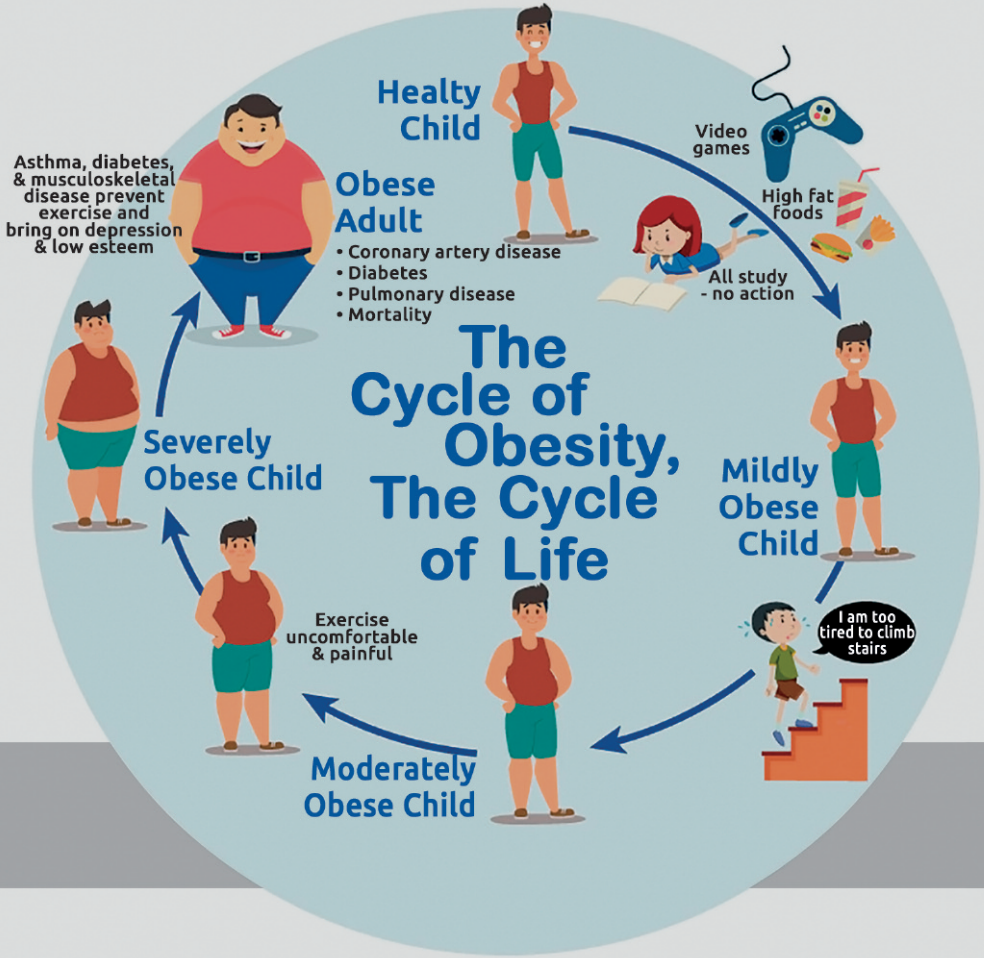
Obesity and Nutrition in the 21st Century

VIII Symposium Ciber Fisiopatología de la Obesidad y Nutrición

Madrid - June 2017



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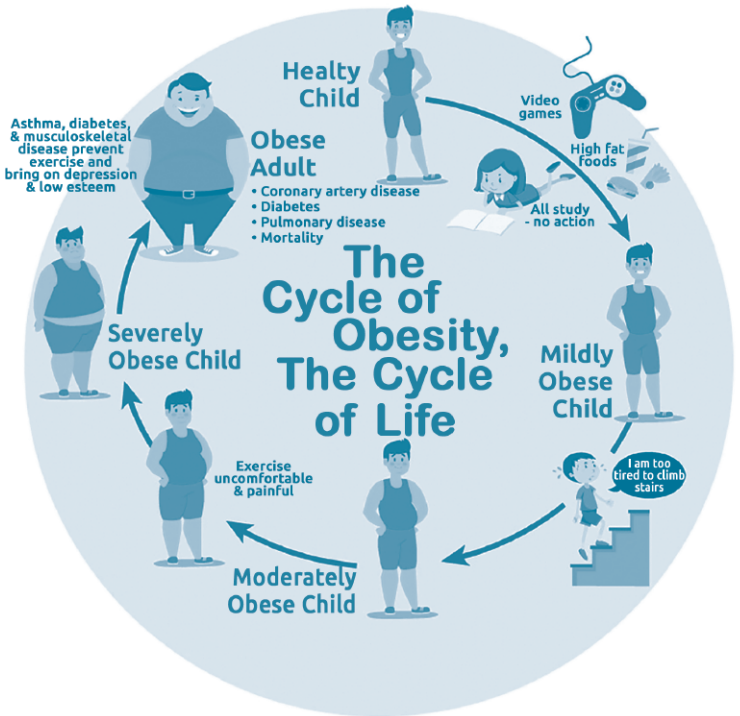

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Centro de Investigación Biomédica en Red

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GENERAL INFORMATION

Venue

ILUNION Atrium
Calle de Emilio Vargas, 3,
28043 Madrid

Date

June 28-29, 2017

Posters

Poster are to be mounted by 09:00 of June 28 and retired on June 29.

Norma

The identification card will be required for access to all scientific sessions, poster area and lunches.

PROGRAM

Obesity and Nutrition in the 21st Century

VIII Symposium Ciber Fisiopatología de la Obesidad y Nutrición

Madrid - June 2017

Wednesday 28 JUNE 2017

09:00-09:40 **Registration**

09:45-10:00 **Welcome & Opening**
Chairs: Manuel Tena Sempere (Córdoba)
& Dolores Corella (Valencia)

10:00-11:30 **Symposium 1**: *Current understanding of central food intake regulation and metabolic homeostasis* (30 min. talks)
Chair: Javier Martínez-Botas (Madrid)

10:00-10:30 Rubén Nogueiras (Santiago Compostela):
Hypothalamic pathways controlling appetite and adiposity
10:30-11:00 Nuria Casals (Barcelona):
Central metabolic pathways and the control of body weight homeostasis: Role of CPT1c
11:00-11:30 José María Moreno-Navarrete (Girona):
The importance of antimicrobial proteins in metabolic homeostasis: from intestine to brain

11:30-12:00 **Coffee break**

12:00-13:45 **Symposium 2**: *Childhood obesity epidemic: Challenges for prevention, management and health consequences* (25 min. talks)
Chair: Luis Moreno (Zaragoza)

12:00-12:25 Mercedes Gil (Córdoba):
New strategies in the prevention of childhood obesity
12:25-12:50 Julio Álvarez (Valencia):
Childhood obesity and early-onset hypertension: A dangerous liaison
12:50-13:15 Gabriel A. Martos Moreno (Madrid):
Childhood Obesity: Pathophysiological relevance of insulin resistance
13:15-13:40 Marcela González-Gross (Madrid)
Metabolic health and its association with sedentary time, physical activity, and fitness

13:45-15:00 **Lunch & Poster viewing/presentations**

15:00-16:00 **Short Oral Communications (I):** 4 x 12 min. Presentations
Chair: Mª Puy Portillo (Vitoria)

15:00-15:12 R. Barragán (Valencia):
BMAL1-Nutrigenetics (Abstract 43)
15:15-15:27 S. Jiménez-Murcia (Barcelona-IDIBEL):
Obesity, gambling, substance abuse (Abstract 29)
15:30-15:42 M. Pardo (Santiago de Compostela):
EV-Adipose (Abstract 3)
15:45-15:57 S. Ezquerro (Pamplona):
Ghrelin, NAFLD, gastrectomy (Abstract 9)

16:00-18:00 **Symposium 3**: *SEEDO-CIBEROBN Joint Activity*
Moderadores: Felipe Casanueva (Santiago de Compostela) & Carlos Diéguez (Santiago de Compostela)

Fernando Rodríguez Artalejo (Madrid):
Epidemiología de la Obesidad
Dolores Corella (Valencia): Influencia genética y epigenética en el desarrollo de la obesidad
Francesc Villarroya (Barcelona):
El BAT como diana terapeútica de la obesidad.
Francisco Tinahones (Málaga):
Avances en el tratamiento de la obesidad

18:15 **Traslado en autobús al Auditorio Nacional de Música de Madrid**
"Aligera tu vida"

Thursday 29 JUNE 2017

09:00-10:00 **PLENARY LECTURE (I)**.
Nathalie Farpurt-Lambert (Geneva, Switzerland):
Chairs: Felipe Casanueva (Santiago de Compostela) & Francisco Tinahones (Málaga)
The European perspective to tackle childhood obesity

10:00-11:00 **Short Oral Communications (II):** 4 x 12 min. presentations
Chair: Marta Giralt (Barcelona)

10:00-10:12 JA Martínez (Pamplona): *DNA methylation in sweet taste genes: BMI and carbohydrate intake (Abstract 41)*
10:15-10:27 Ll. Serra-Majem (Las Palmas Gran Canaria): *The Island in your plate (Abstract 22)*
10:30-10:42 R. Casas (Barcelona-Predimed): *Mediterranean diet-Image (Abstract 23)*
10:45-10:57 R.M. Luque (Córdoba): *Obesity, hepatic steatosis and splicing (Abstract 44)*

11:00-11:30 Coffee break

11:30-13:15 Symposium 4: *New frontiers in Nutritional Research*
(25 min. talks)
Chair: Zaida Agüera (Barcelona)
& Andreu Palou (Palma de Mallorca)

11:30-11:55 Álvaro Hernáez (Barcelona): *Advances in the molecular mechanisms by which Mediterranean diet exerts the protective effects.*
11:55-12:20 Antonio Camargo (Córdoba): *Nutrient-microbiome interactions and their impact on metabolic homeostasis.*
12:20-12:45 Nuria Rosique (Reus): *PrediMed Plus: Present and Future.*
12:45-13:10 Mariona Palou March (Palma de Mallorca): *Health claims on food today: one-size-fits-all or precision nutrition?*

13:30-16:00 Lunch and working sessions of the different scientific programs

16:00-17:30 CLOSING SESSION: State-of-the-art in Obesity Research
Chairs: Julie Chowen (Madrid)
& Carlos Diéguez (Santiago de Compostela)

CLOSING LECTURE (I) Sabrina Diano (New Haven, USA)
Mitochondria and central control of glucose metabolism
CLOSING LECTURE (II) Tamas Horvath (New Haven, USA):
New concepts in the central control of body weight: From mitochondria to behavior

17.45-18:00 Closing remarks *by CIBEROBN Scientific Director*

ABSTRACTS

HUMAN PERIPHERAL BLOOD MONONUCLEAR CELL IN VITRO SYSTEM TO TEST THE EFFICACY OF FOOD BIOACTIVE COMPOUNDS: EFFECTS OF N-3 POLYUNSATURATED FATTY ACIDS AND THEIR RELATION WITH BMI

M. Cifre[1,2], R. Díaz-Rúa[1,2], R. Varela-Calviño[3], B. Reynés[1,2], J. Pericás-Beltrán[4], P. Oliver[1,2], A. Palou[1,2]

[1]CIBEROBN, [2]Laboratory of Molecular Biology, Nutrition and Biotechnology (LBNB), Universitat de les Illes Balears, Palma de Mallorca, [3]Department of Biochemistry and Molecular Biology, University of Santiago de Compostela, Santiago de Compostela, [4]Research Group on Evidence, Lifestyles & Health, Universitat de les Illes Balears, Palma de Mallorca

Introduction: An increasing number of food components, such as n-3 long-chain polyunsaturated fatty acids (LCPUFA), are being studied in the basis of their health effects. Health protective effects of food compounds can be easily assessed using animal models; however, translation to humans is not always simple. Culture of peripheral blood mononuclear cells (PBMC) is emerging as an interesting possibility to test food compounds.

Objective: To analyse usefulness of PBMC to rapidly/easily reflect n-3 LCPUFA effects on lipid metabolism/inflammation gene profile, and evaluate if these effects are BMI-dependent.

Methods: We set up an *in vitro* system of human PBMC from normoweight (NW) and overweight/obese (OW/OB) individuals to study direct effects of physiological doses (10 µM) of docosahexaenoic (DHA), eicosapentaenoic (EPA), or their combination. After treatments, mRNA expression of selected genes involved in immune response and lipid metabolism was analysed by real-time RT-PCR in PBMC.

Results: PBMC reflected increased beta-oxidation capacity (*CPT1A* expression) characteristic of liver and adipose tissue, but only after DHA treatment, with independence of BMI. However, an impaired n-3 LCPUFA response was evident in OW/OB for the studied lipogenic genes: both LCPUFA diminished *FASN* and *SREBP1C* mRNA expression in NW, but no effect was observed for DHA in PBMC from OW/OB. This insensitivity was also evident for inflammatory genes: DHA, EPA or the combination decreased the expression of these genes in NW; nevertheless, no effect was observed in OW/OB after DHA treatment, and EPA effect was impaired. Considering the different genes analysed, *SLC27A2*, *IL6*, and *TNFα* PBMC analysis resulted of special interest to determine obesity-related insensitivity to LCPUFA treatment.

Conclusion: A PBMC-based human *in vitro* system reflects n-3 LCPUFA effects on lipid metabolism/inflammation which is impaired in OW/OB. These results confirm the utility of PBMC *ex vivo* systems for bioactive-compound screening to promote functional food development and to establish appropriate dietary strategies for obese population.

Acknowledgements: CIBEROBN is an initiative of the ISCIII. This work was supported by was funded by the Spanish Government (INTERBIOBES -AGL2015-67019-P- and EPIMILK -AGL2012-33692-) and by the University of the Balearic Islands (IBIFLEX, FA38/2016).

E-mail: marga.cifre@uib.es

LEPTIN INTAKE AT PHYSIOLOGICAL DOSES THROUGHOUT LACTATION IN RATS RESTORES THE ALTERED STOMACH SYMPATHETIC DRIVE CAUSED BY MILD GESTATIONAL CALORIE RESTRICTION

N. Szostaczuk, J. Sánchez, J. Konieczna, A. Palou, C. Picó

Laboratory of Molecular Biology, Nutrition and Biotechnology (Nutrigenomics), University of the Balearic Islands and CIBER de Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Palma de Mallorca, Balearic Islands, Spain.

Introduction: Gestational undernutrition in rats has been associated with lower sympathetic innervation in offspring, affecting peripheral tissues such as the stomach. This has been linked to lower gastric secretion and decreased circulating levels of ghrelin. Considering the essential role of leptin intake during lactation to prevent obesity and reverse developmental malprogramming effects, we aimed to assess whether leptin supplementation reverses the decreased gastric sympathetic drive caused by mild gestational calorie restriction.

Methods: Three groups of male rats were studied at a juvenile age and adulthood: the offspring of ad libitum fed dams (controls), the offspring of 20% calorie restricted dams during the first part of pregnancy (CR), and CR rats supplemented with physiological doses of leptin throughout lactation (CR-Leptin). Tyrosine hydroxylase (TyrOH) levels and the density of TyrOH-immunoreactive ($TyrOH^+$) fibers, used as indicators of sympathetic innervation, were determined in the stomach. Plasma leptin and ghrelin were determined.

Results: At 25 days, CR rats displayed lower density of $TyrOH^+$ fibers and lower TyrOH levels in the stomach than controls. These alterations were not found in CR-Leptin animals, suggesting that the altered sympathetic innervation was reverted by leptin treatment. This alteration was mitigated at the age of 6 months, and differences between control and CR animals were not significant. Nevertheless, the trend to a lower density of $TyrOH^+$ fibers in CR animals compared to controls was also reverted in CR-Leptin animals. Accordingly, CR animals, but not CR-Leptin ones, also showed lower serum ghrelin levels compared to controls, particularly at the age of 3 months, and a higher leptin/ghrelin ratio.

Conclusion: These findings show that leptin intake during lactation is able to reverse the malprogrammed alterations in the stomach sympathetic drive and normalise the increased leptin/ghrelin ratio linked to a mild maternal calorie restriction during gestation in rats, supporting the relevance of leptin as an essential factor during lactation.

Acknowledgements: Spanish Government (AGL2012-33692; AGL2015-67019-P), the European Union's Seventh Framework Programme FP7 2007-2013 under grant agreements n. 244995 (BIOCLAIMS Project), and the Instituto de Salud Carlos III, Centro de Investigación Biomédica en Red Fisiopatología de la Obesidad y Nutrición, CIBERobn.

E-mail: nara.szostaczuk@uib.es

ADIPOSE TISSUE SHEDS DEPOT-SPECIFIC EXTRACELLULAR VESICLES

Camino Tamara[2], Pérez-Sotelo Diego[2], Bravo Susana Belén[3], Sueiro Aurelio[2,5], Baltar Javier[4], Baamonde Ivan[4], Casanueva F Felipe[1,5], Pardo María[1,2].

[1]CIBER Fisiología de la Obesidad y Nutrición, Instituto de Salud Carlos III, Santiago de Compostela

[2] Grupo Obesidómica, Instituto de Investigación Sanitaria de Santiago de Compostela (IDIS), Xestión Integrada de Santiago (XXIS/SERGAS)

[3]Unidad de Proteómica (IDIS), (XXIS/SERGAS)

[4]Servicio de Cirugía General, (XXIS/SERGAS)

[5]Laboratorio de Endocrinología Molecular y Celular, Instituto de Investigación Sanitaria de Santiago (IDIS), (XXIS SERGAS)

INTRODUCTION: The role of adipose tissue (AT) as an endocrine organ is currently reaching an unprecedented dimension due to its capacity to release, in addition to classical soluble factors, extracellular vesicles (EVs). EVs have been currently rediscovered as involved in multiple pathological processes and defined as biomarkers and therapeutic tools and targets. They are shed from the cell membrane (microvesicles), or from multivesicular bodies (exosomes) and they contain lipids, proteins, DNA and RNAs. Interestingly, VEs can activate membrane receptors and signalling pathways in a target cell/tissue, transfer molecules, and they can be used as vehicles to deliver strategic molecules. At this moment, there is barely any research in relation to AT communication through EVs. Previous work from our group with human obese AT secretome using a quantitative proteomics approach revealed that a high percentage of proteins were classified as from extracellular vesicle exosomes.

OBJECTIVE: The aim of the present work is to optimize the isolation and to characterize adipose tissue released vesicles and determine the existence of depot specific EVs.

METHODS: EVs from differentiated adipocytes (C3H10T1/2 cells) were isolated by three different methods: Exo-spin (CELL guidance systems), *Total exosome isolation reagent* (Invitrogen) and ultracentrifugation. EVs from human obese VAT and SAT secretomes explants culture in vitro obtained after bariatric surgery were also isolated. Proteomics analysis of VEs content was performed by liquid chromatography – mass spectrometry LC-MS/MS (ABSciex) and preliminary functional studies established.

RESULTS: Ultracentrifugation was the best method for EVs isolation. Differentiated adipocytes and human obese AT shed EVs of exosomal nature (average size of 100nm and CD63+/CD9+). Obese AT-exosomes proteome analysis shows that although VAT and SAT share common constituents, there is a characteristic protein profile for each adipose depot. Functional analysis of obese exosomes shows proteins implicated in extracellular matrix remodelling, cell growth and maintenance, protein metabolism, inflammation and insulin resistance.

Conclusions: AT-secreted EVs analysis suggests the secretion of cell and tissue specific vesicles with specific functionality that represents a new way of para/endocrine communication probably implicated in the development of obesity related comorbidities.

Acknowledgments: CIBERobn (CB06/03) is an initiative of ISCIII. This work was supported by FISPI16/01212. Pardo M is a Miguel Servet II Fellow (ISCIII).

tamara_cm_10294@hotmail.es

STRESS-INDUCED OPPOSITE EXPRESSION AND DISTRIBUTION OF TOLL-LIKE RECEPTOR 2 AND 3 IN BLOOD AND ADIPOCYTES HAS CONSENSUS WITH OBESITY AND METABOLIC INFLAMMATION

Francisco J. ORTEGA[1,2,3], José M. MORENO-NAVARRETE[1,2,3],*

Jèssica LATORRE[1,2,3], Mónica SABATER[1,2,3], Maria Buxó[2],

José I. RODRIGUEZ-HERMONSA[2,4], Jordi GIRONES[2,4], Wifredo RICART[1,2,3],

*Ramón VILALLONGA[5], Rafael SIMÓ[6], José M. FERNÁNDEZ-REAL[1,2,3]**

[1] CIBEROBN and Instituto de Salud Carlos III (ISCIII) - Madrid, Spain

[2] Institut d'Investigació Biomédica de Girona (IdIBGi) - Girona, Spain

[3] Department of Diabetes, Endocrinology and Nutrition (UDEN), Hospital of Girona "Dr Josep Trueta" - Girona, Spain

[4] Department of Surgery, Hospital of Girona "Dr Josep Trueta" - Girona, Spain

[5] Servicio de Cirugía General, Unidad de Cirugía Endocrina, Bariátrica y Metabólica, Hospital Universitario Vall d'Hebron, European Center of Excellence (EAC-BS) - Barcelona, Spain

[6] Diabetes and Metabolism Research Unit, Vall d'Hebron Research Institute, Universitat Autònoma de Barcelona, CIBERDEM and Instituto de Salud Carlos III (ISCIII) - Barcelona, Spain

Background: Obesity is characterized by chronic low grade inflammation and the systemic immune activation that eventually dampens insulin sensitivity and modifies metabolism. In this context, the immunometabolic capacity of pathogen-sensing systems activated downstream toll-like receptors (TLR) is not fully recognized.

Objectives: The current study aimed the identification of TLR being expressed in whole blood and human adipose tissue by either major immune cell subsets or mature adipocytes, and the systematic characterization of changes accounting upon acute and chronic inflammation in association with obesity and metabolic impairment.

Methods: We explored the effects of different inflammatory / anti-inflammatory paradigms on the expression of subcutaneous (SAT) and visceral (VAT) adipose tissue and whole blood. Among the former, we evaluated the effects of macrophage conditioned media *in vitro* and acute surgery stress *in vivo* on TLR expression. Weight loss was chosen as an anti-inflammatory model (adipose tissue TLR were analyzed before and after ~2 years of bariatric surgery-induced weight loss, n=22). We also evaluated cross-sectionally the associations of TLR mRNAs with inflammatory parameters in a cohort of 80 non-obese and morbid obese participants, in whole blood (n=72), and in *ex vivo* isolated adipocytes / stromal-vascular cells (SVC, n=32 paired samples).

Results: Acute surgery stress raised TLR1 and TLR8 mRNA in SAT, and TLR2 in both SAT and VAT depots, while decreasing VAT TLR3 and TLR4. In partial agreement, macrophage-induced inflammation let to increased expression of TLR2, and dampened TLR3, TLR4, and TLR5 mRNA in fully differentiated mature adipocytes. On the other hand, the anti-inflammatory impact of weight loss was concomitant with decreased TLR1, TLR3, and TLR8 in SAT, and cross-sectional associations confirmed the marked increase of V/SAT TLR1 and TLR8 (but decreased TLR3) found in morbid obese patients with and without diabetes, as compared with non-obese participants with normal glucose

tolerance. As expected, TLR were predominant in SVC and adipocyte precursor cells, even though the expression of all of them but TLR8 (very low levels) was found in differentiated adipocytes in close association with the inflammatory state of activation. Noteworthy, the opposite patterns shown for TLR2 and 3 in V/SAT and inflamed adipocytes were identified in whole blood as well, being TLR3 mRNA more likely linked to lymphocyte numbers instead of neutrophils.

Conclusions: Changes in expression and distribution of TLR found in blood and AT, namely TLR2 and 3, have consensus with acute and chronic immune activation and inflammatory signatures.

Acknowledgments: We are indebted to the IDIBGI Biobank, integrated in the Spanish National Biobank Network, for the sample and data procurement. This study was supported by the CIBER de la Fisiopatología de la Obesidad y la Nutrición (CIBERobn), by funds from the Agència de Gestió d'Ajuts Universitaris de Recerca (AGAUR, FI-DGR 2015 to Jèssica Latorre), the Fondo Europeo de Desarrollo Regional (FEDER), and the CIBER de la Fisiopatología de la Obesidad y la Nutrición (CIBERobn). The CIBERobn is an initiative from the Instituto de Salud Carlos III (ISCIII).

F.J. Ortega: fortega@idibgi.org

LYSOZYME AS NEW PLAYER IN OBESITY-RELATED ADIPOSE TISSUE INFLAMMATION

Jèssica Latorre[1,2,3], José M. Moreno-Navarrete[1,2,3], Francisco J Ortega[1,2,3], Mònica Sabater[1,2,3], Amaia Rodríguez[4], Sara Becerril[4], Gema Frühbeck[4], Ramón Vilallonga[5], Rafael Simó[6], Wifredo Ricart[1,2,3], José M. Fernández-Real[1,2,3]

[1]Institut d'Investigació Biomèdica de Girona (IdIBGi) - Girona, Spain

[2]CIBER de la Fisiología de la Obesidad y la Nutrición (CIBERobn) – Madrid, Spain

[3]Department of Diabetes, Endocrinology and Nutrition (UDEN), Hospital of Girona "Dr Josep Trueta" - Girona, Spain

[4]Laboratorio de Investigación Metabólica, Clínica Universidad de Navarra (IdiSNA) – Pamplona, Spain

[5]Servicio de Cirugía General, Unidad de Cirugía Endocrina, Bariátrica y Metabólica, Hospital Universitario Vall d'Hebron, European Center of Excellence (EAC-BS) - Barcelona, Spain

[6]Diabetes and Metabolism Research Unit, Vall d'Hebron Research Institute, Universitat Autònoma de Barcelona, CIBERDEM and Instituto de Salud Carlos III (ISCIII) - Barcelona, Spain

Introduction: Lysozyme (LYZ) is an antimicrobial enzyme that is expressed in white blood cells. The pathophysiology of obesity implies a chronic low-grade inflammation of adipose tissue associated to macrophages infiltration.

Objectives: In the present study, we aimed to investigate LYZ in adipose tissue and plasma according to obesity status, inflammation and insulin resistance.

Methods: LYZ gene expression and circulating levels were cross-sectionally analysed in subcutaneous and visceral adipose tissue (real-time quantitative PCR) and in plasma (ELISA) from subjects with a wide range of fatness and insulin resistance. Adipose tissue LYZ gene expression was also analysed after bariatric surgery-induced weight loss, after high-fat diet-induced weight gain (in rats), and immediately after surgical procedure. The mRNA and protein of LYZ were also investigated in human primary mature adipocytes and macrophages before and after inflammatory conditions.

Results: The amount of *LYZ* mRNA expression was comparable to lipogenic genes in adipose tissue. Although LYZ was expressed in adipocytes, its main expression was detected in cells of the stromal vascular fraction, specifically in $CD14^+$ cells. In both subcutaneous and visceral adipose tissue, *LYZ* mRNA was increased concurrently with body mass index ($p<0.0001$), percent fat mass ($p<0.0001$) and obesity-associated metabolic disturbances (fasting serum glucose, fasting triglycerides, HOMA-IR and C-reactive protein). In addition, adipose tissue *LYZ* mRNA was significantly and positively associated with expression of adipose tissue inflammation markers, such as tumor necrosis factor alpha, leptin or lipopolysaccharide binding protein, while negatively with markers of adipogenesis. Bariatric surgery-induced weight loss resulted in decreased subcutaneous fat *LYZ* mRNA (-68.3%, $p<0.0001$) in parallel to reduction of adipose tissue inflammation and the improvement of adipogenesis. The high-fat diet-induced weight gain led to increased expression (141.5%, $p=0.0003$). Bariatric surgery *per se* acutely increased LYZ expression, both in subcutaneous (124%, $p=0.014$) and in visceral (157%, $p=0.012$) adipose tissue. Similar to adipose tissue *LYZ* mRNA, plasma LYZ was also increased with obesity and weight gain, and significantly correlated with obesity-associated

metabolic disturbances. *In vitro* experiments revealed that inflammatory factors promoted LYZ biosynthesis and secretion in both adipocytes and macrophages.

Conclusion: Altogether these findings suggest LYZ as a new player in obesity-associated adipose tissue inflammation and dysfunction.

Acknowledgements: We are indebted to the IDIBGI Biobank, integrated in the Spanish National Biobank Network, for the sample and data procurement. This study was supported by the CIBER de la Fisiopatología de la Obesidad y la Nutrición (CIBERobn), by funds from the Agència de Gestió d'Ajuts Universitaris de Recerca (AGAUR, FI-DGR 2015 to Jèssica Latorre), the Fondo Europeo de Desarrollo Regional (FEDER), and the CIBER de la Fisiopatología de la Obesidad y la Nutrición (CIBERobn). The CIBERobn is an initiative from the Instituto de Salud Carlos III (ISCIII).

J Latorre: jlatorre@idibgi.org

HDL FUNCTION AND LDL ATHEROGENICITY: INDEPENDENT ASSOCIATIONS WITH CARDIOVASCULAR RISK

Álvaro Hernáez[1,2,3], María Trinidad Soria-Florido[2,3], Daniel Muñoz-Aguayo[1,2], Gemma Blanchart[2], Sònia Gaixas[2], Emilio Ros[1,4], Xavier Pintó[1,5], Ramón Estruch[1,4], Jordi Salas-Salvadó[1,6], Dolores Corella[1,7], Fernando Arós[1,8], Lluis Serra-Majem[1,9], Miguel Ángel Martínez-González[1,10], Miquel Fiol[1,11], José Lapetra[1,12], Rosa María Lamuela-Raventós[1,13], Montserrat Fitó[1,2,]*

1. CIBER de Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, Madrid, Spain.
2. Cardiovascular Risk and Nutrition Research Group, REGICOR-Study Group, Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain.
3. PhD Program in Food Sciences and Nutrition, Universitat de Barcelona, Barcelona, Spain.
4. Department of Internal Medicine, Hospital Clinic, University of Barcelona, Barcelona, Spain.
5. Lipids and Vascular Risk Unit, Internal Medicine, Hospital Universitario de Bellvitge, Hospitalet de Llobregat, Barcelona, Spain.
6. Human Nutrition Department, Hospital Universitari Sant Joan, Institut d'Investigació Sanitaria Pere Virgili, Universitat Rovira i Virgili, Reus, Spain.
7. Department of Preventive Medicine, Universidad de Valencia, Valencia, Spain.
8. Department of Cardiology, Hospital Universitario de Álava, Vitoria, Spain.
9. Department of Clinical Sciences, Universidad de Las Palmas de Gran Canaria, Las Palmas, Spain.
10. Department of Preventive Medicine and Public Health, Universidad de Navarra, Pamplona, Spain.
11. Balearic Islands Institute for Health Research, Hospital Son Espases, Palma de Mallorca, Spain.
12. Department of Family Medicine, Research Unit, Distrito Sanitario Atención Primaria Sevilla, Sevilla, Spain.
13. Department of Nutrition and Bromatology, Faculty of Pharmacy, Universitat de Barcelona, Barcelona, Spain.

ABSTRACT

Background. Functional characteristics of high-density lipoproteins (HDLs) (cholesterol efflux capacity, antioxidant functions, vasodilatory capacity, oxidation, size, and composition) and atherogenic traits of low-density lipoproteins (LDLs) (resistance against oxidation, size, composition, and cytotoxicity) reflect the role of both particles on cardiovascular health more accurately than the quantity of HDL or LDL cholesterol. However, studies on the independent connections of these traits with cardiovascular risk are scarce.

Objective. Our aim was to determine the relationship between HDL functionality and LDL atherogenicity characteristics and the Framingham-REGICOR cardiovascular risk score, as well as their independent associations with cardiovascular risk factors (diabetes, hypercholesterolemia, hypertension, excess weight, and smoking), age, and sex.

Methods. We performed a cross-sectional analysis in sub-samples of volunteers of the PREDIMED trial at baseline for HDL functionality characteristics (*N*=296) and LDL pro-atherogenic traits (*N*=210).

Results. Greater cardiovascular risk scores were associated with low cholesterol efflux values; oxidized, triglyceride-rich, small HDL particles; and small LDL particles with low resistance against oxidation (*P*-trend<0.05, all). Diabetes contributed particularly to this profile (diabetic patients presented low cholesterol efflux capacities, and more oxidized, smaller, triglyceride-rich LDLs; *P*<0.033, all), as well as excess weight (linked to dysfunctional, small, triglyceride-rich HDLs and low estimated LDL size; *P*<0.039, all), male gender (associated with low cholesterol efflux values; oxidized, small HDLs; and oxidized, small, triglyceride-rich, cytotoxic LDLs; *P*<0.044, all), and advanced age (related to oxidized, small, cytotoxic LDL particles; *P*<0.037, all).

Conclusions. High cardiovascular risk states (particularly due to diabetes, overweight, male gender, and advanced age) are deeply associated with dysfunctional HDL and pro-atherogenic LDL particles.

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First author's e-mail: alvaro.hernaez1@gmail.com

HYPOTHALAMIC GRP78 INDUCES BROWNING OF WAT

Cristina Contreras[1,2], Ismael González-García[1,2], Laura Liñares Pose[1,2], Eva Rial Pensado[1,2], Patricia Seoane-Collazo[1,2], Noelia Martínez-Sánchez[1,2], Carlos Diéguez[1,2], Rubén Nogueiras[1,2] & Miguel López[1,2]

[1] Department of Physiology, CIMUS, University of Santiago de Compostela-Instituto de Investigación Sanitaria, Santiago de Compostela, 15782, Spain

[2] CIBER Fisiopatología de la Obesidad y Nutrición (CIBERobn), Santiago de Compostela, 15706, Spain

Introduction: Obesity and its associated pathologies, such as diabetes, cardiovascular disease, or some cancer types, have an increasing prevalence, being considered a disease by the HWO. Obesity has been related with alterations in endoplasmic reticulum (ER) alterations in peripheral tissues such as liver, pancreas or skeletal muscle (Ozcan et al., 2009; Hosoi et al., 2008; Ropelle et al., 2010; Martínez de Morentin and López, 2010; Cnop et al., 2012), and more recently to central level (Schneeberger et al. 2013, Contreras et al, 2014). The chaperone GRP78/Bip (glucose regulated protein 78 KDa/binding immunoglobulin protein) acts upstream the unfolded protein response (UPR) to modulate protein folding in reply to cellular insults that lead to ER stress.

Aim: The aim of this study was to investigate the role of hypothalamic ER stress in the control of energy balance during obesity, specially the possible involvement in the activation of the thermogenesis in the white adipose tissue (WAT), process known as *browning*.

Methods: High fat diet fed rats were used as model of obesity, which was stereotaxically treated with adenoviruses encoding GRP78/BiP, specifically in the ventromedial nucleus of hypothalamus (VMH), improving the protein folding so reducing the ER stress. Metabolic parameters and browning in gonadal and subcutaneous WAT were studied in this model.

Results: Here, we demonstrate that in diet-induced obese rats, which are characterized by hypothalamic ER stress, genetic overexpression of GRP78 specifically in the ventromedial nucleus of the hypothalamus (VMH) is enough to revert the obese and metabolic phenotype. Of note those effect are related to induced of browning WAT.

C**onclusion:** This evidence indicates that modulation of GRP78 activity (and then reducing ER stress) in specific hypothalamic nuclei may be a potential strategy against obesity and associated comorbidities.

BENEFICIAL EFFECTS OF SLEEVE GASTRECTOMY IN WEIGHT LOSS AND METABOLIC PROFILE IN OBESITY-SUSCEPTIBLE RATS

Becerril S[1,5,6]; Moncada R[2,5,6]; Rodríguez A[1,5,6]; Méndez-Giménez L[1,5,6]; Valentí V[3,5,6]; Ramírez B[1,5,6]; Catalán V[1,5,6]; Gómez-Ambrosi J[1,5,6] and Frühbeck G[1,4,5,6]

[1]Metabolic Research Laboratory, Departments of [2]Anesthesia, [3]Surgery and [4]Endocrinology & Nutrition, Clínica Universidad de Navarra, Pamplona, Spain; [5]CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, Spain; [6]Obesity & Adipobiology Group, Instituto de Investigación Sanitaria de Navarra (IdiSNA), Pamplona, Spain.

Background: The response to dietary fat represents an important factor in the onset of obesity,being associated with a notable inter-individual variation. Some individuals are prone to weight gain (obesity-prone, OP), while others are not susceptible to develop obesity (NSO). Numerous differences between obesity prone (OP) rats and non-susceptible animals to obesity (NSO) have been reported.

Objective: Our aim was to evaluate whether the beneficial effects of the restrictive bariatric procedure sleeve gastrectomy (SG) on weight loss and metabolic profile are preserved even in a context of high obesity susceptibility.

Methods: Male OP (n=13) and NSO (n=14) Wistar rats were submitted to surgical (sham operation and SG) or dietary interventions (pair-fed to the amount of food eaten by sleeve-gastrectomized rats) after 12 months fed a high-fat diet. Body weight and food intake were periodically registered. Fat pad weights and metabolic profile were analyzed 4 weeks after these interventions.

Results: SG decreased body weight in both OP and NSO rats as compared to sham-operated and pair-fed groups ($P<0.05$), mainly due to reductions in adiposity ($P<0.001$). Total weight loss achieved in sleeve-gastrectomized OP and NSO rats was higher than that of pair-fed ones ($P<0.05$), suggesting that the effect of SG is beyond caloric restriction. As expected, NSO rats exhibited a lower weight loss with an increased relative food intake and lower food efficiency ($P<0.05$) compared to OP ones. Sleeve-gastrectomized rats exhibited an increased thermogenesis supported by higher rectal temperature and increased UCP-1 expression in brown fat.

Conclusion: Our findings provide the first evidence that OP rats respond effectively to SG,as evidenced by the weight reduction and the metabolic improvement.

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Mail: sbecman@unav.es

Available for oral communication or poster presentation

IMPLICATION OF GHRELIN ISOFORMS IN THE RESOLUTION OF NAFLD AFTER SLEEVE GASTRECTOMY IN DIET-INDUCED OBESE RATS: EFFECTS ON HEPATIC LIPOGENESIS, β-OXIDATION AND AUTOPHAGY

Silvia Ezquerro[1,5], Leire Méndez-Giménez[1,5], Sara Becerril[1,5], Rafael Moncada[2,5], Víctor Valenti[3,5], Victoria Catalán[1,5], Javier Gómez-Ambrosi[1,5], Gema Frühbeck[1,4,5], Amaia Rodríguez[1,5]

[1]Metabolic Research Laboratory and Departments of [2]Anesthesia, [3]Surgery and [4]Endocrinology & Nutrition, Clínica Universidad de Navarra,IdiSNA, Pamplona, [5]CIBEROBN, Instituto de Salud Carlos III (ISCIII), Madrid.

Introduction: Sleeve gastrectomy is a restrictive bariatric surgery procedure that improves non-alcoholic fatty liver disease. This pathology is also associated with alterations in total ghrelin concentrations.

Objective: The aim of the present study was to analyze the potential participation of acylated and desacyl ghrelin in the amelioration of hepatosteatosis after sleeve gastrectomy in diet-induced obese rats.

Methods: Male Wistar rats (n=161) were subjected to surgical (sham operation and sleeve gastrectomy) or dietary interventions (fed *ad libitum* a normal or a high-fat diet or pair-fed).

Results: Obese rats developed fatty liver and showed a decrease (P<0.05) in plasma desacyl ghrelin, without changes in acylated ghrelin levels. After sleeve gastrectomy, desacyl ghrelin levels were significantly reduced (P<0.05), but an increased (P<0.05) acylated/desacyl ghrelin ratio was found. Furthermore, sleeve-gastrectomized rats showed a reduction (P<0.05) in hepatic triacylglycerol content, a downregulation of lipogenic enzymes *Mogat2* and *Dgat1*, an enhancement in mitochondrial DNA content, as well as an induction of AMPK-activated mitochondrial FFA β-oxidation and autophagy to a higher extent than caloric restriction. Primary rat hepatocytes treated with both acylated and desacyl ghrelin (10, 100 and 1,000 pmol/L) exhibited a significantly increased (P<0.05) triacylglycerol accumulation, triggered AMPK-activated mitochondrial FFA β-oxidation and autophagy.

Conclusion: Our data suggest that the beneficial effects of bariatric surgery on NAFLD are mediated via a reduction in lipogenesis as well as an enhancement in autophagy and mitochondrial β-oxidation. The decrease in desacyl ghrelin after sleeve gastrectomy contributes to the reduction of lipogenesis, whereas the increased acylated/desacyl ghrelin ratio activates factors implicated in mitochondrial FFA β-oxidation and autophagy in obese rats, thereby ameliorating hepatoesteatosis.

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E-mail: sezquerro.1@unav.es

Available for oral communication or poster presentation

BENEFICIAL EFFECT OF TWO HEALTHY DIETS ON ENDOTHELIAL DAMAGE AND REGENERATIVE CAPACITY PROCESSES: FROM THE CORDIOPREV STUDY

Elena M Yubero-Serrano[1,2], Carolina Fernandez-Gandara[2], Antonio Camargo[1,2], Jose David Torres[2], Oriol Rangel-Zuñiga[1,2], Juan F Alcala-Diaz[2], Javier Delgado-Lista[1,2], Pablo Perez-Martinez[1,2], Jose Lopez-Miranda[1,2].

[1]CIBEROBN

[2]Lipid and Atherosclerosis Research Unit, Reina Sofia University Hospital/IMIBIC /University of Cordoba, Córdoba, Spain.

Background: Endothelial dysfunction is considered an important step in the development of cardiovascular disease (CVD). Endothelial damage and regenerative capacity are processes underlying endothelial dysfunction that show a high potential as a diagnostic/prognostic tool in CVD.

Objectives: Our aim was to determine whether long-term consumption of two healthy diets produce a differential effect on both endothelial damage and repair mechanisms.

Methods: 806 patients with coronary heart disease (CHD), from the CORDIOPREV study (NCT00924937), were classified according their endothelial dysfunction degree: 253 patients with severe endothelial dysfunction [flow-mediated dilation (FMD) of the brachial artery <2%] and 553 patients with non-severe endothelial dysfunction (FMD>2%), after a year of dietary intervention [Mediterranean diet (35% fat, 22% MUFA) vs Low-fat diet (28% fat, 12% MUFA)]. Endothelial damage [endothelial microparticles levels (EMPs), and *in vitro* reactive oxygen species (ROS) levels, apoptosis and cell senescence] and endothelial regenerative capacity [endothelial progenitor cells (EPCs), and *in vitro* cell proliferation and angiogenesis] were evaluated at baseline and after the dietary intervention.

Results: A Mediterranean diet decreases activated EMPs levels, apoptotic EMPs:EPCs ratio and *in vitro* endothelial damage processes, while increases EPC levels and *in vitro* endothelial regenerative capacity processes, independently of the degree of endothelial dysfunction. However, a low-fat diet increases EPC levels in patients with non-severe endothelial dysfunction but increases apoptotic EMPs:EPCs ratio in patients with severe endothelial dysfunction, while increases *in vitro* endothelial damage processes and decreases *in vitro* endothelial regenerative capacity mechanisms independently of the degree of endothelial dysfunction.

Conclusions: Our results provide the possibility to establish new and personalize strategies that improve endothelial dysfunction and regenerative capacity, through different dietary patterns, by recommending consumption of a Mediterranean diet to CHD patients, in particular, to those with severe endothelial dysfunction in which consumption of a low-fat diet did not provide a beneficial effect. Those patients with non-severe endothelial dysfunction could benefit indistinctly from both dietary models.

Email: *helese35@hotmail.com*

OBESITY-INDUCED CARDIOMYOPATHY: ROLE OF FIBROBLAST GROWTH FACTOR-21

Anna Planavila[1,2,3], Celia Rupérez[1,2,3], Carles Lerin[3], Alexandra Mas-Stachurska[4], Marta Sitges[4], Marta Giralt[1,2,3], Francesc Villarroya[1,2,3]

[1]CIBER Fisiopatología de la Obesidad y Nutrición, [2]Department of Biochemistry and Molecular Biomedicine and Institut de Biomedicina (IBUB), University of Barcelona, [3]Institut de Recerca Sant Joan de Déu, [4]Cardiology Department, Thorax Institute, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Spain.

Introduction: High-fat diet-induced obesity leads to development of cardiac dysfunction through molecular mechanisms poorly known. We have recently shown that fibroblast growth factor-21 (Fgf21), an endocrine member of the FGF family, is produced by the heart and exerts protective effects preventing cardiac hypertrophy development. The aim of this study was to determine the effects of Fgf21 on the cardiomyopathy associated with obesity development.

Methods: Studies *in vivo* were performed in wild-type and *Fgf21*-null mice. Two-month-old mice were fed a high-fat diet (45% fat content) for 16 weeks to induce obesity. Systemic metabolic and hormonal profile, echocardiographic measurements, cardiac gene expression analysis, oil-red O staining, and dynamic measurement of fatty acid oxidation rates were determined.

Results: We found that high-fat diet-induced obesity significantly increased the plasma levels of Fgf21. Furthermore, high-fat feeding was associated with an increase in the heart weight/tibia length (HW/TL) ratio in wild-type mice, indicating cardiac hypertrophy. *Fgf21*-null mice presented enhanced HW/TL compared with wild-type mice after high-fat feeding. Accordingly, ecocardiographic measurements (left ventricle internal diameter, internal ventricular septum, posterior wall thickness and end-diastolic volume) confirmed enhanced cardiac hypertrophy in *Fgf21*-null mice. At the cellular level, the area of the cardiomyocytes was increased in *Fgf21*-null mice treated with the high-fat diet and was accompanied by induced expression of the hypertrophic marker gene α-Actinin. Furthermore, fatty acid oxidation in the hearts of mice fed a high-fat diet was induced in *Fgf21*-null mice. Finally, the mRNA expression levels of genes involved in lipolysis such as hormone-sensitive lipase or adipocyte triglyceride lipase were down-regulated in *Fgf21*-null mice compared to wild-type mice fed a high-fat diet. Oil-red O staining revealed the presence of higher amounts of lipid droplets in the hearts of *Fgf21*-null mice fed with a high-fat diet relative to wild-type mice fed this same diet.

Conclusions: Our data indicate that lack of Fgf21 confers more susceptibility to the cardiomyopathy induced by obesity. Furthermore, we demonstrate that this cardiac dysfunction was associated with deleterious lipid accumulation in the heart.

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aplanavila@ub.edu

USE OF THERMOGRAPHY FOR THE ASSESSMENT OF BROWN FAT ACTIVITY IN CHILDREN

Rubén Cereijo[1,2], David Sánchez-Infantes[3], Palmira Llorens[1,2], José C. Moreno[4], Verónica Nebreda[4], Marta García[4], Marta Giralt[2,3], Francesc Villarroya[2,3]

[1]CIBER Fisiopatología de la Obesidad y Nutrición, [2]Department of Biochemistry and Molecular Biomedicine, University of Barcelona, and Institut de Recerca Sant Joan de Déu, [3]Department of Endocrinology and Nutrition, Institut d'Investigació en Ciències de la Salut Germans Trias i Pujol, Badalona; [4]Institute for Medical and Molecular Genetics (INGEMM), La Paz University Hospital, Madrid, Spain.

Introduction: Obesity in children is a growing concern. Brown adipose tissue (BAT) activity is protective against obesity and associated metabolic alterations. PET-scan is the standard method for measuring BAT activity in humans; however, costs and ethics considerations preclude an extensive use, especially in pediatric populations. High resolution infrared thermography at the supraclavicular area has been proposed as a potential non-invasive method to assess BAT activity.

Objectives: Here we determined thermography-based BAT activity in relation to age, gender and responsiveness to cold and to a single meal.

Methods: Two study populations: 1) male/female healthy children (2-5 year-old, N=7; and 5-7 year-old, N=6) and adults (40-55 year-old, N=30); 2) female children (7-8 year-old), adolescents (16 year-old) and adults (50-55 year-old). No individual showed obesity or overweight on the basis of BMI. Thermal imaging was recorded using a 2.3 Megapixel Infrared Camera (FLIR Systems). Individuals were at 21° C ambient temperature. Thermal infrared pictures were obtained before and 5 min after placement of the hand into water at 18° C. In study population 1, the procedure was also performed before and 20 min after ingestion of a single meal (300 Kcal, 59% carbohydrate, 6% protein, 35% fat). The peak temperature and the surface area with a significant rise in temperature were determined at the supraclavicular fossa area as indices of activated BAT, and individually corrected for changes in surface at the non-BAT containing deltoid area.

Results: The highest rates of thermography-estimated BAT activity were found in children. Significant, but lower, BAT activity appeared in adolescents, and a minor activity was found in adults. No differences due to gender were found. In children, BAT activity was induced not only by cold but also after a single meal. The basal skin temperature at the supraclavicular BAT area correlated negatively with the BMI in children.

Conclusions: Thermography-based estimations of BAT activity evidence the strong age-dependent decline. BAT activation was responsive not only to cold but also to a single meal, at least in children. Thermography-based methodologies despite several limitations, appear useful for studies of BAT activity in pediatric populations.

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rcereijo@ub.edu

MODULATION OF HUMAN SUBCUTANEOUS ADIPOSE TISSUE MICRORNAS PROFILE ASSOCIATED TO CHANGES IN ADIPOSITY-RELATED

Simona Giardina[1,2], Pablo Hernández-Alonso[1,2], Jordi Salas-Salvadó[1,2], Toni Rabasa-Soler[1], Mònica Bulló[1,2]

1 Human Nutrition Unit, Faculty of Medicine and Health Sciences, Institute of Health Pere Virgili, Universitat Rovira i Virgili, Reus, Spain.

2 CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III (ISCIII), Madrid, Spain.

Introduction: In the last few years evidences have pointed out the importance of microRNAs (miRNAs) in the development of obesity and its related disorders, especially targeting the adipose tissue. However, there is a lack of information regarding whether changes in adipose tissue miRNAs' expression are due to the magnitude of weight lost or the quality of dietary interventions.

Objective: In the context of the GLYNDIET study, we aimed to analyze the effect of three caloric-restricted diets, differing in the amount and quality of carbohydrates, on the subcutaneous adipose tissue miRNAs' profile.

Methods: The GLYNDIET study is a 6-month, parallel, randomized clinical trial conducted on overweight and obese subjects randomized to one of the following dietary intervention group: 1) a moderate-carbohydrate and low glycemic index diet (LGI), 2) a moderate-carbohydrate and high glycemic index diet (HGI), and 3) a low-fat and high glycemic index diet (LF). The genome-wide adipose tissue's miRNA profile was assessed by TaqMan Low Density Array (TLDAs) assay in 8 randomly selected participants. The most relevant miRNAs (n=13) were validated in 48 subjects at baseline and after the dietary interventions.

Results: None of the miRNAs analyzed showed significant changes in their expression between the intervention groups. However, changes in some of them correlated with changes in biochemical and anthropometric variables. Stratifying our population according to tertiles of percentage change in body weight, waist circumference and fat mass, we observed a significant down-regulation of miR-210 in those subjects with higher reductions in weight (Tertile 1) compared to Tertile 3. Stratifying our population by tertiles of waist circumference, miR-132, miR-29a, miR-34a and miR-378 were found down-regulated, but the highest degree of down-regulation was observed in T2 compared to T3 (U-shape). Furthermore, when stratified by tertiles of fat mass, we observed also the significant down-regulation of miR-132 in T1.

Conclusion: The macronutrient composition of a caloric restricted diet does not affect the expression of the miRNAs analyzed, while changes in adiposity play a primary regulator role.

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PLASMA TRIMETHYLAMINE-N-OXIDE AND RELATED METABOLITES INVOLVEMENT WITH THE RISK FOR TYPE 2 DIABETES IN THE PREDIMED TRIAL

Christopher Papandreou[1,2], Mònica Bulló[1,2], Yan Zheng[3], Miguel Ruiz-Canela[2,4], Edward Yu[3], Marta Guasch-Ferré[1,2,3], Estefanía Toledo[2,4], Clary Clish[5], Dolores Corella [2,6], Ramon Estruch[2,7], Emilio Ros[2,8], Montserrat Fitó[2,9], Fernando Arós[2,10], Miquel Fiol[2,11], José Lapetra[2,12], Lluís Serra-Majem[2,13], Enrique Gómez-Gracia[14], Liming Liang[15], Georgios A. Fragkiadakis[16], Cristina Razquin[2,4], Frank B Hu[3,15,17], Jordi Salas-Salvadó[1,2].

[1]Human Nutrition Unit, Faculty of Medicine and Health Sciences, Institut d'Investigació Sanitària Pere Virgili, Rovira i Virgili University, Reus, Spain; [2]CIBER Fisiopatología de la Obesidad y Nutrición (CIBERObn), Instituto de Salud Carlos III, Madrid, Spain; [3]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA; [4]University of Navarra, Department of Preventive Medicine and Public Health, Pamplona, Spain; [5]Broad Institute of MIT and Harvard University, Cambridge, MA, USA; [6]Department of Preventive Medicine, University of Valencia, Valencia, Spain; [7]Department of Internal Medicine Department of Endocrinology and Nutrition Institut d'Investigacions Biomediques August Pi Sunyer (IDI- BAPS), Hospital Clinic, University of Barcelona, Barcelona, Spain; [8]Lipid Clinic, Department of Endocrinology and Nutrition Institut d'Investigacions Biomediques August Pi Sunyer (IDI- BAPS), Hospital Clinic, University of Barcelona, Barcelona, Spain; [9]Cardiovascular and Nutrition Research Group, Institut de Recerca Hospital del Mar, Barcelona, Spain; [10]Department of Cardiology, University Hospital of Alava, Vitoria, Spain; [11]Institute of Health Sciences IUNICS, University of Balearic Islands and Hospital Son Espases, Palma de Mallorca, Spain; [12]Department of Family Medicine, Primary Care Division of Sevilla, San Pablo Health Center, Sevilla, Spain; [13]Department of Clinical Sciences, University of Las Palmas de Gran Canaria, Las Palmas, Spain; [14]Department of Preventive Medicine, University of Málaga, Málaga, Spain; [15]Departments of Epidemiology and Statistics, Harvard T.H. Chan School of Public Health, Boston, MA, USA; [16]Department of Nutrition & Dietetics, Technological Education Institute of Crete, Crete, Greece; [17]Channing Division for Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, MA, USA.

Introduction: The role of trimethylamine-N-oxide (TMAO) in type 2 diabetes (T2D) is currently partially understood and even controversial.

Objective: We aimed to investigate possible associations between TMAO and metabolites involved in related pathways, with the risk of T2D.

Methods: This study is a case-cohort design within the PREDIMED trial, with 251 incident T2D cases and 694 non-cases. We used liquid chromatography-tandem mass spectrometry to measure plasma TMAO, L-carnitine, betaine, lyso-phosphatidylcholine (LPC) and lyso-phosphatidylethanolamine (LPE) species, phosphocholine, alpha-glycerophosphocholine and choline, both at baseline and after 1-year follow-up. We examined possible associations of T2D, TMAO and the other metabolites by using weighted Cox proportional hazard models, while accounting for the weighted case-cohort design by using the Barlow method.

Results: After adjusting for age, sex, body mass index, glucose, smoking and other T2D risk factors, individuals in the highest quartile of baseline TMAO and alpha-glycerophosphocholine appeared to have lower risk of T2D compared to those in the lowest quartile; hazard ratio (HR) 0.52 (95% CI

0.29-0.89) and 0.46 (95% CI 0.24-0.89), respectively. The HR (95% CI) comparing the extreme quartiles of betaine was 0.41 (0.23-0.74, *P*-trend= 0.003), with similar trends were observed for C16:0 LPC, C18:1 LPC, C18:0 LPC, C20:4 LPC, C22:6 LPC, C18:1 LPC plasmalogen and C16:0 LPE (*P*-trend< 0.05). After 1-year, in the highest quartile of increase in TMAO, LPC, C16:0 LPE, and alpha-glycerophosphocholine, significant associations with decreased T2D risk were observed.

Conclusions: We detected inverse associations between plasma TMAO and related metabolites levels with T2D risk. Whether they are causal factor in T2D pathophysiology or participate in an epiphenomenon is not clear yet.

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Christopher Papandreou. E-mail: papchris10@gmail.com

DIETARY SKIN WALNUT SUPPLEMENTATION DELAYS PROGRESSION OF ATHEROSCLEROSIS LESION IN APOE-DEFICIENT MICE IN COMPARISON WITH PALM OLIVE OIL

Sonia Gascón[1]; Luis Vicente Herrera [2]; Cristina Barranquero [2]; Roberto Martínez-Beamonte [2]; Joaquín Surra[2, 4]; Carmen Arnal[3,4]; Jesús de la Osada García[2,4]; María Ángeles Navarro[2,4].

[1]Departamento de Farmacología y Fisiología. Facultad de Veterinaria, CiberObn, Zaragoza ES. [2]Departamento de Bioquímica y Biología Molecular y Celular. Facultad de Veterinaria. Universidad de Zaragoza- CiberObn, Zaragoza, ES. [3]Departamento de Patología Animal. Facultad de Veterinaria. Universidad de Zaragoza, CiberObn, Zaragoza, ES. [4]Instituto de investigación sanitaria de Aragón. IIS, Zaragoza, ES.

Introduction and objective: Epidemiological studies have demonstrated benefits of nut consumption in a healthy pattern on cardiovascular risk factors and coronary heart diseases, attributed to their fatty acid profile, rich in unsaturated fatty acids, and also to other nutrients. The nut components contribution in the development of atherosclerosis remains incomplete.

Methods: The effect of walnuts on the atherosclerotic lesion was studied in female and male *Apoe*-knockout mice fed a diet supplemented with 3% (w/w) walnut and compared with mice receiving an isocaloric diet of similar fat content provided as palm oil and a third group of mice receiving only the walnut skin to evaluate its antioxidants. After 11 weeks, plasma lipid parameters, *Pcyox1* and paraoxonase family hepatic mRNA and aortic en face lesions were measured.

Results: Males receiving walnut diet had lower plasma triglycerides than palm oil group, and both sex groups receiving walnut diet had lower plasma HDL cholesterol than mice receiving the palm oil diet. Hepatic *Pon2* mRNA increased in skin walnut containing diet compared with palm oil group in both sexes, and no change was observed in *Pcyox1* expression. Females consuming the walnut and skin walnut diets showed lower hepatic *Pon3* mRNA than females consuming palm oil, and a decrease of hepatic *Pon1* mRNA was observed in males supplemented with skin walnut compared with palm oil group.

Males and females consuming the skin walnut diet showed smaller aortic lesion areas than those consuming palm oil.

Conclusions: Our results suggest that the antiatherosclerotic effect of skin walnut intake in *Apoe*-deficient mice may be attributed to higher hepatic mRNA *Pon2* expression

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Email: gasconmsonia@hotmail.com

SQUALENE AND SEPSIS

Sonia Gascón[1,2], Mª José Felices[2], Sara Escusol[2], Roberto Martínez-Beamonte[1,3], Cristina Barranquero[1,3], Joaquin Surra[1,3], Jesús Osada[1,3] and Mª Jesús Rodríguez-Yoldi[1,2]

[1] CIBEROBN. [2]Department of Pharmacology and Physiology, Veterinary Faculty. University of Zaragoza. [3]Department of Biochemistry and Molecular Biology, Veterinary Faculty. University of Zaragoza

Introduction. The septic state can cause alterations in different physiological functions of the small intestine affecting its most important function which is the absorption of nutrients. Lipopolysaccharide (LPS) is a complex polymer forming part of the outer membrane of Gram negative bacteria.

Olive oil, the main source of the fat in the Mediterranean diet, is a functional food which besides having high amounts of monounsaturated fatty acid contains minor components with biological properties such as squalene. This component is a natural lipid belonging to the terpenoid family and a precursor of cholesterol biosynthesis.

Aim. Study if rabbit feed with a rich squalene diet could change the LPS effect on intestinal absorption of D-galactose.

Methods. In rabbit, we used two different ways to infection: acute (intravenous administration of LPS) and chronic (the endotoxin was administrated through intraperitoneal osmotic pump). Animals were divided in two groups: standard or rich squalene diet.

Results. Squalene reduces the effects of bacterial sepsis induced by LPS in rabbits regarding processes fever and intestinal galactose malabsorption.

High LPS doses increased D-galactose uptake through paracellular via but also decreased the active sugar transport because the protein levels of SGLT1 were diminished. At the same time, we observed an increased in protein expression of Resistin-like molecule-β (RELM-β) which could cause a decrease of the protein levels of SGLT1. We also studied the interaction between LPS and MLCK, protein of paracellular way. The results showed that the endotoxin activates MLCK protein and therefore could produce an increase of sugar transport through tight junctions.The effect of LPS on paracellular way seems to be more important than on the transcellular route.

Conclusions. Since LPS inhibits the expression of SGLT1 through NF-kB and this factor is related to the anti-inflammatory effect of natural compounds such as squalene and also the endotoxin modified the MLCK expression, we can conclude that this triterpene could inhibit the effect of LPS on D-galactose intestinal absorption through NF-kB factor and MLCK protein.

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Email: gasconmsonia@hotmail.com

QUANTITATIVE ANALYSIS OF RAT ADIPOSE TISSUE CELL RECOVERY, AND NON-FAT CELL VOLUME, IN PRIMARY CELL CULTURES

Xavier Remesar[1,2,3], Floriana Rotondo[1,2], María del Mar Romero[1,2,3], Ana Cecilia Ho- Palma[1], José Antonio Fernández-López[1,2,3] and Marià Alemany[1,2,3]

[1] Department of Biochemistry and Molecular Biomedicine, Faculty of Biology, University of Barcelona, Barcelona.

[2] Institute of Biomedicine, University of Barcelona, Barcelona.

[3] CIBER OBN.

Background. White adipose tissue (WAT) is a complex, diffuse, multifunctional organ which contains adipocytes, but also other cell types, active in defence, regeneration and signalling functions. Studies with adipocytes often require their isolation from WAT by breaking up the matrix of collagen fibres; however, it is unclear to what extent adipocyte number in primary cultures correlates with their number in intact WAT, since recovery and viability are often unknown.

Experimental Design. Epididymal WAT of four young adult rats was used to isolate adipocytes with collagenase. Careful recording of lipid content of tissue, and all fraction volumes and weights, allowed us to trace the amount of initial WAT fat remaining in the cell preparation. Functionality was estimated by incubation with glucose and measurement of glucose uptake and lactate, glycerol and NEFA excretion rates up to

48 h. Non-adipocyte cells were also recovered and their sizes (and those of adipocytes) were measured. The presence of non-nucleated cells (erythrocytes) was also estimated.

Results. Cell numbers and sizes were correlated from all fractions to intact WAT. Tracing the lipid content, the recovery of adipocytes in the final, metabolically active, preparation was in the range of 70_75%. Cells showed even higher metabolic activity in the second than in the first day of incubation. Adipocytes were 7%, erythrocytes 66% and other stromal (nucleated cells) 27% of total WAT cells. However, their overall volumes were 90%, 0.05%, and 0.2% of WAT. Non-fat volume of adipocytes was 1.3% of WAT.

Conclusions. The methodology presented here allows for a direct quantitative reference to the original tissue of studies using isolated cells. We have also found that the ``live cell mass'' of adipose tissue is very small: about 13 mL/g for adipocytes and 2 mL/g stromal, plus about 1 mL/g blood (the rats were killed by exsanguination). These data translate (with respect to the actual "live cytoplasm'' size) into an extremely high metabolic activity, which make WAT an even more significant agent in the control of energy metabolism.

xremesar@ub.edu

REGULATION OF DIET-INDUCED THERMOGENESIS BY HYPOTHALAMIC CPT1C AND THE ENDOCANNABINOID SYSTEM

R. Rodríguez-Rodríguez [1], C. Miralpeix [1], L. Herrero[2,3]; D. Serra[2,3]; N. Casals [1,2],

[1]. Facultad de Medicina y Ciencias de la Salud, Universitat Internacional de Catalunya, Sant Cugat del Vallés, Spain

[2]. CIBER Fisiopatología de la Obesidad y la Nutrición (CIBEROBN), Instituto de Salud Carlos III, Madrid, Spain

[3]. Facultad de Farmacia. Universitat de Barcelona, Barcelona, Spain.

Brain-specific carnitine palmitoyltransferase-1C (CPT1C) is implicated in central regulation of food intake and energy homeostasis. CPT1C-KO mice show increased susceptibility to diet-induced obesity and an impaired regulation of food intake. However, it is completely unknown whether CPT1C is involved in hypothalamic regulation of thermogenesis. Here we explore the role of CPT1C in leptin- and diet-induced thermogenesis in brown adipose tissue (BAT) and the mechanisms involved.

CPT1C KO and WT mice were fed a standard or high fat diet (HFD) for 7 days. In WT mice, HFD significantly increased interscapular BAT (iBAT) temperature and thermogenic markers expression, while these parameters were lower in CPT1C KO mice. Moreover, KO animals showed a reduced increase of BAT thermogenesis in response to intracerebroventricular injection of leptin. Phenotype reversion studies identified the mediobasal hypothalamus (MBH) as the area of CPT1C activity responsible for those effects.

Evaluation of the mechanisms involved revealed increased levels of ER stress markers and dysregulation of leptin signaling in MBH from CPT1C KO mice compared to WT mice. In order to elucidate the molecular mechanism of CPT1C effects, we performed proteomic analysis to identify the main interactors of CPT1C. Results revealed ABHD6, a hydrolase that regulates the levels of the endocannabinoid 2-AG, as one of the main interactors of CPT1C. FRET analysis and co-immunoprecipitation studies confirmed the interaction. Moreover, CPT1C KO mice showed increased 2AG levels in the hypothalamus, which is known to be related with an obesogenic phenotype.

Therefore, our data demonstrate that CPT1C is crucial in the hypothalamic control of BAT thermogenesis in response to HFD or leptin signaling through the regulation of ABHD6 and endocannabinoid levels.

DIETARY IMPACT ON THE CENTRAL AND CIRCULATING IGF SYSTEMS

Santiago Guerra-Cantero[1,2], Francisca Díaz[1,2], Purificación Ros[3,4], Alejandra Freire-Regatillo[1,2,4], Pilar Argente-Arizón[1,2], Vicente Barrios[1,2], Julie A. Chowen[1,2], Jesús Argente[1,2,4,5]

[1]CIBEROBN, [2]Department of Endocrinology, Hospital Infantil Universitario Niño Jesús, Instituto de Investigación La Princesa, [3]Hospital Universitario Puerto de Hierro-Majadahonda, Madrid, [4]Department of Pediatrics, Universidad Autónoma of Madrid, Madrid, [5]IMDEA Food Institute, CEI UAM + CSIC, Madrid.

Introduction: Insulin-like growth factor (IGF) exerts both metabolic and neuroprotective effects, but little is known regarding the role of the new members of the IGF system (pappalysins and stanniocalcins) in these processes. Moreover, as astrocytes mediate the neuroprotective effects of IGF1, we hypothesized that the IGF system of these glial cells could be modified by dietary signals.

Objectives: 1) Analyze the IGF system in serum and the hypothalamus in response to short-term high fat diet (HFD) or low fat diet (LFD) intake. 2) Determine if palmitic acid (PA) modifies the IGF1 system in primary astrocyte cultures. 3) Examine if exogenous IGF1 blocks the toxic effects of PA in astrocytes.

Methods: Male and female Wistar rats were given a HFD (60% fat, 5.1 kcal/g), LFD (10% fat, 3.76 kcal/g) or normal rat chow (Ct, 3.1 % fat, 2.9 kcal/g) for 1 week (n = 6). Primary astrocyte cultures were treated 24h with PA (0.25 or 0.5 mM), IGF1 (10 or 50 ng/ml) or both. Gene expression in the hypothalamus and in astrocyte cultures was measured by RT-PCR. Serum hormone levels were measured by ELISA.

Results: Males on a HFD gained more weight than those on a LFD or chow, with no effect in females. Males had higher levels of total and free IGF1, IGFBP3 and BP5 than females, while females had higher PAPP-A2 levels. These factors were not affected by the short-term dietary change. In the hypothalamus, LFD increased IGF2 mRNA levels, but this was only statistically significant in male LFD rats ($p<0.02$). In both hypothalamic and hippocampal astrocyte cultures, PA induced a marked decrease in the IGF1 system, except in PAPP-A which increased. Markers of cell stress and cytokine production were also increased. Exogenous IGF1 was unable to revert the harmful effects of PA.

Conclusions: 1) The hypothalamic expression of IGF2 is altered by LFD intake and this deserves further investigation. 2) Palmitic acid markedly alters the IGF1 system in astrocytes, which could potentially be involved in the cell damage caused by this fatty acid.

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santiguerra8@gmail.com

ASSOCIATION OF PHYSICAL ACTIVITY AND SEDENTARISM WITH CARDIORESPIRATORY FITNESS (MAXIMAL OXYGEN UPTAKE) IN THE PREDIMED-PLUS TRIAL

L. Tojal [2], I Salaverría[1], A Alonso-Gómez [1,2], J Rekondo[1,2] , F Arós[1,2]

[1] CIBEROBN, [2] Department of Cardiology, OSI Araba, University Hospital Vitoria-Gasteiz, Spain

INTRODUCTION: Physical activity is a measure of primary and secondary prevention of cardiovascular disease related to the cardiorespiratory fitness which is an independent predictor of cardiovascular mortality. However, physical fitness is rarely determined in an objective manner by ergoespirometry in the absence of cardiovascular disease. On the other hand, sedentary behaviors have been linked to increased cardiovascular morbimortality

OBJECTIVES: The aim of this study is to examine the association between self-reported physical activity and sedentarism with the cardiorespiratory fitness evaluated by ergoespirometry with direct determination of maximal oxygen uptake

MATERIALS AND METHODS: The present investigation is a cross-sectional analysis on baseline data from participants in one center (Vitoria-Gasteiz) of the PREDIMED PLUS trial (multicenter, randomized, primary cardiovascular prevention clinical trial in patients with overweight/obesity who met at least three components of metabolic syndrome). At entry patients performed a maximal exercise testing on treadmill according to ramp Bruce protocol with expired gas analysis (Vitoria-Gasteiz is the only center of PREDIMED PLUS study where a ergoespirometry was included in the protocol). In addition, following the general protocol, patients completed the validated questionnaires: NHS (Nurses Health Study) for sedentary lifestyle and the REGICOR , RAPA 1 (Rapid Assessment of Physical Activity) and chair test for physical activity

RESULTS: Of the 274 patients recruited in Vitoria, 243 fulfilled the criteria of maximal exercise testing (age: 65±5 years; BMI: 32,5±3,4; 66,3%:male). According RAPA 1 and chair test classification groups (slightly active, moderately active and active) pphysical activity reached a maximal oxyen uptake of 21,3±4,6 vs 18±4,4 ml/min/kgr of patients with < 150 min/week. Television time as a proxy for sedentary behaviors was not associated to differences in oxygen consumption: ≤ 2 h/day, 2-4 h/day, >4 h/day: 22.5±4,5; 20,5±5; 19,4±4,7 respectively (p:. 310)

CONCLUSIONS: In patients with overweight/obesity and metabolic syndrome, physical activity assessed by validated questionnaires is properly associated to peak oxygen consumption while sedentary behaviors do not seem to influence the physical fitness.

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e-mail: L. Tojal Sierra: lutojal@hotmail.com

FACTORS ASSOCIATED WITH STUNTING AMONG CHILDREN AGED 0 TO 59 MONTHS FROM THE CENTRAL REGION OF MOZAMBIQUE

Loida María García Cruz[2,3], Gloria González Azpeitia[2,4], Desiderio Reyes Súarez[2,4], Alfredo Santana Rodríguez[3], Juan Francisco Loro Ferrer[4] and Lluis Serra Majem[1,5,]*

1. CIBEROBN (CB06/03), Instituto Carlos III, Spanish Government, 28029 Madrid, Spain
2. Research Institute of Biomedical and Health Sciences, University of Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain
3. Clinical Genetics Unit, Complejo Hospitalario Insular-Materno Infantil, 35016 Las Palmas de Gran Canaria, Spain
4. Department of Clinical Sciences, University of Las Palmas de Gran Canaria, 35016 Las Palmas de Gran Canaria, Spain
5. Research Institute of Biomedical and Health Sciences, University of Las Palmas de Gran Canaria / Nutrition Without Borders, 35016 Las Palmas de Gran Canaria, Spain

INTRODUCTION: Undernutrition is a major public health problem that increases the global health burden of premature mortality and morbidities during childhood. It accounts for 45% of all deaths in children under five years of age. More than two million children under five years of age die each year due to undernutrition around the world. 'The UNICEF's Annual Reports' consistently show the prevalence of stunting in Sub-Saharan Africa to be around 30–40%, varying per country or region or urban versus rural environment. According to 'The 2016 Global Nutrition Report', the prevalence of stunting in Mozambique in children under the age of five years is still high (43.3%) while the underweight (19%) and wasting (5.9%) categories are decreasing.

OBJECTIVE: The objective of this study was to identify the major socio-demographic, health, and environmental determinants of stunting among children aged 0–59 months from the Tete province (Mozambique) and offering useful information for future healthcare strategies and interventions.

MATERIAL AND METHODS: A case-control study was conducted among 282 (162 boys; 120 girls) children under five years of age from the central region of Mozambique between 1 May and 3 June 2014. Children with stunting (HAZ < 2 SD according to the WHO Child Growth Standards in 2006) were considered as cases and those who had a Z-score < 2 SD were considered as controls. We collected data related to mothers and children and their environment, and they were assessed in two groups to find a possible association. The software used for data analysis was the SPSS® (version, 21.0) using descriptive statistics, t-test, ANOVA, chi-square analyses, bivariate comparisons, and stepwise multiple logistic regression analysis.

RESULTS: The results showed that birth weight, mother's educational status, maternal occupation, living in a rural area, family size, number of children under five years of age in the household, cooking with charcoal, inhabiting wooden or straw housing or housing without proper floors, overall duration of breastfeeding as well as duration of exclusive breastfeeding, and time of initiation of complementary feeding were significantly related to stunting.

CONCLUSIONS: Thus, appropriate nutritional intervention programmes considering these determinants and the dissemination of knowledge at the population level related to undernutrition are necessary to ameliorate the children´s nutritional status.

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Correspondence: lluis.serra@ulpgc.es

LA ISLA EN TU PLATO (THE ISLAND ON YOUR PLATE)

Ll. Serra-Majem[1,2,4]E. González-Padilla[2], C. Ruano-Rodríguez[1,2], A.L. Álvarez-Falcón[1,3], Álvarez Pérez J[1,2],

[1] CIBER OBN, Instituto Carlos III, Spanish Government, 28029 Madrid, Spain

[2] Nutrition Research Group of the Research Institute of Biomedical and Health Sciences, University of Las Palmas de Gran Canaria (ULPGC), Canary Islands, Spain.

[3] University Hospital of Gran Canaria "Doctor Negrín", Canary Islands, Spain.

[4] UNESCO Chair of Local Health Systems and Food Systems, Research Institute of Biomedical and Health Sciences, University of Las Palmas de Gran Canaria (ULPGC), Canary Islands, Spain.

INTRODUCTION: The Mediterranean Diet is considered to be the epitome what a Sustainable Diet means. "The Island on Your Plate" is a project that intends to draw attention towards the gastronomic diversity of the island of Gran Canaria (Canary Islands, Spain). Doing so through a proactive intervention on the dietary pattern of the island of Gran Canaria to encourage a more sustainable diet by adapting the local habits to a traditional Mediterranean-Diet. The main goals of this initiative include the revitalization of the concept of a traditional proximity diet; the promotion of the consumption of local products that meet the standards of freshness, sustainability and diversity; as well as the empowerment and diffusion of the traditional food system of Gran Canaria and the benefits of the Mediterranean Diet style. As a secondary goal, it aims to open the dialogue for the creation of a Museum of Mediterranean Diet in Gran Canaria.

MATERIAL AND METHODS: A study was conducted regarding the various food groups integrated in the local and traditional production in Gran Canaria, taking the basic elements of the Mediterranean Diet. Afterwards, a thorough analysis took place collecting the details related to the production and elaboration process, popular culture and an assortment of traditional recipes that shape a sustainable diet on the island.

RESULTS AND DISCUSSIONS: As a result, a document on ebook format was elaborated to bring attention to the richness of Gran Canaria's gastronomy and the importance that it has over the health status, the environment, the culture and the local economy. Alongside, this project has manifested the possibility to make a significant change on Gran Canaria's dietary pattern to promote and encourage a sustainable diet of proximity that is balanced, varied, and healthy and to bring it closer to the Mediterranean Diet pattern. Moreover, an Expert Meeting took place, in collaboration with other National and International Institutions, that culminated on the elaboration of the Decalogue of a Healthy Diet in the Community: Gran Canaria Declaration. A video has been elaborated and distributed in different channels. In addition, an online platform was created to divulge information regarding other initiatives -both public and private- that promote the ideology behind food sustainability. This platform invites citizens and professionals alike to interact with other departments and institutions with a similar interest for the creation of future sustainability plans and policies.

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de Municipios de las Medianías de Gran Canaria, CIHEAM, Ayuntamiento de la Villa de San Mateo, Research Institute of Biomedical and Health Sciences, University of Las Palmas de Gran Canaria (ULPGC), IACON, CHSMAN.

Correspondence: lluis.serra@ulpgc.es

EFFECT OF MEDITERRANEAN DIET ON ATHEROSCLEROTIC BURDEN PROGRESSION MEASURED BY IMAGING TECHNIQUES

Rosa Casas[1,2], Miguel Camafort[1,2*], Gabriel Frontana[2], Ana M. Ruiz-León[1,2], Marina Sadurní[1,2], Aleix Sala-Vila[1,3], Rosa Gilabert[4], Emilio Ros[1,3], Montse Fitó[1,5], Xavier Pintó[1,6] and Ramon Estruch[1,2]*

[1]CIBER de Fisiopatologia de la Obesidad y la Nutrición (CIBEROBN 0603), Instituto de Salud Carlos III; [2]Department of Internal Medicine, Hospital Clínic, Institut d'Investigació Biomèdica August Pi i Sunyer, Universitat de Barcelona, Spain; [3]Lipid Clinic, Endocrinology and Nutrition Service, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Hospital Clínic, Barcelona, Spain; [4]Diagnostic Imaging Centre, IDIBAPS, Hospital Clínic, Barcelona, Spain; [5]Cardiovascular Risk and Nutrition and REGICOR research group, Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain; [6]Lipids and Vascular Risk Unit, Internal Medicine, Hospital Universitario de Bellvitge, Barcelona , Spain; *Equal contribution.

Introduction: Several epidemiological studies have shown that greater adherence to the Mediterranean Diet (MD) is associated with a lower incidence of coronary heart disease and mortality. However, how the MD exerts its effects is not fully known.

Objectives: The aims of this study were to compare the effects of an intervention with MD plus extra-virgin olive oil (EVOO) or nuts with a control group, to evaluate the plasma concentrations of inflammatory biomarkers and to correlate the data with changes at medium-term in intima-media thickness of the common carotid artery (CCA-IMT) and plaque height measured by ultrasonography in elderly healthy subjects at high risk for CVD.

Methods: We evaluated 120 participants from Primary Care Centers affiliated with the Hospital Clínic of Barcelona and the "Principes de España" Hospital who were randomized into 3 groups: MD plus extra-virgin olive oil (EVOO) or nuts, and a low-fat diet (LFD). Using standard carotid ultrasonography we assessed ICA-IMT and carotid plaque height at baseline and after a mean of 2.4 years of dietary intervention.

Results: After 2.4 y of follow-up, participants allocated to MD+nuts group and with the same $plaque_{max}$ at baseline experienced a significant reduction in the maximum plaque height (0.17-0.26 mm) because of changes in plasmatic concentrations of sVCAM-1, sICAM-1, MCP-1, TNF-α, IL-6, IL-18 and hs-CRP compared with the LFD (P<0.05;all). This group, with the same $ICA\text{-}IMT_{max}$ at baseline, showed a statistically significant reduction of the maximum ICA-IMT (0.20-0.22 mm) because of changes in plasmatic concentrations of MCP-1, IL-1α, IL-6, IL-10 and hs-CRP after the MeDiet+nuts intervention group compared with the LFD (P<0.05;all). $ICA\text{-}IMT_{max}$ was also reduced (0.17- 0.21 mm) because of changes in concentrations of sVCAM-1, TNF-α, IL-6 after MeDiet+EVOO intervention compared with LFD.

Conclusions: A dietary intervention with MD+nuts seems to have an immunomodulatory effect on the inflammatory molecules that is correlated with ultrasonography carotid changes (plaque height and ICA-IMT, mainly). This beneficial effect could be related to a decreased recruitment of macrophages into the arterial wall.

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*rcasas1@clinic.ub.es

THE EFFECTS OF THE MEDITERRANEAN DIET ON GENE EXPRESSION RELATED WITH CARDIOVASCULAR DISEASE

Rosa Casas[1,2]; Mireia Urpi-Sarda[3]*; Emilio Sacanella[1,2], Dolores Corella[2,4], Cristina Andres-Lacueva[3], Rafael Llorach[3], Gloria Garrabou[1], Francesc Cardellach[1], Emilio Ros[5], Miguel Ruíz-Canela[6], Montserrat Fitó[7], Jordi Salas-Salvadó[8], Ramon Estruch[1,2].*

[1]Department of Internal Medicine, Hospital Clinic, Institut d'Investigació Biomèdica August Pi i Sunyer (IDIBAPS), Villarroel 170, 08036 Barcelona, Spain; [2]CIBER 06/03: Fisiopatología de la Obesidad y la Nutrición, Instituto de Salud Carlos III; [3]Department of Nutrition, Food Science and Gastronomy, Faculty of Pharmacy and Food Sciences, Campus Torribera, University of Barcelona, Sant Coloma de Gramanet, 08921, Spain; [4]Department of Preventive Medicine, University of Valencia, Valencia, Spain; [5]Lipid Clinic, Service of Endocrinology & Nutrition, IDIBAPS, Hospital Clinic, Barcelona, Spain; [6]Department of Preventive Medicine and Public Health, School of Medicine, University of Navarra, Pamplona, Spain; [7]Cardiovascular Risk and Nutrition (Regicor Study Group), Hospital del Mar Research Institute (IMIM), Barcelona, Spain.; [8]Human Nutrition Unit, Hospital Universitari de Sant Joan de Reus, IISPV, Universitat Rovira i Virgili, Reus, Spain. *Equal contribution.

Introduction: A reduced incidence of coronary heart disease and mortality is associated with a higher adherence to a Mediterranean diet (MD). The signaling pathways related to atherogenesis that could be affected by the MD at gene levels are still unknown.

Methods: A total of 285 participants in the PREDIMED (Prevención con Dieta Mediterránea) trial were randomly assigned into 3 intervention groups: MD supplemented with extra-virgin olive oil (MD-EVOO) or nuts (MD-Nuts), and a low-fat diet (LFD). Fourteen plasma inflammatory biomarkers and high sensitivity C-reactive protein (hs-CRP) were determined by Luminex and standard enzyme-linked immunosorbent assay, respectively, at baseline and after 3 years. In addition, the expression of 10 genes related to atherosclerosis were determined by RT-PCR.

This trial was registered at controlled-trials.com as ISRCTN35739639.

Results: After 3 y. participants following one of the two MDs showed significantly decreased plasma levels of MCP-1 (P<0.001, both), MIP-1β (P<0.036, both), ENA78 (P<0.001, both), IL-1β (P<0.05, both), IL-6 (P<0.014, both), IL-8 (P<0.034, both), TNF-α (P<0.047, both), IFN-γ (P<0.027, both) and hs-CRP (P<0.015, both), while no significant changes were observed in these biomarkers in the LFD group (P>0.05), except for hs-CRP that showed a trend to reduction (P=0.066). We detected a significant increase (P<0.05) in gene expression levels for TLR2 and CCR2 by 10%, TLR6 by 10%, CCR5 and CXCR3 by 6% and CXCR2 by 23% and after 3 y of LFD, while no changes were observed after intervencion with MD in both MDs groups.

Conclusions: A MD pattern decreases plasma levels of inflammatory molecules and avoids changes in gene expression related to atherosclerosis after 3 years in elderly subjects at high cardiovascular risk, while a LFD promotes gene expression of inflammatory markers. These results could imply that the MD modulates inflammation related to aging over the time.

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*rcasas1@clinic.ub.es

HEPATIC P63 REGULATES STEATOSIS VIA IKKβ/ER STRESS

Begoña Porteiro[1,2], Marcos F. Fondevila[1,2], Teresa C. Delgado[3], Cristina Iglesias[1], Monica Imbernon[1,2], Paula Iruzubieta[3], Bárbara González-Terán[4], Sulay Tovar[1,2], Anxo Vidal[1], Julia Sánchez-Ceinos[2,5], Maria del Mar Malagón[2,5], Celia Pombo[1], Juan Zalvide[1], Arkaitz Carracedo[3], Xabier Buque[6,7], Carlos Dieguez[1,2], Guadalupe Sabio[4], Miguel Lopez[1,2], Patricia Aspichueta[6,7], María L. Martínez-Chantar[3], Ruben Nogueiras[1,2]

[1] Department of Physiology, CIMUS, University of Santiago de Compostela-Instituto de Investigación Sanitaria, Spain

[2] CIBER Fisiopatología de la Obesidad y Nutrición (CIBERobn), Spain

[3] CIC bioGUNE, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Technology Park of Bizkaia, Spain

[4] Centro Nacional de Investigaciones Cardiovasculares Carlos III, Madrid, Spain

[5] Instituto Maimónides de Investigacion Biomédica de Córdoba, Hospital Universitario Reina Sofia/University of Cordoba, Spain

[6] Department of Physiology, University of the Basque Country UPV/EHU, Spain.

[7] Biocruces Research Institute, Spain.

Introduction: p53 family members control several metabolic and cellular functions. p63 modulates cellular adaptations to stress and plays a major role in cell maintenance and proliferation.

Objectives: We demonstrate the role of endogenous p63 in hepatic lipid metabolism.

Methods: We perform *in vivo* adeno-associated and lentiviral gene transfer to over-express and silencing p63 in the mice liver by tail vein injection. TAp63 was silenced in THLE2 cells (human cell line of primary hepatocytes) treated with oleic acid using a siRNA. THLE2 cells were transfected with a plasmid encoding p63 and then co-transfected with a siRNA IKKb. After treatments, biochemical analysis were performed: bodipy immunofluorescence, hepatic triglyceride content, real time PCR and western blot.

Results: Mice with liver-specific p53 deletion develop steatosis and show increased levels of p63. Down-regulation of p63 attenuates liver steatosis in these mice and in diet-induced obese mice. The activation of p63 in THLE2 induces lipid accumulation through IKKβ activation and ER stress, and their inhibition rescues the hepatic phenotype. TAp63, IKKβ and XBP1s are increased in the liver from obese NAFLD patients.

Conclusions: Our data show an unexpected role of the p63/IKKβ/ER stress pathway in liver disease.

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begona.porteiro@usc.es

RELATIONSHIP BETWEEN TOTAL BILIRUBIN AND PRECLINICAL CAROTID AND FEMORAL ATHEROSCLEROSIS IN FAMILIAL DYSLIPIDEMIA

Antonio J. Amor[1,2]; Aleix Sala-Vila[1,2]; Montserrat Cofán[1,2]; Emilio Ortega[1,2]; Emilio Ros[1,2]

[1]CIBEROBN; [2]Lipid Clinic, Endocrinology and Nutrition Service, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Hospital Clínic, Barcelona

BACKGROUND: Bilirubin, an endogenous antioxidant, has been inversely associated with preclinical atherosclerosis in some studies, but information in familial dyslipidemia is lacking.

AIM: We aimed to assess the associations between total bilirubin with preclinical carotid and femoral atherosclerosis in this high-risk group.

METHODS: We studied 464 subjects with familial dyslipidemia (n=240, familial hypercholesterolemia; n=82, autosomic dominant hypercholesterolemia; n=142, familial combined hyperlipidemia). Bilateral carotid and femoral arteries were imaged by B-mode ultrasound with a standardized protocol. Mean and maximum intima-media thickness and plaque presence (intima-media thickness≥1.2 mm) were recorded. Cross-sectional relationships between serum total bilirubin and preclinical atherosclerosis variables were assessed in age- and sex-adjusted and fully-adjusted models (including other cardiovascular risk factors, lipid profile and statin use).

RESULTS: Of the total cohort, 56% were men and median age was 48 years. Atheroma plaques were found in 78%. In the overall sample, age- and sex-adjusted models showed an inverse relationship between total bilurrubin tertiles and mean intima-media thickness of all carotid segments (common, bulb and internal carotid; $p<0.05$ for all), without major changes in fully-adjusted models. Total bilirrubin also related to carotid plaque presence (odds ratio [95% confidence interval]; 0.33 [0.14-0.79]) and presence of ≥3 carotid plaques (0.38 [0.12-0.65]). The familial combined hyperlipidemia group (with higher inflammation-related variables, $p<0.05$ between groups) showed the strongest associations in the carotid and femoral territories. Thus, in fully-adjusted models, carotid plaque presence (0.19 [0.04-0.91]), ≥3 carotid plaques (0.14 [0.02-0.83]) and the maximum height of femoral plaques (β=-0.176, p=0.034) were inversely associated with total bilirrubin.

CONCLUSIONS: In our sample of individuals with familial dyslipidemia, total serum bilirubin was independently and inversely associated with preclinical atherosclerosis, especially in familial combined hyperlipidemia. This finding, which might be explained by the strong antioxidant capacity of bilirubin, supports the use of this simple and widely available biochemical parameter as a biomarker of atherosclerosis in this high-risk group.

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E-mail: ajamor@clinic.cat

OMEGA-3 INDEX RELATES TO LOWER PREVALENCE OF DIABETES: PROVISIONAL RESULTS OF THE DI@BET.ES STUDY

Aleix Sala-Vila[1,2]; Montserrat Cofán[1,2]; Antonio J. Amor[1,2]; Emili Ros[1,2]; Emilio Ortega[1,2]

[1]CIBEROBN; [2]Lipid Clinic, Endocrinology and Nutrition Service, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Hospital Clínic, Barcelona

BACKGROUND: The issue of whether dietary omega-3 fatty acids protect against diabetes remains controversial. Clinical data on the topic is limited to several epidemiological studies, mostly conducted in United States. Very few used objective biomarkers of long-term intake of omega-3 fatty acids. A similar study has not been conducted in a Mediterranean country.

AIM: In the frame of the study Di@bet.es, which comprises a population representative of all the Spanish territory, we cross-sectionally related the omega-3 index (the sum of the erythrocyte membrane proportions of the marine omega-3 fatty acids eicosapentaenoic and docosahexaenoic) at the time of enrolment to different categories of glucose metabolism: normal glucose regulation, pre-diabetes (impaired fasting glucose and/or impaired glucose tolerance), unknown diabetes, and diagnosed diabetes.

METHODS: From the Di@bet.es study cohort, stored blood is available in 4856 participants. To date we have determined the omega-3 index by gas chromatography in 1332 subjects. We constructed multivariate logistic regression models to search for associations between the omega-3 index and the prevalence of prediabetes, total diabetes, and known diabetes, adjusting for age, gender, smoking status and physical activity.

RESULTS: The study population (57% women, mean age 49±17 years, range 18-89 years) was distributed as follows: normoglycemia = 991 (74.4%); prediabetes = 162 (12.2%); unknown diabetes = 55 (4.1%); known diabetes = 124 (9.3%). The mean value of the omega-3 index was 5.88±1.53. Compared to participants in the lowest quartile of omega-3 index, those in the highest quartile showed lower prevalence of total (known and unknown) diabetes (Odds Ratio [OR]=0.465, 95% confidence interval [CI] 0.280-0.771, P=0.003; P for trend=0.023). An inverse association was also observed for known diabetes (OR=0.387, CI 0.170-0.878, P=0.023, P for trend=0.140). No association was found for prevalence of prediabetes.

CONCLUSIONS: Our preliminary results point to an inverse association between the omega-3 index and diabetes in a Mediterranean population. A longitudinal study of the Di@bet.es cohort is underway to determine whether diabetes incidence also relates to the omega-3 index, which would provide a higher level of evidence for the protective effect of marine omega-3 fatty acids.

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E-mail: asala@clinic.ub.es

POSTPRANDIAL ENDOTOXEMIA MAY INFLUENCE THE DEVELOPMENT OF TYPE 2 DIABETES MELLITUS

Antonio Camargo[1,2], Elena M. Yubero-Serrano[1,2], Javier Lopez-Moreno[1,2], Rosa Jimenez-Lucena[1,2], Cristina Vals-Delgado[1,2], Juan F. Alcala-Diaz[1,2], Oriol A. Rangel-Zuñiga[1,2], Pablo Perez-Martinez[1,2], Jose Lopez-Miranda[1,2].

[1]CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, Cordoba, Spain. [2]Lipids and Atherosclerosis Unit, GC9 Nutrigenomics, Maimonides Biomedical Research Institute of Cordoba (IMIBIC), Reina Sofia University Hospital, University of Cordoba, Spain.

Introduction: Intestinal absorption of bacterial components activates the toll-like receptors inducing inflammation, and this in turn, insulin resistance.

Objective: We aimed to assess the differences in LPS and LBP levels in a postprandial test (fat challenge), before and after the development of type 2 diabetes (New-DIAB) as compared with patients who did not develop diabetes during this period (Non-DIAB).

Research Design and Methods: The study was performed with 462 patients included in the CORDIOPREV study, who had not been diagnosed with diabetes. Of these, 107 patients developed type 2 diabetes (T2DM) according to the American Diabetes Association (ADA) diagnosis criteria after a median follow-up of 59 months.

Results We observed a postprandial increase in LPS levels in the New-DIAB at baseline (*P<0.001*), whereas LPS levels were not modified in the Non-DIAB. Moreover, the patients who developed T2DM underwent a higher postprandial TAG increase than Non-DIAB (*P=0.034*). In addition, the development of T2DM was accompanied by an increase in LBP and TNF-α levels plasma levels (*P=0.035* and *P=0.034*). Disease-free survival curves based on the LPS postprandial fold change improved T2DM Risk Assessment as compared with the previously described FINDRisk score (hazard ratio of 2.046, 95%CI 1.156-3.619 *vs*. 1.596, 95%CI 0.870-2.927). Moreover, disease-free survival curves combining the LPS postprandial fold change and FINDRisk score together showed a hazard ratio of 3.745 (95%CI 1.433-9.784), linked to high values of both parameters.

Conclusion Our results suggest that a high postprandial endotoxemia precedes the development of T2DM. Our results also showed the potential use of LPS plasma levels as a biomarker predictor of T2DM development.

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Email: antonio.camargo@imibic.org

DECISION MAKING IMPAIRMENT: A SHARED VULNERABILITY IN OBESITY, GAMBLING DISORDER AND SUBSTANCE USE DISORDERS?

S. Jimenez-Murcia[1,2,3], N. Mallorquí-Bagué[1,2], AB. Fagundo[1,2], R de la Torre[2,4], RM. Baños[2,5], C. Botella[2,6], FF. Casanueva[2,7], AB. Crujeiras[2,7], JC. Fernández-García[2,8], JM. Fernández-Real[2,9], G. Fruhbeck[2,10], R. Granero[2,11], A. Rodríguez[2,10], I. Tolosa-Sola[1], FJ. Ortega[2,9], FJ. Tinahones[2,8], E. Alvarez-Moya[1], C. Ochoa[1], JM. Menchón[1,3,12], F. Fernández-Aranda[1,2,3]

[1] Department of Psychiatry, University Hospital of Bellvitge-IDIBELL, Barcelona. [2]CIBER Fisiopatología de la Obesidad y Nutrición (CIBERobn), Instituto Salud Carlos III, Madrid. [3]Department of Clinical Sciences, School of Medicine, University of Barcelona, Barcelon. [4]Integrated Pharmacology and Systems Neurosciences Research Group, Neuroscience Research Program, IMIM (Hospital del Mar Medical Research Institute), Barcelona. [5]Department of Psychological, Personality, Evaluation and Treatment of the University of Valencia, Valencia. [6]Department of Basic Psychology, Clinic and Psychobiology of the University Jaume I, Castelló. [7]Endocrine Division, Complejo Hospitalario U. de Santiago, Santiago de Compostela. [8]Department of Endocrinology and Nutrition, Hospital Clínico Universitario Virgen de Victoria, Málaga. [9]Department of Diabetes, Endocrinology and Nutrition, Institut d'Investigació Biomèdica de Girona (IdlBGi) Hospital Dr Josep Trueta, Girona. [10]Department of Endocrinology and Nutrition, Clínica Universidad de Navarra, University of Navarra, Pamplona. [11]Departament de Psicobiologia i Metodologia, Universitat Autònoma de Barcelona, Barcelona. [12]CIBER Salud Mental (CIBERSAM), Instituto Salud Carlos III, Madrid.

Introduction: Obesity is an increasing worldwide problem that shares similar patterns to addictions. Addictions are associated with decision making impairments.

Objective: The present study explores decision making in Substance use disorder, Gambling disorder and Obesity when assessed by Iowa Gambling Task and compares them with healthy controls.

Method: 591 participants (194 controls, 113 obese, 178 gambling disorder and 106 substance use disorder patients) were assessed, completed a sociodemographic interview and conducted the Iowa Gambling Task.

Results: clinical patients present impaired decision making when compared to the healthy controls in the overall task and task learning, however no differences are found for the overall performance in the Iowa Gambling Task among the clinical groups. Results also reveal some specific learning across the task patterns within the clinical groups: obese maintains negative scores until the third set where learning starts but with a less extend to controls, substance use disorder patients presents an early learning followed by a progressive although slow improvement, and gambling disorder patients present more random choices with no learning.

Conclusion: Results can help understanding the underlying mechanisms of obesity and addiction behaviors as well as improve current clinical treatments

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E-mail: sjimenez@bellvitgehospital.cat

MODULATION OF IRISIN AND PHYSICAL ACTIVITY ON EXECUTIVE FUNCTIONS IN OBESITY AND MORBID OBESITY

Z. Agüera[1,2], A.B. Fagundo[1,2], S. Jiménez-Murcia[1,2,3], C. Giner-Bartolomé[1,2], S. Sauchelli[1,2], M. Pardo[2,4], A.B. Crujeiras[2,4], R. Granero[2,5], R. Baños[2,6], C. Botella[2,7], R. de la Torre[2,8], J.M. Fernández-Real[2,9], J.C. Fernández-García[2,10], G. Frühbeck[2,11], A. Rodríguez[2,11], N. Mallorquí-Bagué[1,2,] S. Tárrega[5], F.J. Tinahones[2,10,] R. Rodriguez[9,] F. Ortega[2,9,] J.M. Menchón[1,3,12], F.F. Casanueva[2,4], F. Fernández-Aranda[1,2,3]

[1]Department of Psychiatry, University Hospital of Bellvitge-IDIBELL, Barcelona. [2]CIBER Fisiopatología Obesidad y Nutrición (CIBERObn), Instituto Salud Carlos III, Madrid. [3]Department of Clinical Sciences, School of Medicine, University of Barcelon, Barcelona. [4]Endocrine Division, Complejo Hospitalario U. de Santiago, Santiago de Compostela. [5]Departament de Psicobiologia i Metodologia, Universitat Autònoma de Barcelona, Barcelona. [6]Department of Pyschological, Personality, Evaluation and Treatment of the University of Valencia, Valencia. [7]Department of Basic Psychology, Clinic and Psychobiology of the University Jaume I, Castellón. [8]Human Pharmacology and Clinical Neurosciences Research Group, Neuroscience Research Program, IMIM-Hospital del Mar Research Institute, Parc de Salut Mar, Barcelona. [9]Service of Diabetes, Endocrinology and Nutrition, Institut d'Investigació Biomèdica de Girona (IdlBGi) Hospital Dr Josep Trueta, Girona. [10]Service of Diabetes, Endocrinology and Nutrition, Hospital Clínico Universitario Virgen de Victoria, Málaga. [11]Department of Endocrinology and Nutrition, University of Navarra, Pamplona. [12]CIBER Salud Mental (CIBERSAM), Instituto Salud Carlos III, Madrid.

Introduction: Whether the executive profile is different between obesity and morbid obesity remains unclear. Recent evidence suggests that physical activity can act as a cognitive enhancer. Irisin is a recently discovered hormone associated with some of the positive effects of physical activity.

Objective: The objective of the study was to investigate the executive profile in obesity and severe obesity, and to explore the role of physical activity and irisin.

Method: 114 participants were included (21 obese, 44 morbid obese and 49 healthy controls) in the study and assessed with the Wisconsin Card Sorting Test, Stroop Color and Word Test, and Iowa Gambling Task. All participants were female, aged between 18 and 60 years.

Results: Results showed a similar dysfunctional profile on decision making in obese and morbid obese compared with controls. Thus, no specific neuropsychological profiles between obese and morbid obese can be clearly observed in our sample. However, a negative correlation was found between irisin and executive functioning.

Conclusion: These results demonstrate a specific executive profile in obese and a relevant and negative modulation of irisin on executive functioning. Although irisin might be a promising target for the treatment of obesity, its effects on cognition might be considered when thinking about its therapeutic use.

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E-mail: zaguera@bellvitgehospital.cat

AN EVALUATION OF THE EFFECTS ON LIPIDOMA AFTER DHA SUPPLEMENTATION IN PATIENTS WITH CYSTIC FIBROSIS

Lamas Ferreiro A[1], Guzmán Lafuente A[1], Serna Ferrón J[1], Busto Durán R[1,2], Lasunción MA[1,2], Pastor Rojo O[1,2].

[1]Hospital Universitario Ramón y Cajal-IRYCIS, Madrid. [2]CIBEROBN.

Introduction: Confirmation of the beneficial effects of omega-3 supplementation, like docosahexaenoic acid (DHA), in humans requires of reliable markers of its incorporation in the body. The reference method for the evaluation of DHA, gas chromatography (GC), is difficult to apply in the clinical practice due to its low throughput and does not provide information about specific incorporation of DHA in lipid species and other potential effects over lipid classes.

Objectives: 1) Evaluate changes in lipid species in response to DHA supplementation. 2) Compare values in DHA containing lipid species with the reference method for DHA analysis. 3) Simplify the analysis of lipid species and obtain a rapid measurement of DHA and arachidonic acid (AA) content in plasma.

Methods: We selected 50 patients with cystic fibrosis (NCT01783613), 25 supplemented for 1 year with a seaweed oil equivalent to 50 mg/kg/day DHA (DHA-basic®, CASEN Fleet) and 25 with placebo. Plasma samples (baseline, 6 and 12 months) were analyzed by GC-MS and the lipidoma was obtained by LC-MS and MALDI-MS.

Results: The percentage of total DHA (GC) tripled after 12 months of supplementation (1.7±0.18 *vs* 4.73±0.4, P <0.001, baseline *vs* 12 months), however, no changes were observed in the AA content . Lipidomic analysis revealed changes in 41 lipid species out of 192 analyzed (LC-MS). The increase of DHA (%) occurred mainly in cholesterol ester species (3.3±0.34 *vs* 7.6±0.6, P<0.001) and phosphatidylcholine (8.24±0.61 *vs* 15.6 ± 0.89, P<0.001), and a decrease in the percentage of AA-containing phosphatidylethanolamine species was observed (25.4±1.24 *vs* 18.9±0.79, P <0.001). The DHA/AA ratio obtained from lipidomic measurements (LC-MS or MALDI-MS) correlated with the reference method (r = 0.8983 and r=0.7602, P <0.001).

Conclusions: Lipidomic measurements provide a complete information about the effects of DHA supplementation on plasma lipid molecules. The quantification of DHA in choline phospholipids by MALDI-MS is an excellent, rapid and simple method to evaluate DHA levels in plasma.

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Correspondig author: oscar.pastor@salud.madrid.org

STUDY OF THE ROLE OF LIPID HOMEOSTASIS IN MALE MICE INFERTILITY ASSOCIATED WITH OBESITY

Casado ME[1,2], Ulloa V[1], Huerta L[2], Pastor O[3], Lasunción MA[1,2], Martín-Hidalgo A[1,2]

[1]CIBEROBN, [2]Hospital Universitario Ramón y Cajal-IRyCIS, Madrid, Spain

Introduction: Obesity alters lipid homeostasis and fertility. Obesity in men is associated with a decrease in sperm concentration, motility, alterations in sperm morphology, chromatin integrity and hormonal profile. There is a close relationship between lipid metabolism and development of germinal cells. The decrease in adiposity improves the concentration of spermatozoa reverting infertility.

Objectives : 1) To study the pathophysiological mechanisms causing gonadal dysfunction and infertility associated with obesity in a mouse model fed with high fat diet (HFD) compared with low fat diet (LFD), and 2) to analyze whether weight loss and fat mobilization in obese mice with control diet or polyphenols (ellagic acid, EA), improves lipid parameters and reverses infertility.

Methods: The experimental groups were: 1) LFD 10 weeks; 2) HFD 10 weeks; 3) LFD 18 weeks; 4) LFD 10 weeks and LFD + EA (100 mg/ml) 8 weeks; 5) LFD 10 weeks and LFD + EA (150 mg/ml) 8 weeks; 6) HFD 18 weeks; 7) HFD 10 weeks and HFD + EA (100 mg/ml) 8 weeks; 8) HFD 10 weeks and HFD + EA (150 mg/ml) 8 weeks; 9) HFD 10 weeks and LFD 8 weeks; 10) HFD 10 weeks and LFD+EA (100 mg/ml) 8 weeks;.and 11) HFD 10 weeks and LFD+EA (150 mg/ml) 8 weeks. Seminal fluid was obtained from epididymis for spermatozoa counts and motility. Plasma testosterone was measured by ELISA. Plasma glucose, triglycerides, cholesterol, HDL and LDL were measured by colorimetric/enzymatic methods.

Results: The mice fed with high fat diet had increased body weight, food efficiency rate and liver weight, and a decrease in testis weight/body weight ratio. These mice showed an increase in plasma cholesterol, HDL and LDL compared with mice fed with LFD. Finally, obese mice exhibited a decrease in sperm counts and plasma testosterone levels.

Conclusions: The HFD altered lipid homeostasis and caused hypogonadism and a decrease in sperm count in obese mice. These alterations may underlie the infertility associated to obesity in male mice.

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E-mail: m.e.casado4@gmail.com

EFFECTS OF AN ONLINE INTERVENTION ("LIVING BETTER") TO PROMOTE HEALTHY LIFESTYLES IN HYPERTENSIVE OVERWEIGHT POPULATION: EFFECTS AT 3, 6 AND 12 MONTHS

M. Mensorio[1,7], J. Navarro[1], A. Cebolla[1,6], E. Rodilla[2], G. Palomar[3], J.F. Lisón, C.Botella, [5.6.], R.M. Baños[165]

[1] Universitat de València, Spain, [2] Unidad de hipertensión y riesgo vascular. Hospital de Sagunto, Spain , [3] Atención Primaria Centro de Salud, Quartell, Spain, [4] Universidad CEU Cardenal Herrera, Valencia, Spain, [2] Universitat Jaume I, Spain, [5]CIBER Fisiopatología de la Obesidad y la Nutrición, Santiago de Compostela,,Spain, [6] CAPES, Brasil.

Introduction: Changes in lifestyles are considered key elements in the prevention and treatment obesity and hypertension but the usual treatments in health services to promote these changes are not effective enough. The use of new technologies has been demonstrated as an effective alternative tool for development of interventions for this population.

Objective: To evaluate the effectiveness of an online intervention to promote healthy lifestyles in patients with obesity and hypertension, analyzing their effect on relevant medical and psychological variables.

Method: 106 patients (BMI M= 30.1 kg/m2; 59 males, age M= 50,02; SD=3.5) under medical supervision in a Hypertension Unit. Participants were randomized into 2 groups: Experimental (EG-online intervention) and Waiting list (WLG). The intervention (totally self-applied) is composed by 9 modules (3 months duration) and uses cognitive-behavioral strategies and psychoeducation for the promotion of healthy eating habits and increased physical activity. Physiological-medical data (BMI, Waist circumference, hip circumference, glycemia, insulin, cholesterol, triglycerides, and blood pressure) and lifestyle/psychological variables (quality of life, self-efficacy, physical activity, Mood, and intake styles) were assessed before and after the intervention, and in follow-up at 6 and 12 months. The GLE also received the intervention after the GE.

Results: EG had improvements in all medical variables after the intervention, and significant differences were observed between EG and WLG in: BMI, waist perimeter, glycemia, and Insulin ($p<.01$). Regarding the psychological variables, EG also showed improvement in all variables, with a significant reduction in the external eating style, anxiety symptoms and stress ($p<.01$). Follow-up data indicate that the changes obtained after treatment in the EG are maintained in BMI, waist and hip circumference, and external eating style, furthermore EG patients reduced diastolic blood pressure and fat mass percentage. After receiving the online treatment, the WLG also improved physical and psychological condition ($p<.01$).

Conclusion: The data suggest that the online program can have positive effects in promoting changes in lifestyles, acting on the medical and psychological condition, even on the long-term. These findings highlight the benefits of using a totally self-applied program in this particular clinical population, since it can reduce costs and reach a large number of patients in a practical and effective way.

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MANIPULATING SELF-EFFICACY TO INCREASE PHYSICAL ACTIVITY THROUGH THE USE OF AVATARS IN OBESE AND OVERWEIGHT WOMEN

Navarro, J[1]., Cebolla, A[1]., Botella, C.[2,3]. Baños, R.M.[1 3].

[1]Departamento de Personalidad, Evaluación y Tratamiento Psicológico, Universidad de Valencia, España.

[2]Departamento de Psicología Básica, Clínica y Psicobiología, Universidad Jaume I, España

[3]CIBER Fisiopatología Obesidad y Nutrición (CIBERObn), Instituto Salud Carlos III, Valencia, España.

Introduction: Low levels of physical activity (PA) are considered important contributors to the increasing prevalence of obesity and overweight. It is necessary to design interventions to enhance the adoption and maintenance of regular PA. Self- efficacy, has been identified as a key factor in increasing PA. Recently, virtual reality (VR) has proved to be useful for learning healthy behaviors such as the acquisition of PA habits through the use of avatars (virtual representations of the person) and the influence they exert on self-efficacy. **Objective:** To explore how the use of avatars and the changes in these body representations in virtual worlds influence on self-efficacy towards PA.

Method: Overweight women (IMC>25) (N=42) with an age between 18 and 64 years are randomized to three conditions: "Ideal Avatar" (ideal body dimensions), "Real Avatar" (actual body dimensions) and control group (without avatar). In all conditions, the participants receive an online motivational intervention. Subsequently, they perform aerobic PA for two minutes with the use of a VR program designed for this purpose. In the "Ideal Avatar" and "Real Avatar" conditions, the virtual experience is recorded on video for the participants to visualize it every day during the next week. In the control group, the participants are not represented by any avatar. Finally, all participants are assigned a weekly PA goal. **Results:** It is a work in progress. A mixed ANOVA 3(inter) x 2 (intra) will be performed for self-efficacy. Participants in the "ideal avatar" condition are expected to show higher scores on this variable the other two conditions. **Conclusions:** VR could contribute to an increase in PA through its influence on self-efficacy. Therefore, VR could help to prevent and treat the obesity and overweight.

Acknowledgements: CIBEROBN is an initiate of the ISCIII

Mail: Jessica.Navarro@uv.es

COMPARATIVE EFFECTS OF RESVERATROL AND ENERGY RESTRICTION ON LIVER FAT ACCUMULATION AND HEPATIC FATTY ACID OXIDATION

Milton-Laskibar I[1,3], Aguirre L[1,3], U. Etxeberria[2], F.I Milagro[2,3] J.A. Martínez [2,3], Portillo MP[1,3],

[1]Nutrition and Obesity Group, Department of Nutrition and Food Science, University of the Basque Country (UPV/EHU), Vitoria, Spain.

[2]Department of Nutrition, Food Sciences and Physiology; Centre for Nutrition Research; University of Navarra, Pamplona, Spain

[3]CIBERobn Physiopathology of Obesity and Nutrition, Institute of Health Carlos III, Spain.

Introduction: Energy restriction is an effective approach in preventing liver steatosis. However, compliance with this treatment protocol is often very poor. Resveratrol, a natural polyphenolic compound has been widely reported to imitate the effects of energy restriction.

Objective: To compare the effects of resveratrol and a mild energy restriction on liver fat accumulation and hepatic fatty acid oxidation.

Methods: 36 male six-week-old rats were fed a high-fat high-sucrose diet for 6 weeks in order to induce steatosis. Then, rats were divided into four groups and fed a standard diet for 6 additional weeks: control group (C), resveratrol group (RSV, resveratrol 30 mg/kg/d), restricted group (R, 15 % energy restriction) and combined group (RR, 15 % energy restriction and resveratrol 30 mg/kg/d). Liver triacylglycerols (TG) and total cholesterol contents were measured by using commercial kits. Carnitine palmitoyl transferase 1a (CPT 1a) and citrate synthase (CS) activities were measured spectrophotometrically. TFAM (mitochondrial transcription factor A) and peroxisome proliferator-activator receptor alpha (PPARα) protein contents, as well as the ratio acetylated peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α)/Total PGC1α were analyzed by Western blot. Statistical analysis was performed by using one way ANOVA and Newman-Keuls as post-hoc test.

Results: No differences were observed among the four groups regarding liver weight and cholesterol content, but the three treated groups showed reduced TG when compared to the control group, being the restricted groups the ones showing the lowest values. Higher CPT 1a and CS activities were observed in the groups supplemented with resveratrol (RSV and RR). The acetylated PGC1α /total PGC1α ratio was lower in the treated groups (RSV, R and RR) than in the control group. As far as TFAM protein expression is concerned, only the RR group reached a higher value. Finally, no changes were observed in PPARα protein expression.

Conclusions: Resveratrol administration is an effective intervention for liver triacylglycerol content reduction, but a mild energy restriction is even more effective. The mechanisms of action of these two strategies are different. Thus resveratrol, but not energy restriction, seems to act by increasing fatty acid oxidation. When both treatments (resveratrol administration and a mild energy restriction) were combined, no additive or synergic effects were appreciated.

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Email: inaki.milton@ehu.eus

EFFECTIVENESS OF AN INTERVENTION PROGRAM TO PROMOTE FRUIT AND VEGETABLE CONSUMPTION AMONG CHILDREN. PRELIMINARY DATA

Arrizabalaga-Lopez M[1], Rada-Fdez. de Jáuregui D[2], Portillo-Baquedano MP[1,5], Martínez O[3], Etaio I[4], Rodríguez VM[1,5].

[1]Nutrition and Obesity Group, Dept. of Pharmacy and Food Science, Faculty of Pharmacy, UPV/EHU

[2]Dept. of Preventive Medicine and Public Health, Faculty of Pharmacy, UPV/EHU

[3] Dept. of Pharmacy and Food Science, Faculty of Pharmacy, UPV/EHU

[4] Sensory Analysis Laboratory LASEHU, Dept. of Pharmacy and Food Science, Faculty of Pharmacy, UPV/EHU

[5]CIBERobn Physiopathology of Obesity and Nutrition, Institute of Health Carlos III, Spain

Introduction: After checking that the consumption of fruit and vegetables of the child population of Vitoria-Gasteiz was low, an intervention program was proposed at school level. This intervention is based on theories of behavior, as they have been proved to be the most effective in achieving changes.

Objectives: The main aim of the present study is to increase consumption of fruit and vegetables in school children aged 8 to 11 years in Vitoria.

Methods: In a controlled intervention (n = 100 intervention group; n = 100 control group), the intervention group received 14 sessions of 60 minutes during an academic year (October to June). These sessions, designed by a multidisciplinary team, were based on behavioral theories and aimed to modify attitudes, subjective norms, perceived control, the intention of consumption, and the consumption of fruit and vegetables itself. Both the process and the evolution of consumption were evaluated (before, during and after) using validated surveys, 7 day food records and 24 hour reminders.

Results: Preliminary results indicate that intake of fruit and vegetables increased significantly in the intervention group (fruit: p=0.014; vegetable: p=0.004), but not in the control group (fruit: p=0.461; vegetable: p=0.248).

Conclusions: The intervention program based on theories of behavior seems to be effective for promoting the consumption of fruit and vegetables in children aged 8 to 11.

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Contact: maria.arrizabalaga@ehu.eus

RELATION BETWEEN ADHERENCE TO THE MEDITERRANEAN DIET AND INFLAMMATORY MARKERS IN BALEARIC ISLANDS POPULATION

A Sureda, MM Bibiloni, JM Gámez, I Llompart, A Pons, JA Tur

University of Balearic Islands, Palma de Mallorca and CIBEROBN (Fisiopatología de la Obesidad y la Nutrición CB12/03/30038) Instituto de Salud Carlos III, Madrid, Spain.

Introduction: A protective effect of the Mediterranean diet has been evidenced against various chronic diseases, including a favourable effect on total mortality, cardiovascular disease, several types of cancer and inflammatory diseases. Adherence to a healthy dietary pattern has been shown to be inversely associated with Metabolic Syndrome. Chronic low-grade inflammatory status is present in many metabolic syndrome associated pathologies.

Objectives: To assess levels of inflammatory markers among adults and adolescents from the Balearic Islands on relation with the adherence to the Mediterranean diet.

Methods: A cross-sectional nutritional survey carried out in the Balearic Islands, Spain with a random sample (n=598, 219 male and 379 female) of the population (12-65 years) was included in the study. Participants were interviewed, anthropometrically measured, and provided a fasting blood sample. Circulating plasma levels of inflammatory makers were measured. Dietary habits were assessed by means of two 24 h recalls, and a quantitative food-frequency questionnaire. Adherence to the Mediterranean diet pattern was also analyzed.

Results: The prevalence of metabolic syndrome increased with age in both sexes. The adherence to the Mediterranean diet in males was 51.3% in adolescent and 45.7% in adults. In females was 53.1% in adolescent and 44.3% in adults. In males, higher adherence to the Mediterranean diet was associated with higher levels of adiponectin and lower levels of leptin, TNF-α, PAI-1 and hs-CRP in adults but not in young subjects. In females, higher adherence was associated with lower levels of TNF-α in young group, PAI-1 in adults and hs-CRP in both groups.

Conclusions: With increasing age in both sexes, increases metabolic syndrome (%), but lower the adherence to MD. Evidence that overeating and adiposity contribute to systemic inflammation and development of the metabolic syndrome raises the possibility that lifestyle interventions may provide effective means of reducing risk.

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e-mail: nucox@uib.es

EFFECTS OF RED WINE AND DIFFERENT DOSES OF POLYPHENOLS FROM DEALCOHOLIZED RED WINE ON ENDOTHELIAL FUNCTION IN SUBJECTS WITH METABOLIC SYNDROME

Gemma Sasot[1,2,3], Anna Creus-Cuadros[1,2], Mercè Mercader-Martí[5], Rosa M. Lamuela-Raventós[1,2,3], Ramon Estruch[2,4]*

[1]Nutrition, Food Science and Gastronomy Department, Pharmacy and Food Science School, University of Barcelona, Av. Joan XXIII 27, Barcelona, Spain.

[2]CIBER Physiopathology of obesity and nutrition (CIBEROBN). Institute of Health Carlos III, Spain.

[3]INSA-UB, Nutrition and Food Safety Research Institute, University of Barcelona, Spain.

[4]Department of Internal Medicine, Hospital Clinic, Institute of Biomedical Investigation August Pi i Sunyer (IDIBAPS), University of Barcelona, Spain.

[5]Miguel Torres, Vilafranca del Penedés, Barcelona, Spain

Introduction: Cardiovascular disease is the leading cause of death in the developed world. Several studies pointed out that mortality and risk from cardiovascular disease are higher in subjects with Metabolic Syndrome, which is considered as a cluster of metabolic conditions including central obesity, reduced HDL-cholesterol and elevated triglycerides, blood pressure and fasting blood glucose.

Epidemiological studies and intervention clinical trials have shown that dealcoholised red wine and moderate consumption of red wine are inversely associated with cardiovascular risk factors. Indicating a possible additional protective effect due to the non-alcoholic fraction of red wine

The aim of this study was to evaluate the effect of polyphenols on circulating endothelial cells, as a potential marker of the endothelial damage, and endothelial progenitor cells, useful in the repair of damaged endothelium.

Methods: A randomised, open, prospective and controlled clinical trial, running in parallel was performed in 72 subjects with metabolic syndrome; 130 mL/day or 260 mL/day of red wine for women and men, respectively, 375 mL/day of dealcoholised red wine, dealcoholised red wine with grape extract or water were administered during three months.

Peripheral blood mononuclear cells were isolated by Ficoll density-gradient centrifugation and, a FACS Calibur Flow Cytometer and CellQuest software were used to analyse levels of endothelial progenitor cells and circulating endothelial cells.

Results: After the dealcoholised interventions, the number of circulating endothelial cells significantly decreased, while after red wine it shows a noticeable decrease. There is a significant increase in the number of endothelial progenitor cells after de red wine intervention and just a low increase in the dealcoholised red wine intervention enriched with grape extract.

Conclusions: The non-alcoholic fraction of wine, rich in polyphenols, may reduce circulating endothelial cells, known marker of severity of cardiovascular disease, and increase endothelial progenitor cells, a marker of endothelial regeneration, in a population at high risk of cardiovascular disease. These features might explain why dealcoholised red wine and moderate red wine consumption suggest an improvement in the condition of the vascular endothelium and possibly contribute to delay the development of atherosclerotic plaques.

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gemmamsf@gmail.com

MEDITERRANEAN DIET AND TRANSITION BETWEEN METABOLIC PHENOTYPES IN OBESE AND NON-OBESE SUBJECT

J Konieczna[1,2], A Colom[1,2], N Babio[1,3], E Toledo[1,4], JV Sorlí[1,5], Estruch R[1,6], F Arós[1,7], J Lapetra[1,8], M Fiol[1,2], D Romaguera[1,2], PREDIMED investigators.

[1]CIBEROBN; [2]Instituto de Investigación Sanitaria Illes Balears; [3]Universitat Rovira i Virgili; [4]Universitad de Navarra; [5]Universidad de Valencia; [6]Hospital Clínic de Barcelona; [7]Hospital Txagorritxu; [8]Centro Salud San Pablo Sevilla.

Introduction: Although the concept of obesity phenotypes is controversial, some studies have suggested that metabolically healthy obese individuals are not at an increased risk of cardiovascular disease compared to their non-obese counterparts. Little is known about the lifestyle determinants of obesity phenotypes.

Objective: To determine the effect of a Mediterranean diet (MedDiet) enriched with extra-virgin olive oil (EVOO) or nuts versus advices on following a low-fat diet (control group) on the transition between metabolic phenotypes in obese and non-obese participants from the PREDIMED study.

Methods: A total of 5793 participants at high cardiovascular risk from the PREDIMED trial (www.predimed.es) were included in the present study; at baseline, obesity phenotypes were defined based on their BMI and prevalence of the metabolic syndrome (MetS) in four categories: 1 – metabolically abnormal obese (MAO); 2 – metabolically healthy obese (MHO); 3 – metabolically abnormal non-obese (MANO); 4 – metabolically healthy non-obese (MHNO); Cox regression models were built to determine the effect of PREDIMED interventions (follow-up 4.8 years) on transition between metabolic phenotypes (incidence or reversion of MetS) in obese and non-obese subjects, adjusting for centre, sex, age, baseline adherence to the MedDiet, total energy intake, physical activity, smoking status, alcohol consumption, and educational level; as sensitivity analyses, models were further adjusted for annual weight change.

Results: At baseline, 37.2% participants were classified as MAO; 10.2% as MHO; 26.8% as MANO; and 25.8% as MHNO. The two intervention arms (MedDiet + EVOO or nuts) were associated with transition to healthier metabolic phenotypes in metabolically unhealthy obese and non-obese participants, but did not prevent transition to unhealthy phenotypes in metabolically healthy participants. MAO participants allocated to any of the MedDiet interventions were 34% (95% CI 6-68%) more likely to become MHO; likewise, MANO allocated to any of the MedDiet interventions were 35% (95% CI 12-63%) more likely to become MHNO. These associations persisted after taking into account weight change during follow-up.

Conclusions: Results of this study suggest that an intervention based on the promotion of MedDiet + EVOO or nuts improved the metabolic profile of obese and non-obese participants at high cardiovascular risk, allowing the transition of healthier phenotypes, independently of concomitant weight change.

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Email: jadzia.konieczna@gmail.com

MARESIN 1 MITIGATES LIVER STEATOSIS IN DIET-INDUCED OBESE MICE

Laiglesia LM[1,2], Lorente-Cebrián S[1,2,3], Martínez-Fernández L[1,2], Sáinz N[2], Burrell MA[4], Rodríguez-Ortigosa CM[5,6], Martínez JA[1,2,3,7], Moreno-Aliaga MJ[1,2,3,7]

[1]University of Navarra, Department of Nutrition, Food Science and Physiology, Pamplona, Spain

[2]University of Navarra, Centre for Nutrition Research, Pamplona, Spain

[3]Navarra Institute for Health Research (IdiSNA), Pamplona, Spain

[4]University of Navarra, Department of Histology and Pathology, Pamplona, Spain

[5]Hepatology Program, Centre for Applied Medical Research, University of Navarra, Pamplona, Spain

[6] Centro de Investigación Biomédica en Red en el Área temática de Enfermedades Hepáticas (CIBERehd), Institute of Health Carlos III (ISCIII), Madrid, Spain

[7] Centro de Investigación Biomédica en Red de la Fisiopatología de la Obesidad y Nutrición (CIBERobn), Institute of Health Carlos III (ISCIII), Madrid, Spain

Background: Obesity has been tightly related to non-alcoholic fatty liver disease, which is characterized by excessive lipid accumulation within hepatocytes leading to their dysfunction. Maresin 1 (MaR1) is a DHA-derived pro-resolving lipid mediator that improves insulin sensitivity and attenuates adipose tissue inflammation in obese mice.

Objective: The aim of this study was to characterize the ability of MaR1 to alleviate obesity-related liver steatosis and to elucidate the mechanisms involved.

Methods: The effects of MaR1 (50 µg/kg, oral gavage for 10 days) on fatty liver disease were tested in diet-induced obese (DIO) mice. MaR1 actions were also evaluated in primary cultured hepatocytes.

Results: MaR1 decreased serum transaminases and reduced liver weight and triglycerides content. MaR1-treated mice exhibited reduced hepatic lipogenic enzymes content (FAS) or activation (by phosphorylation of ACC), along with upregulated expression of fatty acid oxidation-related genes such as carnitine palmitoyltransferase (*Cpt1a*) and acyl-coenzyme A oxidase (*Acox1*). Moreover, MaR1 induced autophagy-related proteins 5 and 7 (*Atg 5-7*) gene expression, in parallel to an increased number of autophagic vacuoles and reduced p62 protein levels. MaR1 also promoted AMP-activated protein kinase (AMPK) phosphorylation in both DIO mice and primary hepatocytes. Interestingly, AMPK inhibition reversed MaR1 actions on *Cpt1a, Acox1, Atg5* and *Atg7* expression.

Conclusion: MaR1 ameliorates liver steatosis by decreasing lipogenic enzymes, while inducing fatty acid oxidation related genes and autophagy, which may be mediated through AMPK activation. Therefore, MaR1 may be a new therapeutic candidate for reducing fatty liver in obesity.

Prof. María Jesús Moreno-Aliaga

E-mail: mjmoreno@unav.es

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DNA METHYLATION PATTERNS AT SWEET TASTE-TRANSDUCING GENES ARE ASSOCIATED WITH BMI AND CARBOHYDRATE INTAKE IN AN ADULT POPULATION

Ramos-Lopez O,[1] Arpón A,[1] Riezu-Boj JI,[1,2] Milagro FI,[1,3] Mansego ML,[1] Martinez JA,[1,2,3,4] on behalf of the MENA project.[5]

[1] Department of Nutrition, Food Science and Physiology, and Center for Nutrition Research, University of Navarra, Pamplona, Spain. [2] Navarra Institute for Health Research (IdiSNA), Pamplona, Spain. [3] Centro de Investigación Biomédica en Red de la Fisiopatología de la Obesidad y Nutrición (CIBERobn), Carlos III Institute, Madrid, Spain. [4] Madrid Institute of Advanced Studies (IMDEA Food), Madrid, Spain. [5] Others members of the MENA project in alphabetical order are: Abete I, Crujeiras AB, Cuervo M, Goni L, Marti A, Martinez-Gonzalez MA, Moreno-Aliaga MJ, Navas-Carretero S, San Cristobal R, Santos JL, Zulet MA.

Background: Individual differences in taste perception may influence appetite, dietary intakes, and subsequently, disease risk. In this context, the increased consumption of sweet energy-dense foods is considered a contributor to the rising prevalence of obesity.

Objective: The aim of this study was to investigate the association between DNA methylation patterns at taste-transducing genes and obesity and dietary intake in an adult population.

Methods: A nutriepigenomic analysis within the Methyl Epigenome Network Association (MENA) project was conducted in 474 adults. DNA methylation in peripheral white blood cells was analyzed by a microarray approach. KEGG pathway analyses were performed concerning the characterization and discrimination of genes involved in the taste transduction pathway. Adjusted FDR values ($p<0.0001$) were used to select those CpGs that showed best association with BMI. Furthermore, associations between taste methylation patterns and dietary intakes were screened in available individuals with the requested data (n=212).

Results: A total of 29 CpGs at taste-transducing genes met the FDR criteria. However, only 12 CpGs remained statistically significant after linear regression analyses adjusted for age and sex. The selected CpGs were cg15743657 (*TAS1R2*), cg02743674 (*TRPM5*), cg01790523 (*SCN9A*), cg15947487 (*CALHM1*), cg11658986 (*ADCY6*), cg04149773 (*ADCY6*), cg02841941 (*P2RY1*), cg02315111 (*P2RX2*), cg08273233 (*HTR1E*), cg14523238 (*GABBR2*), cg12315353 (*GABBR1*) and cg05579652 (*CACNA1C*). Interestingly, most of them were implicated in the sweet taste signaling pathway, except *CACNA1C* (sour taste). In addition, *TAS1R2* methylation at cg15743657 was strongly associated with total energy ($p<0.0001$) and carbohydrate intakes ($p<0.0001$). **Conclusion.** This study suggests that DNA methylation in genes related to sweet taste transduction pathway could be an epigenetic mechanism associated with obesity and a basis for precision nutrition in obesity.

Prof. J. Alfredo Martinez

E-mail: jalfmtz@unav.es

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UMAMI TASTE: PERCEPTION, RELATIONSHIPS WITH DIET AND OBESITY AND GENOME-WIDE ASSOCIATION STUDY OF ITS GENETIC DETERMINANTS

Barragán R[1,2], Fernández-Carrión R[1,2], Carrasco P[1,2], Asensio EM[1,2], González-Monje I[1], Portolés O[1,2], Sorlí JV[1,2], González JI[1,2], Osma-Santiago R[1], Giménez-Fernández F[1,2], Ferriz E[1], Corella D[1,2], Coltell O[2,3]

[1]Department of Preventive Medicine and Public Health, School of Medicine, University of Valencia, Valencia; [2]CIBER Fisiopatología de la Obesidad y Nutrición, Instituto de Salud Carlos III, Madrid; [3]Department of Computer Languages and Systems. University Jaume I, Castellón.

Introduction: The greater or lesser perception of different flavors has been associated with food consumption, and obesity. The umami taste has recently been recognised as the "fifth taste", after salt, sweet, sour and bitter. It can be described as a pleasant "brothy" or "meaty" taste. Human umami taste perception is typically elicited by select amino acids, such as glutamate and aspartate.. Umami taste is hypothesized to have evolved to guide the ingestion of foods rich in these compounds, including certain vegetables (mushrooms, petit pois, sweetcorn and sweet cherry tomatoes are high in glutamate) as well as any fermented, aged, or cooked foods Interestingly, human milk is one of the highest glutamate-containing mammalian milks. We aimed to analyze umami taste perception as well as its geneetic determinants and associations with obesity and food intake in a Mediterranean population.

Material and Methods: Cross-sectional study of 300 participants in the PREDIMED PLUS-Valencia study. Umami tastes was determined through laboratory tests on the perception of their intensity (a score from 0 to 5). Monosodium l-glutamate (MSG) was used as an umami taste substance, and the highest concentration tested was 200mM. A genome-wide association study (GWAs) genotyping was undertaken with the Human OmniExpress Illumia array (700K) and PLINK. Top-ranked SNPs were identified. Associations with antropometric and dietary variables (17-item adherence to the Mediterranean diet score) were analyzed.

Results: Prevalence of non-tasters (0 points), 1, 2, 3, 4 and 5 (super-tasters) categories for the umami (MSG) taste were: 15.3%, 27.5%, 23.1%, 18.8%, 10.6% and 4.7%, respecively. There were no significant differences between the mean umami perception in men and women (1.86+/-0.11 vs 2.05+/-0.11, respectively; P=0.300). A higher umami perception was associated with lower body-mass index (BMI) even after adjustment for sex and age (beta: -0.051+/.0.02; P=0.024). Several associations with food items were found and the most significat association was detected with vegetable intake. Subjects having a low vegetable intake (less than 2 servings per day), had a lower score in the umami test perception than subjects with higher vegetable intake (-0.455+/-0.156; P=0.005 after adjusment for sex, age and BMI). New genes associated with umami taste were identified (P<0.00001). The top ranked polymorphsims in the GWAs were: rs3846739-intergenic; rs34459426-BAZ2B; rs12822660-intergenic; rs12320148-intergenic, rs10958403-intergenic, and rs4483229-EPB41L4B.

Conclusions: Umami taste perception greatly varies in the Mediterranean population and was associated both with BMI and dietary intake. New genetic factors associatd with the umami taste have been identified.

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E-mail: rocio.barragan@uv.es

GENETIC VARIANTS IN THE BMAL1 CIRCADIAN GENE ARE ASSOCIATED WITH TYPE-2 DIABETES AND INCIDENCE OF CARDIOVASCULAR DISEASES IN A HIGH RISK MEDITERRANEAN POPULATION

Sorli JV[1,2]; Barragán R[1,2], Fernández-Carrión R[1,2], Carrasco P[1,2], Asensio EM[1,2], González-Monje I[1], Portolés O[1,2], Sorlí JV[1,2], González JI[1,2], Ferriz E[1], Coltell O[2,3], Corella D[1,2]

Background: Many aspects of physiology and behavior follow a circadian rhythm. Circadian disturbance affects glucose metabolism and some polymorphisms in circadian (clock) genes have been associated with type-2 diabetes and cardiovascular diseases (CVD). The Aryl hydrocarbon receptor nuclear translocator-like (ARNTL) gene, also called BMAL1, is one of the most relevant clock genes. Some polymorphisms in the BMAL1 genes have been associated with type-2 diabetes, but the association with CVD has been less investigated. In mice, Baml1 influences critical heart functions, such as development of dilated cardiomyopathy, contractile function, as well as life span. Therefore, our aim is to study the association of polymorphisms in the BMAL1 gene with type-2 diabetes and CVD incidence in a high-risk cardiovascular population.

Methods: We have carried out an observational study at baseline and longitudinally in the PREDIMED-Valencia trial including (n=1094) men and women aged 67+/-7 y. PREDIMED is a dietary intervention trial with Mediterranean diet (MedDiet). Prevalence of type-2 diabetes was analyzed at baseline, and participants were followed-up a median of approx. 5 years to analyzed incidence of CVD (including myocardial infarction, stroke and cardiovascular death were). BMAL1 polymorphisms were determined by dense genotyping. Multivariable logistic regression at baseline and Cox regression models in the follow-up were fitted.

Results and conclusions: We focused on five BMAL1 polymorphisms. Linkage disequilibrium among these SNPs was low (r2 ranging from: 0.25 to 0.65). rs2290037 and rs7123257 were significantly associated with prevalence of type-2 diabetes, whereas rs10832027, rs1982350 and rs7924734 were significantly associated with CVD incidence. The strongest associations were found for BMAL1-rs1982350. Prevalence of this SNP was 51%GG, 39%GA and 10%AA. Carriers of the variant allele (A) had higher CVD incidence (2.7%, 5.6% and 8.2%) in wild-type homozygous, heterozygous and homozygous for the variant allele, respectively; P=0.004). In the Cox model adjusted for age, sex, dietary intervention and diabetes, the HR for CVD per variant allele (additive model) was 1.56; 95%CI:1.07-2.37; P=0.023. We also found a significant association of this SNP with higher risk of myocardial infarction, this being the first time that the association between this polymorphism and CVD incidence in humans has been reported. Moreover, the association with CVD was higher in type-2 diabetic patients. Similar patterns of association with CVD were found for the rs10832027 and rs7924734, suggesting a relevant role of this gene both in type-2 diabetes and CVD incidence in type-2 diabetic patients.

[1]Department of Preventive Medicine and Public Health, School of Medicine, University of Valencia, Valencia; [2]CIBER Fisiopatología de la Obesidad y Nutrición, Instituto de Salud Carlos III, Madrid; [3]Department of Computer Languages and Systems. University Jaume I, Castellón.

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E-mail: sorli@uv.es

HEPATIC STEATOSIS DEVELOPMENT IN OBESE WOMEN IS ASSOCIATED WITH A SEVERE DYSREGULATION OF KEY SPLICING MACHINERY COMPONENTS

Del Río-Moreno M[1,2,3,4,5], Alors-Pérez E[1,2,3,4,5], González-Rubio S[2,3,6,7,8], Ferrín G[2,3,6,7,8], Reyes O[2,3,9], Rodríguez-Perálvarez M[2,3,6,7,8], Ventura S[2,3,9], Kineman RD[10], de la Mata M[2,3,6,7,8], Castaño JP[1,2,3,4,5], Gahete MD[1,2,3,4,5], Luque RM[1,2,3,4,5].

[1]CIBER Physiopathology of Obesity and Nutrition (CIBERobn), [2]Maimonides Institute of Biomedical Research of Cordoba (IMIBIC), Cordoba; [3]Reina Sofia University Hospital (HURS), Cordoba; [4]Department of Cell Biology, Physiology and Immunology, University of Cordoba (UCO); [5]Agrifood Campus of International Excellence (CeiA3), Cordoba; [6]CIBER Liver and Digestive Diseases (CIBERehd); [7]Liver Transplantation Unit (HURS), Cordoba; [8]Department of Medicine (Medicine, Dermatology and Otorhinolaryngology), University of Cordoba (UCO); [9]Department of Computer Sciences, University of Cordoba (UCO), Cordoba, Spain; [10]Research and Development Division, Jesse Brown Veterans Affairs Medical Center; Section of Endocrinology, Diabetes, and Metabolism, Department of Medicine, University of Illinois at Chicago, Chicago, Illinois, USA.

Introduction: Hepatic steatosis is a common obesity-associated pathology, wherein accumulation of fat within the liver can progress to liver fibrosis, cirrhosis and, ultimately, lead to hepatocellular carcinoma. Emerging evidence indicates that alternative mRNA splicing, the key mechanism providing transcript and protein diversity, is dysregulated in many tissues under adverse metabolic conditions such as obesity and diabetes. Moreover, expression of aberrant splicing variants could contribute to the comorbidities of these pathologies.

Objective: Since generation of alternative splicing variants might be linked to a dysregulation of the cellular machinery responsible for this process, i.e., spliceosome components and splicing factors (SFs), the objective of the present study was to determine the association between the expression pattern of the components of this machinery and hepatic steatosis.

Methods: Liver biopsy samples from obese women (IMC>30) with (n=32) or without (n=9) hepatic steatosis were collected and RNA was extracted and retro transcribed to determine the expression levels of selected components of the major (n=13) and minor (n=4) spliceosomes and SFs (n=28) using a qPCR-based, custom-made Fluidigm array. In vitro functional approaches were also performed using different liver cell-lines.

Results: The liver of steatotic patients exhibited a severe dysregulation of certain spliceosome components and SFs compared to non-steatotic patients. Although these alterations did not appear to associate with the level of hepatic steatosis, a non-supervised clustering analysis revealed the existence of groups of steatotic patients with specific alterations in spliceosome components and SFs, which also presented distinctive hepatic and clinical-metabolic alterations (e.g. ALT, hyperglycemia, hyperinsulinemia, etc.). Importantly, modulation (silencing) of selected splicing machinery components altered fat accumulation in hepatic cell-lines. Conversely, fat accumulation did not alter the expression of those spliceosome components, indicating that the alteration of the splicing machinery components could be a driver factor of hepatic steatosis development and not its consequence.

Conclusion: Although further confirmatory studies are needed, our results suggest that the development of hepatic steatosis and its associated comorbidities could be linked to the dysregulation of the splicing machinery, which may provide novel diagnostic/therapeutic tools for this pathology.

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E-mail: raul.luque@uco.es

MECHANISMS AND CONSEQUENCES OF OBESITY-INDUCED HYPOGONADISM: ROLE OF A NOVEL HYPOTHALAMIC MIR-137/KISSPEPTIN PATHWAY

MS Avendaño[1-4]; MJ Vázquez[1-4]; I Velasco[2,4]; A Barroso[1-4]; E Torres[2,4]; C Perdices-López[2,4]; F Ruiz Pino[1-4]; V Heras[2,4]; M Lara-Chica[2-4], MA Calzado[2-4], JM Castellano[1-4]; L Pinilla[1-4]; M Tena Sempere[1-4].

[1]CIBER Physiopathology of Obesity and Nutrition (CIBEROBN), Instituto de Salud Carlos III, [2]Maimonides Institute of Biomedical Research of Cordoba (IMIBIC), Cordoba; [3]Reina Sofia University Hospital (HURS), Cordoba; and [4]Department of Cell Biology, Physiology and Immunology, University of Cordoba14004 Córdoba, Spain

Introduction: Obesity is a life threatening condition associated with numerous comorbidities. Among them, central hypogonadism, i.e., low circulating levels of testosterone, has been recently suggested as putative contributor to the metabolic complications of obesity, especially in men. The mechanisms for obesity-induced hypogonadism (OIH), and its contribution to the generation/evolution of the metabolic alterations of obesity remain ill defined. Recent data has suggested that OIH may be caused by suppression of hypothalamic Kiss1 system; kisspeptins being potent activators of the reproductive axis that ultimately stimulate testosterone secretion. However, the mechanisms for Kiss1 suppression in obesity remains unknown.

Objective: Our recent evidence suggests that microRNAs (miRNAs) are putative regulators of the Kiss1 system. In this work, we aimed to identify novel miRNAs capable of regulating kisspeptin expression and to evaluate their potential contribution to OIH.

Methods and Results: Bioinformatic analyses on *KISS1* gene were conducted with different algorithms (http://www.targetscan.org/; http://www.ebi.Ac.uk/enright-srv/microcosm /htdocs/ targets/v5/; http://zmf.umm.uni-heidelberg.de/apps/zmf/mirwalk2/; http://www.microrna. org/ microrna/home.do) to seek for potential miRNA regulators. Selection of miRNA candidate(s) was based on the following criteria: 1) to be identified in at least two different databases; 2) to show an evolutionary conserved seed region (rat, mouse, human); and 3) to be deregulated by metabolic alterations, associated with changes in hypothalamic kisspeptin expression. Using these criteria, miR-137 was selected as a robust putative modulator of *KISS1*. This was tested biochemically using a luciferase reporter assay, which documented a repressive interaction of miR-137 at the 3'UTR of *KISS1*. Further confirmation was obtained in vivo, using a *Target Site Blocker* (TSB) approach. A TSB, tailored to block the repressive interaction of miR-137 selectively at Kiss1 3'UTR, was injected centrally in a male rat model of OIH, with severe suppression of testosterone (T) and gonadotropin (LH) levels, and marked metabolic alterations: increased systolic blood pressure (SBP), glucose intolerance and insulin resistance. TSB administration not only restored T and LH levels, and increased hypothalamic kisspeptin, but also ameliorated insulin resistance, glucose intolerance, SBP and cardiac hypertrophy, without detectable changes in body weight.

Conclusions: Our results are the first to provide conclusive evidence about the relevant role (and eventual therapeutic value) of a novel central miR-137/kisspeptin pathway in OIH, and strongly suggest that central hypogonadism is a major contributor for the metabolic complications of obesity.

E-mail: Marisol.avendanno@gmail.com; fi1tesem@uco.es

EFFECT OF A MEDITERRANEAN DIET ON THE PRIMARY PREVENTION OF ATRIAL FIBRILLATION AND MAJOR CARDIOVASCULAR EVENTS IN HYPERTENSIVE PATIENTS WITH HIGH CARDIOVASCULAR RISK: RESULTS OF ICFAMED STUDY

J Lapetra[1,2], JM Lozano-Rodríguez[3], MR Caballero-Valderrama[4], JM Santos-Lozano[1,2], M Ortega-Calvo[1,2], FJ García de la Corte[1,2], L Miró-Moriano[2].

[1]Department of Family Medicine, Unit Research, Distrito Sanitario Atención Primaria Sevilla (Servicio Andaluz de Salud). [2]CIBER de Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, Spain. [3]Distrito Sanitario Atención Primaria Sevilla-Norte (Servicio Andaluz de Salud). [4]Department of Cardiology. Hospital Universitario Virgen del Rocío, Sevilla (Servicio Andaluz de Salud).

Introduction. Not well known the effect of a Mediterranean-type diet (MedDiet) on the occurrence of atrial fibrillation (AF), stroke, ischemic heart disease (IC) and heart failure (HF) in high-risk cardiovascular hypertensive patients.

Objective. To evaluate the effect of a MedDiet, compared with a low fat diet (LFD), on the incidence of this group of diseases in hypertensive patients with high cardiovascular risk (CVR) in a situation of primary prevention (PP).

Methods. Clinical trial of dietary intervention, randomized, controlled, simple blind and multicenter (ISRCTN27497769), performed entirely in primary care. 180 participants (62.8% women), hypertensive patients with a high CVR in PP. Random assignment to 2 intervention groups (IG): 90 to MedDiet; 90 to LFD. For at least 2 years, they received dietary advice (individual and group) every three months. Primary outcome variable (POV): variable composed of AF, stroke, IC and HF. The occurrence of POV was detected by the annual ECG, periodic contact with patients and their family physicians, and consultation medical history. Intention-to-treat analysis. Descriptive, comparative analysis, calculation of hazard ratios (HR) and survival analysis. Level of significance was $p < 0,05$.

Results. After a mean follow-up of 27.6 ± 5 (SD) months there were 16 events: IG-MedDiet: 5 (FA: 2; IC: 2; stroke: 1); IG-LFD: 11 (FA: 6; CI: 2; stroke: 3). The crude rate for the occurrence of events per 1000 patient-months of follow-up was 1.97 (95% CI: 0.6-4.6) for the IG-MedDiet and 4.51 (95% CI: 3-8,1) for IG-LFD. The HR for patients with IG-MedDiet compared to IG-LFD was 0.44 (95% CI: 0.15-1.26, p> 0.05). Survival analysis showed the protective effect of MedDiet vs LFD after 15 months of follow-up.

Conclusions. In hypertensive patients at high CVR, in a PP situation, the 2.3-year follow-up of a MedDiet compared to a LFD resulted in a reduction in the risk of cardiovascular complications related to hypertension (AF, stroke, IC and HF) of 56%. This effect was mainly due to the decrease in the incidence of AF and stroke.

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E-mail: jlapetra@ono.com, jmlozano27@gmail.com

METABOLIC AND INFLAMMATORY STATUS IN PREPUBERAL CHILDREN WITH A HISTORY OF EXTRAUTERINE GROWTH RESTRICTION OR PREMATURITY

M Gil Campos[1], K Flores Rojas[1], J Olza Meneses[2], C Aguilera-García[2], JL Pérez Navero[3], MC Muñoz Villanueva [4], MD Diaz Ordonez[3].

[1]Metabolism Unit and Pediatric Research. IMIBIC.Reina Sofia University Hospital, University of Córdoba, Ciberobn.

[2]Institute of Nutrition and Food Technology. University of Granada. Ciberobn.

[3]Metabolism Unit and Neonatology Unit. Reina Sofia University Hospital. IMIBIC, University of Córdoba.

[4] Unit of Methodology in Investigation, IMIBIC.

Introduction: Extrauterine Growth Restriction is defined as a growth values lower than the 10th-percentile at 36 weeks corrected gestational age or at discharge. Intrauterine growth restriction has been related with a higher risk of cardiovascular diseases in later life.

Aim: To study metabolic risk variables in prepubertal extrauterine growth restriction children and in prematurity children, compared with a healthy group.

Material-methods: A total of 211 were enrolled including 38 children with antecedents of extrauterine growth restriction, 50 children who were preterm and 123 healthy term infants. The anthropometric parameters, blood pressure levels and general biochemical parameters were analyzed. Plasma levels of relevant interleukins, C-reactive protein, hepatocyte growth factor, chemoattractant factor of macrophages type 1, tumor necrosis factor alpha, inhibitor plasminogen activating factor 1, adipokines and antioxidant enzymes were determined.

Results: Lower body mass index Zscore and higher blood pressure and higher glycemia, hepatocyte growth factor, chemoattractant factor of macrophages type 1, tumor necrosis factor alpha, resistin levels, and lower adiponectin levels were observed in children with antecedents of extrauterine growth restriction compared with the other two groups. Preterm group showed the highest levels for inhibitor plasminogen activating factor 1, insulin, insulin resistance index and leptin. In both groups the concentrations of C-reactive protein and interleukin-8 were higher and the values of HDLcolesterol and glutation peroxidase were significantly lower compared with controls. In the extrauterine growth restriction group, leptin exhibited the strongest association with body mass index Z-score, insulin, insulin resistance index and hepatocyte growth factor; and adiponectin with HDLcolesterol. In the logistic regression analysis, the predictors of metabolic status of the EUGR children were blood pressure levels, glucose, resistin and tumor necrosis factor alpha, as well as lower values of body mass index-Zscore, adiponectin, HDLcolesterol and glutation peroxidase.

Conclusions: In prepubertal children with antecedents for extrauterine growth restriction or prematurity, an alteration in metabolic programming conditioning a higher risk of inflammation and oxidative status can be present. These findings could condition a greater risk of metabolic syndrome and cardiovascular disease in later stages.

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INSULIN RESISTANCE IS ASSOCIATED WITH A SPECIFIC METHYLATION PROFILE OF VISCERAL ADIPOSE TISSUE IN OBESE PATIENTS

Izquierdo AG[1], Díaz-Lagares A[2], Moreno-Navarrete JM[3], Carreira MC[1], Sandoval J[4], Amil M[1], Esteller M[2], Casanueva FF[1], Fernández-Real JM[3], Crujeiras AB[1].

[1]Laboratory of Molecular and Cellular Endocrinology, Instituto de Investigación Sanitaria (IDIS), Complejo Hospitalario Universitario de Santiago (CHUS) and Santiago de Compostela University (USC), Santiago de Compostela, Spain; CIBER Fisiopatología de la Obesidad y la Nutrición (CIBERobn), Madrid, Spain. [2]Cancer Epigenetics and Biology Program (PEBC), Bellvitge Biomedical Research Institute (IDIBELL), L'Hospitalet, Catalonia, Spain. [3]Department of Diabetes, Endocrinology and Nutrition, Institut D'investigació Biomédica De Girona (IdIBGi); CIBER Fisiopatología de la Obesidad y la Nutrición (CIBERobn), Madrid, Spain.[4]Laboratory of Personalized Medicine, Epigenomics Unit, Medical Research Institute La Fe, Valencia, Spain.

Introduction: Obesity is characterized by an excessive accumulation of body fat that exerts a detrimental effect on insulin action. Elucidating the potential mechanisms involved in controlling this process is an important priority in counteracting obesity-associated diseases. Epigenetic regulation, such as DNA methylation, lead to changes in gene activity and it may influence the development of metabolic disorders. Therefore, we propose that an epigenetic regulation can mediate the susceptibility to insulin resistance in obesity.

Objective: To disentangle the epigenetic basis of insulin resistance by performing a genome-wide epigenetic analysis in visceral adipose tissue from morbidly obese patients.

Methods: The insulin sensitivity was determined by the clamp technique in morbidly obese patients. DNA isolated from visceral adipose tissue of insulin-resistant and insulin-sensitive patients was hybridized in the HumanMethylation450 Infinium BeadChip array.

Results: Comparing DNA methylation levels between insulin-resistant and insulin-sensitive, 982 CpG sites were identified with significant differences between both groups. These differentially methylated CpGs were associated with 538 genes, which were able to completely distinguish patients insulin-resistant of and insulin-sensitive. The Gene Ontology analysis determined a high number of genes were linked to signal transduction, transcription regulation and cell adhesion. Most of the genes associated with the differentially methylated CpGs were significantly ($P < 0.001$) related with insulin signalling pathways and 10% of them were associated with Diabetes according to the "Human Diabetes Proteome Project". The current work identified novel IR-related genes epigenetically regulated in VAT, such as COL9A1, COL11A2, CD44, MUC4, ADAM2, IGF2BP1, GATA4, TET1, ZNF714, ADCY9, TBX5, and HDACM.

Conclusion: This study demonstrates the existence of a methylome profile associated with insulin resistance in VAT. The results identify potential epigenetic biomarkers and novel therapeutic targets in the prevention and treatment of disturbances in insulin sensitivity associated with obesity. The observations of the current work are of foremost relevance as they provide tools for additional personalized treatment for prevention of type 2 diabetes based on epigenetic biomarkers.

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andrea.gonzalez.izquierdo@hotmail.com

CARDIORESPIRATORY FITNESS AS A TOOL IN THE ASSESSMENT OF EARLY CARDIOVASCULAR RISK IN OBESE YOUTH

Pau Redon (1,2), Guido Grassi (3), Julio Álvarez (1,2), MI Torró (1,2), Empar Lurbe (1,2)

1. CIBEROBN, Health Institute Carlos III, Madrid-SPAIN,

2. Cardiovascular Risk Unit, Hospital General Universitario University of Valencia, Valencia, SPAIN

3. Dipartimento di Scienze della Salute, Clinica Medica, Universitá Milano-Bicocca. Milano, Italy.

Over the last decades the prevalence of obesity in children and adolescents has increased worldwide. This fact affects health expectancy and quality of life and then, assessment of cardiovascular risk factors has been emphasized. Among cardiovascular risk factors in adults, the relevance of cardiorespiratory fitness has been highlighted by the American Heart Association (*AHA, Circulation 2016*).

Objective: To assess the cardiorespiratory fitness and its relationship with the cardiac autonomic neural activity, a marker of early cardiometabolic risk, in youths with abnormally increased body weight.

Methods: Sixty-four overweight and obese subjects, 9 to 17 years, of both sexes, stratified according to the international body mass index cut-off, were enrolled. Continuous electrocardiogram was recorded during 15 minutes in resting and supine conditions, and afterwards heart rate variability was analysed in the time and frequency domain as well as non-linear dynamics. In addition, cardiorespiratory fitness in effort conditions was assessed (VO_{2peak}).

Results: Among the obese youths, cardiorespiratory fitness was the lowest in severe obese despite that no significant differences were observed regarding heart rate nor heart rate variability in time and frequency domain. A positive and significant relationship, independent of the degree of obesity, pubertal stage and breathing rate under resting conditions, were observed between cardiorespiratory fitness (assessed by VO_{2peak}) and sympatho-vagal balance, estimated by standard deviation of the NN interval (SDNN: $r=0.268$, $p<0.05$) and the long term variation using the Poincaré plot (P_{S1}: $r=0.275$, $p<0.05$; P_{S2} $r=0.273$, $p<0.05$),

Conclusion: The key finding of the present study was the presence of a link between cardiorespiratory fitness and cardiac autonomic nervous system activity, independent of the degree of obesity. This emphasises that cardiorespiratory fitness can be a relevant tool in the assessment of early cardiovascular risk in obese youths.

UNRAVELING THE URIC ACID IN THE CLUSTER OFCARDIOMETABOLIC RISK FACTORS EARLY IN LIFE: A PROSPECTIVE STUDY

J Alvarez (1,2), I Torro (1,2), P Redon (1,2), F Aguilar (1,2), E Lurbe (1,2)

1. CIBEROBN, Health Institute Carlos III, Madrid-SPAIN,

2. Cardiovascular Risk Unit, Hospital General Universitario University of Valencia, Valencia, SPAIN

Objective. The present prospective research, starting at birth, was undertaken to analyze factors related to the uric acid in children at 5 years old.

Subjects and methods. One hundred and fifty four Caucasians of both sexes (77 females), of European origin, born at term were included. After the initial evaluation on the second day of life, infants were followed up and growth pattern prospectively recorded. At five years, office BP measurements were performed and fasting blood sample was obtained to measure glucose, insulin, lipid profile, and uric acid. All subjects were normotensives, no diabetes neither dyslipidemia were present.

Results. In this prospective study, uric acid at five years depends positively on the increment of weight from birth ($p<0.001$) and inversely of the birth weight ($p<0.05$). Furthermore, uric acid was significantly correlated with current weight ($r=0.25;p=0.003$), current height ($r=0.17;p=0.04$), office SBP ($r=0.23;p=0005$), insulin ($r=0.36;p=0.001$), and HDL ($r=-0.30;p=0.001$). In a multiple regression analysis insulin, and HDL cholesterol were independent determinants of uric acid when, sex, current weight, birth weight, SBP, and Log triglycerides were also included ($r^2=0.23$). The weighted impact of uric acid on metabolic parameters and office SBP, adjusted by sex and body weight, are shown in the Table.

Conclusions. Uric acid is associated with metabolic parameters independent of office BP. Metabolic status at 5-year-old in children born at term may be influenced by perinatal events and postnatal rapid weight gain with clinical implications that require active intervention to prevent or reverse upward crossing of weight percentiles.

	Uric acid tertiles			
	First	**Second**	**Third**	***p-value***
Number	53	47	54	
Uric acid (mg/dl)	3.06 (0.39)	3.91 (0.14)	4.70 (0.64)	<0.001
Fasting insulin	5.48 (0.65)	6.34 (0.72)	9.33 (0.62)	<0.001
HOMA index	1.10 (0.14)	1.31 (0.16)	1.77 (0.14)	<0.001
C-HDL (mg/dl)	55.9 (1.7)	53.2 (1.9)	50.4 (1.6)	ns
Log-TG (mg/dl)	1.81 (0.02)	1.89 (0.03)	1.87 (0.02)	0.045
Office SBP (mmHg)	93.9 (1.1)	91.5 (1.3)	96.4 (1.1)	0.013

Values are average (standard error)

THE EPIGENETIC REGULATION OF THE VITAMIN D SYSTEMN AND INFLAMMATORY STATE OF ADIPOSE TISSUE IN COLORECTAL CANCER DEVELOPMENT

Manuel Macias-Gonzalez [1,2],Daniel Castellano-Castillo[1]; Sonsoles Morcillo[2]; Mercedes Clemente Postigo[1], Esperanza Torres[3], Msc; Francisco José Tinahones [1,2]*

1. Unidad de Gestión Clínica Endocrinología y Nutrición. Instituto de Investigación Biomédica de Málaga (IBIMA), Complejo Hospitalario de Málaga (Virgen de la Victoria)/Universidad de Málaga (Spain).
2. CIBER Pathophysiology of obesity and nutrition (CB06/03), Spain.
3. Unidad de Gestion Clinica de Oncología Intercentros Hospital Universitario Virgen de la Victoria, Málaga, Spain.

ANTECEDENTS: Adipose tissue dysfunction has been related to a low-grade inflammatory state, which in turn could promote diseases like cancer. Furthermore, lack of vitamin D has been associated with colorectal cancer (CRC). Vitamin D is believed to have an effect over the epigenetic landscape.

AIM: The aim of this study was to explore the relationship between serum 25(OH)-Vitamin D , adipose tissue gene expression of the vitamin D receptor (VDR), NFκB1 and the epigenetic factor DNMT3A as well as VDR promoter methylation in CRC.

METHODS: Blood and visceral adipose tissue from 57 CRC subjects and 50 healthy controls subjects were collected. Serum vitamin D as well as biochemical and anthropometric variables were measured. VDR, NFκB1 and DNMT3A gene expression as well as VDR promoter DNA methylation was determined by Qrt-pcr and Pyrosecuencing respectively

RESULTS: We observed, that CRC subjects showed lower serum vitamin D levels and higher adipose tissue VDR gene expression and were negatively associated in CRC group. Serum CRP and adipose tissue NFκB1 gene expression were higher in CRC than in controls. CRP correlated negatively with serum vitamin D and positively with adipose tissue NFKB1 and VDR gene expression, only in the cancer group. CRC showed higher DNMT3A mRNA levels, which was negatively associated to serum 25(OH)D and positively to adipose tissue VDR DNA methylation in the CRC group.

CONCLUSIONS: our results suggest fo the first time that adipose tissue may be a key factor in CRC development. The low vitamin D levels and high adipose tissue VDR expression in CRC can at least in part be mediating this relationship by modifying adipose tissue DNA methylation and promoting inflammation.

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Email: mmacias.manuel@gmail.com

ABSTRACT

RESEARCH GROUP

INDEX

ABSTRACT

FIRST AUTHOR

INDEX

FONDO EUROPEO DE DESARROLLO REGIONAL
Una manera de hacer Europa
FONDO SOCIAL EUROPEO
El FSE invierte en tu futuro