during the post-prandial response, wherein expression of several splicing factors (e.g. Magoh, SRSF2, SRSF4, Tra2beta) was drastically induced in T2D-developing individuals compared to control patients, not developing T2D after 3-years of follow-up. These results reveal the existence of pre-TD2 development-associated spliceosome alterations, which could be related to the loss of phenotypic flexibility, and could help to predict, as a "splicing fingerprint", development of T2D in high-risk patients.

V.c Relationship between intake and urinary phosphate excretion in patients with chronic kidney disease (CKD).

Authors: *Mª Victoria Pendón, Mª Dolores Salmerón, Rafael Santamaría, Erena Ruiz, Noemí Vergara, Mª Dolores López, Juan Muñoz, Pedro Aljama, Mariano Rodríguez.*

Group: GC13 Calcium metabolism. Vascular calcification.

Introduction: High phosphate is associated with cardiovascular risk. Protein intake entails a greater input of phosphate in the diet. Urinary excretion of urea reflects protein intake. In addition, dietary phosphate from salts and additives is easily absorbed. It is possible that excessive intake of phosphate as additives distort the association between urinary excretion of urea and phosphate. Objective: To characterize the relationship between the dietary content of both protein and phosphate with the urinary excretion of urea and phosphate. Methods: Cross-sectional study of 50 patients with metabolic syndrome, CKD II-III without hyperphosphatemia and with minimal albuminuria (<0.3mg/g). Demographic, clinical and laboratory variables (blood test and 24 hours urinalysis) were analyzed. Dietary survey was also taken (3 days). Results: Average age: 61±9 years; men: 76%; Hypertension: 100%; diabetes: 52%; dyslipidemia: 82%; BMI: 32.3 ± 4.1; Hyperuricemia: 60% and smokers: 16%. The calculated amount of phosphate intake was not correlated with the urinary excretion of phosphate (24h) (p=0.6). By contrast there was a significant correlation between phosphate/creatinine ratio (P/Cro) and urea/creatinine ratio (U/Cro) (r^2=0.75, p<0.0001). Further analysis revealed that for patients with similar excretion of urea, the values of P/Cr in urine correlated with the calculated amount of phosphate intake (p = 0.05). Conclusions: Urinary excretion of phosphate is related to phosphate intake if it is corrected for urea excretion. It is likely that a moderate amount of absorbable dietary phosphate makes a large impact in urinary phosphate excretion.

V.d Factors influencing telomere length and cardiovascular disease. From the CordioPrev Study.

Authors: *Cristina Moyano Hidalgo, Javier Delgado Lista, Ruth Blanco Rojo, Oriol Rangel Zuñiga, Elena Yubero Serrano, Antonio Camargo, Antonio Garcia Rios, Carmen Marin, Jose Lopez Miranda, Pablo Perez Martinez.*

Group: GC9 Nutrigenomics and Metabolic Syndrome.

Introduction: A relationship between the development of atherosclerosis and premature cellular aging has been suggested, and telomere shortening is one of the primary mechanisms influencing cellular senescence. However, if coronary heart patients have shortened telomeres and whether this fact relates to different cardiovascular risk factors has not been studied. Objective: To determine whether the presence of coronary disease implicates a telomere shortening, and to investigate possible factors that may influence telomere length in coronary heart patients compared to a control population. Methods: In the setting of the NUTRICLOCK substudy of the CORDIOPREV study, we selected 115 subjects with coronary heart disease and 40 healthy matched controls, and we compared telomere length in both groups adjusting by potential confounders. We also performed linear regression models with more than 30 variables related to inflammation, oxidative stress and factors related to atherosclerosis, seeking to determine the factors related to telomere length in both samples. Finally, we evaluated the R2 of the models, to check the prediction level of the final models, both in the coronary heart disease patients and the general population. Results: Coronary patients showed a reduced telomere length (1.03± 0.23, vs. 1.64± 0.11, P 0.037) compared to controls. In the sample of coronary patients, our final regression model showed an R2 > 80%, meaning that this model exhibited a really high accuracy in predicting telomere length. Control population, on the contrary, may have different determinants of telomere length, as our set of potential influencing factors (>30 factors) did not properly predicted this length in these patients. Conclusions: In our study, we discovered that telomere length is shortened in people with coronary heart disease and we were able to build a highly precise prediction model for telomere length in these patients.

V.e Changes in gut microbiota according to the progresion of metabolic syndrome.

Authors: Sonia García-Carpintero, Carmen Haro, Ana León Acuña, Isabel Pérez-Corral, Beatriz Gómez Marín, Javier López-Moreno, Francisco Pérez-Jiménez, Antonio Camargo.

Group: GC9 Nutrigenomics and Metabolic Syndrome.

Introduction: The gut microbiota is an ecological community formed by a diverse range of bacterial species that contributes in the health or disease of host. Recent evidence suggests that gut microbiota is an important contributing factor to obesity and its metabolic disorders, such as the Metabolic Syndrome (MetS). Objective: The aim of this study was to identify a pattern of gut microbiota associated with the development of MetS. Methodology: 410 patients within the CORDIOPREV study were divided into 4 groups according with their evolution of MetS during three years follow up and under two healthy diets Mediterranean diet and Low-fat diet. Sequencing of 16S rRNA gene has been used to analyze the stable changes in the microbiota composition at basal and after three years of dietary intervention. In addition, we have determined the endotoxemia effect by meassurements of the plasma levels of LPS and LBP and their relationship with the microbiota composition changes. Results Multivariated analysis (PCA-PLSDA) showed that the microbiota before and after development MetS were different. We observed change in relative abundance of Proteobacteria, Roseburia, B.dorei, P. vibrio, P,xylaniovans, R.faecis, S.bovis, Bacilli, Lactobacillaceae, Blantia, Faecalibacterium, F. prausnitzii, B.cocoides, Desulfovibrionales, A. crotonatoxidans according with the progression of MetS ($p<0.05$). The species richness index decreased when development MetS and increased phylum and genus richness index ($p<0.001$). At 3 years of study the species and phylum diversity increased in patients with MetS ($p=0.04$;$p=0.020$). We observed postprandial increased of LPS that development MetS at three years of study ($p=0.002$). MetS patients showed higher plasma levels of LBP ($p=0.016$) as compare to control group without MetS. Postprandial level of LBP decreased in patients that lost MetS at three years of study ($p=0.002$). Conclusion: Collectively, these findings suggest that manipulation of gut microbiota communities might be a novel target in the treatment of MetS.

V.f Hypothalamic GRK2, via GPR54, modulates puberty onset.

Authors: *MS Avendaño; F Ruiz Pino; MJ Vázquez; I Velasco; V Heras; E Torres; JM Castellano; J Roa; L Pinilla; M Tena-Sempere.*

Group: GC10 Hormonal regulation of energy balance, puberty and reproduction.

Worrying trends changes in the age of puberty have been reported recently, mostly in girls. The reason for this phenomenon, which may have durable consequences in later health, remains unknown. This urges for a better understanding of the basis of puberty and its alterations. The G protein-coupled receptor kinase 2, GRK2, is a ubiquitous serine/threonine protein kinase that is able to phosphorylate and desensitize the active form of several G protein coupled receptors (GPCR). Compelling, as yet limited, evidence in vitro has 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, in vivo remains unexplored. We report herein a series of expression and functional analyses addressing the putative role of central (hypothalamic) GRK2 in the regulation of puberty. 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. Models of delayed puberty, due to postnatal under-nutrition or manipulation of neonatal sex steroid milieu, displayed an exaggerated increase of hypothalamic GRK2 expression. In addition, central injection of a GRK2 inhibitor enhanced LH and FSH secretion in response to acute kisspeptin-10, but not to NKB, administration. Furthermore, chronic central GRK2 inhibition caused an advancement of puberty onset, evidenced by earlier vaginal opening and first ovulation, together with increased ovarian and uterus weights. Alike, GRK2 inhibition partially rescued the delay in puberty onset caused by postnatal under-nutrition. Altogether, our results demonstrate that GRK2 regulates hypothalamic Gpr54 signaling in vivo and provide conclusive evidence for a crucial role of GRK2 in the fine tuning of pubertal timing, likely via modulation of kisspeptin actions, in normal and metabolically/hormonally compromised conditions.

SESSION VI

Cancer
(Oncology and Oncohematology)
Active ageing an fragility

VI.a Differential sensitivity of prostate cancer cells to galiellalactone. A proteomic approach.

Authors: Víctor García, Juan Carranza, Marco A. Calzado and Eduardo Muñoz.

Group: GC4 Inflammation and cancer.

Prostate cancer (PCa) is the second most common cancer in men. Initially, PCa patients respond to androgen deprivation therapy but they usually develop castration-resistant PCa (CRPC), requiring a second-line therapy still unavailable. The small molecule Galiellalactone (GL) is a dual NF-KB and STAT3 inhibitor that reduces tumor growth and early metastatic dissemination of PCa, indicating its potential use as a therapeutic compound in advanced metastatic PCa. We have recently shown that GL also induces cell cycle arrest and a DNA damage response through the ATM/ATR pathway in androgen-independent cell lines (DU145 and PC3) but GL did not induce cell-cycle arrest in androgen-dependent (LNCaP) and/or normal prostate epithelial (RWPE) cell lines. In order to investigate the differential response to GL among different PCa cell lines we analyzed and compared the proteomic profiling of DU145 and LNCaP cells under basal and GL-treated conditions. Through peptide digestion and LC–MS/MS analysis we have identified large differences between DU145 and LNCaP. Under basal conditions DU145 constitutively express several proteins whose genes are regulated by the Nrf2 transcription factor that can be explained because the Keap1 gene is methylated and repressed in this cell line. Interestingly, reconstitution of Keap1 in DU145 cells prevented GL-induced cell cycle arrest and enhanced GL-induced apoptosis. Proteomic analysis also showed that GL induced the expression of several key proteins of the spliceosome machinery such as RBMX, HNRNPA2B1, HNRNPH3, DHX9, SNRPD3, HNRNPU and others. Among them, RBMX (RNA Binding Motif Protein, X-Linked) has also been described to exert tumor suppressor activity and we have found that reconstitution of Keap1 prevented GL-induced RBMX expression in DU145 cells. In conclusion, GL is a multi-target compound that is being developed for the treatment of CRPC and our results showed for the first time a potential connection between the Keap1/Nrf2 pathway and RMBX in cancer cells.

VI.b Functional role of somatostatin receptor subtype 1 (sst1) in prostate cancer: an in vitro approach.

Authors: Sergio Pedraza-Arévalo, Daniel Hormaechea-Agulla, Luke A. Selth, Justo P. Castaño, Raúl M. Luque.

Group: GC8 Hormones and cancer.

Prostate cancer (PC), the most commonly diagnosed malignancy among men, is a complex and heterogeneous disease highly influenced by the endocrine environment, making difficult the identification of novel therapeutic biomarkers to treat this pathology. Somatostatin is a pleiotropic neuropeptide which exerts its multiple biological functions, including tumor cell regulation, through a family of receptors (named sst1-5). Particularly, in this study we found that sst1 is overexpressed in human PC samples compared with normal prostate (NP). Therefore, our objective was to determine the relevance of sst1 in PC analyzing functional parameters in response to two sst1-agonists and sst1 silencing/overexpression. Moreover, we analyzed potential microRNAs (miRNAs) that could regulate sst1 expression in PC and then, some selected miRNAs were used to perform functional assays. Treatment with sst1-agonist reduced PSA secretion and decreased, while silencing of sst1 expression increased, cell proliferation in 22Rv1 cells. These effects of sst1-agonist were probably mediated through the regulation of AKT. In silico analyses revealed four miRNAs (miR-24/27/383/488) that could interact with sst1 at the 3'UTR. Interestingly, these miRNAs were negatively correlated with sst1 in 414 tumors (using the TCGA data portal). Moreover, overexpression of miR-24 decreased sst1 expression, cell proliferation and migration, but increased cell death, in 22Rv1 and/or C42B cells. Finally, an inverse correlation between sst1 and miR-24 expression was found using the MSKCC dataset which include the combined analysis of 29 NP, 131 primary PC and 19 metastatic PC samples. In conclusion, our results indicate that sst1 is over-expressed in PC, where it can exert a relevant pathophysiological role by decreasing cell proliferation through AKT signaling pathway. The observation that miR-24 can regulate sst1 expression and aggressiveness features in PC cells supports the idea that the combination of sst1 and miR-24 expression might be used as a novel tool to explore therapeutic targets in PC.

VI.c Recent advances in human sweat metabolomics for lung cancer screening.

Authors: *M. Calderón-Santiago, M.M. Delgado-Povedano, B. Jurado-Gámez, F. Priego-Capote, M.D. Luque de Castro.*

Group: GC21 Metabolomics Identification/Quantification of Bioactive Components.

Lung cancer is the leading cause of cancer related mortality owing to the advanced stage at which it is usually detected and the invasive nature of the existing diagnostic tests. For this reason, different biofluids have been studied to find new screening tools to detect lung cancer at earlier stages. However, these studies need to be validated to find a robust panel of markers. In this research, sweat samples from two batches (a first cohort of 35 patients recruited from March to August 2012 and a second cohort composed by 34 patients recruited from November 2012 to October 2014) were combined to increase the robustness of potential biomarkers. First of all, the variability between cohorts and the individual predictive capability of each metabolite were studied. The proposed biomarkers panels was oriented to discriminate between lung cancer patients and smokers as control individuals of the two cohorts, the samples from whom were collected and analyzed at different times. The resultant two panels of metabolites were configured using the PanelomiX tool as an attempt to reduce false negatives (at least 95% specificity) and false positives (at least 95% sensitivity). The first panel (96.9% specificity and 81.1% sensitivity), was composed by histidine, monoglyceride MG(22:2), nonanedioic acid, suberic acid, and a tetrahexose, while the second panel (84.4% specificity and 97.3% sensitivity) was composed by the monoglyceride MG(22:2), phenylalanine, a tetrahexose, a trisaccharide phosphate, and urocanic acid.

VI.d Assessment of RIFLE and AKIN criteria to define acute renal dysfunction for HIPEC procedures for ovarian and non ovarian peritoneal malignances.

Authors: *J. Cabrera-Bermon, A. Cadenas-Febres, A. Arjona-Sanchez, F.C. Muñoz-Casares, A. Casado-Adam, J.M. Sanchez-Hidalgo, M. Lopez-Andreu, J. Briceño-Delgado, S. Rufian-Peña.*

Group: Others.

Background: The acute renal dysfunction (ARD) is a common complication in cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC). Our aim is evaluate the ARD post-HIPEC procedures using the RIFLE and AKIN criteria. Evaluate the risk factors and analyze ARD's impact on postoperative course. Methods: From 2011 to 2014, in a retrospective way using a prospective database were operated by HIPEC procedure. The ARD was analyzed by RIFLE and AKIN criteria. The perioperative features were analyzed and a multivariate analysis was performed to define the risk factors to develop the ARD. Results: 141 patients were treated and analyzed. The ARD was detected in 30.5% (Injury 18.4% and Failure 12.1%) when RIFLE criteria were applied. The multivariate analysis detected that decrease of pH during HIPEC [OR ¼ 29.39 (5.09e169.76)], PCI [OR ¼ 1.07 (1.01e1.15)] and ureteral catheters [OR ¼ 12.71 (1.44e111.85)] were associated to the development of acute renal injury (ARI) post-HIPEC. Decrease of Na during HIPEC [OR ¼ 1.15 (1.01e1.30)], intraoperative inotrope use [OR ¼ 3.83 (1.12e13.09)] and PCI [OR ¼ 1.06 (1.0e1.14)] were associated to acute renal failure (ARF) post-HIPEC. The ARD was related to a higher length of stay hospital (17.2 11 vs. 13.8 8 days) (p ¼ 0.05) but no impact in early survival was observed in ARD group. Conclusions: The widespread use of RIFLE criteria for ARD would have major benefits in terms of accurately diagnosing patients undergone HIPEC procedures. The ARD has a detrimental impact in length of stay hospital. The knowledge of risk factors helps us to prevent the ARD post-HIPEC by means of an aggressive and multidisciplinary perioperative management.

VI.e The truncated somatostatin receptor, sst5TMD4, is overexpressed in prostate cancer, where it increases malignant features by altering key signaling pathways and tumor suppressors/oncogenes.

Authors: *Juan M. Jiménez-Vacas, Daniel Hormaechea-Agulla, Enrique Gómez-Gómez, Fernando L-López, Julia Carrasco-Valiente, José Valero-Rosa, María M. Moreno, Rafael Sánchez-Sánchez R, Rosa Ortega-Salas, Francisco Gracia-Navarro, Michael D. Culler, Alejandro Ibáñez-Costa, Manuel D. Gahete, María J. Requena, Justo P. Castaño, Raúl M. Luque.*

Group: GC8 Hormones and cancer.

Prostate cancer (PC), one of the most common malignancy in men around the world, is deeply influenced by endocrine inputs. In line with this, somatostatin (SST) exerts multiple biological functions, including tumor cell regulation, through a receptor family (sst1-5). We recently identified an aberrant spliced truncated variant, sst5TMD4, which displays unique molecular/functional features, and is expressed in various endocrine-related tumors (i.e. breast, neruroendocrine and pituitary tumors), wherein it exacerbates malignant characteristics. In this study, we aimed at characterizing the presence, functional and pathological role and mechanisms of actions of sst5TMD4 in preclinical and human prostate cancer (PCa) models, in vivo and in vitro. Specifically, prostate tissues from patients with low/intermediate PCa-risk [n=25 (tumoral/non-tumoral paraffin-embedded regions)], high PCa-risk (n=52; fresh-tumoral biopsies), and healthy-prostates (n=12; from cystoprostatectomies) were examined. Additionally, in vitro functional (proliferation/migration) and mechanistic (gene expression) assays were performed in PCa-cell lines (VCaP-, DU145- and PC3-cells) and tumor progression was monitored in xenograft-models (nude-mice) injected with PC3-cells overexpressing sst5TMD4. We found that sst5TMD4 was overexpressed at mRNA and protein level in PCa-samples and associated to an altered frequency of two SNPs. Remarkably, sst5TMD4 expression was higher in metastatic tumors. sst5TMD4 overexpression increased cell proliferation and migration in PCa-cells and induced larger tumors in nude-mice, while its silencing decreased proliferation/migration. sst5TMD4 overexpression activated multiple key intracellular-pathways (ERK/JNK, MYC/MAX, WNT and RB), altered the expression of oncogenes (GCA/CAV2/IL-6) and tumor suppressor genes (SFRP1/NRIP1/LOXL1/CDKN2A/RARB2/APC/IGFBP5), and disrupted the normal response to SST-analogs in PCa-cells. Altogether, we found that sst5TMD4 is overexpressed in PCa where is associated to metastasis and to an altered frequency of two SNPs and demonstrate a pathological role of sst5TMD4 in PCa-cells (proliferation and migration) and the mechanisms underlying these changes, suggesting that sst5TMD4 might have a potential value as biomarker and/or therapeutic target.

VI.f Age related paramethers can be improved by a mediterranean diet supplemented in hydroxytyrosol.

Authors: Andreea Corina, Javier Delgado-Lista, Ana Lean Acuña, Oriol Alberto Zuñiga, Pablo Pérez Martínez, José López-Miranda, Francisco Pérez Jiménez.

Group: GC9 Nutrigenomics and Metabolic Syndrome.

Objective: To study whether a Mediterranean diet supplemented in an olive extract containing hydroxytyrosol can improve endothelial function and oxidative stress parameters in healthy elderly patients. Subjects and Methods: The study was conducted in 23 subjects, 12 men and 11 women, olther than 65 years. They underwent two intervention periods of four weeks each. The subjects followd a crossover latin square design, being randomized in two groups: 1. Mediterranean Diet and hydroxytyrosol (MedD+H): participants received 100 mg of product containing hydroxytyrosol per day, in the form of capsules (5 capsules of 20mg of product registered HT80 ©, BIOMASLINIC SL), 2. Mediterranean Diet and placebo (MedD+P): participants received 5 capsules containing placebo a day. The study of endothelial function was performed by calculating the post-ischemic reactive hyperemia and parameters of oxidative stress were also studied. The results were analyzed using repeated measures ANOVA test, Bonferroni corrections where applied for randomization group, age, sex, diagnosis of dyslipidemia and diagnosis of Type 2 Diabetes Mellitus. Results: Studying the endothelial function, we observed that after the intervention with MedD+H there is a significant increase in the post-ischemia hiperemia area comparing to the pre-intervention point (26115 ± 2704 vs. 17016 ± 3629, p = 0,008). After the intervention with MedD+P this phenomenon is not observed (22463 ± 2852 vs 17016 ± 3629, p = 0,364). The results of the oxidative stress study show an increase in reduced glutathione/ oxidized glutathione ratio after MedD + H (18.20 ± 15.98) compared to pre-intervention phase (8.13 ± 3.72), p = 0,044. Conclusions: A Mediterranean diet supplemented in 100 mg of a mix containing hydroxytyrosol, daily (HT80 © registered product, S.L. BIOMASLINIC) can improve arteriosclerosis and age related parameters as endotelial function and oxidative stress in elderly patients.

POSTER
Abstracts

POSTER SESSION

Active Ageing and Fragility

P1. **Phenotypic changes in human NK cells related to ageing and CMV-infection.**

Authors: *López-Sejas N, Simarro C, Hassouneh F, Pera A, Solana R, Campos C.*

Group: GC1 T and NK immunosenescence. Antiviral immune response.

The immune impairment associated with aging is known as immunosenescence. Previous studies show that NK cells are affected by age, modifying its phenotype. These changes have been associated with CMV infection. The aim of this work was to analyze the effect of CMV-seropositivity and ageing on the surface receptors expression in the NK cells. 67 healthy donors were included, stratified by age and CMV-seropositivity. Peripheral blood samples were obtained in heparinized tubes and peripheral blood mononuclear cells (PBMCs) were isolated. Plasma from all donors was tested for CMV-specific IgG and IgM by ELISA. The percentage of cells expressing CD57, CD300 y CD161 in NK cell subsets (defined by CD56 and CD16 expression) were analyzed by multiparametric flow cytometry. Data were analyzed using FlowJo software. Our results showed an increase in CD300 expression on total, CD56dim and CD56brightNK cells from elderly CMV-seropositive donors compared to young (CMV-seropositive and CMV-negative) and middle-age CMV-seropositive. CD161 expression was decreased in total, CD56dim and CD56brightNK cells from elderly, middle-age and young donors (all CMV-seropositive) compared to young CMV-negative. CD57 expression was also increased on total and CD56dimNK cells from CMV-seropositive donors (young and elderly) compared to young CMV-seronegative. These results show that aging and CMV infection are associated to changes in phenotype and function of the NK cells. Thus, whereas CMV-seropositivity of healthy young donors is associated to the increased CD57 expression and to the decreased CD161 expression on the major CD56dim cell subset, aging is associated to the increased CD300 expression on all subsets of NK cells. These results indicate that changes of NK cell subsets in the elderly are related not only with age but also with exposure to CMV and emphasize the relevance of including the determination of CMV serostatus in those studies addressed to analyze the immune response in the elderly.

***P2.* Dietary fat and aging has an impact on glomerular and proximal convoluted tubule cells ultrastructure as well as modulate autophagic and mitochondrial dynamics proceses in kidney of caloric restricted mice.**

Authors: *Miguel Calvo-Rubio; Mª Isabel Burón; Guillermo López-Lluch; Plácido Navas; Rafael de Cabo; Jon J. Ramsey; José M. Villalba and José A. González-Reyes.*

Group: Others. Grupo Biomembranas, antioxidantes y estrés oxidativo | BIO-276 | UCO.

Calorie restriction (CR) has been repeatedly reported to prevent cancer, diabetes, hypertension and other age-related diseases in a wide range of animals, including nonhuman primates and humans. In rodents CR also increase life span constituting a powerful tool to study the aging process. Recently it has been reported in mice that the dietary fat plays an essential role in the determination of life span extent on a basis of 40% CR. In these conditions, animals fed lard as dietary fat showed an extra life span extension compared with mice fed soybean or fish oils. In this paper we study the effect of these dietary fats on structural and physiological parameters of kidney from mice submitted to 40% CR for 6 and 18 months. Analyses were performed using quantitative electron microcopy techniques and protein expression in western blots. Although CR mitigated most of the analyzed parameter related to aging in kidney, lard fat had an optimal effect in most of them. These measure parameters include number glomerular basement membrane and foot processes thickness as well as filtration slits width along with mitochondrial mass in convoluted proximal tubules and mitochondrial dynamics together with autophagic markers in renal homogenates. These results point out that dietary fat modulates the beneficial effects of CR and plays an essential role in the determination of life and health span in rodents.

P3. Female sex and burden of caregivers of people with Alzheimer's disease as triggers of social loneliness.

Authors: *Patricia Luque-Carrillo, Ignacio Morales-Cane, Pablo Jesús López-Soto, Juan Manuel Carmona-Torres, María Aurora Rodríguez-Borrego.*

Group: GA2 Comprehensive care nurses - a multidisciplinary perspective.

Introduction: Informal caregivers spend most or all of their time to perform the role of caregiver (Toribio-Díaz et al., 2013), what causes changes that may affect their physical and psychological health, as well as their family and social life (Joling et al., 2010). The aim of the study is to know what factors interfere in the emergence of social loneliness on caregivers. Methods: Quasi-experimental study "pretest-posttest" during which two interventions are carried out: a motor intervention to the patients and a group therapy intervention based on problem solving to the caregivers. Before and after the implementation of the interventions, an assessment of the functional state of patients and an assessment to caregivers in terms of burden, depression, anxiety and social loneliness is carried out. Simple random sample of 63 patients with their caregivers, other 63 people. Results: This communication reports data obtained in the pre-test evaluation of caregivers. Average age of caregivers was of 58,15, being women in a 75,8%. They present an average social loneliness of 8,25 ± 4,24, what means low-medium level. Positive correlations were detected between the level of social loneliness of caregivers and: • Female sex of themselves (p=0.005). • Their level of burden (p=0.001). • Caregiver's age (p=0.001). On the other hand, it has been detected a negative correlation between the level of social loneliness of caregivers and having a college education (p=0.003). Discussion/ Conclusions: The establishment of burden and its relationship with social loneliness in informal caregivers of patients with Alzheimer's disease highlights relational aspects to consider, among which may be having support on decisions making. That is why data obtained reaffirm the decision of introducing the proposed intervention in the quasi-experimental study, training caregivers on decision making.

P4. **Kaempferol, a dietary polyphenol, produce alterations of mitochondrial physiology and autophagy markers in an in vitro model.**

Authors: *Gutiérrez Casado Elena, Fernández del Río Lucía, Villalba José Manuel.*

Group: Others. Grupo Biomembranas, antioxidantes y estrés oxidativo | BIO-276 | UCO.

Deleterious effects of reactive oxygen species (ROS) are suppressed by many antioxidant substances. Kaempferol (3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one) is a flavonoid found in many edible plants, which has been used in traditional medicine. Kaempeferol can behave both as antioxidant and as pro-oxidant in a concentration-dependent manner (1). When used at high concentrations, it can induce autophagy and apoptosis (2, 3), whereas at low concentrations it is capable of neutralizing superoxide anion (1). Recent results obtained by our research group indicate that this substance produces a significant increase in the levels of coenzyme Q, an endogenous antioxidant, in mouse kidney cells. The goal of the present study was to determine how mitochondrial physiology, as well as the autophagy flux were affected by kaempferol under the same experimental conditions previously tested. Moreover, since this polyphenol is known to activate the mitochondrial sirtuin Sirt3, we wanted to test out the effects of the combined treatment with kaempferol and nicotinamide, a general competitive inhibitor of sirtuin activity acting at the NAD+ site of the deacetylases, which however can also behave as a sirtuin activator at low doses by acting as a NAD+ precursor (4). Cultures of a mouse kidney proximal tubule cell line (TKPTS) were treated with 10 μM kaempferol during 48 hours in the presence of absence of 10 mM nicotinamide. After that, different mitochondrial and oxidative stress-related parameters were measured, including mitochondrial abundance, intracellular levels of superoxide and peroxides, mitochondrial superoxide and mitochondrial membrane potential. Proteins related with autophagy were also measured by western blot. Our results indicate that kaempferol can modulate ROS levels and mitochondrial function in TKPTS cells.

***P5*. Impact of CPAP therapy on quality of life related to health in patients over 65 years with apnea-hypopnea.**

Authors: Leiva-Cepas, Fernando; López Macías, Isabel; Serrano Merino, Jesús; Conesa Pedrosa, Isabel; Soriano Gómez, Fátima; Alcalá Grande, Alberto José.

Group: Grupo de Investigación GIEAP- Unidad docente de Medicina Familiar y Comunitaria de Córdoba.

Objectives: To assess the impact of CPAP (CPAP) therapy on quality of life related to health (HRQOL) in patients with apnea-hypopnea syndrome (SAHS) and daytime sleepiness in> 65 years. Compare HRQOL with/without SAHS. Methods: A quasi-experimental longitudinal, prospective study, pre-post intervention, multicenter (OSAS cohort of patients> 65 years). TCPAP impact was assessed by comparing results of HRQOL questionnaires, SF-36 and SAQLI, preTCPAP and 3 months later; and control without DAHS cohort. Test comparison of means or proportions (95%). Results: 100 preselected patients (75% diagnosis SAHS); 67.7% men. Age 70.70 years and BMI 33,18kg / m2. Differences pre-post test SAQLI therapy were significant: "Daily Operation" (0.87 ± 0.95; 95% CI 0.64 to 1.09; p <0.001) "Social interactions" (0.59 + 0 , 65, 95% CI: 0.44 to 0.75; p <0.001), "emotional Operation" (0.90 + 0.77, 95% CI: 0.71 to 1.07; p <0.001) and "SAQLI Total "(0.71 + 0.80, 95% CI: 0.52 to 0.90; p <0.001). The SF-36 test was significant: "Physical Function" (10.83 + 16.82, 95% CI 6.88 to 14.79; p <0.001), "physical role" (22.22 + 41.44, 95% CI 12.48 to 31.96; p <0.001), "Vitality" (16.02 + 28.07, 95% CI 9.43 to 22.62; p <0.001), "social function" (12 29 + 25.86, 95% CI 6.21 to 18.37; p <0.001), "emotional role" (15.23 + 29.01, 95% CI 8.42 to 22.05; p <0.001), "Mental health" (12.19 + 16.95, 95% CI 8.21 to 16.17; p <0.001), "Transition of health" (25.13 + 26.02, 95% CI: 19 , 02 to 31.25; p <0.001) and "body pain" (24.94 + 88.53, 95% CI 4.14 to 45.75; p = 0.019). Epworth test decreased by an average of 3.75 + 6.43 (95% CI 2.22 5.27; p <0.0001). Conclusions:> 65 years with SAHS, the TCPAP improved HRQOL and daytime sleepiness. No significant differences in HRQOL in patients with / without SAHS.

***P6*. Dual task of motor-cognitive interference as marker of cognitive impairment in patients with subjective memory complaints.**

Authors: *C. Conde-Gavilán, C. Bahamonde, A. Jover, M.A. Peña-Toledo, S. Molina, A. Galvao-Carmona, R. Valverde, M. Latorre M, A.I Giraldo, E. Agüera, F. Sánchez López, R. Lillo, I. Túnez.*

Group: GE1 Oxidative stress and nutrition.

Introduction and Objectives: The management of walking requires a high degree of cortical processing, especially during the performing of concurrent cognitive tasks. The aim of this study was to determine if the assessment of the walking process and a simultaneous cognitive task is a good marker of cognitive decline in patients with subjective memory complaints. Material and Method: 28 patients and 14 healthy controls were evaluated with a dual task of motor cognitive interference during the walking process. Additionally, all the patients performed Symbol Digit Modalities Test (SDMT). Results and Discussion: The patients displayed signs of slowing in all the dual task measures ($F_{1, 40}=23,14$; $p<0.001$), as well as a greater effort of the cognitive task during walking ($F_{2,80}=19,31$; $p<0.001$). In addition, our patients showed scores in the SDMT that evidenced cognitive decline and significant differences between patients and control subjects ($t=8,7$; $p<0.001$). Finally, the study showed the correlation between SDMT and motor cognitive interference ($r=-0,9$; $p<.05$). Conclusions: The measuring of the motor-cognitive interference during walking may be a good and a straightforward marker of cognitive decline in patients with subjective memory complaints.

P7. Effect of aging and CMV-seropositive on phenotype of human T cells.

Authors: *Fakhri Hassouneh , Nelson López-Sejas , Alejandra Pera, Rafael Solana and Carmen Campos.*

Group: GC1 T and NK immunosenescence. Antiviral immune response.

Immunosenescence is a progressive deterioration of the immune system with ageing. It affects both, innate and adaptive immunity limiting the response to pathogens and to vaccines. As chronic cytomegalovirus (CMV) infection is probably one of the major driving forces of immunosenescence, the aim of this study was to analyze the effect of CMV-seropositivity and ageing on the surface receptors expression on Both CD4, CD8 T-cells and NKT-like cells. Three age groups consist of 67 healthy donors stratified by CMV-serostatus and age. Peripheral blood from each subject was collected and followed by PBMCs isolation from each blood sample and CMV-specific IgG and IgM was determined by ELISA from plasma or sera of each sample. The percentage of cells expressing CD57, CD300 and CD161 was measured on CD4, CD8 T Cells and NKT-Like cells. Samples were acquired by multiparametric flow cytometry and analysed with FlowJo v X 10.0.7 software. Our results showed an increase in CD57 and CD300 expression on CD4+, CD8+ T cells and NKT-like cells from elderly CMV-seropositive donors compared to young (CMV-seropositive and CMV-negative) and middle-age CMV-seropositive.The expression of CD161 on CD4+, CD8+ T cells and NKT-like cells from elderly, middle-age and young donors (all CMV-seropositive), was decreased compared with its expression on lymphocyte from young individuals. These results show that both, CMV latent infection and age, contribute differentially to the phenotype of the T-cells subsets studied. Thus, whereas the expression of CD161 was affected by ageing but not by CMV-serostatus, the expression of CD57 on CD4+ and CD8+ but not in NKT-like T-cells was affected by both CMV and age. On the contrary the expression of CD300 in CD4+ T cells was due to combination of both CMV and age, where in CD8+ and NKT-like is only due the effect of age.

P8. **Comorbility and social-demographyc factors asociated to kidney stone in subject between 40 and 65 years: an epidemiologycal study of population base.**

Authors: Arias Vega R 1,3,8, Jiménez García C 2,3,8, Pérula de Torres LA 3,4,8, Carrasco Valiente J 5, Requena Tapia MJ 5, Cano Castiñeira R ; Silva Ayçaguer LC 7, Alcala Grande AJ6 .

Group: Unidad Docente de Medicina Familiar y Comunitaria de Córdoba. Distrito Sanitario Córdoba y Guadalquivir. Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC)/Hospital Universitario Reina Sofía/Universidad de Córdoba. Avda. Menéndez Pidal, s/n. Córdoba (Spain)

Background: The kidney Stone is one of the highest magnitude phatology due to its clinical and social significance, cost and an increasing prevalence in the world in the last decades. It seems to be related to with different sociodemographyc factors, climate, lifestyle and previous comorbilities. The objetive is to study the relation among certain chronic diseases, sociodemographyc variables and renal urolithiasis in Spanish population who are between 40 and 65 years old.

Methods: We develope an observational, cross-sectional study with population base, selecting spanish population of 40 to 65 years. We combined two aleatory samples (PreLiRenA and PreLiRenE study) which are stratified by sex and age. Data were obtained by telephone interviews that were conducted using a questionnaire that covered several sociodemographic and morbility variables. The average of anual temperature of each Spanish región were also obtained. The prevalence-ratio was calculated and was done an analisis of multiple logistic regression.

Results: PreLiRenA study survey 2439 subject and PreLiRenE 2445 subject. The 51.3% (n=2504) were women. The 25.0% (n=1223) were between 40 – 45 years old. The 36.0% (n=1795) have primary study level and the 31.4% (n=1565) came from lower-class. Using multivariable analisis, the following variables showed estatistical relation with the kidney Stone: subject with age between 46 – 50 years old (OR=1.31; CI 95% = 1.02 – 1.69) and 60 – 65 years old (OR = 1.39; CI 95% = 1.06 – 1.8), belonging to social upper-class (OR = 1.98; CI 95% = 1.29 – 2.62), family history of kidney Stone (OR = 2.22; CI 95% = 1.88 – 2.65), arterial hypertension (OR = 1.68; CI 95% = 1.39 – 2.02) overweight/obesity (OR = 1.31; CI 95% = 1.12- 1.54). Statistical realtion was not found between kidney Stone and sex. Moreover kidney Stone is not statistical related to the study level, hipercolesterolemia, diabetes or hiperuricemia of the subject.

Conclusions: It is objectified the relation among kidney stone and age, the belonging to a higher social class, the existence of family history, and health problems like hypertension and overweight/obesity.

POSTER SESSION

Cancer
(Oncology and Oncohematology)

P9. Search for prostate cancer potential biomarkers in urine by LC–QTOF.

Authors: *M.A. Fernández-Peralbo, E.Gómez-Gómez, M. Calderón Santiago, J. Carrasco-Valiente, M.J. Requena-Tapia, J. Ruiz-García, F. Priego-Capote, M.D. Luque de Castro.*

Group: GC21 Metabolomics Identification/Quantification of Bioactive Components.

The accurate detection of prostate cancer (PCa) is urgently needed to reduce overdiagnosis and over-treatment, while maintaining a reduction in mortality. In this sense, the existing clinical biomarkers for PCa diagnosis are far from ideal, as is the case with prostate specific antigen serum (PSA) level that suffers from lack of specificity, thus giving place to frequent false positives. For this reason, minimum invasive tests based on markers from biological samples such as blood or urine that could complement or replace PSA represent a goal in PCa research. Recent advances in analytical instrumentation have facilitated the development of metabolomics, providing an insight into the metabolic state and biochemical processes of the organism. In this research, a comprehensive global analysis by LC–QTOF have been applied to urine from 62 patients with a clinically significant PCa and 42 healthy individuals, both groups confirmed by biopsy. An unpaired t-test (p-value<0.05) revealed 42 significant metabolites tentatively identified in urine, that were considered to develop a partial least squares–discriminant analysis (PLS–DA) model, characterized by 86.05 and 92.85% of sensitivity and specificity, respectively. Then, an external validation using the 30% of the samples reported a sensitivity and specificity of 73.68% and 78.57%, respectively. These 42 urinary metabolites are involved in key biochemical pathways like amino acids metabolism (e.g. lysine degradation, taurine, and tryptophan metabolism), the urea cycle and purine and pyrimidine metabolism, among others. These results indicate that deregulation of amino acids metabolism may be specific for the PCa metabolic phenotype, which can be also associated to abnormal cell growth and intensive cell proliferation. These preliminary results emphasize the necessity for a large scale study to validate the proposed metabolites, as well as to include urine from less advanced PCa stages.

***P10.* Towards precision medicine in colorectal cancer: relationship between nitric oxide and molecular subtypes.**

Authors: *Rafael Mena-Osuna, Jon Peñarando, Álvaro Jiménez-Arranz, Macarena Centeno, Rafael Sánchez, Carlos Villar, César Díaz, José Barbadillo, Enrique Aranda, Antonio Rodríguez-Ariza.*

Group: GC6 New therapies in cancer.

The heterogeneity within colorectal cancer (CRC) patients compels the development of personalized treatments. Thus, recent studies have described different CRC molecular subtypes based on gene expression signatures. Besides, experimental evidence highlights the importance of nitric oxide (NO) in cancer biology, particularly in the acquisition and maintenance of stem characteristics. Nevertheless, there are no studies about the link between NO and the CRC molecular subtypes. Therefore, the objective of the present study was to characterize the NO-related gene expression in CRC molecular subtypes, and to determine its prognostic and/or diagnostic value. Forty human adenocarcinoma samples were selected and the expression of 36 genes grouped into 5 categories (Housekeeping genes, Stem genes, Wnt target genes, NO-metabolism related genes, and CRC subtypes classifier genes) were analyzed by using the nCounter (NanoString) technology. Of the 40 tumors, 6 were classified as Stem-like subtype, 11 as CS-TA subtype, 6 as Goblet-like subtype, 4 as Enterocyte subtype and 2 as Inflammatory subtype. Each subtype showed differential anatomical distribution throughout the colon. Regarding stage, Stem-like subtype showed a higher proportion of stage III tumors, a more advanced stage associated with poor prognosis and survival, and an increase of stem-related genes expression (such as CD44, ALDH1A1 and BMI-1). Importantly, Stem-like subtype was characterized by high expression of NO-related genes, such as ADH5, TXNRD1, NOS1 and NOS3. In the case of NOS3, all stem-like tumors expressed notably higher levels of this endothelial isoform of NO synthase than the other CRC subtypes. In conclusion, the expression analysis of a discrete number of classifier genes allows to assign tumors to different CRC subtypes. Furthermore, the NO metabolism plays a key role in the CRC pathology, confirming the relationship between NO and stem characteristics in intestinal tumors, and suggesting novel therapeutic strategies in the personalized treatment of this disease. Funded by PI13-00553.

P11. Impact of histological features of hepatocellular carcinoma on mTOR pathway. Expression after liver transplantation.

Authors: *Marta Guerrero Misas, Manuel Rodríguez-Perálvarez, Marta Guerrero-Misas, Gustavo Ferrín, Lydia Barrera, Marina Sánchez-Frías, Jose María Álamo, Rubén Ciria, Francisco Serrano, Carmen Bernal, Javier Briceño, Miguel Ángel Gómez-Bravo, Jose Luis Montero, Manuel De la Mata.*

Group: Others.

Background and Aims: We aimed to investigate whether mTOR pathway expression is influenced by histological features of hepatocellular carcinoma (HCC) in candidates for liver transplantation. Methods: Prospective study including patients with HCC who underwent liver transplantation from June 2012 to October 2015. mTOR pathway expression was evaluated in the explanted liver (tumoral and peritumoral tissue) by using the "PathScan Intracellular Signaling Array Kit" (Cell Signaling). The "QProteome FFPE Tissue Kit" (Qiagen) was used to extract proteins. The active signaling molecules (phosphorylated) were quantified in spot intensity per surface unit (I/mm2), and correlated with HCC histological features. Results: Forty-six patients were included (average age 56.9±6.1 years, 13% females). The most frequent underlying liver disease was hepatitis C (65.2%). Pretransplant locoregional therapies were used in 31 patients (67.4%). Eleven patients were beyond Milan criteria (23.9%). p-mTOR was over-expressed in peritumoral tissue as compared with tumoral tissue (1.02±0.2 I/mm2 vs 0.87±0.2 I/mm2; ΔSignal 13.8%; p<0.001). The p-mTOR activators were also increased in peritumoral tissue (p-Akt ΔSignal 13.7%, p=0.015 and p-AMPKa ΔSignal 23.5%, p<0.001), as they were the downstream effectors responsible for cell growth and survival (p-P70S6K ΔSignal 19.8%, p<0.001 and p-S6RP ΔSignal 23.3%, p<0.001). Pretransplant locoregional therapies decreased the expression of p-mTOR in tumoral tissue (p=0.007), but not in peritumoral tissue (p=0.38). Patients beyond Milan criteria showed increased p-MTOR in tumoral and peritumoral tissue (ΔSignal 14.1% in both; p=0.043 y p=0.015 respectively). The p-MTOR expression was higher in patients with multinodular HCC, both in tumoral (0.97±0.2 I/mm2 vs 0.79±0.2 I/mm2; p=0.008) and peritumoral tissue (1.15±0.2 I/mm2 vs 0.92±0.2 I/mm2; p=0.001). However p-MTOR was not influenced by the presence of microvascular invasion (tumor p=0.09; peritumor p=0.92), tumor differentiation (tumor p=0.48; peritumor p=0.99), diameter of the main nodule (tumor p=0.90; peritumor p=0.43) and total tumor volume (tumor p=0.14; peritumor p=0.16). Conclusions: mTOR pathway is over-expressed in peritumoral tissue and it is not hindered by locoregional ablative therapies. This study provides the first rationale to use mTOR inhibitors preferably in liver transplant patients with multinodular HCC, although this hypothesis deserves further validation in clinical trials.

P12. Hypofractionated radiotherapy in prostate cancer: analysis of toxicity.

Authors: *Fabiola Romero Ruperto, Fátima Ginés Santiago, Sonia García Cabezas, Amalia Palacios Eito.*

Group: GC8 Hormones and cancer.

Introduction: Conventional fractionation schemes are considered the standard in radical intent treatment to localized prostate cancer. Hypofractionated schemes have demonstrated non-inferiority against normofraccionated schemes, in terms of local control. The potential greater toxicity requires these schemes be administered with highly conformational techniques with a large gradient of doses between the treatment volume and organs at risk such as IMRT (Intensity-Modulated Radiation Therapy) and/or VMAT (Volumetric Modulated Arc Therapy). Objective: To analyze early and late toxicity in patients diagnosed with localized prostate carcinoma who received radiotherapy following a hypofractionated schedule by VMAT technique in our center. Material and methods: Between October-2013 and July-2015, 137 patients diagnosed of prostate cancer were treated with IMRT/VMAT technique. Patients of any risk group were included and treated by an hypofractionated scheme (60 Gy in 20 sessions). A retrospective analysis was performed to identify early and late toxicity using the RTOG (Radiation Therapy Oncology Group) scale, and a descriptive study of the patients treated. Results: The mean age of patients analyzed was 69±14 years (45-83). In 26% of cases patients received previously hormonal blockade. The mean PSA was 12.3 ng/ml (2.4-112). Gleason score 7 was the most frequent (43.8%), followed by 6 (41.6%). In relation to tumor stage, most corresponded to T1c (59.9%), followed by T2a (20.4%). Early genitourinary toxicity was: G0: 61%; G1: 41.6%; G2: 11.7%; and G3: 2.2%. There were not early toxicity G4. Early gastrointestinal toxicity was: G0: 64.2%; G1: 22.6% and G2: 13.2%. There were no acute toxicity G3-G4. As late toxicity: genitourinary G1-G2 was 11.8%. Three patients had gastrointestinal toxicity G2. There was no late toxicity G3-4. The median duration was 32.4 months (7.4-82.4). Biochemical failure rate was 1.5%. Two patients had distant metastases. Conclusion: This hypofractionated radiotherapy by VMAT is well tolerated, associated with aceptable early and low late toxicity.

P13. Insulin and IGF-I play a relevant role in the regulation of normal and tumoral prostate cell function.

Authors: *Fernando López-López, André Sarmento-Cabral, Manuel D. Gahete, Justo P. Castaño, Raúl M. Luque.*

Group: GC8 Hormones and cancer.

Obesity represents one of the most serious global health threats. Obesity is associated with an increase in the incidence of certain cancer types, such as prostate cancer (PC), a hormone-related, heterogeneous, and complex cancer with high incidence. Although the precise endocrine-metabolic mechanisms linking obesity and higher incidence/aggressiveness of PC are still uncertain, growth factors altered in obesity, such as insulin and IGF-1, might play a key role. Therefore, to elucidate the role of insulin and IGF-I in normal and tumoral prostate cell function, especially in the context of obesity, we employed a multifaceted approach including the generation of a mouse model of high-fat diet (HFD)-induced obesity, as well as normal mouse prostate (NP) tissues, primary NP cell cultures from mice and two human PC cell lines (PC3 and LNCaP). These studies demonstrated that obesity altered the expression (by quantitative PCR) of different components of the insulin/IGF-I regulatory axes. Specifically, expression of IGF1 binding protein-3 was elevated while GLUT4 expression was decreased in prostates of obese-mice compared with control-mice. Interestingly, although the acute effect of insulin on Akt activation was blunted in prostates of HF-fed mice, prostates of obese mice remained responsive to insulin despite peripheral (i.e. liver and fat) insulin resistance. Remarkably, acute insulin treatment affected the expression of specific genes (i.e. GH and IGF1 binding protein-3 were decreased) in prostates of obese compared with vehicle-treated controls. Furthermore, in vitro models demonstrated both insulin and IGF-1 treatment directly regulate the expression of their receptors and increased the proliferation and migration of PC cell lines, while they did not alter PSA secretion. Altogether, our data indicate that insulin and IGF-1 could play a relevant role in the regulation of prostate cell function under normal and obesity conditions, as well as on the control of malignancy features in prostate tumor cells.

P14. Engrailed-2 as a novel biomarker for prostate cancer

Authors: *Enrique Gomez Gomez, Sergio Pedraza-Arévalo, Julia Carrasco-Valiente, Daniel Hormaechea-Agulla, José Valero Rosa, Alejandro Ibañez-Costa, María del Mar Moreno, Manuel D. Gahete, J. Pablo Campos Hernández, Justo P. Castaño, María José Requena-Tapia, Raúl M. Luque.*

Group: GC8 Hormones and cancer.

Prostate-cancer (PC) is the most common malignancy in the male population however; molecular diagnostic/prognostic-markers that better define this pathology are limited and frequently found to be unspecific (i.e. PSA-levels). Therefore, it is necessary to provide new clues for novel diagnostic/prognostic/therapeutic-targets in PC. The family of homeodomain-containing transcription-factors, which determine cell/tissue identity during normal embryonic development, have been shown to be re-expressed in different tumoral cell-types. Interestingly, some studies have indicated that the engrailed variants (EN1 and EN2) might be used as a potential diagnostic-markers of early-PC; however; these few studies are conflicting/incomplete and, to date, limited information is available concerning the presence of these variants in PC-cells. Therefore, the main goals of this study were to analyse the expression levels of EN-variants in PC-tissues and cell-lines and the urinary levels of EN2-variant in patients with and without PC and, to determine the functional role of EN2-variant in PC-cells. To that end, we implemented a triple strategy by using: 1) paraffin-embedded PC-tissues obtained from radical-prostatectomies and its adjacent normal-control tissues and fresh-tissues from prostate-biopsies and cystoprostatectomies; 2) normal (RWPE-1) and androgen-dependent (LnCaP/VCaP/22Rv1) and androgen-independent (DU145/PC3) PC-cell lines and; 3) Urinary-fluids from patients with PC and control-patients. Our results revealed that EN2 was overexpressed in both paraffin-embedded and fresh PC-tissues compared to normal-controls and, in PC cell-lines (LnCaP>DU145>VCaP>PC3>22Rv1) compared with normal prostate cells (RWPE-1; no-expression was found in these cells). Treatment with, and overexpression of, EN-2 increased proliferation in RWPE1-cells and migration in PC3-cells. Notably, urine EN2 levels were higher in patient with PC compared with healthy-control patients under non-stimulated conditions; however, we found no-differences in urine EN2 levels between patients with PC vs. controls after prostate-massage. Altogether, our results demonstrate that EN2 could play an important pathophysiological role in PC-cells and that its urine-levels could be used as useful-biomarker in PC

P15. Identification of new roles for kinase DYRK2 and their implications in cancer cell signaling.

Authors: *Morrugares R, Lara-Chica M, Jiménez-Jiménez C, Muñoz E & Calzado MA.*

Group: GC4 Inflammation and cancer.

Dual-specificity tyrosine-regulated kinases (DYRKs) enclose a family of protein kinases found in 4 of the 5 main taxa which participate in several signalling pathways critical for cellular growth and homeostasis. DYRKs family is composed by 5 different proteins –DYRK1A, DYRK1B, DYRK2, DYRK3 and DYRK4-, amongst which DYRK1A stands out due to its relevance in Down syndrome. Although the function of DYRK2 has not been widely described, its role in several crucial processes such as cell cycle control in response to DNA damage by p53, c-Myc or c-Jun regulation should be emphasized. Therefore, studying new functions of this particular kinase emerges valuable in cancer cell signalling. To determine new roles of DYRK2, several of its potential substrates should be identified. To allow this, various techniques have been carried out. First of all, we performed a kinase array and obtained a number of possible candidate proteins to DYRK2 substrate. In parallel, a different approximation based on immunoprecipitation (IP), followed by the analysis of the sample by HPLC and tandem mass spectrometry (MS/MS), were performed. In this case, HEK 293T cells were transfected with a flag-tagged DYRK2 vector to facilitate protein IP. Afterwards, screening of MS results was carried out combining them with the kinase array, thus obtaining a short list of hit proteins. Among them, several molecules related to cell cycle control, splicing and intracellular transport stand out. DYRK2 interaction with some of them was validated by co-immunoprecipitation experiments. Taken together, all these results suggest that the study of DYRK2 interactome is a promising area. The knowledge of new roles for this kinase and their implications in several diseases that may depend on cell cycle deregulation, such as cancer, open a road to the development of new therapeutic strategies.

***P16*. Clinical-histological and molecular characteristics of neuroendocrine lung carcinoids.**

Authors: *Herrera-Martínez AD, Gahete MD, Sánchez-Sánchez R, Ortega-Salas R, Serrano-Blanch R, Salvatierra A, Luque RM, Gálvez MA, Castaño JP.*

Lung carcinoids (LCs) are rare tumors that comprise 1-5% of lung malignancies but represent 20-30% of neuroendocrine tumors. Unfortunately, their incidence is progressively rising and better characterization of these tumors is required. Alterations in ghrelin and somatostatin (SST)/cortistatin (CORT) systems have been associated to development/progression of various endocrine-related cancers, wherein they may serve as useful diagnostic, prognostic and treatment biomarkers. Here, we aimed to evaluate the expression levels of ghrelin and SST/CORT systems components in LCs, as well as to explore their putative relationship with histological/clinical characteristics. In this observational retrospective study, 75 LC patients with clinical/histological characteristics were included. Formalin-fixed paraffin-embedded samples from 47 individuals were processed to isolate mRNA from tumoral and adjacent non-tumoral region and the expression levels of ghrelin and SST/CORT systems components, determined by quantitative-PCR, were compared to those of 6 normal controls tissues. Patient cohort was characterized by mean age 53 ±15 years, 48% males, 71.7% with tobacco exposure; 71.4/38.6% typical/atypical tumors, 21.7% incidental tumors, 4.3% functioning tumors, 17.7% with metastasis. Ghrelin and SST/CORT system components were expressed in tumors, adjacent non-tumor tissues and normal lung tissues at variable levels. SST, sst4, sst5, GHS-R1a and GHS-R1b were overexpressed in tumor tissue compared to normal tissue ($p<0.05$). Tumor sst3 levels were higher in patients with tobacco smoke exposure ($p<0.05$). Incidental tumors overexpressed sst5, while non-functional and metastatic tumors overexpressed GHS-R1a ($p<0.05$). LCs with parenchymal localization overexpressed GHS-R1b ($p<0.05$), while those with bronchial localization or invasion tended to overexpress ghrelin ($p=0.057$). Necrotic tumors overexpressed GOAT ($p<0.05$) and vascular invasion was negatively correlated to ghrelin expression ($p<0.05$). Altogether, these data reveal a notable, widespread expression of key SST/CORT/ghrelin system components in LCs, where they display relevant associations with clinical-histological features, which could provide novel, valuable markers for the management of neuroendocrine tumor patients.

P17. Comparison of tomosynthesis plus synthesized mammography and digital mammography in a population-based screening program.

Authors: *Sara Romero Martín; Marina Álvarez Benito; José Luis Raya Povedano; María Cara García; Ana Luz Santos Romero; Margarita Pedrosa Garriguet; Cristina Amate Rivas.*

Group: Others.

Purpose: to evaluate the performance of breast tomosynthesis compared with conventional 2D mammography in terms of breast cancer detection rates and callbacks reduction in a population-based screening program. Materials and Methods: cross-sectional study including women between 50 and 69 years living in the Province of Córdoba and participating in the breast screening program between January 2015 and December 2016. Once the patient has accepted the informed consent, a conventional 2D mammography and a tomosynthesis are performed. After these tests, a synthesized 2D mammography is also obtained. Three interpretation models are carried out by the radiologists: 1) conventional 2D mammography; 2) tomosynthesis + synthesized; 3) tomosynthesis + synthesized mammography + conventional mammography. Six radiologists read independently and blindly each interpretation model. Results: 8750 examinations interpreted by using mammography alone and mammography plus tomosynthesis. Detection rates, including those for invasive and in situ cancers, were 4.0 per 1000 examinations for mammography alone and 4.68 per 1000 examinations for mammography plus tomosynthesis (17% increase; P=.001). Seven additional cancers have been detected with mammography plus tomosynthesis. Recall rates were 5.68 per 100 examinations with mammography alone and 4.60 examinations per 100 with mammography plus tomosynthesis (19% decrease; P=.001). Positive predictive values for recalled patients with cancers verified later were comparable (7.04% with mammography alone and 10.17% with mammography plus tomosynthesis). Conclusion: the use of mammography plus tomosynthesis in a population–based screening program results in a significantly higher cancer detection rate and decreased recall rate.

P18. KIR genes as a predictor of response to the anti-HER therapy in solid tumors

***Authors*:** Morales-Estévez, C; Manzanares-Martín, B; De la Haba-Rodríguez, J; González-Fernández, R; Porras-Quintela, I; Ortiz-Morales, MJ; López-González, J; Gómez-España, MA; Cano-Osuna, MT; Moreno-Vega, A; Sánchez-Mauriño; Serrano-Blanch, R; Rubio-Pérez MJ; Aranda-Aguilar, E.

***Group*:** Oncology Department, Maimonides Institute of Biomedical Research (IMIBIC), Reina Sofía Hospital, University of Córdoba, Córdoba, Spain

Background: KIRs are an important receptor in NK cells; these cells play a role in ADCC response due to monoclonal antibodies therapy. It is unknown whether the extensive polymorphism killer cell immunoglobulin-like receptors (KIRs) and/or their HLA ligands might influence the response to treatment with monoclonal antibodies (MABs).

Methods: We select in this study 39 pacients treated with MABs (anti-HER: Trastuzumab for advanced breast cancer and Cetuximab for advanced colorectal and advanced head and neck cancer). All the pacients had progressed to the MABs therapy and were grouped in two groups taking into account the TTF duration (<or=6m and >or=10m). KIR genotyping (16 polymorphisms) was performed by PCR sequence-specific primer technique and KIR-ligand typing was performed for HLA-B & -C loci by reverse PCRSSO methodology and for HLA-C alleles by direct sequencing.

Results: Subjects carrying the KIR2DS1/HLAC2C2-C1C2 showed longer TTF than non carriers (14,76 m vs 3,73 m, $p<0.001$) and KIR3DS1/HLAw4w4-w4w6 (14,93 m vs 4,6 m, $p=0.005$). No other significant differences were observed.

Conclusions: Two activator combinations of KIRs and their HLA ligands predicts longer TTF of patients treated with anti-EGFR therapy. These findings increase the overall knowledge on the role of specific variants related with anti-EGFR treatment in solid tumors responsiveness and highlight the importance of assessing gene polymorphisms related with cancer medications. These result must be confirm in future trials on going.

***P19*. Role of temperature on the pharmacokinetics of paclitaxel in intraperitoneal intraoperative administration in the surgical treatment of peritoneal carcinomatosis from ovarian cancer. Hyperthermia versus Normothermia.**

Authors: *Casado-Adam A, Muñoz-Casares F.C, Arjona-Sánchez A, Fernández Peralbo M.A, Luque de Castro M.D, Muñoz Villanueva M.C, Sánchez Hidalgo J.M, Caro Cuenca T, Ortega Salas R, Rufián Peña S.*

Groups: GC18 Translational research in surgery of solid organ transplants.

Background: The treatment of ovarian carcinomatosis with cytoreductive surgery and HIPEC (hyperthermic intraperitoneal chemotherapy) is still controversial. The effect and pharmacokinetics of drugs used are under consideration at present. Our objetive is to analyze the effect of temperature on palitaxel´s pharmacokinetics (tissue, plasma and serum concentration) in his intraperitoneal intraoperative administration. Patients and method: Randomised, single centre, simple blind, prospective clinical trial was performed between July 2012 and November 2014. 32 patients diagnosed with primary or recurrent ovarian peritoneal carcinomatosis where incluyed and underwent cytoreductive surgery and intraoperative intraperitoneal chemotherapy with paclitaxel (16 in hypertermic and 16 in normothermic conditions). In every patient, tissue, serum and plasma samples were taken before and after intraperitoneal chemotherapy to measure the concentration of paclitaxel. Also demographic, surgical and morbidity characteristics were analyzed. Results: Degree of cytoreduction achieved, peritoneal carcinomatosis index (PCI), type of peritonectomy procedure and other demographic data were similar between the two groups except BMI (body mass index) , which was higher in the normothermia group against hyperthermia (29(5) against 25(3), respectively; p=0,007). Surgical morbidity (Clavien >III), haematotoxicity and nephrotoxicity according CTCAE v4.0 were similar in both groups. Paclitaxel levels in serum and plasma immediately after administration were slightly superior in the hyperthermia group, while levels in serum, plasma and tissue 1 hour after administration were higher in the normothermia group. These differences were not statistically significant (p=0,372; p=0,856; and p=0,525; p=0,119 and p=0,252, respectively). Conclusion: Paclitaxel has proven adequate pharmacokinetics to treat peritoneal carcinomatosis of ovarian origin, reaching optimal concentrations in tissue and minimal in serum and plasma when administered in the peritoneal cavity during cytoreductive surgery. However there were no differences observed between the group treated with normothermia and the group treated with hyperthermia.

POSTER SESSION

Chronic and inflammatory diseases

P20. Work-related stress among nursing personnel in a teaching hospital.

Authors: *Silvia Portero de la Cruz, Jesús Cebrino Cruz, Manuel Vaquero Abellán.*

Group: GA2 Comprehensive care nurses - a multidisciplinary perspective.

Background: Numerous studies have explored job stressors within the healthcare professions, but there is still considerable debate regarding the factors increasing the risk of stress among nursing staff, and further research is required. Objectives: To assess the degree of work-related stress among nursing staff at a teaching hospital belonging to the Andalusia Public Health System in southern Spain, and to examine potential correlations between stress levels and social and employment-related variables. Design and Method: Observational, descriptive, cross-sectional study of a sample comprising 210 nurses and nursing assistants. An original, specific questionnaire was used to collect social and employment data, and the Nursing Stress Scale was administered to all subjects. Data were subjected to descriptive and inferential statistical tests, and multivariate analysis was applied. Results: A total of 55.24% of subjects were nurses (95%CI 48.24%-62.08%). Mean subject age was 49.21± 7.13 (95%CI 48.39-50.33). The mean work-related stress score was 44.38±12.70 points (95%CI 42.65-46.10). Stress levels did not vary significantly as a function of the subject's length of service in his/her current post ($p = 0.19$). Conclusions: Average scores were recorded for overall perceived stress. Uncertainty regarding treatments was the subscale associated with the highest level of stress among nursing staff, while the lowest stress level was reported for peer relations. Finally, social and employment variables correlating with increased work-related stress levels included non-statutory contracts and length of service in current post. Responsibility for trainee supervision was associated with a decrease in stress levels.

P21. **Ileal–ureter substitution: Contemporary indications and outcomes.**

Authors: *Enrique Gomez-Gomez, Julia Carrasco Valiente, Sachin Maldea, Marco Spilotrosa, P. J. Shaha, Juan Pablo Campos Hernandez, Jose Luis Carazo Carazo, Maria José Requena Tapia, Tamsin J. Greenwell and Jeremy L. Ockrima.*

Group: GA7 Urology and sexual medicine.

Objective. Complex ureteric stricture disease in contemporary practice is typically related to prior pelvic surgery, radiotherapy, or complicated, repeated retrograde stone surgery, although outcomes in this group have not been well studied. The aim of this study was to report medium-term outcomes with ileal–ureter substitution for complex ureteric stricture disease. Materials and methods: All patients who had undergone ureteric reconstructive surgery using small bowel over a 5 year period between 2010 and 2015 were identiEed from the theatre database and their case notes reviewed. Data were collected on aetiology of ureteric stricture, prior surgery or radiotherapy, baseline renal function and comorbidity. Postoperative complications were recorded using the Clavien– Dindo classification, and overall outcome and need for further intervention were documented. Results. Nine patients underwent ileal–ureter substitution for complex ureteric stricture disease over this period, with four having bilateral ileal interpositions. Median age was 48 years (38–62 years) with a median follow-up of 17 months (1–40 months). Simple untailored ileal segments and refluxing anastomoses were used in all cases. One case of anastomotic leak and restricture required reintervention, but all others had favourable outcomes with no stricture and no requirement for further intervention. Two patients reported recurrent cystitis following surgery but there was no deterioration in renal function in any patient, with no metabolic complications reported. Conclusion. Ileal–ureter substitution surgery is a valuable option for selected patients with complex, difficult-to-treat ureteric defects that cannot be bridged by other methods. Simple onlay techniques do not seem to affect renal or metabolic function. Avoiding the extra complexity of tailored and tunneled anastomoses may reduce the potential morbidity and reintervention rate in patients with challenging surgical fields.

P22. Integrated Analysis of MicroRNA and mRNA Expression Profiles related to Cardiovascular disease in monocytes from Systemic Lupus Erythematosus patients.

Authors: *C. Pérez-Sánchez, MA Aguirre, P. Ruiz-Limón, N. Barbarroja, Y. Jiménez-Gómez, MC Abalos, I. Arias de la Rosa, M Galindo, E. Collantes-Estévez, MJ Cuadrado, and Ch. López Pedrera.*

Group: GC5 Systemic and chronic inflammatory autoimmune diseases of the locomotor system and connective tissue.

Background: This interplay between miRNA and their mRNA might constitute an important mechanism in the regulation of the proatherothrombotic status of SLE patients.
Objetive: To investigate the contribution of deregulated miRNAs to the altered gene profile associated to cardiovascular disease in SLE.
Methods: Thirty three SLE patients and 27 healthy donors were included in the study. Gene Expression Microarray and nCounter microRNA Expression Array were performed, respectively, to analyze mRNA and miRNA expression profiles on isolated monocytes. Putative microRNA-mRNA target pairs, were identified by using the Igenuity Pathway Analysis Software (IPA). The resulting identified interactions were revalidated by RT-PCR on the whole cohort of SLE patients.
Results: Comparative analysis of the mRNA profiles showed significantly different expressions of 1222 genes in SLE monocytes in relation to healthy monocytes, of which 658 were found up-regulated and 564 were down-regulated. Functional analysis by using IPA showed that about 30% of altered genes were involved in inflammation and cardiovascular disease (CVD). Comparative analysis of the microRNA profiles showed significantly different expressions of 37 microRNAs in SLE monocytes, of which 29 were up-regulated and 8 were down-regulated. Functional IPA analysis showed that microRNAs altered were mainly related to connective tissue disorders, inflammatory response and reproductive system disease. A total of 63 genes were inversely correlated, and predicted as CVD-related target genes of 23 differentially expressed microRNAs in SLE monocytes. An interaction network of those genes and some microRNAs differentially expressed in SLE monocytes (such as miR-130a-3p, miR-149-5p) was also identified and validated, including targets related to inflammation and CVD such as PPARG, STAT-3 and CMKLR.
Conclusion: We have identified novel microRNA-mRNA regulatory networks related to CVD in SLE, thus delineating a novel genetic control of the diverse biological processes and factors related to the cardiovascular pathology present in this autoimmune condition.

***P23*. Tocilizumab might prevent cardiovascular disease in rheumatoid arthritis patients through the modulation of endothelial dysfunction, NETosis and monocyte-mediated inflammation.**

Authors: *Ruiz-Limon P, Ortega R, Arias de la Rosa I,Abalos-Aguilera MC,Perez-Sanchez C, Gimenez-Gomez Y, Peralbo-Santaella E, Font P, Ruiz-Vilches D, Ferrin G, Collantes-Estevez E, Escudero-Contreras A, Lopez Pedrera Ch, Barbarroja N.*

Group: GC5 Systemic and chronic inflammatory autoimmune diseases of the locomotor system and connective tissue.

Tocilizumab (TCZ) is an effective treatment for rheumatoid arthritis (RA). However, the changes occurred after TCZ therapy on endothelial dysfunction, monocyte activity, NETosis, and oxidative stress, principal effectors of atherosclerosis and cardiovascular disease, have not been analyzed. Whit this objective, twenty RA patients treated with subcutaneous TCZ for 6 months were evaluated. TCZ significantly restored endothelial function and decreased oxidative stress in RA leukocytes. Percentage of low density granulocytes and NETosis generation were reduced. The proinflammatory and prothrombotic status of RA monocytes were also reversed through modulation of specific intracellular pathways. All these results were recapitulated after in vitro treatment with TCZ of RA monocytes and neutrophils, and in co-cultures with endothelial cells. Plasma levels of miRNA-223, miRNA-146 and miRNA-23 were upregulated by TCZ. In conclusion, TCZ prevents CVD through the restoration of the endothelial function, oxidative stress reduction, inhibition of monocytes' prothrombotic and inflammatory profile, and abridged NETosis generation.

P24. Cannabidiol quinol derivatives for the treatment of scleroderma.

Authors: *Carmen del Rio, I. Cantarero, M. Luz Bellido, Giovanni Appendino, Maria Gómez-Cañas, Ruth Pazos, Javier Fernández-Ruiz, Marco A. Calzado and Eduardo Muñoz.*

Group: GC4 Inflammation and cancer.

Scleroderma is a group of rare diseases that involve the hardening and tightening of the skin and connective tissues. There are two major forms of scleroderma: localized scleroderma and systemic sclerosis, which affect up to 30% of the patients. Scleroderma is associated with early and transient inflammation and vascular injury, followed by progressive fibrosis affecting both the skin and multiple internal organs. Fibroblast activation is the hallmark of scleroderma, and disrupting the intracellular TGFβ signaling may provide a novel approach to controlling fibrosis. In addition, pro-inflammatory factors known to have an important role in the pathogenesis of the disease might be released or activated by immune cells. Because of its potential role in modulating inflammatory and fibrotic responses, PPARγ and CB2 receptors represent attractive targets for the development of cannabinoid-based therapies. We have previously found that resorcinyl-to-paraquinol oxidation of CBG (VCE-003) and CBD (HU-331) increases their PPARγ agonistic activities. However, both VCE-003 and HU-331 are unstable electrophilic compounds. As part of our study on the SAR of CBD we have developed a non-thiophilic and chemically stable derivative of the CBD quinol (VCE-004.3) that behaves as a dual agonist of PPARγ and CB2 receptors. VCE-004.3 inhibited TGFβ-induced Col1A2 gene transcription and collagen synthesis without interfering with SMAD2 phosphorylation. VCE-004.3 also inhibited TGFβ-mediated αSMA induction and myofibroblast differentiation and impaired wound-healing activity. We also found that VCE-004.3 inhibited TCR-induced IL-17 transcriptional activity in T cells and modulated M1/M2 macrophage differentiation. The anti-inflammatory efficacy in vivo was investigated in an inflammatory model of dermal fibrosis induced by bleomycin. VCE-004.3 reduced dermal thickness and prevented mast cell degranulation, the infiltration of inflammatory cells and downregulated the expression of several key genes associated with fibrosis and inflammation, qualifying this semi-synthetic cannabinoid as a novel compound for the management of scleroderma and, potentially, other fibrotic diseases.

P25. Diagnostic evaluation of a cohort of patients with undifferentiated arthritis.

Authors: *J. Calvo Gutierrez, R. Ortega Castro, M. Castro Villegas, P. Font Agalde, A. Escudero Contreras, E. Collantes Estevez.*

Group: GC5 Systemic and chronic inflammatory autoimmune diseases of the locomotor system and connective tissue.

Objectives: 1) To evaluate prognostics factors in patients with UA (undifferentiated arthritis) that allow us to predict evolve to defined RA. 2) Analysis of other clinical characteristics predictive of progression to RA.
Methods: Descriptive observational study of a cohort of patients who, after a first clinical evaluation are diagnosed with UA, from 2005 to 2015, presenting arthritis in one or more joints lasting less than one year of evolution and not meet ACR1987 diagnostic criteria for RA. Of the patients evaluated at that time, 200 were diagnosed with UA and subsequently followed for more than 3 years. Were analyzed baseline and diagnosis characteristics for each patient
Results: Of the 200 patients with UA, 72 were women (52.2%) with a mean age of 48.4 (17-87) years. During the 12-month follow-up, 40 (20%) evolved RA, 52 (26%) a palindromic rheumatism, 53 (26.5%) to other rheumatic disease and 52 (26%) remained as UA. Of the group of patients who evolved RA, 53.6% were women, with an average age of 51.7 (18-82) years. Introducing a form of polyarticular onset in 27 (67.5%), small and medium joints affected 22 (55%), symmetrical involvement 36 (90%). 75 % were FR+, OR = 2.49 (95% CI = 2.11 to 8.13) and 78,5% were ASPA +, while it was negative in patients with UA remained as an OR = 9.77 (95% CI 4.18 to 22.8). At 3 years of follow-up only 5.1% remained as undifferenciated forms.
Conclusions: For early diagnosis, it is essential to identify patients with UA to develop an RA. A quarter of the patients analyzed in our study diagnosed with UA, evolved RA. Patients evolved RA debuted in more than half of the cases with a predominance of polyarticular involvement and medium and small joints affected. The presence of RF and ASPA are predictors of evolution RA.

P26. Structural damage distribution at vertebral level in patients with axial spondyloarthritis.

Authors: *J. Calvo-Gutiérrez; J.L. Garrido-Castro, C. Gonzalez-Navas, M.C. Castro-Villegas, C. Lopez-Medina, R. Ortega-Castro, P. Font-Ugalde, E. Collantes-Estevez.*

Group: GC5 Systemic and chronic inflammatory autoimmune diseases of the locomotor system and connective tissue.

Objectives: To analyze vertebral distribution of structural damage in the spine of patients with ankylosing spondylitis according to the mSASSS index criteria.

Methods: 103 AS patients (69 men and 34 women, mean age 41.9 ± 11.1 years, 14.4 ± 0.4 evolution years, 90% HLAB27 positive) participated in the study. Analyzing radiographic images of the lumbar and cervical spine, individual scores of structural damage were obtained at each vertebra, obtaining the mSASSS index. In addition the metrological index UCOASMI [1] and the activity index ASDAS was measured.

Results: For each vertebra analyzed, the percentage of individuals with the vertebra affected (mSASSS>= 1) and percentage with severe structural damage (mSASSS >=2) are shown in graph. Severity ratio calculated as the ratio between these two parameters is represented in the secondary vertical scale. Average evolution time in years, structural damage (mSASSS), mobility (UCOASMI) and activity (ASDAS) categorized by gender and structural damage were also calculated.

Conclusions: This study has allowed to analyze the areas that are more often damaged in AS patients as it increases the degree of structural damage. The most affected are those belonging to the middle of the cervical and lumbar region (C5 and L4). The mSASSS index was higher in men than in women, a fact already known. The mobility according UCOASMI was decreasing as structural damage increases. The ASDAS index was similar in all groups (although statistical differences between men and women were found). Following a logical structure the vertebrae most commonly affected should have a greater presence of spinal fusion, however, according to the ratio of severity, are not the central but the extreme vertebrae which have a higher severity ratio. Especially in those vertebrae that have less mobility, bone bridges appear earlier. This can highlight the idea of the need of increased physical activity and exercise adequate flexibility in these patients to delay ankylosis.

P27. Short-term efficacy and safety of new biologic agents targeting IL-23/Th17 pathway for moderate to severe plaque psoriasis: a systematic review and network meta-analysis.

Authors: Sanz Cabanillas JL, Gómez F, Gay-Mimbrera J, Gonzalez-Padilla M, Isla-Tejera B, Velez A, D. Epstein, J. Ruano.

Group: GE3. Enfermedades Inflamatorias Cutáneas Inmunomediadas (EICI).

A new generation of biologics targeting IL-23/Th17 pathway has been developed. This study aimed to assess the short-term effectiveness and safety of these new agents using a network meta-analysis. Twenty seven randomized clinical trials (n=10,629) were identified by a comprehensive systematic literature review (PROSPERO 2015:CRD42015025472). Quality of evidence was assessed following Cochrane compliant rules. Efficacy was compared, based on rates of 75% and 90% reductions in the Psoriasis Area and Severity Index (PASI) responses at weeks 10-16, using a random-effects network meta-analysis within a Bayesian framework to estimate pooled odds ratios (OR) of direct and indirect comparisons among the therapeutic options. Infliximab 5 mg.kg-1 Q8W was ranked the most effective, followed by secukinumab 300 mg Q4W, and ustekinumab 90 mg Q12W. Infliximab had the highest Surface Under the Cumulative RAnking probability (SUCRA) for PASI 75 (92.2%) and PASI 90 (86.3%), followed by secukinumab (PASI 75: 83.1%; PASI 90: 83.9%) and ustekinumab (PASI 75: 84.1%; PASI 90: 82%). There were 6 direct drug-to-drug comparisons in the network, with a high degree of consistency between the direct and the indirect evidence. From the available evidence, infliximab, secukinumab, and ustekinumab were found to be the most efficacious short-term treatments. However, when compared with placebo, secukinumab, but not infliximab or ustekinumab presented higher risks of total adverse events (AE) and infectious AE. Future treatment recommendations should consider economic evaluation.

***P28.* Descriptive Analysis of cardiovascular risk factors in a cohort of Anglo patients with Rheumatoid arthritis.**

Authors: *Jiménez Gasco R, Estrach-Roig C, Goodson N, Escudero Contreras A, Collantes Estévez E.*

Group: GC5 Systemic and chronic inflammatory autoimmune diseases of the locomotor system and connective tissue.

Objectives: To describe CV risk profile in patients with long-standing RA in order to optimize its assessment in RA-affected patients in the annual review clinics. Methods: A descriptive study was carried out using a group of 81 anglo-saxon patients aged over 18 years that had been diagnosed with RA (ACR criteria 1987/EULAR2010) from the annual review clinic. Mean and standard deviation of quantitative variables and frequencies and percentages of qualitative variables were calculated. Mean intervals were estimated with 95% confidence. Data were collected from case notes including a period ranging from January 2015 to December 2015. Demographic variables and comorbidities were collected. Data were analyzed using SPSS v17 program. Results: Patients were mostly females (n = 54; 66. 7%) with a mean age of 66.17±12.50 years in patients with long standing disease 7. 69 ±4.88 years of evolution and mean DAS 28: 2.68 ±1.80. Out of 81 patients, 22.2 % were smokers and 30% of patients were suffering from at least one risk factor.Out of 81 patients 43.2% had hypertension, 16% DM and 37% had dyslipidemia. Five patients (6.2%) were on no treatment with DMARDs and 49 (61.5 %) were on combination therapy. The Cardiovascular risk of 78 patients was calculated using the QRISK2 calculator, which is used to work out a risk of suffering heart attack or stroke over the next 10 years. Out of 78 patients, 47 (58%) had a QRISK 2 above 15% of which 51% had hypertension, all of them being under treatment. Conclusions: There is a high CV risk in the population of patients with well-controlled RA. Recent evidence suggests that factors of CV risk must be managed in RA patients, and that identification of these risk factors is crucial as a first step aimed to reducing CV-related morbidity and mortality in RA.

P29. Microvesicles from endothelial cells and monocytes in chronic kidney failure: could help us in the diagnosis of the disease?

Authors: *A. Carmona, P. Buendía, F. Guerrero, MJ. Jiménez, S. Soriano, MA. Álvarez de Lara, A. Martín Malo, R. Ramírez, P. Aljama, J. Carracedo.*

Group: GC7 Nephrology. Cell damage in chronic inflammation.

INTRODUCTION: Cardiovascular disease has a high incidence and is the major cause of mortality in patients with chronic kidney disease (CKD). Microvesicles (MVs) are membrane vesicles produced by cells as a result of activation and/or apoptosis and are increased in CKD patients. The levels of apoptotic MVs (CD31+/ Annexin V+), proinflammatory monocytes MVs (CD14+/CD16+) and proagulant activity MVs (CD144+/TF+) may serve as markers endothelial dysfunction in those patients. OBJECTIVE: The aim of this study was to analyze if different phenotypes of MVs could be useful as a biomarkers of endothelial damage in patients with CKD. MATERIAL AND METHOD: We performed a prospective study in 16 CKD patients (stage 4-5; Phase I) and 6 months after starting hemodialysis therapy (HD; Phase II). 56.25% of patients are male. The mean age was 64 ± 3.45 years. The MVs were obtained from plasma by serial ultracentrifugation and were quantified by flow cytometry: CD31 + / Annexin V + (MV/µl), CD14 + / CD16 + (MV/µl) and CD144 + / TF + (MV/µl). RESULTS: The results are expressed as mean ± SEM. In phase II patients was observed a significant decrease in the number of CD31 + / annexinV + MVs ($p<0.001$) and CD14 + / CD16 + MVs ($p<0.001$). However, the CD144 + / TF + MVs did not decrease significantly when patients are treated with HD therapies (see table). CONCLUSION: HD treatment reduces the number of MVs from endothelial cells and inflammatory monocytes in patients with advanced CKD. The study of these MVs may offer a new tool for assessing endothelial dysfunction, inflammatory state and even adequacy of hemodialysis.

P30. Optimization strategies of biological therapy in rheumatoid arthritis (RA). CREATE registry results after two years of follow-up.

Authors: *R. Ortega Castro, J. Calvo Gutiérrez, M. C. Castro Villegas, D. Ruiz Vilchez, M. Romero Gómez, M. Cárdenas Aranzana, S. De la Fuente Ruíz, P. Carreto Font, A. Escudero Contreras, E. Collantes Estévez, P. Font Ugalde.*

Group: GC5 Systemic and chronic inflammatory autoimmune diseases of the locomotor system and connective tissue.

Introduction: The primary target for RA treatment should be a state of clinical remission. After this, there are different therapeutic approaches to consider. Optimization of Biological Therapy (BT) is a strategy, consists in a dose reduction or an extended dose interval, searching a minimum effective dose for each patient, which limits the occurrence of adverse effects and promotes economic savings

Patients and methods: RA patients (ACR criteria 1987) of CREATE registry that November 1, 2013 had clinical remission (DAS28 value <2.6) of at least 6 months constituted the cohort of patients who were optimized. According to the consensus of the Spanish Society of Rheumatology and hospital pharmacy, dose optimization involved the reduction of between 20 and 50% of it.

Results: We performed a prospective observational cohort study in 70 RA optimized patients. Optimization occurred in 41.4% of patients in the first year and 58.8% in the second year (p = 0.001). 64 patients completed 24 month of follow-up, suffering 36 (56.3%) clinical relapse (mean DAS28 2.81 (0.88)) at 1 year, reason why they return to the usual dose reaching again clinical remission after 2 years (DAS 28 2.59 (0.58).

43.8% patients maintained optimization after 2 years of follow-up without suffering relapse (mean DAS28 2.19 (0.84)).

Statistically significant differences were found when comparing the mean baseline DAS 28 between both groups, being lower in the subgroup of patients who maintains remission (1.97 (0.85) vs 2.44 (0.66)) (p = 0.012)

Conclusions:

- The use of an extended dose interval maintained remission status in patients with established RA who are in clinical remission it is possible in 41.2% patients after 2 years of follow-up in clinical practice (CREATE registry).
- This strategy is possible in patients with controlled disease persistently and, we might consider that those patients who have a lower level of activity at onset optimization, are less likely to relapse and therefore maintain this strategy.

P31. **Effects of olive oil on oxidative stress in an experimental model of multiple sclerosis.**

Authors: *M. Bahamonde, C. Conde, E. Luque, M. LaTorre, A.I. Giraldo, M. Feijóo, R. Lillo, B.M. Escribano, A. Galán, E. Agüera, I. Túnez.*

Group: GE1 Oxidative stress and nutrition.

Objective: The aim of the present work was studied the effects of administration of extra-virgin olive oil (EVOO) in a myelin oligodendrocyte glycoprotein (MOG)-induced experimental autoimmune encephalomyelitis (EAE) model, similar to reproduce human multiple sclerosis (MS). Material and Methods: Twenty male Dark Agouti rats, weighing 180-200 g and 2 months old were used in the study. The rats were divided into 4 groups of 5 as follow: i) control; ii) vehicle; iii) EAE; and iii) EAE+EVOO. Rats were injected with an emulsion containing myelin oligodendrocyte glycoprotein (MOG) supplemented with heat-inactivated Mycobactirium tuberculosis H37Ra. EVOO was administered orally using catheter, representing 10% of calorie intake (in weight terms) in the total standard daily diet of rat. EVOO was applied during 21 days, starting 14 days after inoculation with MOG. Results: Our data showed a significant decrease score as well as a reversion towards to normality in the oxidative stress biomarkers after EVOO supplementation. Conclusions: The EVOO administration shows positive and protective effects in EAE animals. However, more experimental and clinical studies in this line are required multiple sclerosis.

P32. Dietary magnesium supplementation prevents and reverses vascular and soft tissue calcifications in uremic rats.

Authors: *Noemi Vergara, Alan Peralta-Ramirez, Mariano Rodriguez, María E Rodríguez-Ortiz, Ana I Raya, Ignacio Lopez, Carmen Herencia, Addy Montes de Oca, Kristina Gundlach, Janine Büchel, Sonja Steppan, Julio M Martínez-Moreno, Juan M Diaz-Tocados, Antonio Canalejo, Arnold Felsenfeld, Yolanda Almadén, Escolástico Aguilera-Tejero, Juan R Muñoz-Castañeda.*

Group: GC13 Calcium metabolism. Vascular calcification.

Although magnesium (Mg) has already been shown to prevent vascular calcifications (VC) in vitro, controlled in vivo studies in uremic models are limited. To determine whether dietary Mg intake protects against the development of VC, 5/6 nephrectomized Wistar rats were fed with different Mg content diet (from 0.1 to 1.1%). In addition, uremic rats with established VC were fed a diet with either normal (0.1%) or moderately high (0.6%) Mg. In uremic rats an increase in dietary Mg resulted in a marked reduction in VC. A moderate change from 0.1% to 0.3% Mg in the diet was associated with a 15-fold reduction in aortic calcium (Ca) content together with an improvement in mineral metabolism parameters. The protective effect of Mg was not limited to its action as phosphate binder, Mg supplementation resulted in improvement of renal function and a significant reduction of blood pressure. In a different experiment in uremic rats that had already developed VC, the change in dietary Mg from 0.1% Mg to 0.6% reduced mortality rate from 52% to 28%, this could be explained by the observed reduction of VC. In conclusion, increasing dietary Mg reduced VC and mortality in uremic rats.

P33. Abnormalities in skeletal muscle fibers by a defective regeneration.

Authors: *Fernando Leiva-Cepas, Ignacio Ruz-Caracuel, Rubén Giovanneti-González, Ignacio Jimena, Rafael Villalba & José Peña.*

Group: GE1 Oxidative stress and nutrition.

INTRODUCTION: skeletal muscles exhibit a high capacity to regenerate after injury, but various reintegrative factors (revascularization, reinnervation and longitudinal tension) are required in order to make the process effective. We are using adipose tissue to reconstruct a volumetric loss of skeletal muscle. However,in our experimental model, regeneration takes place in a defective microenvironment due to reintegrative factors are reduced or absent. OBJECTIVE: the aim of this study was to determine the cytoarchitectural changes that may occur in the regenerative muscle fibers when they grow in a microenvironment with altered reintegrative factors. METHODS: Wistar rats were anesthetized and a piece of muscle was extracted from the belly of anterior tibial muscles using a cylindrical punch (Ø 6 x 5 mm length). After this we implanted in the muscle defect adipose tissue obtained from the inguinal space. We use as a group control, rats injured with mepivacaine. Rats were sacrificed at 7, 14, 21, 28 and 90 days postimplantation, and muscles were removed, frozen in isopenthane previously cooled in liquid nitrogen. Cryosections were stained using histological, histochemical and immunohistochemical techniques. RESULTS: the muscle reconstruction was mainly derived from the regenerative response that originates from the edges wounded. However the regenerating muscle fibers showed several cytoarchitectural changes that included: fibers with myonuclei clumps, ringer fibers, snake-coiled, central spot, split and fragmented muscle fibers. These changes did not occur in the control group. CONCLUSIONS: considering that new muscle fibers formation occurs under a lack of integration, we propose that an altered regeneration leads to an abnormal development of regenerating muscle fibers. The results indicate that some changes observed in human pathologic muscle can be explained by the alteration of muscle fiber regeneration.

P34. Computerized tomography indication in mild traumatic brain injuries.

Authors: *Manuel Vaquero Álvarez, Fco Javier Fonseca del Pozo, Joaquín Valle Alonso.*

***Group*:** Others. Unidad Gestión Clínica Linares (Jaén). Centro Salud San José.

Patients with mild traumatic brain injuries (TBI) represent 95% of all TBI, and up to 20 % with lesions on computerized tomography (CT). Overuse of CT scan is a current problem, because of the expense involved and the risks from exposure to radiation.

Objective: to guide emergency physicians to minimize the unnecessary use of CT and ensure a more accurate diagnosis in mild TBI.

Methods. Longitudinal study of 217 patients with mild TBI treated in the emergency department of a regional hospital in Andalusia, between 2011 and 2013. The affected had included: head trauma with loss of consciousness and / or amnesia and / or diffuse headache and / or vomiting; score on the Glasgow Coma Scale (GCS) of 14 or 15 points; occurred in the last 24 hours, which CT cranial is performed as part of the internal protocol. Receiver operator characteristic curves (ROC) were carried out and the area under the curve (AUC) was calculated to know which explanatory variables best predict the multivariate model. It has also developed a clinical decision tree to determine the normal degree of prediction against disease or CT.

Results. The variables used in the predictive model were: vomiting (OR 26.75, 95% CI 7.55 to 94.8), headache (OR 6.6, 95% CI 1.4 to 29.9), score 14 GCS (OR 4.7, 95% CI 1.3 to 17.1) and age ≥ 65 years (OR 3.9, 95% CI 1.5 to 10.1). According to the clinical decision tree when a patient suffers a TBI, the two variables that are associated with your pathological CT have been in this order: present two or more vomiting and age greater than or equal to 65 years.

Conclusions. When a person suffers from a mild head injury and has two or more vomiting would indicate CT scan, helping to protect our patients from the side effects of radiation.

POSTER SESSION

Infectious and immunological diseases. Organ transplantation.

P35. Survival of adult cardiac arrest in Spain: a systematic review.

Authors: Morales-Cané, Ignacio; Luque-Carrillo, Patricia; Valverde-León, María del Rocío; Rodriguez Borrego, Mª Aurora

***Group*:** GA02 Cuidados enfermeros integrales. Perspectiva multidisciplinar.

Aim. To know scientific production about out- of-hospital cardiac arrest and in-hospital cardiac arrest and to analyze the survival and prevalence of shockable rhythms. Method. Systematic review of scientific production between 2005 and 2015; we extracted numerical data about the number of reanimations practiced, initial rhythms, patients with re-turn of spontaneous circulation, witnessed cardiac arrest, reanimation previous to emergency teams and response time of emergency teams. Results. We selected 13 observational studies that met inclusion criteria and quality standards whose proportions of re-turn of spontaneous circulation after cardiopulmonary resuscitation were between 10.87% and 52.50% in out-of-hospital cardiac arrest and the proportions were between 20% and 43.45% in-hospital cardiac arrest. The survival to discharge were between 10.4% and 38%. 1867 patients had a shockable rhythms (19.03%; CI95% 17.25-19.81) which reversed 870 (46.60%; CI95% 43.28-48.86) who survived to hospital admission 529 (60.80%; CI95% 56.64-64.05). Conclusions. There is a large geographical variability of community-acquired survival due to geo-demographic factors, although in general survival cardiac arrest is low compared to countries like the US.

***P36.* HLA-B18 as risk factor of fast progression to severe liver fibrosis in HIV/HCV co-infected patients with minimal or moderate fibrosis: Implications for timing of therapy.**

Authors: *Mario Frias, Francisca Cuenca-Lopez, Diego Rodriguez-Cano, Ana Gordon, Ismael Zafra, Laura Ruiz-Torres, Angela Camacho, Antonio Rivero-Juarez, Antonio Rivero.*

Group: GC3 Infectious diseases.

Background: Treatment is currently prioritized for patients with severe stages of fibrosis (F3-F4), although patients with no or minimal fibrosis are not exempt from rapid progression. However, the risk factors of accelerated progression remain unclear. The aim of our study was to analyze the influence of HLA-B molecules on liver fibrosis progression in HIV/HCV patients. Methods: A retrospective longitudinal study included HIV/HCV patients in follow-up between 2007 and 2014. Inclusion criteria were: a) at least two determinations of Liver Stiffness Measurement (LSM); b) ≥12 months of total follow-up; c) active HCV infection. Exclusion criteria were: a) HCV treatment previous to follow-up; b) cirrhosis at baseline (LSM≥14.6kPa). Analytical, demographic and clinical variables were collected. Outcome variables were: 1) fibrosis stage progressedat least one stage; 2) fibrosis progressed up to severe liver fibrosis (F3-F4). Results: 104 patients fulfilled the criteria. HLAB-18 allele (B18pos n=15; B18neg n=89) was the only factor associated with progression of liver fibrosis [n=11 (73.3%) vs. n=34 (38.2%); p=0.011]. 69.2% B18pos patients with no or mild-to-moderate developed advanced or severe fibrosis during the follow-up period, while only 28.2% B18neg patients with stages F0-F2 progressed to F3-F4. Survival analysis compared the probability of the degree of liver fibrosis increasing among B18pos/neg patients and found differences at 1, 2, 3 and 5 years (p<0.001) and also showed a higher probability of progression to severe fibrosis in B18pos patients at 1, 2, 3 and 5 years (p<0.001). Multivariate Cox regression showed that HLAB-18 was the only independent risk factor associated with liver fibrosis progression, adjusted for other clinical variables (p<0.001;HR=6.62,95%CI[2.74-16]). Conclusions: HIV/HCV patients carrying allele HLAB18 were more likely to progress more rapidly to developing advanced and severe fibrosis (F3-F4) than HLA-B18neg patients. These results could help make decisions about the timing of HCV therapy in F0-F2 patients at risk of accelerated progression.

P37. KIR2DS2 is a strong predictor of secondary thrombocytopenia to pegylated interferon-alpha treatment: lesson from HIV/HCV co-infected patients.

Authors: *Francisca Cuenca-Lopez, Mario Frias, Diego Rodriguez-Cano, Salvador Barea, Rafael Gonzalez, Barbara Manzanares-Martin, Angela Camacho, Teresa Brieva, Laura Ruiz, Ismael Zafra, José Peña, Antonio Rivero, Antonio Rivero-Juarez.*

Group: GC3 Infectious diseases.

BACKGROUND: Thrombocytopenia is the leading cause of interferon dose reduction, early therapy discontinuation and worse clinical outcome such bleeding complications. Here, we evaluate the role of the killer immunoglobulin-like receptor (KIR) of the natural killer cells (NK) genotype in the development of secondary thrombocytopenia to Peg-IFN therapy in HIV/HCV co-infected patients. METHODS: HIV-infected patients with chronic hepatitis C bearing genotype 1, naïve to HCV treatment and receiving a first course of Peg-IFN/RBV combination therapy, were enrolled in the study. At baseline, a whole blood sample was collected for genetics determination KIR genotyping was performed using sequence-specific primers able to detect the presence of 16 different KIR genes. These KIRs associated with decline in the platelet total count was selected. Reductions in platelet count were analyzed for KIRs genotype between baseline and weeks 1, 2, 4, 8 and 12. Then, the association between the time to the development thrombocytopenia and KIRs genotype was assessed. RESULTS: Fifty-eight HIV/HCV infected patients were enrolled in the study. KIRs 2DL2, 2DL5, 2DS1, 2DS2, 2DS3, 2DS4FULL, 2DS5 and 3DS1 were included in the analysis. The absence of KIR2DS2 was strongly associated with the development of thrombocytopenia during Peg-IFN treatment (Absence of KIR2DS2: 13/24 [54.2%]; Presence of KIR2DS2: 7/34, [22.5%], p = 0.012). Those patients bearing KIR2DS2 had a bigger time to be free of thrombocytopenia than those patients without KIR2DS2 (Log-rank test = 0.008) (6.6 weeks and 10.3 weeks in those patients with absence or presence of KIR2DS2, respectively). CONCLUSIONS: The absence of the KIR2DS2 is associated with a higher decline in platelet count during HCV treatment with Peg-IFN in HIV/HCV co-infected patients. The determination of this genetic marker before starting HCV-treatment could identify those patients with a high chance to experience thrombocytopenia during first 12 weeks of therapy, and help to individualize treatment regimen.

P38. Clinical manifestations and analytical alterations associated with acute hepatitis e virus in HIV-infected patients

Authors: *Francisca Cuenca-Lopez, Antonio Rivero-Juarez, Antonio Martinez-Peinado, Angela Camacho, Ismael Zafra, Mario Frias, Salvador Barea, Diego Rodriguez Cano, Laura Ruiz-Torres, Antonio Rivero.*

Group: GC3 Infectious diseases.

BACKGROUND: The aim of this study is to evaluate clinical manifestations and analytical alterations of HEV seroconversion in HIV-infected patients. The natural history of HEV infection in HIV-infected patients has not been established and could differ from that of HEV infection reported in the general population. METHODS: A prospective longitudinal study whose study population consisted of HIV-infected patients who were seronegative for HEV antibodies at the start of the study. All patients included in the study were followed up every 3-6 months during the study period. ELISA for anti-HEV IgG and IgM was performed for all patients at every visit. In patients who developed HEV seroconversion, a data collection protocol was conducted to identify associated clinical manifestations. An analytical alteration was defined as a transitory increase or decrease in a laboratory parameter measured coincident with the time of seroconversion. RESULTS: Forty-one patients developed detectable anti-HEV antibodies. Among HEV-seroconverted patients, 32 (78.04%) presented any symptom and/or analytical alteration. 26 patients (63.4%) showed clinical manifestation, been the most frequent (and 30 patients (66.6%) developed clinical manifestations and laboratory abnormalities, respectively, during the seroconversion period. Of these patients, 15 (36.5%) experienced HIV blips at the time of HEV seroconversion. During the study, 50 total patients (7.9%) experienced HIV blips, indicating that HEV seroconversion is associated with HIV blips (36.5% vs. 7.9%; $p < 0.001$). CONCLUSION: In our study, HEV seroconversion was frequently siymtomatic and interestingly, it was also associated with HIV blips and CD4+ decline. The impact of blips on HIV infection outcomes is unknown, but they could be linked with subsequent virological failure. Consequently, the identification of HEV seroconversion as a factor associated with blips suggests that this may be an important element to consider in the clinical management of HIV-infected patients.

P39. First Isolation of Hepatitis E Virus From Breast Milk During Acute Infection.

Authors: *Francisca Cuenca-Lopez, Mario Frias, Diego Rodriguez-Cano, Ismael Zafra-Soto, Laura Ruiz-Torres, Teresa, Salvador Barea, Angela Camacho, Antonio Rivero, Antonio Martinez-Peinado, Antonio Rivero-Juarez.*

Group: GC3 Infectious diseases.

Background: A 34-year-old woman, who was a breastfeeding mother of a boy of 18 months, was diagnosed of acute HEV infection. Here, we evaluate if the Hepatitis E Virus (HEV) can be detected in breast milk during the acute phase of infection. Methods: Breast milk was collected in disposable plastic labware, centrifuged to obtain milk plasma, and tested in duplicate for HEV RNA using a made-in-house PCR assays. HEV RNA was monitored in serum and breast milk. For viral quantification, total viral RNA was isolated from 200 µL of serum and 200 µL of milk plasma using the QIAamp Mini Elute Virus Spin Kit (Qiagen, Hilden, Germany). Presence of the virus was determined by reverse transcription polymerase chain reaction using the LightCycler 480 instrument (Roche Diagnostics, France). The World Health Organization standard strain for hepatitis E virus RNA (PEI code 6329/10) was used to quantify the virus. Results: Analysis of samples collected simultaneously revealed the presence of HEV RNA in breast milk, showing a similar titer to the serum. During follow-up, milk and serum showed similar HEV RNA titers and time points for viral clearance (9 November 2015: 2130UI/ml in blood and 1930 UI/ml in milk; 30 November 2015: 670UI/ml in blood and 500UI/ml in milk; 18 December 2015: Negative in both samples, blood and milk). Conclusion: Our study constitutes the first isolation of HEV in brest milk during the acute phase of infection. These data suggest that breastfeeding could be a potential route of HEV transmission from mother to child.

***P40.* Association of HEV seroconversion and liver decompensation in cirrhotic patients.**

Authors: *Francisca Cuenca-Lopez, Antonio Martinez-Peinado, Angela Camacho, Ismael Zafra, Mario Frias, Salvador Barea, Diego Rodriguez Cano, Laura Ruiz-Torres, Antonio Rivero, Antonio Rivero-Juarez.*

Group: GC3 Infectious diseases.

BACKGROUND: HEV infection in HIV-infected patients with an active hepatotropic viral co-infection, such hepatitis C or B could trigger an acceleration towards liver cirrhosis and end-stage liver disease. In this study we are going to evaluate the clinical impact of HEV seroconversion in HIV-infected and cirrhotic patients. METHODS: A prospective longitudinal study, whose study population consisted of HIV-infected cirrhotic patients who were seronegative for HEV antibodies at the start of the study. All patients included in the study were followed up every 3-6 months during the study period. ELISA for anti-HEV IgG and IgM was performed for all patients at every visit. Liver decompentation was defined as hepatocelular carcinoma (HCC), portal hypertensive gastrointestinal bleeding (PHGB), ascites, hepatorrenal syndrome (HRS), spontaneous bacterial peritonitis (SBP), and hepatic encephalopathy (HE), were diagnosed according to criteria stated elsewhere. This collected data was combined starting with the last seronegative visit and ending with the seroconversion visit. RESULTS: 83 patients had liver cirrhosis at the time of inclusion. Of these patients, 60 (72.2%) presented with an active, chronic HCV infection, 18 (21.6%) with a successfully treated chronic HCV infection, and 5 (6.2%) with an active HBV infection. Eight cirrhotic patients (9.6%) experienced HEV seroconversion during the study. During the follow-up, four cirrhotic patients (4.8%) suffered a cirrhotic decompensation (3 ascites and 1 PHGB). All four liver decompensations occurred in patients with active chronic HCV (n = 3) or HBV (n =1) hepatitis. The presence of liver decompensation was more common in patients who experienced HEV seroconversion (2/8; 25%) than in those who did not (2/75; 2.6%) (p = 0.023). CONCLUSION: HEV seroconversion in cirrhotic patients was associated with liver decompensation. Due to this clinical impact in a high-sensitivity group, preventive measures against risk factors associated with transmission must be considered.

P41. Incidence of acute hepatitis e virus in HIV-infected patients and associated risk factors.

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Group: GC3 Infectious diseases.

Background: Hepatitis E virus (HEV) incidence is not yet properly documented in developed countries. The outcome variable was HEV seroconversion, defined as the development of detectable anti-HEV antibodies (IgG and/or IgM) and the risk factors for infection. Methods: A prospective longitudinal study, whose study population consisted of HIV-infected patients who were seronegative for HEV antibodies at the start of the study. All patients included in the study were followed up every 3-6 months during the study period. ELISA for anti-HEV IgG and IgM was performed for all patients at every visit. The accumulated incidence, incidence rate of HEV and bivariate analysis comparing the accumulated incidence between groups was carried out to identify variables related to HEV seroconversion, were calculated. Results: 698 patients who tested negative for anti-HEV IgG and IgM constituted the initial study population; 627 (89.9%) accepted to participate in the study and constituted the final study population. The median follow-up (IQR) time was 11.96 months (8.52-14.52), with a median (max-min) number of anti-HEV antibodies per patient of 3 (4-2). During the study period, 41 patients developed detectable anti-HEV antibodies (accumulate incidence: 6.5%). Of these, thirty-six (87.8%) and five (12.2%) tested positive for anti-HEV IgG and IgM, respectively. None tested positive for both IgG and IgM antibodies. The incidence rate was 7.2 cases per every 100 patients/year (95% CI: 5.04-9.16 cases per every 100 patients/year). The incidence rate of HEV seroconversion among patients living in rural areas was 17.4 cases per every 100 patients/year, while the incidence rate in patients living in urban areas was 5.8 cases per every 100 patients/year (log rank tests: $p < 0.001$). Conclusion: We found a relatively high incidence rate for HEV seroconversion in HIV-infected patients (7.2 HEV seroconversions for every 100 patients/year). The rural habitat was the main risk factor for infection

P42. Prevalence of Hepatitis E virus infection in pigs and its potential role as route of transmission to human: Results of the HepEpork Study.

Authors: *Francisca Cuenca-Lopez, María de los Angeles Risalde, Vicente Fernandez, Mario Frias, Diego Rodriguez-Cano, Juan Luis Millan, Ignacio García-Bocanegra, Isamel Zafra-Soto, Laura Ruiz-Torres, Salvador Baena, Antonio Rivero, Jose Carlos Gómez-Villamandos, Antonio Rivero-Juarez.*

Group: GC3 Infectious diseases.

Background: Hepatitis E virus (HEV) is the leading cause of acute viral hepatitis in Europe. Pigs could compose the principal animal reservoir of the HEV, supposing the main route of transmission to humans. Here, we evaluate the prevalence of HEV infection in pigs as potential source of transmission of this zoonotic disease. Methods: Prospective transversal study including pigs farming in Córdoba. A sampling of farms was performed by the Consejería de Agricultura, Pesca y Ganadería of the Junta de Andalucía in Cordoba. Both intensive and extensive farming farms were included. In each farm, 40 animals were randomly selected to be tested for HEV infection in serum. HEV infection was defined as the presence of RNA-HEV in serum samples tested by made-in-house RT-PCR. Descriptive analysis was performed. Results: Twenty-six farms were included. Of this, 9 (34.6%) were extensive farming and 17 intensive farming (65.4%). A total of 1037 animals constituted the study population. The overall prevalence in pigs was 16.2% (n = 168). Of the 26 farms included, 20 showed at least one animal infected, supposing a farm prevalence of 76.9%. Conclusions: Our data shows a high prevalence of HEV infection in pigs, point that support the fact that contact with or consumption of pork could suppose the main route of HEV transmission to human.

P43. Prospective study of allograft outcome in single-kidney transplanted patients with preformed non-C1q-binding donor-specific antibodies

Authors: A. Navas[1-3], J. Molina[1-3], M.L. Agüera[2-3], A. Rodriguez-Benot[2-3], P. Aljama[2-3], R. Solana[1-3]

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Introduction: Evolution of anti-HLA antibody detection tests towards more sensitive ones has improved the determination of unacceptable mismatches of patients in waiting lists. However, this higher sensitivity has raised the calculated panel reactive antibody (cPRA) of sensitized patients, decreasing their transplantation possibilities. In an effort to reduce immunological restrictions, the gold standard single antigen bead (SAB) assay has been modify to detect only those antibodies capable of binding the human C1q complement component. Nevertheless, allograft outcome of transplanted patients with preformed non-C1q-binding donor-specific antibodies (DSA) is still unclear.
Material and Methods: In this study we prospectively analyzed the impact of preformed non-C1q-binding DSA on early allograft function of fourteen single-kidney transplanted patients at Reina Sofia University Hospital (Cordoba, Spain). Comparisons were performed using a control group without preformed DSA.
Results: Our results show that the mean serum creatinine value of the study group in the first, sixth and twelfth month after transplantation was not significantly different of that of the control group ($p>0.05$). Three patients in the study group were diagnosed of T-cell-mediated rejection and two of antibody-mediated rejection, one of them with chronic-active features, whose allograft finally failed. C4d staining was diffused in all cases. The remaining population currently preserve a stable allograft function.
Conclusion: Despite the more frequent rejection events in non-C1q-binding DSA patients, they did not have a different early allograft outcome than patients without DSA. Identification of unacceptable mismatches according to SAB-C1q assay can increase the transplantation possibilities in highly sensitized patients, shortening their waiting time.

P44. The C1q-binding ability of preformed donor-specific antibodies predicts the risk of kidney allograft failure.

Authors: J. Molina[1-3], A. Navas[1-3], M.L. Agüera[2-3], A. Rodriguez-Benot[2-3], P. Aljama[2-3], R. Solana[1-3]

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Introduction: Preformed donor-specific anti-HLA antibodies (DSA) are associated with poorer allograft outcome. Even though the development of single antigen bead (SAB) assay as antibody detection test has increase transplantation succeed, it also has limited the highly sensitized patients' allograft allocation possibilities. Considering the classical complement cascade as the major antibody-mediated harm pathway, a new test to detect only C1q-binding antibodies, was developed. Thus, hypothetically, preformed C1q-binding DSA would more dangerous for allograft outcome.

Material and Methods: We retrospectively analyzed the risk of allograft failure according to the preformed DSA C1q-binding ability, examining the impact of anti-HLA antibodies on allograft outcome of 345 single-kidney transplanted patients between 1995 and 2006 at Reina Sofia University Hospital (Cordoba, Spain).

Results: We found that risk of allograft failure was significantly higher in patients with preformed C1q-binding DSA than in patients without preformed DSA (HR 2.897, CI 95% 1.603-5.235; p<0.001) and with preformed non-C1q-binding DSA (HR 2.235, CI 95% 1.063-4.700; p=0.035). Patients with preformed C1q-binding DSA also had a significantly poorer allograft survival than the remaining population (p<0.001). Interestingly, allograft survival in patients with preformed non-C1q-binding DSA was not different than in patients without preformed DSA (p=0.340), although the firsts showed an increased risk of early antibody-mediated rejection (OR 4.594 CI 95% 1.74-12.10; p=0.002).

Conclusions: Only preformed C1q-binding DSA represent a total contraindication prior to transplantation. Transplantation with preformed non-C1q-binding DSA might be performed successfully. Determining unacceptable mismatches by SAB-C1q assay would increase the likelihood of finding a suitable donor, particularly in highly sensitized patients.

P45. Impact of the implementation of the Spanish National Hepatitis C strategy on HIV co-infected patients in southern Spain: Results of the HERACLES cohort.

Authors: *Cuenca-López F, López-Cortés LF, Castaño M, Merino D, Pineda JA , Rivero A, Ríos Villegas MJ, Márquez M, Vergara A, López-Ruz MA, Collado A, Téllez F, Gómez-Vidal A, Pérez Xpstachowski X, Hernández-Quero J, Girón JA, Fernández-Fuertes E, Delgado C, Almodovar MC, Rivero-Juarez A.*

Group: GC3 Infectious diseases.

Background: In April 2015, theSpanish National Health Systemdeveloped a national strategic plan for the diagnosis,treatment andmanagementof hepatitis C (HCV). We analyze the impact of this on HIV-infected patients included in the HERACLES cohort during the first 6 months of its implementation. Methods:TheHERACLES cohort (NCT02511496) wasset up in March 2015 to evaluate the status and follow-up of chronic HCV infection in patients co-infected with HIV inthe south of Spain. The included population had active chronic HCV infection. In September 2015, the data was analyzed to identify clinical events (death, liver decompensation and liver fibrosis progression) and rate of treatment implementation in thispopulation. Results: The study population compriseda total of 3,474 HIV/HCV co-infected patients. Distribution according to liver fibrosis stage was: 1,152 F0-F1 (33.2%); 513 F2 (14.4%); 641 F3 (18.2%); 761 F4 (21.9%); and 407 with no liver fibrosis(12.3%). During follow-up, 248 patients progressedby at least one fibrosisstage (7.1%; 95% CI: 6.3%-8%).Among cirrhotic patients,52 (6.8%; 95% CI: 5.2%-8.9%) developed hepatic decompensation.In the overall population,50 patients died (1.4%; 95% CI: 1.1%-1.9%). Eight hundred and nineteen patients (23.56%) initiated IFN-free treatment during follow-up. The 38.5%of them were cirrhotic. Conclusion: In our study, during 6 months of follow-up,the 23.56% of HIV/HCV co-infected patients included in our cohort received HCV treatment. However, we observed a high incidence of negativeshort-termoutcomes in our population

POSTER SESSION

Nutrition, endocrine and metabolic diseases.

***P46.* Glucose metabolism control is associated with the presence of carotid atherosclerosis in patients with coronary heart disease. (CORDIOPREV-DIAB study).**

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Group: GC9 Nutrigenomics and Metabolic Syndrome.

Objective: Patients with coexisting coronary heart disease (CHD) and type 2 diabetes mellitus (T2DM) are at high risk cardiovascular recurrence, although it is not well established whether they exhibit an increased intima-media thickness of both common carotid arteries (IMT-CC). Furthermore, if this relationship is inherent to T2DM or depends of glycemic control has not been tested in large cohorts. Our aim was to determine whether clinical categories related of glucose metabolism control were associated to IMT-CC in CHD patients. Methods: 904 patients from CORDIOPREV study (NCT00924937), aged 20-75 years, were classified according to the following clinical categories, depending on the control of glucose metabolism: normal glucose tolerance (NGT), impaired fasting glucose (IFG), impaired glucose tolerance (IGT), controlled T2DM (HbA1c < 6.5%) or uncontrolled T2DM (HbA1c > 6.5%). IMT-C measurement was determined by carotid ultrasound. Results: IMT-CC was higher in T2DM patients with HbA1c > 6.5% compared to T2DM patients with HbA1c < 6.5% ($p = 0.001$), patients with IFG or IGT ($p = 3.11*10-4$) and NGT ($p = 3.31*10-8$). When age is considered, IMT-CC was influenced by glucose metabolism control only in those patients with age < 61 years ($p < 0.05$), while patients aged ≥ 61 years showed no differences in IMT-CC. Conclusions: Our results highlight the importance of properly controlling glucose metabolism in CHD patients, and in particular in younger populations, providing an easy way of categorizing patients with an increased IMT-CC. Moreover, these findings could be an important step for prevention of cardiovascular recurrences, increasing the use of these efficient techniques in practice care vascular health.

P47. Mediterranean diet supplemented with coenzyme Q10 reduces the postprandial levels of advanced glycation end products in elderly men and women.

Authors: *Javier Lopez-Moreno, Gracia M Quintana-Navarro, Antonio Garcia-Rios, Nieves Delgado-Casado, Carmen Marin, Jose D Torres-Peña, José López-Miranda, Elena M Yubero-Serrano.*

Group: GC9 Nutrigenomics and Metabolic Syndrome.

Objective: Advanced glycation end products (AGEs) and elevated oxidative stress (OS) increase with aging and dysmetabolic conditions. Since a Mediterranean diet reduces OS, serum AGEs (sAGEs) levels and expression of genes related to AGEs metabolism in healthy elderly people, we asked whether supplementation with coenzyme Q10 (CoQ) was of further benefit. Methods: 20 participants aged ≥ 65 (10 men and 10 women) were randomly assigned to each of three isocaloric diets for successive periods of 4 weeks in a cross-over design: Mediterranean diet + CoQ (Med+CoQ), Mediterranean diet (Med diet) and a Western high saturated fat diet (SFA diet). After a 12-hour fast, volunteers consumed a breakfast with a fat composition similar to the previous diet period. Analyses included dietary AGEs consumed, serum AGEs (sMG and sCML) and AGER1, RAGE, Gloxl and ERa mRNA levels. Results: Med diet reduced oxidant AGEs levels (sMG and sCML) and increased anti-oxidant defenses (AGER1 and Gloxl mRNA levels) compared to the SFA diet. This benefit was accentuated by adding CoQ, in particular, in the postprandial state. Conclusions: Supplementation of a Med diet with CoQ reduced sAGEs and OS in the postprandial state. Since elevated oxidative stress/inflammation and AGEs are associated with clinical disease in aging, the enhanced protection of a Med diet supplemented with CoQ should be assessed in a larger clinical trial in which clinical conditions in aging are measured.

P48. Circulating miRNAs as tools for early detection of T2DM in patients with cardiovascular disease: study CORDIOPREV.

Authors: *Jiménez-Lucena, R.; Rangel-Zúñiga, OA.; López-Moreno, J.; Jiménez, A.; Zarzuelo, MJ.; Blanco-Rojo, R.; Marín, C.; López-Miranda, J.*

Group: GC9 Nutrigenomics and Metabolic Syndrome.

Objective: To study the clinical relevance of plasma circulating miRNAs as potential biomarkers to the prediction of type 2 diabetes mellitus (T2DM) development. Methods: A sub group of 140 participants in the CORDIOPREV study were selected: 70 cases that developed type 2 diabetes mellitus after two years of baseline and 70 cases which do not developed the pathology (control group). Twenty-eight plasma miRNAs were studied by real-time RT-PCR using the OpenArray platform. After a pathway analysis were selected two target genes of the miRNAs studied and involved in the T2DM development. In turn, it was performed a Receiver Operating Characteristic (ROC) analysis to determine the precision with which the expression of miRNAs could discriminate between people who developed T2DM and people without the disease. Results: The expression levels of miRNAs and genes were compared in the two groups in the baseline time. Five miRNAs (hsamiR107, hsamiR103, hsamiR223, hsamiR28-3p and hsamiR29a) shows significant correlation with glycosylated haemoglobin, disposition index, and insulinogenic index (indexes of β-cell functionality). The expression levels of these miRNAs were lower in patients who developed diabetes than controls and the canonical pathway analysis shows that miRNAs modulate target-genes (INSR and BCL2) involved in PI3K-AKT, p53, mTOR, and HIF-1 pathways. Finally, after the ROC analysis, both hsa-miR-29a and hsa-miR-223 showed an area under de curve (AUC) of 0.854. Conclusion: Changes in the expression profiles of hsa-miR-103, hsa-miR-29a, hsa-miR-28-3p, and hsa-miR-223 could be related with a molecular compensatory system at early stages of T2DM pathogenesis. Likewise, the expression levels on these four miRNAs would represent a set of biomarkers to early diagnosis of T2DM.

P49. The cannabinoid quinol VCE-004.8 inhibits adipogenesis by targeting ERK 1+2 activation and modulates diet-induced obesity.

Authors: *Belen Palomares, Inmaculada Velasco, Carmen del Río, Irene Cantarero, Miguel Angel Sánchez Garrido, Maria L. Bellido, Marco A Calzado, Manuel Tena-Sempere and Eduardo Muñoz.*

Group: GC4 Inflammation and cancer.

Obesity is a growing pandemic and a major contributor to metabolic syndrome and disorders such as type-2 diabetes, cardiovascular disease, dyslipidemia, non-alcohol fatty liver and some cancers. In the past few years it has become evident that the endocannabinoid system (ECs) plays a crucial role in regulating food intake and energy metabolism. Moreover the ECs also regulate different arms of the immune system and the inflammatory process, which is closely linked to obesity and insulin resistance. Therefore, the pharmacological manipulation of the ECs is a major goal for researchers and pharmaceutical companies. Herein, we have investigated the effect of VCE-004.8, a dual agonist of PPARγ/CB2 receptors, in different in vitro models of adipogenesis and in a murine model of metabolic syndrome induced by high fat diet (HFD). Using MEFs, human pre-adipocytes and human MSCs, we found that VCE-004.8 inhibited both ERK 1+2 phosphorylation and adipogenic differentiation measured by quantification of lipid droplets accumulation and determination of adipogenic markers by qPCR. Adult male mice, fed for >8-wks with either HFD or the corresponding low fat, control diet (CD), were used for in vivo validation. Daily intraperitoneal administration of VCE-004.8 (20 mg/kg) for 3-wks induced a significant reduction in food intake and body weight gain, in both HFD and CD mice, with a ~10% drop of BW at the end of the treatment, irrespective of the diet. VCE-004.8 significantly ameliorated also glucose tolerance in both HFD and CD animals reflecting a better response to insulin. Moreover, VCE-004.8 reduced the plasmatic levels of leptin and the expression of phosphorylated ERK 1+2 induced by HFD in the adipose tissue. In conclusion, our studies document the potent biological actions of VCE-004.8 in adipogenesis by inhibiting ERK 1+2 activation and highlight its potential to ameliorate inflammation associated to obesity by targeting also PPARγ and CB2 receptors.

P50. The Calcium-Sensing Receptor modulator AMG641 inhibits PTH releasing but increases bone turnover in uremic rats.

Authors: *Díaz-Tocados JM, Lopez I, Rodríguez-Ortiz ME, Herencia C, Martínez-Moreno JM, Montes de Oca A, Vergara N, Carvalho CG, Frazão JM, Almadén Y, Rodríguez M, Muñoz-Castañeda JR.*

Group: GC13 Calcium metabolism. Vascular calcification.

The actions of extracellular calcium are mediated through the Calcium-sensing Receptor (CaSR). Renal disease patients that develop secondary hyperparathyroidism are treated with calcimimetics, which bind the CaSR in the parathyroid glands and increase its sensibility to calcium decreasing the parathyroid hormone (PTH) secretion. However, the CaSR is expressed in a wide variety of organs, as kidney, gut or bone. In our study we researched whether the calcimimetic AMG641 induces any action on bone independently of its function on parathyroid glands. Uremia was induced in rats by 5/6 nephrectomy (5/6Nx) and animals fed a phosphate 0.9%, calcium 0.6% diet and were divided in two groups, receiving AMG641 or vehicle intraperitoneally. As a decrease in PTH levels was expected, two additional groups of 5/6Nx rats underwent total parathyrodectomy and received constant infusion of PTH (5/6Nx+PTx+PTH), fed the same diet and were treated with AMG641 or vehicle. Sham animals were also included. Bone mineralization was studied by double-calcein labeling. After 3 weeks, 24-hours urine was collected, animals were euthanized and blood samples and organs collected. AMG641 decreased PTH levels and reduced plasma calcium in 5/6Nx rats, however osteoclast activity and osteoblast number remained similar in both groups, and osteoid surface increased in Nx5/6+AMG641 as compared with Nx5/6+Vehicle. Interestingly, in 5/6Nx+PTx+PTH rats, AMG641 administration increased bone turnover as compared with vehicle. Mineralization was similar in both Nx+PTx+PTH groups and bone formation was slightly higher in Nx+PTx+PTH+AMG641 rats, however neither Nx5/6 nor Nx5/6+PTx+PTH improved net bone volume with the CaSR activation by AMG641. In conclusion, calcimimetic AMG641 increases bone turnover in uremic rats even decreasing PTH levels, and reduced serum calcium independently of the osteoclast activity, suggesting an extraosseous effects. This side effect of CaSR activation might be a mechanism to preserve bone calcium store.

***P51.* A lipidomic approach to study adipose tissue from obese and insulin resistant patients.**

Authors: *Fernández-Vega, A. Sánchez-Ceinos, J. Guzmán-Ruiz, R. García Navarro, S. Calderón-Santiago, M. López-Bascón, A. Priego Capote, F. López-Miranda, J. Vázquez-Martínez, R. y Malagón, M.M.*

Group: GC11 Metabolism and adipocyte differentiation. Metabolic syndrome.

Adipose tissue is a dynamic organ that plays a key role in the regulation of lipid homeostasis. Stored lipids are used as energy reservoirs for utilization in other tissues during periods of energy demands, though they can also serve as substrates for the synthesis of both structural (phospholipids) and signaling lipids (eicosanoids, prostaglandins, phosphoinositol, etc). Obesity is characterized by excess lipid accumulation in adipose tissue, which is commonly associated with insulin resistance. Notably, differences exist between subcutaneous (SC) and omental (OM) fat in both their lipid-storage capacity and their contribution to metabolic disease. Herein, we aimed at establishing the lipid signature of adipose tissue in obesity-associated metabolic disease in order to better understand the pathophysiology of obesity and its metabolic complications. To this end, comparative lipidomics of paired samples of SC and OM adipose tissue of obese patients with distinct degrees of insulin sensitivity [normoglycemic (NG), insulin-resistant (IR) or with type 2 diabetes (T2D)] was carried out by LC/QTOF mass spectrometry. This approach enabled the identification of different forms of phospholipids, phosphoglycerides, sphingolipids, fatty acids and tri-, di- and monoglycerides both in OM and SC. Statistical evaluation using the principal component method showed a clear discrimination of samples depending on adipose tissue localization and insulin levels, suggesting that the observed changes in lipid patterns are mainly due to the variables analyzed. Phospholipids and phosphoglycerides underwent the most profound changes depending on insulin sensitivity, especially in OM fat. In particular, multiple comparisons revealed changes in the composition of lysophospholipids among obese patients, supporting a role for these compounds in insulin resistance. Altogether, these results show that changes in adipose tissue lipidome may be related to the development of metabolic disease.

***P52*. Two-dimensional liquid chromatography coupled to tandem mass spectrometry for vitamin D metabolite profiling including the C3-epimer-25-monohydroxyvitamin D3.**

Authors: *A. Mena-Bravo, F. Priego-Capote, M. D. Luque de Castro.*

Group: GC21 Metabolomics Identification/Quantification of Bioactive Components.

The growing interest in the clinical effects of vitamin D and its metabolites has also increased the development of new methods for their determination. In addition to the well known role of vitamin D to maintain calcium homeostasis and prevent rickets and osteomalacia, other diseases such as pathogenesis of autoimmune diseases, cardiovascular disorders, infectious diseases, even inhibition of progression of breast, colon or pancreas cancer have been related to abnormal concentrations or ratios of vitamin D metabolites in humans. Recent studies have also shown the presence of the C3-epimer form of 25(OH)D3 in human serum, thus revealing that vitamin D can be metabolized through a parallel pathway, despite the enzyme responsible for 3-epimerization has not been identified. For these reasons, a method based on automated on-line solid phase extraction coupled to two-dimensional liquid chromatography with tandem mass spectrometry detection (SPE–2DLC–MS/MS) was developed for absolute quantitative profiling of vitamin D metabolites in human serum. Two-dimensional LC was configured with two complementary analytical columns, pentafluorophenyl (PFP) and C18 phases, for determination of 25 hydroxyvitamin D3 epimers and the rest of bioactive metabolites of vitamin D (D3 and D2) —25-hydroxyvitamin D2, 1,25-dihydroxyvitamin D3, 1,25-dihydroxyvitamin D2 and 24,25-dihydroxyvitamin D3. Quantitative determination was supported on the use of a stable isotopic labelled internal standard for each analyte and the resulting method was validated by analysis of a standard reference material certified by the National Institute of Standards & Technology (NIST-972a) and 5 samples provided by the vitamin D External Quality Assurance Scheme (DEQAS). The limits of detection were between 9–90 pg/mL for the eight analytes, and precision, expressed as relative standard deviation, was lower than 11.6%. Two-dimensional LC has shown to be the key to discriminate between 25 hydroxyvitamin D3 epimers in a quantitative analysis also involving dihydroxyvitamin D metabolites.

P53. How would be to feel cardiac patient? Psychosocial determinants of well-being in cardiovascular disease. A pilot study.

Authors: *Tamara Gutiérrez-Domingo, Carmen Tabernero, Esther Cuadrado, Rosario Castillo-Mayén, Bárbara Luque-Salas & Alicia Arenas-Moreno*

Group: Others.

Introduction: Cardiovascular disease is the most prevalent chronic disease in the developed societies and the leading cause of death. Scientific evidence indicates that psychosocial determinants contribute to the development of cardiac disease; therefore the aims of this study are to complement the analysis of the impact of self-efficacy and other psychosocial and motivational variables in promoting the health of patients with cardiovascular disease from a cognitive-social approach. This study has been incorporated into the protocol of a project of the University Hospital Reina Sofia of Córdoba, which guarantee the access to the sample and biomedical data. Method: The sample consisted of 170 participants, students from the University of Cordoba, who completed an online questionnaire. The survey assessed the influence of dispositional variables (positivity), motivational variables (cardiac self-efficacy, anxiety regulation strategies and regulatory negative affect self-efficacy) and psychosocial variables (social support), on both Mediterranean diet adherence self-efficacy and life satisfaction. The same predictive model was proposed for both the hypotheses of adherence to the Mediterranean diet self-efficacy and life satisfaction. Results: The results of the Structural Equation Modeling (SEM) allowed us to determine the weight and interaction of the main motivational variables on both self-efficacies on the Mediterranean diet and on life satisfaction of patients with cardiovascular disease. When running, the predictive model –that explained 31% of the variance for life satisfaction and 27% for Mediterranean diet adherence self-efficacy- with AMOS, the fit indices were excellent. Conclusions: The results point to the need for promoting positivity, self-regulation of emotional control, strategies for regulating anxiety, cardiac self-efficacy and social support in the intervention program with patients with cardiovascular disease in order to increase their adherence to the Mediterranean diet and well-being.

P54. Ionized Serum Calcium Modulates the iFGF23/cFGF23 Ratio.

Authors: *Cristian Rodelo-Haad, Maria Encarnación Rodriguez-Ortiz, Mariano Rodriguez, Maria Luisa Agüera-Morales, Alejandro Martin-Malo, Pedro Aljama.*

Group: GC7 Nephrology. Cell damage in chronic inflammation.

Introduction: Patients in dialysis show extremely high serum levels of Fibroblast Growth Factor-23 (FGF23). Two fractions are recognized: intact (iFGF23), biologically active, and C-terminal (cFGF23). Its simultaneous measurement not only may help evaluate its production but also its cleavage. However, the factors that may modulate and favor one fraction over another need to be elucidated. Objective: to evaluate the factors that may modulate the production and cleavage of iFGF23 and cFGF23 in patients undergoing hemodialysis. Methods and Materials: In a cross-sectional study in hemodialysis patients, we analyzed the factors associated with increased serum iFGF23 and cFGF23. We also determined pre-dialysis ionized Calcium (Ca2+), phosphate (P), Vitamin D and intact parathyroid hormone (iPTH) levels and correlated them with both FGF23 fractions. We analyzed the factors that may modulate the ratio iFGF23/cFGF23. A linear regression model was performed to evaluate which parameters could independently affect the iFGF23/cFGF23 ratio. Resultados: 140 patients undergoing hemodialysis were included. Median iFGF23 serum levels was 462 pg/ml (IQR 152 to 1023) and 912 RU/ml (IQR, 489 to 1623) for cFGF23. We divided the population according to the iFGF23 and cFGF23 median values. We found that serum P levels were associated with higher levels of either iFGF23 or cFGF23 (4.760.77 vs 4.141.02, p=<0.001 for iFGF23 and 4.591.13 vs 4.050.87, p=<0.001 for cFGF23). Furthermore, P showed a positive correlation with both FGF23 fractions (r=0.302, p<0.001 and r=0.307, p=0.001 for iFGF23 and cFGF23 respectively). Ca2+ showed an inverse correlation with cFGF23 (r=-0.230, p=0.012). The iFGF23/cFGF23 ratio correlated with Ca2+ (r=0.200, p= 0.035) although, the correlation of such ratio and P was not significant (r=0.008, p=0.449). Multivariate linear regression model showed that Ca2+ determines independently the iFGF23/cFGF23 ratio (OR 10.37, p=0.022, 95% IC 1.59–19.15). Conclusions: serum Ca2+ promotes a higher iFGF23 fraction whereas it is negatively related to cFGF23.

P55. Dysregulation of the splicing machinery components in the liver of obese mice: influence of metformin.

Authors: *Emilia M. Alors-Pérez, Mercedes del Río-Moreno, André Sarmento-Cabral, Fernando López-López, Sergio Pedraza-Arévalo, Manuel D. Gahete, José López-Mirand, Justo P. Castaño1, Raúl M. Luque.*

Group: GC8 Hormones and cancer.

Obesity, a multifactorial chronic endocrine-metabolic disease, represents one of the most serious/complex global health-threats which is often associated with multiple comorbidities (e.g. diabetes type-2). Obesity, as a source of severe metabolic-dysregulation, alters physiologically homeostasis gene expression-patters in multiple metabolic-tissues (e.g. liver). However, the precise molecular mechanisms underlying this complex association are still unknown. There is emerging evidence that alternative mRNA splicing, the key mechanism providing transcript/protein-diversity, is dysregulated in many tissues under adverse metabolic-conditions, such as obesity. We hypothesized that an alteration in the splicing-machinery could occur in key metabolic-tissues such as the liver during obesity, which might ultimately be associated with the progression of hepatic problems. To address this question, an array of selected components of the major- (n=12) and minor-spliceosome (n=4), and associated splicing-factors (n=28) was developed, and their expression levels were evaluated using a Fluidigm methodology, in the liver of obese compared with control-lean mice. Additionally, we analysed whether the splicing-processes are regulated by metformin (an agent used to treat type-2-diabetes) in livers of obese vs. control-lean mice. Results revealed that expression of some splicing factors was altered in the liver of obese vs. control-lean mice (e.g. up-regulation: RNU1, RNU2, RBM22, SRSF3; down-regulation: RNU11). Interestingly, we found that metformin similarly altered the hepatic expression of two splicing-machinery factors (i.e. up-regulation of SRSF10 and PSF) in obese- and lean-mice. However, many other components of the splicing machinery/associated factors (i.e. RNU1, U2AF1, PRPF40A, PRPF8, RBM22, RNU6atac, CELF1, SRSF5, SRSF6, SRSF9, SNW1, SND1, SFPQ, KHDRBS1) were exclusively up-regulated by metformin under normal-lean, but not obese, conditions which might suggest that the liver of obese-mice (fatty-liver; hyperglycemic/hyperinsulinemic-mice) might be partially resistant to alterations in the splicing-machinery in response to metformin. Ongoing studies would clarify the potential physiological implications of these findings, which may provide novel diagnostic-biomarkers and therapeutic-tools to treat hepatic-diseases.

***P56*. Dietary phylloquinone (vitamin K1) intake modulates pro-inflammatory state and its relationship with aging and insulin sensitivity in patients with coronary heart disease: from the CORDIOPREV study.**

Authors: Gracia M Quintana-Navarro, Elena M Yubero-Serrano, Isabel Pérez-Corral, Vanesa Navarro-Martos, Andreea Corina Baba, José López-Miranda, Pablo Pérez-Martínez.

Group: GC9 Nutrigenomics and Metabolic Syndrome.

OBJECTIVE: To examine whether dietary phylloquinone intake modifies the pro-inflammatory state and its relationship with aging and insulin sensitivity in coronary patients.
METHODS: Baseline analysis of 1002 coronary artery disease patients from the CORDIOPREV study. Dietary intake was collected using a validated food-frequency questionnaire and phylloquinone intake was estimated by using the USDA database. Adherence to the Mediterranean diet was assessed using a validated 14-item questionnaire. Plasma levels of fatty acids, adiponectin and leptin, telomere length, telomerase activity, inflammatory markers [resistin, C-reactive protein, tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6)] and parameters of glycemic control [fasting glucose, plasma insulin, HbA1c, HOMA-beta and HOMA-IR] were determined at baseline. The study population was divided into tertiles of phylloquinone intake. RESULTS: Dietary phylloquinone intake was inversely associated with plasma resistin levels (p= 0.038) and saturated fatty acids (p= 0.003) and directly associated with HOMA-beta (p= 0.044) and telomere length (p= 0.029). A significant association between phylloquinone intake and greater adherence to the Mediterranean diet (p <0.005) was also found. No significant differences were found between phylloquinone intake and other biochemical parameters according to tertiles of dietary phylloquinone intake. CONCLUSIONS: There is a relationship between proinflammatory state and aging-associated diseases such as cardiovascular disease. Our results suggest that dietary phylloquinone intake is associated with a greater adherence to a Mediterranean diet, modulating positively the pro-inflammatory state and its relationship with aging-associated pathophysiologic processes such as insulin resistance in patients with established cardiovascular disease.
Vitamin K, Inflammation, Aging, Insulin sensitivity, Mediterranean Diet.

P57. Proteomic profile of carbonylated proteins and redox status of human adipose tissue from morbid obese patients with different degrees of insulin sensitivity.

Authors: *M Carmen Navarro-Ruiz, Alberto Díaz-Ruiz, Sandra Díaz-del Moral, José López-Miranda, Rafael Vázquez-Martínez, Rocío Guzmán-Ruiz and María M. Malagón.*

Group: GC11 Metabolism and adipocyte differentiation. Metabolic syndrome.

Obesity is characterized by adipose tissue dysregulation, which predispose individuals to the development of insulin resistance (IR). At the molecular level, adipocyte dysfunction has been linked to obesity-triggered oxidative stress. Protein carbonylation, which is the most common oxidative protein modification, serves as a marker of oxidative stress and occurs by direct interaction with reactive oxygen species (ROS) or indirectly, as a result of lipid peroxidation. Herein, we aimed at characterizing the carbonylation targets and the redox status of adipose tissue in obese individuals to further elucidate the role of oxidative stress in obesity-associated insulin resistance. To this end, protein extracts omental (OM) and subcutaneous (SC) adipose tissue from morbidly obese subjects with different degrees of insulin sensitivity [normoglycaemia (NG), IR and type 2 diabetes (T2DM)] were derivatized to 2,4-dinitrophenylhydrazone (DNP), and total carbonylated protein content and carbonylated protein profiles were identified by 1D and 2D-PAGE, respectively. Intracellular ROS were measured using the 2,7'-dichloroflourescein diacetate dye and redox status/clearance was measured as superoxide dismutase 1 (SOD1) and glutathione synthase (GS) expression by immunoblotting. Total carbonylated protein content increased in IR and T2DM vs NG obese subjects in OM fat whereas no differences were detected in SC fat. 2D-PAGE revealed different carbonylated protein profiles between depots, identifying both common (serotransferrin, vimentin, actin and annexin A2) and different (SC: carbonic anhydrase and α-crystallin B; OM: α-1-antitrypsin and tubulin) carbonylated proteins. ROS levels and redox clearance were significantly different between groups in OM, but not in SC adipose tissue. In all, our data provide further evidence on the occurrence of depot-dependent differences in the response of adipose tissue to obesity-induced oxidative stress, with OM fat featuring a more robust adjustment of its redox defences in response to the development of insulin resistance. Funding: MINECO/FEDER (BFU2013-44229-R); JJAA/FEDER (PI-0200/2013; CTS-6606); FIS (PIE14_00005) and CIBERobn (ISCIII).

P58. Use of an in vitro model for the analysis of the impact of circulating factors on adipose tissue function.

Authors: *Julia Sánchez-Ceinos, Rocío Guzmán-Ruiz, José M. Moreno-Navarrete, Laura Molero-Murillo, Rafael Vázquez-Martínez, José M. Fernández-Real, and María M. Malagón.*

Group: GC11 Metabolism and adipocyte differentiation. Metabolic syndrome.

Adipose tissue (AT) plays a central role in managing energy stores and as an endocrine organ. AT dysregulation in obesity severely impacts body homeostasis and predispose individuals to the development of insulin resistance (IR). However, the factors and pathways mediating AT dysfunction in obesity are not fully understood. Indeed, AT research is limited by the availability of tissue samples, which are commonly provided from surgical procedures. In this scenario, the use of cell-conditioned media and/or human serum may be useful to examine the response of AT to changes in the extracellular milieu. Herein, we have developed an in vitro model for the analysis of circulating factors on AT functions. To this end, a group of patients were randomly selected from a cohort of obese patients with different anthropometric and biochemical characteristics. In parallel, an experimental protocol for exposure of 3T3-L1 adipocytes to human sera was optimized. Thus, 3T3-L1 adipocytes at day 10 of differentiation were exposed to 10% human sera during 24 hours and then processed for immunoblotting and functional assays. Our studies show that exposure to sera from different subjects differentially affected adipocyte function. Specifically, different responses were observed in key markers of adipocytes such as insulin sensitivity, inflammation, endoplasmic reticulum stress or browning, measured as pIRS1/IRS1 ratio, pJNK/JNK ratio, CHOP and UCP1 protein levels, respectively. Results showed that levels of pJNK/JNK and pIRS1 positively correlated with fat mass, while UCP1 and CHOP correlated with insulin resistance markers. Finally, AT lipid peroxidation correlated with ferritin plasma levels. Taken together, these results support the use of this in vitro approach for the analysis of AT function, which might be extended to other metabolic targets (pancreas, liver or muscle) and thus, pave the way for the development of integrative metabolic studies. Funding: MINECO/FEDER (BFU2013-44229-R); JJAA/FEDER (PI-0200/2013); FIS/FEDER (PIE14_00005) and CIBERobn (ISCIII).

P59. Hepatic insulin resistance determines postprandial lipoprotein metabolism in prediabetic and diabetic patients: from the CORDIOPREV study

Authors: *León-Acuña, Ana Gómez-Marín, Beatriz Gómez-Delgado, Francisco Delgado-Lista, Javier Pérez-Caballero, Ana Isabel López-Moreno, Javier Pérez-Martínez, Pablo López-Miranda, José.*

Group: GC9 Nutrigenomics and Metabolic Syndrome.

Background/aims: Diabetic patients have shown a prolonged and exaggerated postprandial response with an increase of cardiovascular risk. However, the response in prediabetes has not been established. The objective was to analyze the degree of postprandial lipemia response in the CORDIOPREV population (NCT00924937). Methods: 1002 patients (57 non-diabetic, 364 prediabetic and 581diabetic) were submitted to an oral fat load test meal (OFTT) with 0.7 g fat/kg body weight (12% saturated fatty acids (SFA), 10% polyunsaturated fatty acids (PUFA), 43% monounsaturated fatty acids (MUFA), 10% protein and 25% carbohydrates. Serial blood test analyzing lipid fractions were drawn at 0, 1, 2, 3 and 4 hours during postprandial state. Postprandial triglycerides (TG) concentration at any point >2.5 mmol/L (220 mg/dL) has been established as undesirable response. Additionally, the postprandial response was evaluated according to basal insulin resistance subgroups in patients non-diabetic and diabetic without pharmacological treatment (N=642). Results: Prevalence of undesirable postprandial TG was 35% in non-diabetic, 48% in prediabetic and 59% in diabetic subgroup, respectively ($p<0.001$). Interestingly, prediabetic patients displayed higher plasma TG and large triacylglycerol-rich lipoproteins (TRLs-TG) postprandial response compared with those non-diabetic patients ($p<0.001$ and $p=0.003$ respectively). The area under the curve (AUC) of TG and AUC-TRLs-TG was greater in the prediabetic group compared with non-diabetic patients ($p <0.001$ and $p<0.005$ respectively). Patients with liver insulin resistance (liver-IR) showed higher postprandial response of TG compared with those patients with muscle-IR or without any insulin-resistance respectively ($p<0.001$). Conclusions: Our findings demonstrate that prediabetic patients show a lower metabolic flexibility after external aggression, such as OFTT compared with non-diabetic patients. The postprandial response increases progressively according to non-diabetic, prediabetic and type 2 diabetic state and it is higher in patients with liver-IR. To identify this subgroup of patients is important to treat more intensively in order to avoid future cardiometabolic complications.

P60. Confirmatory and Quantitative Analysis of Fatty Acid Esters of Hydroxy Fatty Acids in Serum by Solid Phase Extraction Coupled to Liquid Chromatography Tandem Mass Spectrometry.

Authors: *María Asunción López-Bascón, Mónica Calderón-Santiago, Feliciano Priego-Capote, María Dolores Luque de Castro.*

Group: GC21 Metabolomics Identification/Quantification of Bioactive Components.

In the last decades, the prevalence of metabolic syndrome has increased in developed countries, mainly because of the rise of obesity. Nowadays, the most common disease in patients affected by metabolic syndrome is diabetes mellitus, which is increasing worldwide at an epidemic rate. Recently, a novel class of endogenous mammalian lipids endowed with anti-diabetic and anti-inflammatory properties has been found. Yore et al. in 2014 referred to this class of natural-occurring lipids as fatty acid-hydroxy fatty acids, abbreviated as FAHFAs. They reported that 6 FAHFAs species were upregulated by GLUT4 overexpression, the unique insulin-sensitive glucose transporter protein. Thus, Yore et al. concluded that the administration of these fatty acids to mice improved glucose uptake from blood, enhanced insulin secretion and relieved obesity-associated inflammation, suggesting that these naturally occurring fats could be used for diabetes therapy. Despite the potential of these novel lipids for future treatments of diabetes, further research is needed to establish their normal physiological levels and study their evolution after a specific treatment on individuals. However, FAHFAs are present in serum and tissues at low nanomolar concentrations. For this reason, it becomes necessary the development of a method with enough sensitivity to determine FAHFAs, even when they are at such low concentration. In this research, an automated qualitative and quantitative method based on the on-line coupling between SPE and LC–MS/MS to maximize sensitivity has been developed for determination of FAHFAs. A standard solution containing four commercial FAHFAs was used to optimize the SPE–LC–MS/MS method. Then, the method was applied to identify other FAHFAs present in serum. The main FAHFAs detected were PAHSA and PAHOA with concentrations around 35 and 25%, respectively, followed by SAHOA, OAHOA and OAHSA, with relative concentrations from 5 to 15%. Finally, the method was applied to a cohort formed by diabetic individuals.

***P61*. Polycystic ovary syndrome: Improving diagnosis for a better management and quality of life.**

Authors: Perdices-López C, Pineda B, Torres-Jiménez E, Lorente J, Arjona-Berral J.E, Romero-Ruiz A, Tena-Sempere M.

Group: GC10 Hormonal regulation of energy balance, puberty and reproduction.

Female reproductive health problems are displaying increasing prevalence in recent decades; a phenomenon whose basis remains largely unknown. Polycystic ovary syndrome (PCOS) is the most common endocrine-reproductive pathology that affects 5-10% of women of reproductive age, with manifestations that usually include hyper-androgenism, oligo- or amenorrhea and cystic ovaries. In addition, PCOS is often associated with metabolic disturbances, such as insulin resistance and obesity. While diagnosis of the syndrome is based in well-defined clinical criteria, it is estimated that >70% of affected women remain undiagnosed and that, in most instance, diagnosis is achieved at a relatively later stage of the disease, as PCOS is though to arise at early maturational periods. These features urge for the development of novel tools for the diagnosis of PCOS, aiming at improving the available protocols for earlier identification and better stratification of patients, as that this will permit (lifestyle, hormonal) intervention at initial stages of the disease. In this communication, we summarize our strategies for the identification of novel biomarkers of PCOS, based on large-scale analyses of circulating factors, differentially expressed between cases and controls. These have included candidate-based (>25) and unbiased, high-throughput analyses of the levels of microRNAs, as well as proteomic studies, in plasma samples of well-defined cohort of patients with PCOS, with either lean or obese phenotype, and their respective control. These on-going studies have allowed us to identify already a panel of plasma miRNAs and proteins, whose levels are selectively up- or down-regulated in patients with PCOS. We are currently validating these factors, with the ultimate aim of developing an integral diagnostic system based on multi-parametric determination in blood samples that would permit better diagnosis and improved case stratification of PCOS in adolescence or early adult age.

P62. Estudio de las complicaciones en el embarazo asociadas a imc ≥ 40 en el área de ginecología y obstetricia del Hospital Universitario Reina Sofía en 2015

Authors: *Jorge Duro Gómez; Maria del Sol Sánchez Ramos.*

Group: Others.

In XXI Century, Obesity has become a true pandemic. It is the first time in history of the humanity that an epidemic is not caused by an infectious disease. From the point of view obstetric-gynaecologic it is associated to a high rate on pregnancy, birth and postpartum complications.

Historically, it is associated with a higher prevalence of hypertensive disorders, missbirth, gestational diabetes, preterm delivery, respiratory disease, tromboembolic, increased risk of cesarean, and also a higher risk of stillbirth.

The aim of our taks is to check which the most prevalent complications of pregnancy, childbirth and postpartum, both maternal and fetal, are in patients with BMI>40 previous pregnancy and in our health area in 2015. We carried out a retrospective case-control study. In it, results of cases of pregnant women will be presented with a BMI >= 40 who were attended in high risk consultation Gynaecology and Obstetrics service in Reina Sofia Hospital since 1 January 2015 to 31 December 2015.

The results will be presented on the poster in table format.

After we established the conclusions of our studies, we pretend to act on these patients in the High Risk Obstetric Consultation, referrals them to Nutrition Consultation in order to try to reduce this disease and its complications

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P63. Incidental hepatocellular carcinoma after liver transplantation: prevalence, histopathological features and prognostic impact

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Background: Incidental hepatocellular carcinoma (iHCC) is a histological finding after liver transplantation (LT) which relevance has been scarcely studied.

Methods: Observational study including 451 consecutive adult LT patients (2000-2013). Median follow-up after LT was 58 months. Multiple Cox's regression was used to assess the prognostic impact of iHCC on tumor recurrence and mortality while controlling for potential confounders.

Results: 141 patients had known HCC before LT (31.3%). Among the remaining 310 patients, the prevalence of iHCC was 8.7% (n=27). In the explanted liver, 33.3% of the patients with known HCC and 25.9% of patients with iHCC trespassed Milan criteria (p= 0.45). Patients with known and iHCC had similar rates of multinodular disease (50.4% vs 55.6%; p= 0.62), macrovascular invasion (6.5% vs 3.7%; p= 0.45), microvascular invasion (12.9% vs 14.8%; p= 0.54) and moderate-poor tumor differentiation (53.9% vs 70.4%; p= 0.09). Tumor recurrence rates after LT were not significantly different in patients with known and iHCC (log rank p= 0.55). Cumulative 5-year overall survival rates were similar between patients with known and iHCC (65% vs 52.8% respectively; log rank p= 0.44), but significantly inferior as compared with patients without HCC (77.8%) (p= 0.002 and p= 0.007 respectively). In the multivariate analysis, iHCC and known HCC had identical recurrence-free survival after controlling for histological features (RR=1.06, 95%CI 0.36-3.14; p= 0.90). However, in the overall cohort, iHCC was an independent predictor of mortality (RR=3.02; 95%CI 1.62-5.65; p= 0.001).

Conclusion: Incidental and previously known HCC have comparable histological features and prognosis. New and intensive efforts should be driven to detect HCC before LT, as it would allow for an adequate selection and prioritization of candidates within the waiting list.

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