SOCIETÀ ITALIANA PER LO STUDIO DELLA ATEROSCLEROSI (SISA)

III Spring Meeting Giovani Ricercatori SISA, SIIA, SIMI

Rimini, 7-8 Aprile 2018

La terza edizione dello "Spring Meeting Giovani Ricercatori" si è svolta quest'anno a Rimini il 6 e 7 Aprile, con il coinvolgimento di oltre 80 giovani ricercatori afferenti da 3 diverse società scientifiche: la Società Italiana per lo Studio dell'Aterosclerosi (SISA), la Società Italiana Ipertensione Arteriosa (SIIA) e la Società Italiana di Medicina Interna (SIMI). I partecipanti delle società sono stati rispettivamente: 46 partecipanti della SISA, 24 della SIIA e 19 della SIMI.
Sono pervenuti 74 abstract che sono stati valutati, in cieco, dai comitati scientifici delle tre società. Sono stati suddivisi in tre sessioni orali ognuna di 7 presentazioni, di ricerca di base e di ricerca clinica, per un totale di 21 orali e 8 sessioni poster moderate per un totale di 49 poster. Complessivamente hanno partecipato al meeting 89 persone di cui 21 tra relatori, moderatori, comitato organizzatore e comitato scientifico e 68 iscritti. Quattro iscritti non si sono presentati.

Il meeting, attraverso il confronto e la discussione di lavori scientifici presentati all'interno di sessioni dedicate, è riuscito nell'intento di favorire l'interazione tra i giovani soci delle società scientifiche coinvolte. Durante le due giornate di lavoro, sono state presentate comunicazioni orali e poster, in cui tutti i partecipanti al meeting (supportati da travel grant forniti dalle 3 società) hanno avuto la possibilità di presentare i risultati dei propri lavori di ricerca clinica o di base.
Quest'anno si è tenuta anche una tavola rotonda su forthcoming project:condivisione di progetti di ricerca tra le tre società.I progetti della SIIA sono stati presentati da Francesca Saladini e Costantino Mancusi; quelli della SIMI da Sebastiano Cicco e Emilia Donnarumma; quelli della SISA da Giuseppe Mandraffino, Manuela Casula e Fabio Nascimbeni.

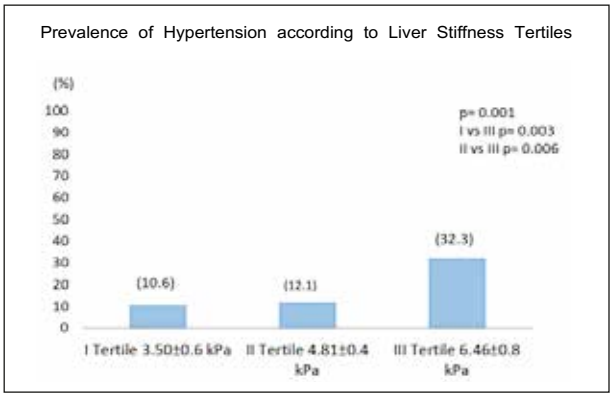
Le tematiche scientifiche affrontate, specchio del diverso background delle società coinvolte, sono state molteplici e si è spaziato dalla ricerca di base a quella clinica e traslazionale. Sono state attivamente partecipate le varie sessioni ma particolarmente stimolante è stata la tavola rotonda su forthcoming projects in particolare quelli presentati dalla SIIA e dalla SISA.
Il meeting si è svolto un clima di serena e sempre attiva discussione da parte dei giovani ricercatori, particolarmente stimolati dal diverso background scientifico dei partecipanti.
Dopo il meeting è stato inviato un questionario di gradimento. Su 66 mail inviate ai partecipanti hanno risposto ad oggi in 38 (5 SIMI, 10 SIIA, 28 SISA). Alla richiesta di dare un giudizio generale sul meeting 20 partecipanti si sono dichiarati molto soddisfatti, 17 soddisfatti, 1 poco soddisfatto, nessuno per nulla soddisfatto.

COMUNICAZIONI ORALI

RELATION BETWEEN ARTERIAL HYPERTENSION AND LIVER STIFFNESS IN UNTREATED HYPERTENSIVE ADULTS

S. Giampà[1], Y Ferro[1], D. de Bonis[1], A. Pujia[1], T. Montalcini[2]
[1]Department of Medical and Surgical Science, Nutrition Unit, Magna Grecia University, Catanzaro;
[2]Department of Clinical and Experimental Medicine, Nutrition Unit, Magna Grecia University, Catanzaro

Background and Aims. Liver disease is a major cause of illness and death worldwide. The factors leading to the progression from simple liver steatosis to severe liver scarring and cirrhosis are not fully clear and the link between liver disease and metabolic components, especially hypertension (HTN) is more complex than previously thought. Recent evidence indicates that angiotensin II (Ang II) may be an important mediator in liver fibrosis. Serum Ang II levels are frequently elevated in patients with cirrhosis and a local renin-angiotensin system is upregulated in experimental hepatic fibrogenesis. It has known that Ang II raises blood pressure (BP) by a number of actions, and that high BP increases the cardiovascular risk. The aim of this study was to evaluate the association between BP and liver stiffness (LS) and to determine the prevalence of HTN in adults.
Methods. In this cross-sectional study, we enrolled 201 consecutive individuals (age 41±15 yrs, 40% male) who underwent a LS measurement by Fibroscan and medical assessment. Patients with a history of hypertension or use of antihypertensive agents were excluded. HNT was defined for SBP ≥130 mmHg and DBP ≥80 mmHg.
Results. The prevalence of obesity was 35%, dyslipidemia 22% and diabetes 3%. The hepatic steatosis was present in 60% and fibrosis in 5% of population. The prevalence of HNT was 18.5%. In particular participants in LS tertile I and tertile II had a lower prevalence of HTN than those in tertile III (p=0.003 and p=0.006 respectively) (Fig. 1). SBP was positively associated with male gender, age, BMI and LS tertiles; DBP was positively associated with BMI, WHR and LS tertiles. At the ROC curve LS value equal to 5.55 kPa achieved adequate specificity (75%) to predict HTN.
Conclusion, We found an association between blood pressure and liver stiffness and also observed the high rate of untreated arterial hypertension in adults with high liver stiffness. These results should encourage performing longitudinal studies to better clarify the timing of the development of hypertension and the role of the liver.



HIGH DENSITY LIPOPROTEINS INHIBIT OXIDATIVE STRESS-INDUCED PROSTATE CANCER CELL PROLIFERATION

E. Giorgio[1], M. Ruscica[2], M. Botta[2], N. Ferri[3], C. Macchi[2], G. Franceschini[4], P. Magni[2], L. Calabresi[1], M. Gomaraschi[1]
[1]Centro Enrica Grossi Paoletti, Dipartimento di Scienze Farmacologiche e Biomolecolari, Università degli Studi di Milano;
[2]Dipartimento di Scienze Farmacologiche e Biomolecolari, Università degli Studi di Milano;
[3]Dipartimento di Scienze del Farmaco, Università degli Studi di Padova;
[4]Dipartimento di Scienze per gli Alimenti, la Nutrizione e l'Ambiente, Università degli Studi di Milano

Background. Recent evidences suggest that oxidative stress is involved in the pathogenesis and the progression of prostate cancer (PCa). Reactive oxygen species (ROS) are normally generated within cell metabolism and can be produced within tumor microenvironment by xenobiotics or infiltrating inflammatory cells. Interestingly, ROS generation is higher in PCa cells compared to normal prostate epithelial cells and this increase is proportional to the aggressive phenotype. High density lipoproteins (HDL) are known to prevent atherosclerosis through different mechanisms, including their antioxidant properties. Aim of the study was to assess whether HDL were able to reduce oxidative stress in two PCa cell lines (LNCaP and PC-3) and the consequent impact on cell proliferation.
Methods and Results. HDL isolated from plasma of healthy human volunteers significantly reduced basal and H2O2-induced oxidative stress in LnCaP and PC-3 cells. ROS production decreased when HDL were given in combination with or before H2O2. The antioxidant effect of HDL was independent from androgen receptor, scavenger receptor BI and ATP binding cassette G1 transporter. When both lines were grown in the presence of H2O2, an increase of cell proliferation rate was observed that was completely blunted by the addition of HDL. Anti-proliferative effect of HDL was due to their capacity to prevent the H2O2-induced shift of cell cycle distribution from G0/G1 towards G2/M phase.
Synthetic HDL made of apolipoprotein A-I and phosphatidylcholine, the main protein and lipid components of HDL, retained the ability of plasma-derived HDL to inhibit ROS production in LNCaP and PC-3 cells.
Conclusions. HDL exert antioxidant activities on PCa cell lines, thus limiting cell proliferation induced by ROS. HDL were effective not only on androgen-dependent PCa cells, but also on castration-resistant ones. Synthetic HDL, which are under clinical development as anti-atherosclerotic agents, retained the antioxidant effects of plasma-derived HDL. These data indicate a possible role of HDL against PCa progression.

CARDIOVASCULAR EVENTS AND TARGET ORGAN DAMAGE IN PRIMARY ALDOSTERONISM: A META-ANALYSIS

S. Monticone, F. D'Ascenzo, C. Moretti, T.A. Williams, F. Veglio, F. Gaita, P. Mulatero
Division of Intenal Medicine and Hypertension Unit (S.M., T.A.W., F.V., P.M.), Division of Cardiology (F.D.A., C.M., F.G.) Depatment of Medical Sciences, University of Torino

Aim. Primary aldosteronism (PA), affecting around 6% of the general hypertensive population is the most frequent form of secondary hypertension. There is conflicting evidence, based on heterogeneous studies, as to whether aldosterone excess results into an increased risk of cardio- and cerebrovascular complications in patients with PA.
We aimed at assessing the relationship between PA and adverse cardiac and cerebrovascular events, target organ damage, diabetes and metabolic syndrome (MetS), compared with essential hypertension (EH), by integrating results of previous studies.
Methods. We performed a meta-analysis of prospective and retrospective observational studies that compared patients with PA and EH, to investigate the association between PA and stroke, coronary artery disease (as co-primary endpoints), atrial fibrillation and heart failure, target organ damage, metabolic syndrome, and diabetes (as secondary endpoints). We also compared PA subtypes, aldosterone producing adenoma (APA) and bilateral adrenal hyperplasia (BAH).
Results. We identified 31 studies including 3,838 patients with PA and 9,284 patients with EH. After 8.8 years [IQR 6.2-10.7] from the diagnosis of hypertension, patients with PA displayed an increased risk of stroke (OR 2.58 [IQR, 1.93-3.45]), coronary artery disease (OR 1.77 [1.10-2.83]), atrial fibrillation and heart failure (OR 3.52 [2.06-5.99] and OR 2.05 [1.11-3.78]). These results were consistent for patients with APA and BAH, without difference between these two subgroups. Similarly, PA increased the risk of diabetes, metabolic syndrome (OR 1.33 [1.01-1.74] and OR 1.53 [1.22-1.91], respectively) and left ventricular hypertrophy (OR 2.29 [1.65-3.17]).
Conclusions. An early diagnosis of PA is of outmost importance because affected patients display an enhanced cardiovascular risk compared to patients with EH.

ROLE OF THE LONG PENTRAXIN 3 IN THE IMMUNOMODULATION OF DIET-INDUCED OBESITY

A. Moregola[1], F. Bonacina[1], A. Baragetti[1,2], R. Porte[3], E. Bonavita[3], K. Garlaschelli[2], A. Salatin[1], L. Grigore[2], F. Pellegatta[2], A. Mantovani[3,4], A.L. Catapano[1,5], C. Garlanda[2], G.D. Norata[1,2,6]
[1]Department of Pharmacological and Biomolecular Sciences, University of Milan;
[2]Centro SISA per lo studio dell'aterosclerosi, Ospedale Bassini, Cinisello Balsamo, Milan;
[3]IRCCS Humanitas Research Foundation, Rozzano, Milan;
[4]Department of Translational Medicine, University of Milan;
[5]IRCSS MultiMedica, Milan;
[6]William Harvey Research Institute, Barts and The London School of Medicine & Dentistry, Queen Mary University, London

Aim. Aim of the project was study the role of PTX3, an essential component of the humoral arm of innate immunity in obesity.
Methods. PTX3 KO and WT littermates were fed a HFD (45% Kcal from fat) for 20 weeks. Body weight was measured weekly; fat distribution (magnetic resonance for imaging, MRI) and glycemia (glucose-GTT and insulin-ITT tolerance tests) was checked at 10 and 20 weeks. Immunophenotyping and gene expression of adipose tissue was performed at 20 weeks. Ectopic fat deposition in h1/h1 and h2/h2 individuals was determined by DEXA.
Results. Here we show that PTX3 KO mice on HFD exhibit a decreased weight gain compared to WT (AUC weight gain WT=190.8±17.45, KO=134.8±10.09), coupled to a decreased accumulation of visceral and subcutaneous fat both at 10 ($p<0.05$) and 20 weeks ($p<0.01$) of diet measured by MRI and confirmed weighing the tissues after the sacrifice (VAT% WT=7.609±0.6776, KO=4.390±0.8235; SCAT% WT=5.953±0.9682, KO=3.144±0.6129, $p<0.05$). Basal glycemia and the results of the glucose and insulin tolerance test were superimposable. PTX3 deficiency results in a reduction of monocytes markers and pro-inflammatory cytokines gene expression in VAT (MCP-1, IL-6, $p<0.05$) associated to a reduced infiltration of monocytes and macrophages in the tissue assessed by cell sorting, while vascularization was enhanced (increased gene expression of CD31 and VEGF in VAT, $p<0.05$). Sorted VAT macrophages showed enhanced expression of molecules associated with M2-polarization (Arg1, YM-1, $p<0.01$). Individuals carriers of h2/h2 haplotype, characterized by lower PTX3 plasma levels, associate with reduced amount of abdominal obesity compare to non-carriers (android fat% h2/h2=45.34±10.32, h1/h1=47.17±9.23, $p<0.05$).
Conclusions. Our results demonstrate that PTX3 deficiency protects from diet induced-obesity. This effect appears to be the consequence of increased M2-macrophages polarization and an enhanced vascularization of VAT.

GENE EXPRESSION PROFILING OF GLUTEAL ADIPOSE TISSUE AFTER PROLONGED BEDREST

R. Colonna, E. dalla Nora, J.M. Sanz, M.A. Miselli, M.L. Morieri, A.M. Sensoli, G. Zuliani, A. Passaro
Azienda Ospedaliero-Universitaria di Ferrara

Aim. According to the WHO, sedentary lifestyle is one of the pillars that support the development and maintenance of chronic diseases and it is recognized as an independent risk factor for cardiometabolic disorders, regardless of concomitant physical activity. The aim of this study was to investigate the effect of physical inactivity on gluteal adipose tissue gene expression in healthy subjects.
Methods. Seven healthy subjects underwent 14 days of total physical inactivity, expressed as absolute bed rest. At basal time and at the end of bed rest we obtained an adipose tissue biopsy for RNA isolation and subsequent microarray analysis, to identify genes differently expressed.
Results. 308 genes were differently expressed in gluteal adipose tissue after bed rest. In silico analysis showed that several of these genes had been previously associated with cardiovascular and metabolic disorders. Particularly, after bed rest, we observed a significant up regulation of genes belonging to the inflammosome such as IL18, IL1β, and NLRP3.
Conclusion. Our data suggest that adipose tissue may be one of the actor playing a role in the detrimental effect of sedentary behaviour, pointing out a possible role of subcutaneous adipose tissue in the pathogenesis of metabolic and cardiovascular complications, associated with physical inactivity. Moreover, we show that inactivity is able to activate the inflammatory cascade, contributing to a low grade systemic inflammation, a known physiopatological mechanism in atherosclerosis development.

THE WRONG OR "RIGHT" EFFECTS OF HCV ON CARDIAC FUNCTION IN PATIENTS WITH LOW-MILD LIVER FIBROSIS: A CASE-CONTROL STUDY

A. Dalbeni[1,2], S. Romano[1], E. Imbalzano[3], M Bevilaqua[1], A. Tagetti[1], G. Torin[1], A. Mantovani[1], G. Cavallon[2], V. Paon[1,2], C. Fava[1], L. Iogna Prat[1,4], F. Capra[2]
[1]Division of General Medicine and Hypertension, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata of Verona;
[2]Division of Liver Unit, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata of Verona;
[3]Division of Internal Medicine, Department of Clinical and Experimental Medicine, University of Messina;
[4]UCL Institute for Liver and Digestive Health, Royal Free Hospital and UCL, London, UK

Introduction. Hepatitis C virus (HCV) infection is one of the most common causes of viral hepatitis. Association between HCV infection and cardiovascular disease has already been described: vascular and cardiac alterations seems to be explained by HCV proinflammatory effects on endothelium and myocardium.
In this study we examined right and left ventricular systolic function in patients affected by HCV infection in low-mild liver fibrosis stage.
Methods. We included 65 consecutive naïve HCV patients with low-mild liver fibrosis stage at Fibroscan referring to our clinic because of eligibility for HCV eradication with DAA (Directly Acting Antivirals) (mean age 58,0±12,8; M 46%). We also included 60 age-sex-BMI and cardiovascular risk factors matched controls.
Transthoracic echocardiography was performed in all participants.
Results. In the two groups the left ventricular function was similar. Left ventricular mass (LVM), dystolic function E/A, mitral annular plane excursion (MAPSE) and ejection fraction (EF%) showed no difference between the two groups. Also left atrial measures showed no difference in the two groups. Conversely, when we analysed the right sections, tricuspid annular plane excursion (TAPSE) and right atrium volume (RA), we found significant differences: TAPSE HCV (mean±SD) was 14,8 ±6,1 mm vs TAPSE controls 18,9±1,9 mm ($p<0.001$); RA HCV 36,9±20,4 mm^3 vs RA controls 25,2±2,9 mm^3 ($p<0.001$). PAPs showed no differences. When we subdivided the HCV patients according to fibrosis stage (1,2 or 3) or viral load (>800.000 copies) no differences were detectable in echocardiographic measures.
Conclusion. our study is the first case-control study that shows right-sided heart alterations due to the presence of HCV which do not seem to be linked to the severity of liver fibrosis and to viral load. Other studies are necessary to understand the right cameras modifications due to HCV infection.

MARKERS OF ARTERIAL STIFFNESS AND SUBCLINICAL VASCULAR DAMAGES IN OBESE CHILDREN

S. Bonafini[1], A. Tagetti[1], P.A. Giontella[1], P. Cavarzere[2], R. Gaudino[2], D. Ramaroli[2], P. Minuz[1], A. Pietrobelli[2], C. Maffeis[2], F. Antoniazzi[2], C. Fava[1]
[1]University of Verona, Department of Medicine, Verona;
[2]University of Verona, Department of Surgery, Dentistry, Paediatrics and Gynaecology, Verona

Aim. In this observational study, we aimed at investigating the influence of weight excess and traditional cardiovascular risk factors on vascular structure and function in a sample of obese children.
Methods. Overweight or obese children (BMI >90th percentile for sex and age) underwent office and ambulatory BP measurements (ABPM) and the assessment of carotid intima-media thickness (cIMT), endothelial function by the Flow Mediated Dilation (FMD) technique and carotid distensibility (cDC) by ultrasounds, and stiffness index (SI) by digital photopletismography.
Results. Sixty-six obese and 4 overweight children were enrolled (age 11.5±2.4 years; female n: 30). Carotid IMT directly correlated with 24 h - and nighttime SBP; cDC showed inverse correlations with BMI and waist circumference and 24 h-BP. Unexpectedly, SI resulted inversely related with several indexes of weight excess. Most of these correlations remained significant after adjustment for age, sex, BMI and BP. In a replication set of 40 obese children SI but not Pulse Wave Velocity (PWV) was still inversely associated with BMI.
Conclusions. These data suggest that arterial structure and elasticity are negatively affected by weight excess and BP levels, even in childhood. Surprisingly, SI might not be a reliable marker of vascular stiffness in obese children, because this measure is probably confounded by other factors including vasodilation.

USE OF PPI AND RISK OF ISCHEMIC EVENTS IN THE GENERAL POPULATION

F. Galimberti[1], M. Casula[1], L. Scotti[2], F. Mozzanica[1], E. Tragni[1], G. Corrao[2], A.L. Catapano[1,3]
[1]Epidemiology and Preventive Pharmacology Centre (SEFAP), Department of Pharmacological and Biomolecular Sciences, University of Milan;
[2]Department of Statistics and Quantitative Methods, Division of Biostatistics, Epidemiology and Public Health, University of Milano-Bicocca;
[3]IRCCS MultiMedica, Sesto S. Giovanni, Milano

The study aimed to evaluate the risk of hospitalization for cardio/cerebrovascular (CV) events in a cohort of incident PPIs users.
A nested case-control study was carried out, using the healthcare utilization databases of Lombardy. All residents (age: 18-70 yy), with a first prescription (index date, ID) of PPIs from 2003/01/01 to 2007/12/31, were selected and followed until the event, death or migration, or 2010/12/31. Patient with antithrombotic therapy or hospitalization for any CV event during 3 years before the ID, or <57days of follow-up, were excluded. For each case, defined by hospitalization for non-haemorrhagic CV event, up to five controls were matched by gender, age, and ID. Exposure was estimated as recency of therapy (defining current, recent and past users) and number of days covered (based on DDD). Conditional logistic regression was used to estimate association between the exposure and outcome, adjusting for several confounding variables. The same design was applied to a cohort of H2-receptor antagonist users.
In our cohort, 17,832 cases and 89,160 controls were identified (males 64.9%; mean age 58.9 years). Cases showed a significantly higher prevalence of diabetes, hypertension, and hypercholesterolemia. In the multivariate-adjusted regression analysis, risk of event was significantly higher for current (OR 1.61; 95%CI 1.55-1.68) and recent users (OR 1.15; 1.06-1.26) compared to past users, regardless of the type of PPI. Analogous results were found separately for cardiovascular (ORcurrent 1.72; 1.63-1.81) and cerebrovascular events (ORcurrent 1.43; 1.34-1.54). Risk was not influenced by antithrombotic or statin use, nor by exposure duration. The analysis on H2-receptor antagonist use showed no significant results.
Consistent with the evidence that PPIs may adversely impact vascular function, in this study current PPI use was independently associated with an increased risk of first-time CV event in the general population. These results underline the need to promote appropriate prescribing of these drugs.

PREDICTIVE ROLE OF AMBULATORY PULSE PRESSURE IN OLDER HYPERTENSIVE EVALUATED TEN YEARS AFTER THE FIRST OBSERVATION

F. Spannella, P. Balietti, F. Giulietti, G. Cocci, B. Bernardi, G. Rosettani, R. Sarzani
Internal Medicine and Geriatrics, Hypertension Excellence Centre of the ESH, IRCCS-INRCA, Ancona; Department of Clinical and Molecular Sciences, University Politecnica delle Marche (UNIVPM) Ancona

Aim: Age-related blood pressure (BP) changes and risk factors associated with pulse pressure (PP) increase in elderly have rarely been studied using ambulatory blood pressure monitoring (ABPM). Our aim is to evaluate ABP changes over ten years, focusing on PP and its associations with mortality, in older hypertensives.
Methods: Observational study on 119 consecutive older hypertensives evaluated at baseline (T0) and after 10 years (T1). We considered clinical parameters at T1 only in survivors (n=87 patients). Patients with controlled ABP both at T0 and at T1 were considered as having sustained BP control. We considered 55 mmHg as a cut-off value for increased ambulatory PP.
Results: Mean age at T0: 69.4±3.7 years. Females: 57.5%. At T1, significant decrease in 24 h, daytime and night-time diastolic BP (all $p<0.05$) coupled with an increase in 24 h, daytime and night-time PP (all $p<0.05$) were observed. Median 24 h PP change between T0 and T1 was +4 mmHg. Non-sustained daytime BP control was significantly associated with a 24 h PP change greater than 4 mmHg (OR 5.0, p=0.011). Patients who have died during the 10 year period had higher 24 h, daytime and night-time PP at T0 compared to survivors (all $p<0.001$). Patients with 24 h PP ≥55 mmHg at T0 had higher risk of death, even after adjusting for covariates (OR=5.2, p=0.032).
Conclusions: ABPM reveals age-related BP changes and ABP control predicts ambulatory PP increase over 10 years, demonstrating the role of hypertension in the progression of vascular damage. Ambulatory PP predicts mortality for values ≥55 mmHg.

ARTERIAL STIFFNESS AND CHRONIC STRESS: ROLE OF GENDER

R. Gherardini
Dipartimento di Medicina Interna Universitaria I, Università di Pisa

Aim. The aim of this study was to evaluate whether exposure to chronic stress is associated with early vascular aging in hypertensive patients and possible gender differences in this relationship.
Methods. Hypertensive patients where recruited in a Hypertension outpatient clinic during a visit for the evaluation of subclinical organ damage. Aortic stiffness was measured as carotid-femoral pulse wave velocity (PWV) by applanation tonometry; common carotid intima-media thickness (IMT) and distensibility were evaluated by automated analysis of carotid ultrasound clips. Chronic stress was assessed using three different standardized scales: Perceived Stress Score 4 (PSS4), Depression Anxiety Stress Scale (DASS) and Chronic Stress Burden (CSB).
Results. Data from 125 patients (age 56.7±12.5 years, 88.5% in antihypertensive therapy) were analyzed. No significant differences were found between men and women in terms of PWV [8.90 (1.9) vs 8.55 (1.8) m/s, p=0.14], carotid distensibility (22.34±8.79 vs 21.17±8.74 mm, p=0.545) and IMT (0.74±0.12 vs 0.70±0.13 mm, p=0.132). Women presented significantly higher scores of PSS4 [7(3) vs 5(3), p=0.007] and CSB (1.42±1.24 vs 0.59±0.85, p=0.004). In the linear multiple regression analysis, CBS was correlated with PWV in the general population (beta=0.37, p=0.050) being responsible for 4% of the variance of the PWV, without significant gender differences. Among the components of CBS, the difficulties in a relationship with someone close to the participant were associated with the increase in PWV only in the female population (p=0.01). In a multiple regression model, this variable tended to be an independent predictor of PWV (beta=0.37, p=0.057), responsible for 7% of the PWV variance. No significant relationships emerged between PWV and chronic stress assessed by PSS4 or DASS.
Conclusions. In hypertensive patients, chronic stress burden is associated with greater arterial stiffness, without significant gender differences; stress related to difficulties in relationships seems to be associated with greater vascular rigidity only in the female sex.

EFFECTS OF RADIATION THERAPY ON LARGE VESSELS IN HODGKIN LYMPHOMA PATIENTS

F. Bertacchini[1], C. Aggiusti[1], A. Paini[1], M. Salvetti[1], C. Agabiti Rosei[1], S.M. Magrini[2], M.L. Muiesan[1]
[1]Internal Medicine, University of Brescia;
[2]Department of Radiation Oncology, University of Brescia

Background. New chemotherapeutic drugs and radiation therapy have significantly improved cancer patient's survival, although the cardiovascular (CV) side effects of cancer treatment are increasingly important. In previous studies, an increased risk of cerebrovascular complications such as stroke and transient ischemic attack was described in patients undergoing neck radiotherapy.
Aim. of our study was to evaluate vascular carotid structural (IMT, plaque) and functional (carotid stiffness) damage, and changes in arterial stiffness (Carotido-femoral pulse wave velocity; cf-PWV) in Hodgkin Lymphoma survivors previously treated with radiotherapy.
Patients and Methods. we enrolled 206 Hodgkin lymphoma survivors (mean age 54±14 years, 51% males, mean follow-up of 9±6 years). CV risk factors were investigated and atherosclerotic carotid damage was assessed by standard carotid ultrasound evaluation for intima-media thickness (IMT) measurement (MeanMax-IMT, CBMax, Tmax; n=167); in 141 patienys radiofrequency-based carotid stiffness analysis (distensibility; distensibility coefficient, DC; compliance coefficient; CC) was also performed. Cf-PWV measurement were obtained in 154 patients.
Results. a significant correlation between radiotherapy dose and: MeanMax-IMT (r=0.20; p<0.05), Tmax (r=0.20; p<0.05), distensibility (r=0.24; p<0.05), DC (r=0.24; p<0.05), CC (r=0.24; p<0.05) was observed. Patients were divided into 4 groups according to radiotherapy dose (Dose: 20-30; 31-36; 37-42; >42 Gy). An increase in Tmax (1.27±0.61, 1.35±0.59, 1.46±0.69, 1.76±1.12 mm, p for trend<0.05) and in the prevalence of carotid plaque (29%, 31%, 47% and 55%, p for trend<0.05) was observed as related to dose-category. One-hundred-seventeen patients received neck irradiation (67 bilateral; 50 unilateral). In unilaterally irradiated patients, MeanMaxIMT was greater in the irradiated side as compared to unirradiated carotid artery and the difference reached statistical significance in the group of patients who received a high radiotherapy dose (0.97±0.35 vs 0.92±0.34 p<0.05). Cf-PWV was significantly greater only in patients that received high dose (>42 Gy), as compared to all the other dose groups (9.7±2.3 vs 8.3±2.2, 8.0±1.5 and 8.3±1.4, p<0.05).
Conclusions. In this large number of Hodgkin Lymphoma survivors, carotid IMT, plaque prevalence and aortic and carotid stiffness were significantly related with radiotherapy doses. Carotid IMT, carotid and aortic stiffness were significantly higher in the irradiated carotid arteries, but only at doses >42 Gy, suggesting that there may be a dose threshold for radiotherapy-induced carotid wall damage.

HDL FUNCTIONALITY AND DIETARY-DERIVED METABOLITES ARE ASSOCIATED WITH DISEASE SEVERITY IN CALCIFIC AORTIC VALVE STENOSIS

C. Marchi[1], D. Kocyigit[2], L. Tokgozoglu[2], K.M. Gurses[3], M. Stahlman[4]; J. Boren[4], M.F.T. Soyal[5], F. Zimetti[1], I. Zanotti[1], H. Canpınar[6], D. Guc[6], A.S. Ayhan[7], T. Hazirolan[8], K. Aytemir[2], N. Ozer[2]
[1]Department of Food and Drug, University of Parma;
[2]Department of Cardiology, Hacettepe University Faculty of Medicine, Ankara, Turkey;
[3]Department of Histology and Embryology, Adnan Menderes University Faculty of Medicine, Aydin, Turkey;
[4]Department of Molecular and Clinical Medicine, University of Gothenburg Institute of Medicine, Göteborg, Sweden;
[5]Department of Cardiovascular Surgery, Medicana International Ankara Hospital, Ankara, Turkey; [6]Department of Basic Oncology, Hacettepe University Institute of Oncology, Ankara, Turkey;
[7]Department of Pathology, Hacettepe University Faculty of Medicine, Ankara, Turkey;
[8]Department of Radiology, Hacettepe University Faculty of Medicine, Ankara, Turkey

Aim. Calcific aortic valve disease (CAVD) is the most prevalent valvular heart disease. Its pathogenesis has not been elucidated clearly. In this study, we aimed to investigate the link between HDL function, evaluated as cholesterol efflux capacity, and the disease severity. In addition, we assessed the levels of some dietary and gut microbiota- derived metabolites and investigated their relationship with CAVD severity.
Methods. Subjects with moderate-severe calcific aortic stenosis (CAS) (n=60), aortic sclerosis (ASc) (n=49) and age - and sex - matched control subjects (n=48) were included in this study. Severity of CAVD determined by echocardiographic, computed tomographic and histopathological examinations. High- density lipoprotein cholesterol efflux capacity (HDL-CEC) was assessed by a radioisotopic technique. Serum choline, betaine and gut microbiota - derived metabolite levels were measured using ultra- performance liquid chromatography - tandem mass spectroscopy.
Results. Patients with moderate- severe CAS displayed significantly lower total HDL-CEC compared to both control (p=0.011) and ASc (p=0.015) groups. Moreover, total HDL-CEC was negatively correlated with parameters suggested to have prognostic implications in AS, such as peak aortic jet velocity (AVmax) (r=-0.302, p=0.002), aortic valve calcium (AVC) score (r=-0.332, p=0.010), coronary artery calcium (CAC) score (r=-0.355, p=0.005). Total HDL- CEC was also found to be negatively correlated with plasma choline levels (r=-0.210, p=0.031). In addition, Average total HDL- CEC were found to be independent associates of AVmax (β: -0.419, SD: 0.139, p=0.005). Patients with moderate-severe CAS had significantly higher plasma levels of choline when compared to both control (p<0.001) and ASc (p=0.006) groups. Betaine and TMAO levels did not differ among groups (p>0.05). Higher quartiles of plasma choline were also found to be associated with AVC score (p<0.001), absolute left ventricular global longitudinal strain (p=0.012) and with mitral annular calcium (MAC) score (p=0.013).
Conclusion. In this work we have demonstrated that HDL functionality, reflected with HDL- CEC, is independently associated with CAVD severity. We have also shown a relationship between presence and severity of CAVD and the plasma levels of dietary-derived metabolites. These findings suggest that HDL function and choline and betaine as well, may be a novel determinant of CAVD besides traditional risk factors.

HIGH SERUM LEVELS OF GALECTIN-3 AND LP(A) IN PATIENTS UNDERGOING CAROTID ENDARTERECTOMY

D. Palma[1,2], M.D. Di Taranto[1,2], M. Savoia[1], L. Agnello[3], F.P. D'Armiento[5], L. del Guercio[6], U.M. Bracale[6], M. Ciaccio[3,4], G. Fortunato[1,2]

[1]Dipartimento di Medicina Molecolare e Biotecnologie Mediche, Università degli Studi di Napoli Federico II, Naples;
[2]CEINGE S.C.a r.l. Biotecnologie Avanzate, Naples;
[3]Sezione di Biochimica Clinica e Medicina Molecolare Clinica, Dipartimento di Biopatologia e Biotecnologie Mediche, Università degli Studi di Palermo;
[4]UOC Medicina di laboratorio, AOUP "P. Giaccone", Palermo;
[5]Dipartimento di Scienze Biomediche Avanzate, Università degli Studi di Napoli Federico II;
[6]Dipartimento di Sanità Pubblica, Università degli Studi di Napoli Federico II, Naples

Aim. Atherosclerosis is considered to be a complex inflammatory process involving various inflammatory players. In particular inflammatory activity is reported associated with a several plaques instability features such as plaque rupture and thrombus formation. We aim to better understand the role of Galectin-3 (Gal-3) and Lipoprotein(a) [Lp(a)] in atherosclerotic process in order to identify possible peripheral markers of plaque instability and of high risk for cardiovascular events.
Methods. Gal-3 and Lp(a) serum levels were measured in samples from 99 patients undergoing carotid endarterectomy and from 61 healthy controls by immunometric assays. Advanced human carotid plaques from patients were classified histologically according to American Heart Association (AHA) guidelines.
Results. Gal-3 and Lp(a) serum levels were significantly higher in the patient than in the control group (19.8±5.8 vs 14.4±3.8 ng/mL, $p<0.0001$ and 8.4(4.0-25.1) vs 4.7(2.4-12.7) mg/dL, $p<0.0001$, respectively). Also normalizing Lp(a) levels for LDL-cholesterol (Lp(a)/LDL ratio) patients showed higher levels than controls [Lp(a)/LDL ratio = 0.11 (0.05-0.27) vs 0.04 (0.02-0.12), $p<0.0001$]. At multivariate logistic regression Gal-3 levels remain associated with the plaque presence independently from age, sex, LDL and Lp(a) levels with an odd ratio of 1.214 (1.088-1.353) and a $p=0.0005$. No differences were found between Gal-3 serum levels among the different plaques types, nor between complicated and uncomplicated plaques.
Conclusion. Our data showed that Gal-3 and Lp(a) are good peripheral analytes discriminating between subjects with and without advanced atherosclerotic plaque. In particular high Gal-3 levels may be considered a risk factor independently from age, sex, LDL and Lp(a) levels. To date, Gal-3 and Lp(a) serum levels cannot be considered markers of plaque instability although a large population should be analyzed.

STEATO-SCORE: A NEW TOOL FOR ASSESSING LIVER FAT CONTENT BY ULTRASOUND IMAGING

N. Di Lascio[1,2], C. Avigo[3], A. Salvati[3,4], N. Martini[5], M. Ragucci[6], S. Monti[7], A. Prinster[6], D. Chiappino[5], M. Mancini[6], D. D'Elia[8], L. Ghiadoni[3], F. Bonino[3,8,9], M. R. Brunetto[3,4], F. Faita[2]

[1]Institute of Life Sciences, Scuola Superiore Sant'Anna, Pisa;
[2]Institute of Clinical Physiology, National Research Council, Pisa;
[3]Department of Clinical and Experimental Medicine, University of Pisa;
[4]Hepatology Unit and Laboratory of Molecular Genetics and Pathology of Hepatitis Viruses, Reference Centre of the Tuscany Region for Chronic Liver Disease and Cancer, University Hospital of Pisa;
[5]Tuscany Foundation G. Monasterio, Massa;
[6]Institute of Biostructure and Bioimages, National Research Council, Naples;
[7]IRCSS SDN, Naples;
[8]University of Pittsburgh Medical Center Institute for Health, Chianciano Terme, Siena;
[9]Fondazione Italiana Fegato, AREA Science Park, Campus Basovizza, Trieste

Non-Alcoholic Fatty Liver Disease (NAFLD) is becoming a global epidemic and represents a risk factor for cardiovascular disease (CVD) independently of the features in common with the metabolic syndrome. This study was aimed at developing a new system for quantitative evaluating liver fat content post-processing ultrasound (US) images.
The study population included 105 subjects and Magnetic Resonance Spectroscopy (MRS) measurements were used as ground-truth. For each subject, US images were acquired and employed for assessing hepatic-renal ratio (HR), hepatic-portal vein ratio (HPV), attenuation-rate (AR), diaphragm visualization (DV) and portal-vein-wall visualization (PVWvis). *Steato-score* was obtained combining these five parameters using multivariate regression analysis. The diagnostic performances of the *Steato-score* were evaluated dividing the population on the MRS base and using previously specified cut-off values correspondent to biopsy steatosis classes S0, S1, S2 and S3. In particular, 3 classifications were performed: S0vsS1S2S3 using a MRS cut-off of 3.12%; S0S1vsS2S3 using a MRS cut-off of 8.77%; S0S1S2vsS3 using a MRS cut-off of 13.69%. In order to test the performances of the system even in cases of overweight and obese subjects, the analysis was repeated using only subjects with BMI>25 kg/m^2.
MRS measurements were significantly correlated with HR, AR, DV and PVWvis; *Steato-score* was dependent on HR, AR, DV and PVWvis. Area under the ROC curve (AUROC) was equal to 0.90, with 81% sensitivity, 88% specificity for the comparison S0 vs S1S2S3, was equal to 0.98, with 100% sensitivity and 88.8% specificity for the comparison S0S1 vs S2S3 and equal to 0.97, with 91% sensitivity and 94% specificity for the comparison S0S1S2 vs S3. These diagnostic performances were confirmed even when considering only subjects with BMI >25 kg/m^2.
This system could be a valid alternative for a non-invasive, simple and inexpensive assessment of intra-hepatic fat.

A TREATMENT WITH ANTI-PROPROTEIN CONVERTASE SUBTILISIN-KEXIN TYPE 9 MONOCLONAL ANTIBODIES IMPROVES LIPID AND INFLAMMATORY PROFILES AND CIRCULATING PROGENITOR CELLS NUMBER

V. Cairo, C.O. Aragona, F. Mamone, F. Savarino, S. Tomeo, M. Scuruchi, S. Loddo, E. Imbalzano, A. Saitta, G. Mandraffino
Department of Clinical and Experimental Medicine, University of Messina

Background. Monoclonal antibodies that inhibit proprotein convertase subtilisin-kexin type 9 (PCSK9) are a new class of drugs that lowers LDL cholesterol levels. Circulating progenitors cells (CPCs) are a heterogeneous population of cells with the ability to differentiate in vivo into a broad range of cell type. They are able to work as proangiogenic support cells, to participate in the turnover of healthy and damaged endothelium, maintaining their importance as regenerative/reparative potential, and also as prognostic markers.
Aims. We investigate whether after six months of treatment with anti-PCSK9 monoclonal antibodies (alirocumab or evolocumab) we can find any improvement of pro-atherogenic profile and of CPC number in patients affected by familial hypercholesterolemia (FH).
Methods. We enrolled 19 FH patients (primary prevention) not at LDL-C target. At enrollment and 6 months later we evaluated anthropometrics, laboratory profile, instrumental, and CPC count.
Results. After 6 months of treatment we found a significant decrease of inflammatory markers (Hs-CRP: -40.9%; Fibrinogen: -20.6%), LDL-C and lipoprotein(a) levels (respectively -66.7% and -37.9%). CPCs appeared to be improved (+22.2%). The variation in CPC number appeared to be correlated with inflammatory markers and LDL-C reduction (Spearman's test). However, the improvement in CPC number appeared to be dependent only on Δfibrinogen and ΔCRP by the multiple regression analysis.
Conclusion. After 6 months of treatment with monoclonal antibodies anti-PCSK9 the levels of CRP, Fibrinogen, LDL-C, and Lp(a), as well as CPC number, were significantly improved as compared to baseline. A treatment with anti-PCSK9 monoclonal antibodies may significantly improve the CPC count in FH patients.

EFFECTS OF AGALSIDASE-B INFUSION ON VASCULAR FUNCTION AND BLOOD PRESSURE IN ANDERSON-FABRY DISEASE

M. De Feo, C.A. Stamerra, C. Ferri, D. Grassi
Department MeSVA, University of L'Aquila

Aim. Anderson-Fabry disease is a lysosomal storage disease caused by a defect in the β-galactosidase A gene. Endothelial dysfunction, related to globotriaosylceramide (GL-3) deposits in the endothelium of the vascular system, is probably one of the most important pathogenetic mechanisms in the development of multisystem complications of Fabry disease. Clinical studies have shown that enzyme replacement therapy (ERT) significantly removes the endothelial GL-3 deposits. However, only a few studies have yet focused on the effects of ERT on vascular function. The aim of our study was to investigate the effects of agalsidase-β treatment on vascular function and blood pressure in 4 adult subjects affected by Fabry disease.
Methods. Office blood pressure, flow mediated dilation (FMD), pulse wave analysis (PWA) and pulse wave velocity (PWV) were evaluated on the day before Agalsidase-β infusion, immediately after the infusion, and on days 4 and 8 after the infusion. Measurements were performed for three consecutive infusions (each dose administered 2 weeks apart) in the first month of treatment.
Results. Agalsidase-β infusion resulted in a steady FMD increase immediately after the infusion and after 4 and 8 days, compared with baseline values. There was a statistically significant increase of FMD after the first month of treatment ($p<0.05$). Although an increase both in systolic blood pressure (SBP) and in diastolic blood pressure (DBP) was detected immediately after each infusion, office blood pressure showed a decreasing trend. The reduction in DBP reached the statistical significance after a month of treatment ($p<0.05$). PWV showed a continuous decrease throughout the follow-up period, with no statistical significance. No substantial change was observed in PWA.
Conclusions. Our study showed that ERT with Agalsidase-β reduced blood pressure and improved FMD and arterial stiffness. These findings suggest that Agalsidase-β might represent a reasonable tool in cardiovascular prevention in subjects suffering from Fabry disease.

ASSESSMENT OF LEFT VENTRICULAR SYSTOLIC FUNCTION IN MASKED, ISOLATED AND SUSTAINED HYPERTENSION IN A GENERAL POPULATION

C. Aggiusti, F. Bertacchini, A. Paini, M. Salvetti, D. Stassaldi, C. Agabiti Rosei, M.L. Muiesan
Internal Medicine, University of Brescia

Background. Previous studies have demonstrated that ambulatory blood pressure monitoring (ABPM) provides useful information in hypertensive patients and in the general population. Few data are available on LV function according to BP categories as defined by clinic and 24 hours BP measurement.
The aim of our study was to evaluate indices of left ventricular (LV) function in normotensive subjects (NT), in patients with isolated office hypertension (IOH), with masked hypertension (MHT) and with sustained hypertension (HT) defined according to clinic and 24 hours blood pressure (BP) monitoring.
Design and Methods. Out of 585 subjects, we identified 294 untreated subjects (mean age 56±9 years, 45% males) participating in our ongoing population study (Vobarno study). All subjects underwent standard laboratory examinations and clinic and 24 hours blood pressure measurement. Standard echocardiography was performed in all patients, and indices of systolic function were calculated. Furthermore in all patients, myocardial mechanoenergetic efficiency (MEE) was calculated as stroke volume/heart rate and indexed to LV mass (MEEi=MEE/LVM) (de Simone et al, 2016).
Results. 39.5% of subjects were classified as NT, 17% as IOH, 18.5% as MH and 25% as HT. MEEi was significantly lower in IOH, MH and HT as compared to NT (0.52±0.12, 0.54±0.13, 0.51±12 vs 0.67±0.16 ANOVA $p<0.05$). The difference between groups remained statistically significant after adjusting for all possible confounders. Midwall fractional shortening (as absolute value and as % of predicted), was lower in IOH, MH and EH as compared to NT. No differences in fractional shortening and ejection fraction were observed.
Conclusions. Left ventricular myocardial mechanoenergetic efficiency and midwall function are depressed not only in patients with sustained hypertension, but also in patients with isolated office and masked hypertension.

ENGINEERED REGULATORY T CELL ADOPTIVE THERAPY AS A NOVEL TOOL FOR THE TREATMENT OF ATHEROSCLEROSIS

F. Bonacina[1], E. Martini[2], S. Garetto[2], F. Sala[1], S. Locatelli[1], A.L. Catapano[1,4], M. Kallikourdis[2], G.D. Norata[1,3,5]
[1]Department of Pharmacological and Biomolecular Sciences, University of Milan;
[2]IRCCS Humanitas Research Foundation, Rozzano;
[3]Centro SISA, Ospedale Bassini, Cinisello Balsamo;
[4]IRCSS MultiMedica, Milano;
[5]School of Biomedical Sciences, Curtin Health Innovation Research Institute, Faculty of Health Science, Curtin University, Perth, Western Australia

Aim. Inflammation is a major contributor of atherogenesis. As loss of anti-inflammatory activity of regulatory Tcells (Treg) is a pathogenic feature of (auto)immune mediated-disease, Treg-Adoptive Cell Therapy (ACT) is emerging as a therapeutic strategy to specifically modulate impaired immune responses. Although ACT has produced encouraging results in animal models, targeting site of action of transferred cells is still lacking. We aim at developing plaque-homing Treg for atherosclerosis treatment in animal models.
Methods. Treg were retrovirally (IRES-EGFP vector) transfected with chemokine receptors or an empty vector and i.v. injected (about $2x10^5$ GFP+ cells/mouse) in male 8-week WTD LDLR KO. Homing of transfected Treg to atherosclerotic plaque and, after 4-week WTD, its progression and composition was analysed by flow cytometry and histology (H&E, picro Sirius staining).
Results. The chemokine CX3CL1 is selectively expressed in the aorta, but not in other tissues (lymph nodes, spleen and liver) ($p<0,01$) of 8 week WTD LDLR KO, contrary to CCL2, usually associated with inflammation during atherosclerosis. Therefore, we compared homing of CCR2- and CX3CR1-transfected Treg to the aorta. Although CCR2-tranfected Treg migrated to the aorta, they didn't show tissue specificity. Conversely, CX3CR1-Treg showed a specific homing to atherosclerotic plaques (2,5% of GFP+ out of lived cell compared to 0.6% of control) while no significant difference was observed in lymph nodes, spleen and liver. Next we investigated whether CX3CR1-Treg reduced atherosclerosis by performing plaque analysis 4 weeks after ACT. Altough levels of plasma cholesterol were comparable (about 560 mg/dL), plaque area was decreased by 72% (5,12% vs 18,78%, $p<0,01$) and stability, measured as collagen content, increased by 26% (9,87% vs 7,81%, $p<0,01$) in CX3CR1- compared to control-Treg treated mice.
Conclusion. Overexpressing CX3CR1 appears a promising ACT to selectively home Treg into the plaque and limit atherosclerosis progression.

PULSE WAVE VELOCITY PROGRESSIONE OVER A 3.7 YEARS FOLLOW-UP: FOCUS ON METABOLIC SYNDROME

A. Maloberti[1,2], P. Vallerio[1], L. D'angelo[1], R. Facchetti[2], L. Occhi[1,2], F. Panzeri[1,2], D. Sirico[1,2], A. Buono[1,2], L. Giupponi[1,2], N. Triglione[1,2], B. Lopez Montero[1], M. Casati[3], S. Signorini[4], A. Moreo[1], G. Grassi[2], C. Giannattasio[1,2]
[1]Cardiology IV, ASST Niguarda Hospital, Milan;
[2]School of Medicine and Surgery, Milano Bicocca University;
[3]Biochemical Laboratory, San Gerardo Hospital, Monza;
[4]Biochemical Laboratory, Desio Hospital, Desio

Objective. The role of classic cardiovascular risk factors on the progression of arterial stiffness has not yet been extensively evaluated particularly regarding Metabolic Syndrome (MS). The aim of the current longitudinal study was to evaluate the determinants of the Pulse Wave Velocity (PWV) progression over a 3.7 years follow-up period in hypertensive subjects focusing on metabolic syndrome.
Design and Methods. We enrolled 448 consecutive hypertensive outpatients 18-80 aged, followed by the Hypertension Unit of St. Gerardo Hospital (Monza, Italy). At baseline anamnestic, Blood Pressure (BP) and laboratory data as well as cf-PWV were assessed. We performed PWV again at a follow-up examination with a median time amounting to 3.7±0.5 years. NCPET-ATPIII criteria were used to define MS as the presence of three or more item. Data are reported as mean±SE.
Results. At T0 the mean age was 53.7±1.1 years, SBP and DBP were 141.3±1.7 and 86.4±1.2 mmHg and PWV was 8.5±0.15 m/s. 125 patients (27.9%) meet the criteria for MS. Those patients were older (56.3±1.0 vs 52.7±0.7, p=0.007) with superimposable baseline SBP and DBP values (141.4±1/87.2±0.6 vs 142.4±1.6/86±1, p>0.05 for both comparison) as well as PWV values (8.7±0.18 vs 8.58±0.1, p=0.43). At follow-up examination MS subjects showed a lower decreas in SBP/DBP (SBP: -4.7±1.7 vs -10.2±1.1; DBP: -5.1±1.1 vs -8.3±0.7, p<0.01 for both comparison) with a higher increase in PWV values (1.1±0.2 vs 0.39±0.1, p=0.03). This difference remain significant also in a multivariate model with age, sex, smoking, baseline PWV and delta MBP as covariates.
Conclusions. Arterial aging and BP values in treated hypertensive subjects during a 3.7 years follow-up seems to be influenced by the presence of MS. In fact subjects with MS showed a worse BP control and an increase in PWV values during the follow-up. PWV changes over time would probably give important information that need further future research studies.

ULTRASONOGRAPHIC DETECTION OF XANTHOMAS IN ACHILLES TENDONS OF SUBJECTS WITH HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

M. Biolo, P. Scarinzi, P. Bigolin, M. Moro, L. Benvegnù, C. Panzavolta, R. Marin, D. Vianello, S. Bertocco, S. Zambon, F. Fabris, E. Manzato, L. Previato, A. Zambon
Medicine Department, DIMED, University of Padova

Aim. To analyse the diagnostic value of the Achilles tendon (AT) ultrasonography to identify xanthomas compared with clinical examination in subjects with Heterozygous Familial Hypercholesterolemia (HeFH).
Methods. We enrolled 101 subjects with HeFH between the age of 18 and 70 years old from January 2016 to October 2017. Medical history, clinical examination, complete lipid profile, and Dutch Lipid Clinic Network (DLCN) score were collected; all the subjects were submitted to bilateral AT ultrasonography to evaluate AT thickness, echo-structure and presence of hypoechogenic formations. Subjects with previous tendon ruptures were not included.
Results. 101 subjects (63 F, and 38 M) with a mean age of 48.0±15.5 years and a mean DLCN score of 10.1±4.9. 10.2% of subjects presented xanthomas at clinical examination (XC) with an echographic pattern compatible with xanthoma (XUS), 51% presented XUS but not XC, and 38% had neither XUS or XC. AT thickness was positively associated with LDL cholesterol at the diagnosis (r=0.411, p<0.001), and this association was maintained in a multivariate logistic regression analysis adjusted for age, sex and lipid lowering therapy (OR 1.020, 95%CI 1.004-1.035; p=0.012).
Conclusions. We have confirmed that ultrasonography is more sensitive than clinical examination to identify xanthomas, and it could represent, with medical history and clinical examination, a useful method to reach an early diagnosis of HeFH.

SHORT-TERM BLOOD PRESSURE VARIABILITY AND CIRCADIAN BLOOD PRESSURE IN SUBJECTS WITH HYPERTENSIVE URGENCIES

S. Ricci[1,2], F. Battista[1,2], R. Sgariglia[1,2], A. Crocetti[1,3], G. Tilocca[1,3], S. Perlini[4], G. Pucci[1,2]
[1]Dipartimento di Medicina, Università di Perugia;
[2]Struttura Complessa di Medicina Interna, Azienda Ospedaliera di Terni;
[3]Struttura Complessa di Cardiologia, Azienda Ospedaliera di Terni;
[4]Dipartimento di Medicina Interna e Terapia Medica, Policlinico "S. Matteo", Università di Pavia

Introduction. Hypertensive Urgencies (HU), classified as abrupt blood pressure (BP) increases above 190/110 mmHg without acute organ damage, could be theoretically conceived as an expression of increased short-term BP variability (BPV). However, few studies systematically explored this association. It is also unknown if subjects experiencing HU are characterized by abnormal BP circadian profiles. We evaluated the association between HU, measures of short-term BP variability, and nocturnal BP dipping in a case-control study.
Methods. We analysed all subjects consecutively admitted to the Emergency Department of the "S. Maria" University Hospital, Terni, with a diagnosis of HU, and subsequently evaluated in the Hypertension Unit by a specialist. All subjects underwent Ambulatory Blood Pressure Monitoring (ABPM) within 5 days from admission. Subjects with hypertensive emergencies (at admission or during the following days) were excluded. Controls were selected in order to be well matched with HU subjects for sex, age, 24 h SBP/DBP, and number of anti-hypertensive drugs. All controls had a negative history for HU. Day-time and night-time standard deviation of SBP (SD-SBP), Systolic BP Average Real Variability (ARV), and weighted 24-h SD of SBP (wSD) were taken as measures of BPV. All subjects were managed according to Guidelines for Good Clinical Practice.
Results. 62 subjects with HU (60±16 years, office BP 190/101±21/10 mmHg, 24 h BP 122/73±13/9 mmHg), were compared with 177 controls. Both groups did not differ in terms of 24 h SBP/DBP, day-time and night-time SBP/DBP, number of anti-hypertensive drugs, and degree of nocturnal BP fall. Subjects with HU had increased wSD (12.0±3 vs 9.2±3 mmHg, p=0.02) and night-time SD-SBP (9±3 vs 8±2 mmHg, p=0.01) as compared to controls. Differences in ARV (8.5±3 vs 6.9±3 mmHg, p=0.29) and day-time SD-SBP (12±4 vs 12±3, p=0.22) were not significant.
Conclusions. As compared to hypertensive patients without HU, subjects referring to the ED for HU showed increased indexes of short-term BPV, expressed as increased wSD and nocturnal SD-SBP. We did not found any differences between groups in terms of nocturnal BP dipping. Our results therefore suggest a possible functional link between increased BPV and the occurrence of HU in hypertensive patients.

FEATURES OF METABOLIC DERANGEMENT WITH PCSK9 DEFICIENCY IN EXPERIMENTAL MODELS AND IN HUMANS

A. Baragetti[1,2], V. Zampoleri[2], L. Da Dalt[2], F. Bonacina[2], L. Grigore[2,3], F. Pellegatta[2,3], U. Guerrini [1], G. Pisano[4], A.L. Fracanzani[4], S. Fargion[4], G.D. Norata[1,5], A.L. Catapano[1,2,3]
[1]Department of Pharmacological and Biomolecular Sciences, Università degli Studi di Milano,
[2]SISA Center for the Study of Atherosclerosis, Bassini Hospital, Cinisello Balsamo;
[3]IRCCS MultiMedica Hospital, Sesto San Giovanni, Milano;
[4]Department of Pathophysiology and Transplantation, Ca' Granda Foundation IRCCS Maggiore Policlinico Hospital, Università degli Studi di Milano;
[5]School of Biomedical Sciences, Curtin Health Innovation Research Institute, Curtin University, Perth, Western Australia

Aim. PCSK9 targets not only the LDLR but also triglycerides (TGs) rich lipoproteins receptors (like VLDLR), significantly expressed in key metabolic tissues (adipose tissue, pancreas). Thus, would PCSK9 reduction affect glucose metabolism and ectopic fat accumulation in vivo?
Methods. An epidemiological study was genotyped for PCSK9 R46L (Loss-of-Function, LoF). Fasting, postprandial lipoproteins as well as gluco-metabolic profiles were evaluated. Abdominal, epicardial adiposity were quantified and presence of hepatic steatosis was evaluated.
Results. LoF carriers showed significantly -11%, -16%, -19% and -35% in plasma LDL-C, ApoB, ApoCIII and PCSK9 (P=0.030, 0.001, 0.013, 0.001 respectively). However, postprandial lipemia after oral fat load challenge was altered in LoF compared to non-carriers, thus questioning the effect of PCSK9 inhibition on broad metabolic features. Moreover, LoF carriers were more obese, showed increased percentage of abdominal fat, two-fold increased prevalence of hepatic steatosis and higher amount of epicardial adipose tissue.
These findings were recapitulated in PCSK9 KO mice fed a high-fat diet, accumulating more visceral adipose tissue vs PCSK9 WT. Despite similar response to insulin, impaired glucose tolerance (+40% vs PCSK9 WT) was reflected by reduced insulin secretion by pancreatic islets; these effects were abrogated when LDLR was defective. Similarly, LoF showed higher glucose levels and -17% beta-cells function index (HOMA-BC), dependently to LDL-C.
KO mice liver and circulating cells from LoF showed altered LDLR, VLDLR, CD36 expression and pro-inflammatory gene pattern, suggesting intracellular relevance of PCSK9 deficiency.
Conclusions. Beside contrasting data on post-prandial TG levels, we question whether altered glucose control and increased ectopic adiposity accumulation are peculiar to genetic PCSK9 deficiency or to circulating protein, target of monoclonal antibodies.

THE PCSK9/LDLR AXIS IMPACTS INSULIN SECRETION AND GLUCOSE RESPONSE

L. Da Dalt[1], G. Balzarotti[1], M. Ruscica[1], F. Bonacina[1], A. Dhyani[1], E. Di Cairano[1], A. Baragetti[2], L. Arnaboldi[1], S. De Metrio[1], M. Botta[1], C. Macchi[1], P. Uboldi[1], C. Perego[1], A.L. Catapano[1,3], G.D. Norata[1,4]
[1]Department of Pharmacological and Biomolecular Sciences, Università degli Studi di Milano;
[2]Centro SISA per lo studio dell'Aterosclerosi, Ospedale Bassini, Cinisello Balsamo;
[3]IRCCS MultiMedica Hospital, Sesto San Giovanni, Milano;
[4]School of Biomedical Sciences, Curtin Health Innovation Research Institute, Faculty of Health Science, Curtin University, Perth, Western Australia

Aim. *PCSK9* genetic variants are associated with lower LDL-Cholesterol levels but also with higher plasma glucose levels and increased risk of T2D. We investigated the molecular mechanisms beyond this association.
Methods. *Pcsk9* KO, WT, *Pcsk9/Ldlr*-DKO, *Ldlr*-KO, albumin (*Alb*)*Cre+/Pcsk9*$^{LoxP/LoxP}$ (liver selective *Pcsk9*-KO mice) and liver selective PCSK9-KO mice were used. GTT, ITT, insulin and C-peptide plasma levels, pancreas morphology and cholesterol accumulation in pancreatic islets were studied in the different animal models.
Results. Glucose clearance was significantly impaired in *Pcsk9*-KO mice fed a standard or a high fat diet for 20 weeks compared to WT animals with both diet (*Pcsk9*-KO AUC was 1.42±0.08 folds higher, $p<0.05$); insulin sensitivity was not affected: both animal models showed a similar decrease in plasma glucose levels during ITT. Plasma insulin and C-peptide levels were reduced in *Pcsk9*-KO mice compared to WT as in fasting and refeeding experiments. A detailed analysis on *Pcsk9*-KO pancreas morphology revealed larger islets with more intracellular accumulation of cholesteryl esters and insulin compared to control (*Pcsk9*-KO Area was 9175,487±1432,97 vs 3629,718±508,26, $p<0,001$). This phenotype was recovered in *Pcsk9/Ldlr* double KO and *AlbCre+/Pcsk9*$^{LoxP/LoxP}$ mice suggesting a key role for the LDLr in determining the phenotype which is independent of circulating PCSK9.
Conclusion. The PCSK9/LDLr axis affects beta cell function and insulin secretion. Our data indicate that this effect is related to local PCSK9 and support the observations available that anti-PCSK9 antibodies or liver specific therapies, such as siRNAs, have a limited impact on glucose metabolism as opposed to statins.

SIMVASTATIN AS A POSSIBLE TOOL TO ALTER EXTRACELLULAR VESICLES FUNCTIONS. IN VITRO STUDIES

F.M. Accattatis[1], L. Merlo[1], A. Granata[1], V. Huber[2], L. Cantone[3], V. Bollati[3], A. Corsini[1], L. Arnaboldi[1]
[1]Dipartimento di Scienze Farmacologiche e Biomolecolari, DiSFeB, Università degli Studi di Milano;
[2]IRCCS Istituto Nazionale dei Tumori, Laboratorio di Immunoterapia dei Tumori Umani, Milano;
[3]Dipartimento di Scienze Cliniche e di Comunità, Università degli Studi di Milano

Extracellular vesicles (EVs) are a highly heterogeneous group of cell-derived membrane structures, which comprise exosomes (50-150 nm) and microvesicles (50-1000 nm). EV are used to transport and deliver lipids, proteins and nucleic acids to distant cells, are present in all body fluids and contribute to homeostasis, diseases development and progression. Since EVs are mainly constituted by cholesterol and phospholipids, it is conceivable that alterations in these components may affect their size, composition and function(s). Therefore, we wanted to assess whether the HMG-CoA reductase inhibitor simvastatin, by inhibiting cholesterol biosynthesis in a lymph-node melanoma metastatic cell line (LM-16), may affect LM-16 derived EV size and composition. We first run experiments to find a concentration-dependent inhibitory effect on cholesterol biosynthesis, without affecting cell proliferation and we used these conditions to assay EV. After a three-days incubation of LM-16 cells with 0.75 µM of simvastatin, we changed the medium with a serum-free one, we maintained it for 24 hrs and then we isolated EV by differential ultracentrifugation; samples were analyzed with or without filtration (0.2 µm, 0.1µm) and analyzed by NanoSight. Our preliminary data show that simvastatin increased EV diameter (from 176.35 to 177.85 nm if non-filtered, from 163.1 to 164.6 nm filtered 0.2 µm, and from 140.2 to 153.9 nm filtered 0.1 µm) while decreased the ratio of 50-150 nm diameter-particles/total ones from 47.92 to 45.13% filtered 0.2 and from 64.57 to 53.89% filtered 0.1. These findings suggest that simvastatin, by increasing EV size and altering the overall particle size distribution, may affect functional properties of EV. We are analyzing the lipid composition of EV and of their parental cells to understand if cholesterol decrease in the latter may cause alterations in EV membrane that can translate into different functional EV properties, with the purpose of finding a pharmacological approach based on modified EV in the treatment of tumors.

FENRETINIDE EXACERBATES ATHEROSCLEROSIS IN SPITE OF BENEFICIAL METABOLIC EFFECTS

S. Manzini[1], M. Busnelli[1], C. Parolini[1], E. Scanziani[2], G. Chiesa[1]
[1]Department of Pharmacological and Biomolecular Sciences, Università degli Studi di Milano; [2]Department of Veterinary Sciences and Public Health, Università degli Studi di Milano

Aim. Fenretinide, a synthetic retinoid derivative first investigated for cancer prevention and treatment, has been shown to ameliorate glucose tolerance and reduce body fat mass. These effects, together with its ability to inhibit ceramide synthesis, have suggested that fenretinide may display anti-atherosclerotic effects.
Methods. To this aim, 9-weeks-old apoE-KO (EKO) female mice were fed for 12 weeks a Western diet, without (control) or with 0.1% w/w fenretinide (n=20 mice/group). Wild-type C57BL/6J (WT) mice were similarly enrolled to rule out possible genotype biases (n=10). Mouse body weight, water and food intake were monitored throughout the study. Shortly before the end of the dietary treatment, plasma lipids and basal glucose levels were measured, and a glucose tolerance test was also performed in EKO. At sacrifice, heart and aorta were harvested to evaluate atherosclerosis development. In addition, liver, spleen, kidney, heart, white abdominal adipose and lung tissue underwent histological analysis.
Results. In EKO, fenretinide administration significantly lowered body weight and glucose levels, as well as plasma levels of total cholesterol, triglycerides and phospholipids. In liver, fenretinide remarkably lessened the storage of glycogen and lipids driven by the Western diet. Unexpectedly, the treatment also led to abnormally enlarged spleens, with severe follicular atrophy and increased prevalence of extramedullary hematopoiesis. This latter finding was also observed in the liver, together with erythrophagocytosis. Heavy renal hemosiderin deposition was observed in fenretinide-treated mice. Finally, atherosclerosis development was markedly increased in fenretinide-treated EKO vs control at the aortic arch (34.6±7.3% vs 26.1±5.8%, +33%), thoracic (14.2±4.9% vs 4.9±2.1%, +190%) and abdominal aorta (7.4±3.3% vs 3.3±1.8%, +124%). Fenretinide treatment to WT also caused body weight and abdominal fat reduction, with less severe spleen enlargement than in EKO. Biochemical and histological evaluations on WT are ongoing.
Conclusions. We first-time demonstrated that, despite beneficial metabolic effects, fenretinide treatment could be severely detrimental for atherosclerosis development.

NORMALIZATION OF LIPOPROTEIN PROFILE DURING PREGNANCY IN LCAT DEFICIENCY

A. Strazzella[1], E. Hanna[2], S. Simonelli[1], A. Ossoli[1], R. Mullan[3], S. Chamney[4], J Chestnutt[2], F. Stewart[5], L. Calabresi[1]
[1]Centro E. Grossi Paoletti, Dipartimento di Scienze Farmacologiche e Biomolecolari, Università degli Studi di Milano;
[2]Department of Biochemistry;
[3]Renal Unit, Antrim Hospital, Northern Health and Social Care Trust, Antrim, UK;
[4]Department of Ophthalmology, Royal Victoria Hospital;
[5]Department of Genetics, Belfast City Hospital, Belfast Health and Social Care Trust, Belfast, UK

Aim. Subjects with genetic LCAT deficiency show marked alterations in plasma lipoprotein profile; among changes, the appearance of an abnormal lipoprotein, Lipoprotein X (LpX), seems to be involved in glomerulosclerosis development. Here we describe the normalization of lipoprotein profile during pregnancy in LCAT deficient woman.
Methods. A 29-year-old multigravida woman compound heterozygote with two LCAT gene mutations initially presented with bilateral corneal clouding, greatly reduced HDL-C and proteinuria (113.7 mg/mmol creatinine). Fasting blood was collected at 22 weeks gestation and 14 weeks post-partum to assess possible changes during pregnancy.
Results. LCAT activity, cholesterol esterification rate, both undetectable, unesterified/total cholesterol ratio, and LCAT mass remained identical during pregnancy and post-partum. Total cholesterol, HDL-C, phospholipids, apoA-I and apoB increased during pregnancy. Her pregnancy was complicated by an hypertriglyceridaemia (613 mg/dL), which was more severe than is seen with normal physiological changes of pregnancy. Surprisingly, the level of proteinuria significantly improved during pregnancy (13.9 mg/mmol creatinine), despite stopping the ACE inhibitor, but it worsened post partum again (131.6 mg/mmol creatinine). Lipoprotein analysis by FPLC and agarose gel electrophoresis of plasma revealed the presence LpX only in post-partum, whereas this abnormal particle disappeared during pregnancy.
Conclusion. LpX is an abnormal lipoprotein particle proposed as a major causative factor in the development of renal disease in carriers of LCAT deficiency. Its disappearance during pregnancy improves proteinuria in this woman and it is probably due to the severe increase of TG that are used, together with phospholipids, to produce VLDL.

SUBCLINICAL IMPAIRMENT OF MYOCARDIAL AND ENDOTHELIAL FUNCTIONALITY IN VERY EARLY PSORIATIC AND RHEUMATOID ARTHRITIS PATIENTS: ASSOCIATION WITH VITAMIN D AND INFLAMMATION

F. Savarino[1], A. Lo Gullo[1], J. Rodríguez-Carrìo[2,3], C.O. Aragona[1], A. Suárez[2,3], F. Atzeni[1,4], A. Saitta[1], G. Mandraffino[1]
[1]Department of Clinical and Experimental Medicine, University of Messina;
[2]Area of Immunology, Department of Functional Biology, Faculty of Medicine, University of Oviedo, Oviedo, Spain;
[3]Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Oviedo, Spain;
[4]Department of Neurology, Robert and Martha Harden Chair in Mental and Neurological Diseases, Sackler Faculty of Medicine, Tel Aviv University, Israel

Aim. The prevalence of subclinical atherosclerosis has been assessed in rheumatoid (RA) and psoriatic arthritis (PsA), but how precociously also myocardial functionality is impaired remains unknown. The aim of this study was to evaluate the myocardial and arterial functionality in RA and PsA patients of recent onset and its associations with circulating CD34+ cells, vitamin D, and disease activity.
Methods. Global longitudinal and circumferential strain (GLS and GCS) were estimated to assess the myocardial functionality in patients with RA (n=41) and PsA (n=35) without traditional CV risk factors, and 58 matched healthy controls (HC). Pulse Wave Velocity (PWV) and carotid intima-media thickness (cIMT) were measured by routine methods. Circulating CD34+ counts were evaluated by flow cytometry, and vitamin D levels by HPLC. Disease activity was also determined by DAS 28, HAQ, VAS and PASI.
Results. GLS and GCS were impaired in RA patients and in PsA patients with higher disease activity. DAS28 was correlated to GLS and GCS in RA. GLS was found to be a predictor of cIMT in PsA. Vitamin D was an independent predictor of decreased CD34+ levels in PsA and RA. CD34+ counts negatively correlated with DAS28, GLS and GCS in RA. moreover, we found DAS28 as main predictor of lower GLS and GCS values.
Conclusions. Subclinical myocardial dysfunction is observed in both RA and PsA patients in the very early phase of the disease. IJD patients with higher disease activity have GLS and GLC lower than those with low disease activity. Disease activity is the main predictor of subclinical myocardial dysfunction in IJD (both RA and PsA).

N-TERMINAL PRO B-TYPE NATRIURETIC PEPTIDE IS INVERSELY CORRELATED WITH LOW DENSITY LIPOPROTEIN CHOLESTEROL IN THE VERY ELDERLY

F. Spannella[1], F. Giulietti[1], G. Cocci[1], P. Balietti[1], M. Bordicchia[2], R. Sarzani[3]
[1]Internal Medicine and Geriatrics, Hypertension Excellence Centre of the ESH, IRCCS-INRCA, UNIVPM, Ancona;
[2]Department of Clinical and Molecular Sciences, University Politecnica delle Marche, Ancona;
[3]Internal Medicine and Geriatrics, Hypertension Excellence Centre of the ESH, IRCCS-INRCA, UNIVPM, Ancona; Department of Clinical and Molecular Sciences, University Politecnica delle Marche, Ancona

Aim. Laboratory studies on human adipose tissue and differentiated adipocytes indicate that natriuretic peptides (NPs) affect lipid metabolism and plasma cholesterol. Few previous clinical studies in non-elderly populations found associations between NPs in the physiological range and cholesterol. Our aim is to evaluate the association between NT-proBNP and lipid profile in very elderly hospitalized patients characterized by a wide range of NT-proBNP levels.
Methods. Cross-sectional study on 288 very elderly patients hospitalized for medical conditions, in which increased NT-proBNP levels are very common. NT-proBNP, total cholesterol (TC), HDL cholesterol (HDLc) and triglycerides were collected just few days before discharge. Patients taking lipid-lowering drugs and patients with an admission diagnosis of acute heart failure were excluded. Calculated LDL-cholesterol (LDLc) was used for the analyses.
Results. Mean age: 87.7±6.2 years; female prevalence (57.3%). Median NT-proBNP: 2949 (1005-7335) pg/ml; mean TC: 145.1±40.3 mg/dl; mean HDLc: 38.4±18.6 mg/dl; median triglycerides: 100 (75-129) mg/dl; mean LDLc: 84.0±29.5 mg/dl. We found negative correlations between NT-proBNP and both TC and LDLc (Rho=-0.157; p=0.008 and Rho=-0.166; p=0.005, respectively), while no correlations emerged between NT-proBNP and HDLc (Rho=-0.065; p=0.275) or triglycerides (Rho=-0.009; p=0.874). These associations were confirmed considering NT-proBNP tertiles. The inverse association between NT-proBNP and LDLc was maintained even after adjusting for confounding factors.
Conclusions. Our real-life clinical study supports the hypothesis that NPs play a role on cholesterol metabolism, given the association found between LDLc and NT-proBNP even in very elderly patients where NT-proBNP values are often in the pathological range.

LIPOPROTEIN(A) SCREENING IN PATIENTS WITH PREMATURE MYOCARDIAL INFARCTION: CLINICAL ROLE AND IMPACT ON DECISION-MAKING

A. Cesaro, F. Gragnano, F. Fimiani, F. Natale, R. Bianchi, M. Crisci, A. Shatri, G. Limongelli, R. Calabrò, P. Calabrò
Division of Cardiology, Department of Cardiothoracic and Respiratory Sciences, University of Campania "Luigi Vanvitelli", Naples

Aim. The association between elevated lipoprotein(a) (Lp(a)) levels and the incidence of the atherosclerotic cardiovascular disease is well established. However, evidence for its clinical role in patients with premature coronary artery disease remains limited. We aimed to elucidate the role of the Lp(a) screening in patients with premature myocardial infarction, to assess its impact on the clinical decision-making and patients' management.
Methods. We prospectively screened for Lp(a) 105 consecutive patients admitted to our division of Cardiology for premature myocardial infarction. Patients were eligible for inclusion if they presented an age <50 years old. All patients were treated according to European guidelines recommendations. Samples for Lp(a) measurement with ELISA were collected during follow-up, in stable clinical conditions. Lp(a) concentration ≥30 mg/dL was considered elevated.
Results. In our premature myocardial infarction population, Lp(a) resulted elevated (≥30 mg/dL) in the 28.5% (n=30) of all subjects, at mean follow-up of 9.6 months. Moreover, the 12.3% (n=13) of patients had a Lp(a) value ≥70 mg/dL, with a clinical indication for Lp(a)-specific apheresis. All patients with high levels of Lp(a) were on optimal medical therapy and with well-controlled risk factors, according to European guidelines.
Conclusions. Elevated levels of Lp(a) are highly prevalent in young patients presenting with myocardial infarction. A systematic screening for Lp(a) might improve their management, contributing (1) to intensify the control of traditional risk factors; (2) to identify subjects that could benefit from Lp(a) apheresis, (3) to start a family screening programme to identify relatives with potentially Lp(a) disorders at risk.

IN VIVO EVALUATION OF OXIDATIVE STRESS, PLATELET ACTIVATION AND ENDOTHELIAL DISFUNCTION IN FAMILIAL HYPOBETALIPOPROTEINEMIA (FHBL): COMPARISON WITH AUTOSOMAL DOMINANT HYPERCHOLESTEROLEMIA (ADH) AND HYPERALPHALIPOPROTEINEMIA (HALP)

A. Giammanco[1], A. Ganci[1], D. Noto[1], A.B. Cefalù[1], G.I. Altieri[1], F. Fayer[1], R. Spina[1], V. Ingrassia[1], C. Scrimali[1], F. Brucato[1], A. Mattina[1], C.M. Barbagallo[1], F. Santilli[2], F. Cipollone[3], G. Davì[2], F. Violi[4], R. Carnevale[5], M.R. Averna[1]
[1]Dipartimento Biomedico di Medicina Interna e Specialistica (DIBIMIS), University of Palermo;
[2]Dept. of Medicine and Aging Science, University of Chieti;
[3]Ce.S.I.-Met, "G. D'Annunzio" University of Chieti;
[4]I Clinica Medica, Atherothrombosis Center, Department of Internal Medicine and Medical Specialties, Sapienza University of Rome;
[5]Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina

Background. Oxidative stress is associated with an increased risk of atherothrombosis and platelet activation as several animal models have been shown. The increased production of reactive oxygen species (ROS) leads to lipids peroxidation of the cell membranes and of lipoproteins, high production of F2-isoprostanes from arachidonic acid, thus modulating the platelet activation induced by thromboxane. 8-iso-$PGF_2\beta$ and 11-deidro-tromboxane (TX)B_2 are *in vivo* markers of oxidative stress and platelet activation, respectively. Recently it has been shown that subjects with low plasma levels of HDL (increased cardiovascular risk) present with high urinary levels of these markers. This excretion is reduced by changing life style and by pharmacological increase of HDL cholesterol.
Aim and Methods. The aim of this study was to evaluate in a group of FHBL subjects (n=10) the urinary levels of 8-iso-$PGF_2\beta$ and 11-deidro-TX B_2 and to compare these finding with ADH (n=10) and HALP subjects (n=10). We have performed also the analysis of plasma markers of inflammation (IL-6), platelet (NOX-2) and endothelial activation (ICAM-1, VCAM-1) to understand the real CV risk in FHBL subjects compared to ADH and HALP patients.
Results. The analysis of oxidative stress, platelet and endothelial activation markers didn't show any significant difference between FHBL and HALP subjects. Non-treated ADH exhibit higher urinary secretion of F2-isoprostanes and plasma levels of NOX-2, ICAM-1, VCAM-1 and IL-6 than FHBL and HALP subjects. After lipid lowering treatment, ADH subjects exhibit a significant decrease of all these markers.
Conclusions. These data confirm a linear correlation between the excretion of rates of F2-isoprostanes and subjects at high CV risk (such ADH subjects). Several limitations include small sample size of our study population. These findings may have important clinical implications for primary and secondary prevention in ADH and HALP subjects underlying possible benefits of low cholesterol plasmatic levels in FHBL subjects.

NON ALCOHOLIC FATTY LIVER DISEASE IS OMEGA-6 FATTY ACIDS DIET DEPENDENT IN A GROUP OF OBESE CHILDREN

A. Dalbeni, A. Mantovani, A.Tagetti, S. Bonafini, V. Paon, R. Gaudino, M. Montagnana, A. Donato, P. Minuz, C. Maffeis, F. Antoniazzi, F. Capra, C. Fava
University and Azienda Ospedaliera Universitaria Integrata of Verona

Aim. Obesity leads to the clustering of metabolic syndrome (MetS) and cardiovascular (CV) risk factors, also in children. Non-alcoholic fatty liver disease often accompanies the MetS and it's described like a new independent CV risk factor. Quality of dietary fat, beyond the quantity, could influence MetS, CV risk profile and the development of NAFLD. The aim of this cross-sectional observational study was to investigate the associations of individual CV risk factors and NAFLD, characterizing the MetS, with erythrocyte fatty acid (marker of average intake), in a group of 70 obese children.
Methods. Enrollment of obese children aged 5-18 years old (BMI >90th percentile). Calculation of Fatty Liver Index (FLI) and Ultrasound (US) abdomen echography for the detection of NAFLD. Anthropometric and ambulatory blood pressure (BP) measurement by calibrated instruments. Laboratory measurement of lipid, glucose and hepatic function indices; Erythrocyte membrane FA gas chromatography.
Results. Mean content of Omega-3 FA was low. Total amount of omega-6 FA were inversely associated with several futures of the MetS: waist circumference (rS=-0.393), triglycerides (rS=-0.294), fasting insulin (rS=-0.341), FLI (rS=-0.435), ALT (rS=-0.297). They were directly correlated with HDL (rS=0.327). Arachidonic acid showed inverse correlations with WC (rS=-0.352), triglycerides (rS=-0.366), fasting insulin (rS=-0.337), FLI (rS=-0.472) and ALT (rS=-0.331). Total content of saturated FA was directly correlated to waist circumference (rS=0.237), triglycerides (rS=0.298), nighttime-DBP (rS=0.251), FLI (rS=0.479), ALT (rS=0.291). Palmitic acid directly correlated with waist circumference (rS=0.354), triglycerides (rS=0.373), insulin (rS=0.287) and HOMA-IR (rS=0.335), FLI (rS=0.515), ALT (rS=0.239).
Conclusions. Our data suggest that omega-6 FA, especially AA, could be protective toward CV risk factors including NAFLD featuring the MetS and also to indexes of hepatic steatosis in obese children, whereas SFA seems to exert opposite effects. The level of omega-3 FA in our sample of obese children, is extremely low so that its putative beneficial effect could have not been detectable. Our findings agree with the current dietary recommendation to reduce the intake of SFA and support a possible beneficial effect of polyunsaturated FA intake, especially omega-6 FA.

PEDIATRIC HYPERCHOLESTEROLEMIA AND HYPERTENSION AS PIECES OF PUZZLE OF ADULT CARDIOVASCULAR DISEASE: AN INTEGRATED VIEW FOR FAMILY PHYSICIANS

G. Mastrogiorgio, P.S. Buonuomo, U. Giordano, I. Rana, A. Bartuli
Rare Diseases and Medical Genetics Unit Bambino Gesù Children's Hospital Rome

Aim. Cardiovascular disease (CVD) has a prolonged subclinical phase of development lasting years and there is increasing evidence that atherosclerosis begins during childhood.
While the majority of children are free of symptomatic CVD, far fewer are free of CVD risk factors. Most clinicians involved in management of chronic diseases (rheumatologic diseases, nephropaties, diabetes, etc.) are familiar with behavioral and pharmacologic strategies for modifying these and other traditional CVD risk factors. Indeed, approaches to the prevention of CVD are often too narrow in scope and initiated too late in children without other risks factors. Through research in the prevention and treatment of adult diseases, it has become clear that many adult diseases have their origins in childhood. Although pediatric clinical guidelines have recommended universal screening for hypertension since 1977 and targeted screening for dyslipidemia since 1992, this screening is not yet common practice in general pediatrics. The American Heart Association (AHA) has defined four health behaviors and four health factors that are strongly correlated with ideal cardiovascular health, suggesting that evaluation of cardiovascular wellness should be applied to evaluation of children and adolescents and targeted as part of primary prevention.
Therefore we propose a model of screening program for all pediatricians.
Methods. In the first part of the study, a complete educational program for pediatricians will be created consisting of lectures, workshops, meetings, videoconferences and a web-based educational platform.
We'll suggest to pediatrician to test cholesterol levels in all children age >2 yrs with a family history of hypercholesterolemia and/or myocardial infarction (anamnestic screening), or in case of blood tests for other medical conditions (universal screening-like).
About hypertension screening, U.S Preventive Services Task Force concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for primary hypertension in asymptomatic children and adolescents to prevent subsequent cardiovascular disease in childhood or adulthood.
However, because of there are increasing evidence that the presence of multiple risk factors increases the cardiovascular risk, we suggest to screen for hypertension our patients with hypercholesterolemia by blood pressure (BD) measurements (three measurements at each of two clinic visits).
Results. The study is recruiting.
Conclusions. We highlight those strategies are most applicable to children and teens and also propose fundamental reframing that recognizes the importance of early choices and life experiences to achieving cardiovascular health.

CHARACTERISTICS OF PATIENTS WITH CLINICAL DIAGNOSIS OF HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA (HEFH) IN THE PRESENCE OR ABSENCE OF PATHOGENETIC MUTATION

F. Brancato, I. Stanca, I. Minicocci, L. D'Erasmo, A. Di Costanzo, A. Montali, D. Pergolini, G. Pigna, M. Arca, M. Maranghi
Policlinico Umberto I, Università La Sapienza, Roma

Aim. The primary objective of the study was to evaluate the clinical and phenotypic characteristics of subjects with clinical suspicion of HeFH according to a DLCN score ≥3 and in the presence/absence of pathogenetic mutations in genes mainly responsible for HeFH (LDL-R, PCSK-9, APOB).
Methods. We consecutively recorded data of subjects with DLCN ≥3 regularly followed o referred for hypercholesterolemia to the Cardiovascular Prevention Clinics of the Department of Internal Medicine and Medical Specialties of Policlinico Umberto I. All subjects signed the informed consent at the recruitment visit (V1). During V1, demographic, clinical, anthropometric, biochemical data and family history were collected and blood samples were taken for DNA extraction and subsequent genetic-molecular diagnosis. Biochemical data prior to V1 were also collected; we define as WV the visit in which the worst LDL-C value has been recorded from patients clinical records.
Data are expressed as mean ±SD or median and min- max for continuous variables and frequencies for categorical ones. SPSS version 20.0 was used for statistical analysis.
Results. We consecutively recruited 169 subjects: 109 subjects (M) resulted heterozygotes carriers of variants in tested genes (105 for LDL-R, 2 for Apo B and 3 for PCSK9) and 60 subjects (non M) resulted non carriers. The two groups were similar for gender distribution, but M subjects were younger at V1 as compared to nonM (41±16 vs 50±10 y; p=0,000).
In our population, 77.6% of M subjects have a DLCN score ≥6 (HeFH clinical diagnosis safe) as compared to 25% in non M.
M subjects show an higher prevalence of hypercholesterolemia onset before age 18 (31,5% M vs 2% non-M p=0,000) and of I degree family members with hypercholesterolemia (67,6% M vs 43,3% non-M p=0,002). They exhibit higher levels of Total and LDL- cholesterol at V1 and WV as compared to non-M subjects, despite being treated with lipid-lowering therapy in higher percentage (LDL-C WV 261 (128-522) vs 217 (74-346) mg/dl, p=0,000; CT WV 335,5 (176-666) vs 307,5 (173-438) mg/dl, p=0,003; LDL-C V1 180±81,4 vs 158±53,4 mg/dl, p=0,03).
In addition, among the mutated subjects, women have higher TC and LDL-C values than men although they do not differ in age and treatment.
Conclusions. Among subjects with possible clinical diagnosis of HeFH according to the DLCN score, those carrying genetic variants exhibit a worst lipid profile, an earlier age of onset and are undertreated as compared to subjects not carrying pathogenetic variants.

PREVALENCE OF METABOLIC SYNDROME IN HYPERTENSIVE PATIENTS AFFECTED BY PERI-IMPLANT DISEASES

V. Bisogni[1], P. Papi[2], V. Saracino[1], B. Di Murro[2], D. Penna[2], A. Concistrè[1], L. Petramala[1], M. Celi[1], F. Olmati[1], G. Iannuccci[1], G. Pompa[2], C, Letizia[1]
[1]Department of Internal Medicine and Medical Specialties, Unit of Secondary Arterial Hypertension, "Sapienza" University of Rome;
[2]Department of Oral and Maxillo-Facial Sciences, "Sapienza" University of Rome

Aim. Several studies have reported a direct relationship between periodontitis and systemic diseases, such as arterial hypertension, dyslipidaemia, and diabetes. Recently, for the first time, has been highlighted a correlation between metabolic syndrome (MS) and peri-odontal diseases (1). However, the evidences about a link between MS and peri-implant diseases are still debate. The aim of this study is to provide the prevalence of MS in hypertensive patients with dental implant(s) complicated by peri-implant diseases.
Methods. We enrolled 32 patients with ≥18 years old of age, referred to our Hypertension Unit. All subjects had diagnosis of hypertension and had ≥1 dental implant(s). They underwent to screening for MS, according to the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]) (2). All participants were submitted to an accurate odontoiatric evaluation to determine the diagnosis of peri-implant diseases: full mouth peri-apical x-rays and probing pocket depth to evaluate as marginal bone loss bleeding at probing and suppuration.
Results. 15 males and 17 females, with mean age 62±13 years, body mass index 27.0±3.5 kg/m^2, mean systolic blood pressure 126±2 mmHg and mean diastolic blood pressure 77±2 mmHg at the 24h-ambulatory blood pressure monitoring, have been studied. 90.6% was affected by peri-implant diseases; among these, diagnosis of MS was made in 18 (62.1%) subjects, presenting ≥3 NCEP ATPIII criteria. The MS subgroup showed significantly higher values of waist circumference and triglycerides (103.4±9.7 *vs* 92.2±11.0 cm, p=0.01, 147.5±62.2 *vs* 87.9±30.4 mg/dl, p=0.002, respectively), and lower HDL cholesterol levels (50.3±16.1 *vs* 66.8±14.5 mg/dl, p=0.01), comparing with patients without MS.
Conclusions. Subjects with dental implants complicated by peri-implant diseases show increased prevalence of MS. MS could be considered a risk factor for developing peri-implant diseases and a potential contraindication for dental implants placement.

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EFFICACY OF MARAVIROC IN MODULATING ATHEROSCLEROSIS AND INFLAMMATION IN HIV INFECTED PATIENTS AT HIGH CARDIOVASCULAR RISK UNDER SUPPRESSIVE ANTIRETROVIRAL THERAPY. A RANDOMIZED, CROSS-OVER, PILOT STUDY

V. Bianconi[1], M.R. Mannarino[1], E. Schiaroli[2], F. Bagaglia[1], D. Francisci[2], F. Baldelli[2], M. Pirro[1]
[1]Unit of Internal Medicine, Department of Medicine, University of Perugia;
[2]Unit of Infectious Diseases, Department of Medicine, University of Perugia

Aim. Experimental CCR5 antagonism with maraviroc in atherosclerosis-prone mice and preliminary data in humans suggest an anti-atherosclerotic effect of the drug. We assessed the impact of maraviroc treatment in HIV-infected patients on several subclinical indicators of atherosclerosis and putative mechanisms for such an effect.
Methods. HIV-treated patients under effective antiretroviral (ART) therapy were recruited if they had a Framingham risk score >20%, brachial flow-mediated dilation (bFMD) <4%, as indices of high cardiovascular risk. Maraviroc (300 mg *per os* for 24 weeks) was administered on top of ART to all participants using a cross-over design. Brachial FMD, carotid-femoral pulse wave velocity (cfPWV) and carotid intima-media thickness (cIMT) were measured as non-invasive markers of atherosclerosis. Vascular competence, as expressed by the ratio of circulating endothelial micro-particles (EMPs) to endothelial progenitor cells (EPCs), as well as markers of systemic inflammation, were assessed.
Results. Maraviroc treatment significantly improved bFMD, cf-PWV and cIMT by 61%, 17%, and 11%, respectively. We also found a beneficial effect of maraviroc on the EMP/EPC ratio [from 1.33 (1.25-1.42) to 1.10 (1.05-1.19), $p<0.001$]. No significant changes in markers of systemic inflammation were observed.
Conclusions. Maraviroc leads to a significant improvement of several markers of cardiovascular risk (*i.e.*, endothelial dysfunction, arterial stiffness and early carotid atherosclerosis), which is accompanied by an amelioration of vascular competence, but not of systemic inflammation. These data support further studies on the use of maraviroc in patients at high cardiovascular risk to prevent atherosclerosis-driven pathologies.

PERIPHERAL ARTERY STENOSIS MAY SUGGEST A SEVERE POLYARTERITIS NODOSA

S.A. Ciampi, S. Cicco, S. Noviello, A.G. Solimando, C. Marasco, A. Cirulli, A. Vacca
Department of Biomedical Sciences and Human Oncology, Section of Internal Medicine, University of Bari Aldo Moro Medical School, Bari

Aim. Polyarteritis nodosa (PAN) is a vasculitis affecting middle-sized arteries. The clinical presentation could be complicated by organ ischemia due to vascular stenosis and tissue hemorrhage. Our aim was to understand how a vascular stenosis in PAN is related to thrombosis and the risk of cardiovascular disease.
Methods. From 2015 to 2018, we observed five patients with PAN, 4F/1M, mean age 54±8 years. In 4 out of the 5 patients, the initial symptoms were asthenia and myalgia associated to pain of the limbs and ulceration. Four patients experienced access to the Emergency Department for abdominal pain with demonstration of visceral vessels involvement. The diagnosis of PAN was made with CT scan or biopsy along with clinical criteria. Immunosuppressive therapy with Cyclophosphamide and Prednisone was associated to antithrombotic agents. In 2 patients, intervention for critical stenosis was needed. In 3 patients, vasodilating agents (Cilostazol or Iloprost) were added to restrain limbs pain.
Results. The ultrasound studies did not demonstrate dysfunction of the heart, but stenosis and altered perfusion were present at the peripheral district. Framigham score ranged from 8 to 23%. After the therapy, an improvement of symptoms was seen, and in 3 cases, the reduction of stenosis was seen at the radiological level. In only one case the therapy with Cyclophophamide failed and an off label protocol with Tocilizumab (anti-IL6 mAb) was started. Vasodilating agents were successful only in 1 out of 3 patients.
Conclusion. Here, we observed that the peripheral involvement in PAN could precede the visceral damage. The immunosuppressive therapy associated to antithrombotic drugs seems to be necessary to reduce the severe case of visceral stenosis. Not the same efficacy is obtained for peripheral stenosis, in which surgical intervention could be the better choice.

LEFT VENTRICLE MASS AND ATRIAL VOLUME IS RELATED TO DISEASE ACTIVITY IN SYSTEMIC LUPUS ERYTHEMATOUS

M. Guarascio, S. Cicco, L. Crudele, V. Racanelli, A. Vacca
Department of Biomedical Sciences and Human Oncology, Section of Internal Medicine, University of Bari Aldo Moro Medical School, Bari

Introduction. Systemic Lupus Erythematosus (SLE) is a chronic inflammatory disease caused by autoimmunity. One of SLE damage is due to vascular inflammation. That's why we looked for a correlation between disease activity, evaluated by SLEDAI score, and heart involvement.
Materials and Methods. We evaluated 23 SLE patients (22 women (96%) and 1 man (4%), aged 43.74±11.98 years) between 01/01/2015 and 31/12/2017. Patients came in follow-up for revaluation and therapy adjustment. The 65.2% of them were treated with steroid therapy, the 39.1% with DMARDs (disease-modifying antirheumatic drugs), 13% with Mycophenolate, 17.4% with Belimumab.
We divided the sample according to SLEDAI score: 13 mild-to-moderate (SLEDAI <12) (12 women, 1 man; aged 44.36±14.40 years) and 10 severe (SLEDAI ≥12) (all women, aged 41.75±8.57 years).
Results. We highlight that patients with severe SLEDAI had an increased left ventricular mass (MLV) both as absolute value (MLV: severe 215.4±61.5 vs mild-to-moderate 169.3±34.6 gr, $p<0.05$) and MLV indexed (MLVi) for body surface area (BSA) (MLVi: severe 133.3±45.2 *vs* mild-to-moderate 101.8±15.6 gr/m^2, p<0-05). At the same time also left atrium (LA) results increased in both as volume absolute value (LAV: severe 65.4±20.1 vs mild-to-moderate 47.5±14.9 ml; $p<0.05$) and LA volume indexed (LAVi) for body surface area (BSA) (LAVi: severe 39.9±15.5 vs mild-to-moderate 28.6 ± 8.4 ml/m^2, $p<0.05$).
Conclusion. These data show a significant increase of LAV and MLV in patients with severe SLEDAI, compared to mild-to-moderate SLEDAI patients. This could suggest heart damage related to SLE disease activity, but further studies are needed to better understand the pathophysiology of this phenomenon.

FLOGOSIS AND HEART INVOLVEMENT IN LARGE VESSEL VASCULITIS

S. Noviello, S. Cicco, S. Ciampi, A.G. Solimando, C. Marasco, A. Cirulli, S. Longo, V. Racanelli, A. Vacca
Department of Biomedical Sciences and Human Oncology, Section of Internal Medicine, University of Bari Aldo Moro Medical School, Bari

Introduction. Many symptoms of large vessel vasculitis (LVV) are related to increased wall thickness. Heart is usually excluded but indirect effect may cause its modifications.
Aim. Of this study was to describe heart involvement in relation to common inflammation parameters.
Materials and Methods. We analyzed 17 LVV (4 M/13F, median age 54±20 years). All patients underwent to laboratory analysis, ultrasound and Doppler of big arteries and heart. Maximum measured Blood pressure (SBP) was considered in this study.
Left ventricular hypertrophy was present in 12 patients. Among others, 3 patients showed a concentric remodeling. Twelve patients gave a diastolic dysfunction. Aortic root normalized for body surface area was dilated (Aoi; 19.1±2.5 mm/m^2) and wall thickened (3.9±0.8 mm). Aortic valve was regurgitant (AR) in 8 patients.
Framingham score was 21.6%±16. Other parameters were: Uric Acid 4±1 mg/dl, CRP 46.3±58.3, ESR 42.8±32.3, C3 1.2±0.2 mg/dl, Systolic BP (SBP) 125.6±21.2 mmHg and Diastolic BP (DBP) 72.5±8.4 mmHg.
Results. A direct correlation was found with SBP and Uric acid (P=0.04), ESR (P=0.008), diastolic dysfunction (P=0.02) and Framingham score (P=0.03), while an inverse correlation was found with aortic wall thickness (P=0.01).
CRP was directly correlated to C3 (P=0.02) but inversely correlated with aortic wall thickness (P=0.04); ESR was directly correlated to C3 (P=0.003), Aoi (P=0.03), but inversely correlated to aortic root thickness (P=0.008). Aortic wall thickness was directly correlated to Aoi (P=0.01), but inversely correlated to diastolic dysfunction grade (P=0.009), SBP (P=0.01), Uric acid (P=0.003), ESR (P=0.008), and CRP (P=0.049). Aoi was directly related to C3 (P=0.009) and to wall thickness (P=0.01).
Conclusion. LVV could lead an increase in heart dimensions neither related to systemic inflammation nor to blood pressure. On the contrary, the reduction in diastolic function may also have an inflammatory genesis. Aortic root presents an increased diameter due to inflammatory status despite active inflammation did not appear the main actor in wall thickening.

CARDIOVASCULAR DISEASE EARLY MARKERS ARE INCREASED IN IBD PATIENTS WITH UNCONTROLLED SYMPTOMS BY CONVENTIONAL THERAPY

S. Tomeo[1], G. Costantino[2], M. Scuruchi[1], A. Lo Gullo[1], C. Oriana Aragona[1], W. Fries[2], A. Saitta[1], C. Zito[3], G. Mandraffino[1]
[1]Internal Medicine Unit, University of Messina;
[2]Inflammatory Bowel disease Unit, University of Messina;
[3]Cardiology Unit, University of Messina

Background. Inflammatory bowel diseases (IBD) are chronic inflammatory conditions affecting the gastrointestinal tract. The relationships between low and high chronic inflammatory status have been assessed in several conditions, including Rheumatoid Arthritis, and are debated in Psoriatic Arthritis and Scleroderma. On the other hand, a cogent challenge is to evaluate the potential link between chronic inflammation in IBD patients and the actual risk to develop CVD, where the current knowledge is to be better focused so far.
Currently, the diagnosis of CVD in these clinical subsets is based on the evidence of "clinic" markers, such as carotid, cardiac, or renal damage, and standard clinical, laboratory and instrumental evaluations allow to identify patients already CV-diseased; the challenge is to detect patients with unfavorable CV risk profile, when standard evaluations are yet in line with a CV non-diseased picture.
Aim and Methods. We aimed to evaluate early cardiac (as evaluated by 2D speckle tracking echocardiography) and artery (as evaluated by arterial stiffness indices) damage as preclinical marker of CVD. Furthermore, we counted CD34+ cells from peripheral blood. We enrolled IBD patients, in detail suffering from Crohn Disease, whose disease has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments); currently, we included 6 patients, age- and gender-matched with 6 healthy controls.
Results. Median age was 48(30), M/F: 5:1. We found that IBD patients had higher fibrinogen plasma levels [407(162) *vs* 262(93), p=0.010], while CRP and ESR were not different (0.589 and 0.126, respectively); PWV was higher in IBD patients [9.2(4.1) *vs* 4.8(1.0), p=0.002], as was impaired GLS% [-16.9(3.7) *vs* -22.5(1.9), p=0.002]; CD34+ count was not different [1.89(0.24) *vs* 1.8(1.84) p=0.818]. Interdependence analysis showed a direct association between Fibrinogen and PWV (beta=0.681, p=0.031) and GLS% (beta=0.800, p=0.005).
Conclusions. These preliminary data suggest that in IBD patients with uncontrolled symptoms by conventional therapy early markers of CVD are higher than healthy subjects, and seem to be associated with fibrinogen plasma levels; CD34+ cell count in peripheral blood resulted not different with respect to healthy subjects.

ACUTE EFFECTS OF PEANUTS CONSUMPTION ON LIPIDS, FAT OXIDATION AND RESTING ENERGY EXPENDITURE IN OVERWEIGHT/OBESE WOMEN

E. Santariga[1], Y. Ferro[1], A. Lico[1], S. Maurotti[1], F. Provenzano[1], T. Montalcini[2], A. Pujia[1]
[1]Department of Medical and Surgical Science, Nutrition Unit, Magna Grecia University, Catanzaro;
[2]Department of Clinical and Experimental Medicine, Nutrition Unit, Magna Grecia University, Catanzaro

Background and Aims. Peanuts are high in fat (albeit largely unsaturated) and are energy dense. However, epidemiological studies document an inverse association between the frequency of nut consumption and body mass index. Limited data suggest that routine consumption is associated with elevated resting energy expenditure (REE) and an optimal lipid profile, but the acute effects of peanuts on energy balance and lipids in individuals with obesity remain still largely unclear. The purpose of this study was to evaluate the effects of acute peanut consumption on total cholesterol, REE and fat oxidation in overweight/obese individuals.
Methods. We conducted a study to evaluate the effect of acute peanut consumption on total cholesterol, respiratory quotient (RQ) and REE as assessed by indirect calorimetry in 15 healthy fasting overweight or obese women [mean BMI: 35±6 kg/m^2]. Participants consumed 1.35 gr of peanuts/kg of body weight (4-4.5 ounces). Glucose, total cholesterol, blood pressure, heart rate, RQ and REE were measured at baseline (0 min) and at 60 min after peanuts consumption.
Results. Data were analyzed with SPSS 20.0. We used a paired T-test. Acute peanut consumption significantly reduced RQ (means±SEMs-60 min: 0.82±0.05 compared with 0.88± 0.05; p=0.001) and increased the REE (1524±195 kcal compared with 1390±192 kcal; p=0.002). Peanut significantly reduced total cholesterol (203±23 compared with 213±27 mg/dL; p=0.029) Glucose blood pressure responses and heart rate were similar with baseline.
Conclusion. The acute consumption of 1.35 gr of peanuts/kg of body weight improved fat oxidation and REE and lipid profile of healthy overweight/obese women. Further research is needed to confirm their effects on anthropometric parameters. In the meantime, the current data suggest that peanuts may affect the energy balance.

PREVALENCE AND RELATION OF WEIGHT EXCESS AND BLOOD PRESSURE WITH ANTROPOMETRIC MEASUREMENTS IN A SAMPLE OF ITALIAN CHILDREN

A. Tagetti[1], S. Bonafini[1], A. Giontella[1], P. Minuz[1], C. Maffeis[2], F. Antoniazzi[2], C. Fava[1]
[1]Department of Medicine, University of Verona;
[2]Pediatric Department, University of Verona

Objective. Weight excess and hypertension represent an increasing epidemics not only in adults but even in children. The aim of the present study was to assess the prevalence of weight excess and high blood pressure (BP) and their relation with other anthropometric measurements in a school-based study.
Design and method: 309 children attending the 3rd and 4th classes of 4 primary schools (mean age 8.64±0.7y) in Verona south district participated. All children underwent anthropometric and vascular measurements at school.
Results. Based on the 85th and 95th percentiles of BMI, 19% of children were classified as overweight and 13% as obese, without significant gender differences. Waist/height ratio was below 0.5 in 93% of normal-weight children, 48% in overweight children and 12% in obese children. When considering the subgroup of children with weight excess (obese + overweight) in comparison to normal weight children, they showed higher systolic BP (including the z-score of systolic BP). Considering BP in the whole sample, 22% resulted above the 95th percentile and 17% between the 90th and 95th percentile whereas the prevalence of BP >95th percentile in obese was 31%. After repetition of BP measurement in standard conditions in a subsample of 25 children with BP >95th percentile at the first visit, only one child confirmed a BP >95th percentile. Systolic and diastolic BP were directly correlated with BMI, waist circumference, hip circumference and waist/height ratio, but the latter showed a weaker correlation with BP in comparison to the other anthropometric characteristics. In obese children, most correlations were still significant and showed a higher correlation coefficient.
Conclusions. Excess weight and high BP is frequent also in Italian children attending the primary school. Measures of adiposity and BP associate calling for preventive actions. Epidemiological studies should pay attention to standardize the conditions of measurement when the exact prevalence of hypertension has to be estimated.

MICROCIRCULATORY IMPROVEMENT INDUCED BY LAPAROSCOPIC SLEEVE GASTRECTOMY IS RELATED TO INSULIN SENSITIVITY RETRIEVAL

S. Ministrini[1], C. Fattori[1], M.A. Ricci[1], V. Bianconi[1], R. Paltriccia[1], M. Boni[2], M.T. Paganelli[3], G. Vaudo[1], G. Lupattelli[1], L. Pasqualini[1]
[1]Department of Medicine, Università degli Studi di Perugia;
[2]General Surgery, "S. Giovanni Battista" Hospital, Foligno (PG), ASL Umbria 2;
[3]General Surgery, "S. Maria della Misericordia" Hospital, Perugia

Aims. Microvascular dysfunction is a potential factor explaining the association of obesity, insulin resistance and vascular damage in morbidly obese subjects. The purpose of the study was to evaluate possible determinants of microcirculatory improvement one year after laparoscopic sleeve gastrectomy (LSG) intervention.
Methods. Thirty seven morbidly obese subjects eligible for bariatric surgery were included in the study. Post-Occlusive Reactive Hyperaemia (PORH) of the forearm skin was measured as Area of Hyperaemia (AH) by laser-Doppler flowmetry before LSG and after a one year follow-up.
Results. After intervention, we observed a significant reduction in BMI, HOMA index, HbA1c and a significant increase of AH in all patients after surgery; this change was significant only in patients with insulin resistance or diabetes/porediabetes. Also, a significant correlation between the increase of AH and the reduction of both HOMA index and HbA1c was observed.
Conclusions. Our study shows that LSG intervention can produce a significant improvement in the microvascular function of morbidly obese subjects; this improvement seems to be related to the baseline degree of insulin-resistance and to the retrieval of insulin-sensitivity post-intervention.

REACHING CARDIOVASCULAR RISK REDUCTION TARGET AND ALL-CAUSE MORTALITY IN A DIABETIC POPULATION: "REAL-LIFE" DATA

M.A. Miselli[1], M.L. Morieri[1], E. Marchetto[1], M. Monesi[2], A. Passaro[1], G. Zuliani[1]
[1]Department of Medical Sciences, Section of Internal and Cardiorespiratory Medicine, University of Ferrara; [2]Unit of Diabetology, ASL Ferrara

Aim. Cardiovascular disease (CVD) is the leading cause of death in type 2 diabetes (T2D). National guidelines suggest an intensive and multifactorial intervention aimed to control of all cardiovascular risk (CVR) factors through life style modification and pharmacological therapies. A series of targets for CVR reduction have been therefore identified by the American Diabetes Association, and these include: glycemic control evaluated with glycated hemoglobin (HbA1c) level, blood pressure (BP) monitoring, achievement of adequate LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C) and triglycerides plasma levels. The aim of this observational study was to evaluate the effect of controls of CVR factors (expressed as ADA-targets), on all-cause mortality, in a group of subject with T2D.
Methods. Our study population was composed of 1917 outpatients with T2D attending the Outpatient Diabetes Clinic of Ferrara over a mean follow-up period of 10 years; Health records included personal, clinical and biochemical data, and pharmacological treatments. Two different model of Cox proportional hazard analysis were performed: Model 1 included age, sex and number of ADA target satisfied (0-5). ADA targets were considered fulfilled when mean values of the parameter of interest (HbA1c, BP, LDL-C, HDL-C and triglycerides) reached guidelines recommendation for each parameter. Model 2 included age, sex and specific ADA target fulfillment for HbA1c, BP, LDL-C, HDL-C and triglycerides (yes/no).
Results. As expected age and male sex where significantly associated with an increase in all-cause mortality in both models. Overall number of ADA target satisfied (0 vs 4: HR:0.46; IC95%: 0.12-0.69) in Model 1, and specific ADA target for HDL-C (HR:0.63; IC95%:0.42-0.97) in Model 2, were significantly associated with a reduction in all-cause mortality.
Conclusions. Our "real life" data support guidelines recommendations to a multifactorial intervention for CVD prevention; nevertheless, HDL-C, which is mainly determined by genetic and lifestyle, appears to be the stronger predictor of all-cause mortality.

ASSOCIATION OF PLASMA IRISIN WITH BODY COMPOSITION, PHYSICAL PERFORMANCE AND METABOLIC PROFILE IN A COHORT OF HEALTHY ELDERLY AND AFTER 14-DAY OF BED REST

A. D'Amuri, D. Francesconi, M. De Candia, C. Mancino, C. Soavi, J.M. Sanz, M.L. Morieri, E. Dalla Nora, G. Zuliani, A. Passaro
Section of Internal and Cardio-Respiratory Medicine, Department of Medical Sciences, University of Ferrara

Aim. Animal studies have shown beneficial properties of Irisin (an exercise-induced myokine) on metabolic and cardiovascular disease, however irisin effect in humans is currently unclear. Our goal was to evaluate the relationship between irisin levels and cardio-metabolic profile in a cohort of elderly subjects, and to evaluate the effect of prolonged immobilization on irisin levels.
Methods. 297 healthy community-dwelling subjects (inclusion criteria were age >60 years and the ability to walk for 2 km) were included in this study (cross-sectional analysis). Additional 23 volunteers were enrolled in a 14 days of experimental horizontal-bed-rest (BR). Each participant underwent a BIA to evaluate body composition and a blood sample collection for laboratory analyses. Cardio-respiratory fitness ($VO2_{max}$) was estimated with the UKK-walk-test.
Results. In the cross-sectional analysis, after adjustment for age and sex, the linear regression analysis showed that irisin was significantly inversely associated with weight, free fat mass (FFM), muscle mass, basal metabolic rate, total cholesterol, LDL cholesterol and triglycerides (all P<0.05). No association was found with VO2 max (P 0,8). The multivariate regression model showed that only female sex (P 0,04) and FFM (P 0,003) were independently associated with irisin levels (although only a small proportion of irisin variability was explained by this model, R2 0,06). As expected over BR, we observed a decrease in FFM (from 59,6 to 55,1 kg; P<0,001) that was paralleled by a significant increase of irisin levels (P 0,01). Irisin levels at the end of bed rest was partially explained by the decrease in FFM (R2 0,16, P=0.06).
Conclusions. Surprisingly we found, both in the general population and in response to an acute immobilization, a negative correlation between FFM and irisin levels. However body composition and metabolic characteristics poorly explain irisin variation. Whether additional measures of muscle function may be more informative will require further studies.

PENTRAXIN 3 AS A MARKER OF INFLAMMATORY STATUS AND CARDIOVASCULAR RISK IN OBESE PATIENTS TREATED WITH LAPAROSCOPIC ADJUSTABLE GASTRIC BANDING

D. D'Ardes, M.T. Guagnano, P. Innocenti, L. Aceto, R. Liani, R. Tripaldi, F. Cipollone, G. Davì, F. Santilli
"G. D'Annunzio", University of Chieti-Pescara

Aim. The long-term effects of LAGB on the components of MetS and on PTX3 levels have not been largely studied. The protein PTX3 represents a biomarker for immunity and inflammation and it seems to exert an important role in modulating the CV system. Previous studies have shown that PTX3 is inversely associated with BMI and is reduced in MetS. Visceral adipose tissue PTX3 gene expression is increased in obesity and has previously been associated with CV risk factors.
The objective of this study was to investigate the long-term effects of LAGB (36-months follow-up) on PTX3 levels.
Methods. Eight (4 M) patients with severe obesity (median BMI 43,9; mean age 41 years) were studied before LAGB, 3-, 6-, 12- and 36-months after LAGB for serum levels of PTX3.
Results. BMI progressively decreased from a median preoperative value of 43.7 kg/m^2 (IQR, 39.8-47.9 kg/m^2) to 34.7 kg/m^2 (32.9-38.4 kg/m^2) after 12 months (P<0.0001) and to 32.6 kg/m^2 (29.5-37.6) after 36 months (P=0.007) after LAGB.
At these time points, plasma PTX3 increased by 214.9% (67.8-678.6%; P<0.0001), at 12 months after LAGB, but decreased afterword and returned to baseline values after 36 months [-16% (-75% - +11%), P=0.237 *vs*. baseline], despite weight maintenance after LAGB in all subjects.
Conclusions. PTX3 is significantly increased at 1 year after LAGB to slowly return at baseline values after 3 years, despite maintenance of successful weight loss achieved with LAGB.
Our results suggest that LABG-induced weight loss may positively affect several components of CV risk and MetS, including levels of PTX3, that emerges as a pro-resolving mediator counteracting inflammation and returning to baseline levels at distance from LAGB, in parallel with a stable adaptation of body weight and of metabolic profile.

Abbreviations
LAGB: laparoscopic adjustable gastric banding
MetS: metabolic syndrome
CV: cardiovascular
PTX3: pentraxin 3
BMI: body mass index

PROPROTEIN CONVERTASE SUBTILISIN-KEXIN TYPE-9 (PCSK9) AND TRIGLYCERIDE-RICH LIPOPROTEIN METABOLISM: A META-ANALYSIS OF RANDOMIZED TRIALS

E. Olmastroni[1,2], M. Casula[1,2], A. Baragetti[2,3], A.L. Catapano[1,2,3,4]
[1]*Epidemiology and Preventive Pharmacology Centre (SEFAP), University of Milan;*
[2]*Department of Pharmacological and Biomolecular Sciences, University of Milan;*
[3]*S.I.S.A. Center for the Study of Atherosclerosis, Bassini Hospital, Cinisello Balsamo, Milan;*
[4]*IRCCS MultiMedica, Milan*

Aim. Emerging data suggest that PCSK9 might play a role in the modulation of triglyceride-rich lipoprotein (TGRL) metabolism. A meta-analysis of randomized clinical trials was performed to evaluate the effects of anti-PCSK9 mAbs added on top of Standard Care of treatment.
Method. Searches were conducted on PubMed, MEDLINE, and EMBASE database, from inception to 30 November 2017. Only trials that met the following criteria were included: (1) English language (2) phase 2 or 3 RCT; (3) PCSK9 antibodies that had been approved (4) comparing PCSK9 antibodies with no PCSK9 antibody; (5) with effects on triglycerides reported; (6) with treatment duration longer than 8 weeks. The average difference (MD) between change in TG levels before and after treatment in the group of patients treated with anti-PCSK9 antibodies and in the control group was considered as primary endpoint. Pooled estimates have been obtained by using the inverse variance-weighted average method. Between-study heterogeneity was measured with the I2 statistics.
Results. After screening, 30 studies with 37,804 randomized patients were included. The addition of anti-PCSK9 mAbs (mainly on top of a statin treatment) caused an additional reduction of TG levels (up to -14%) compared to that achieved with standard care or -3% compared to that achieved with ezetimibe. The low I2 values showed that most of the variability across studies was due to chance rather than heterogeneity. The univariate correlation between baseline TG levels across different interventional trials and TG change after anti-PCSK9 treatment was significant (p-value =0.020) and derived from Pearson univariate correlation (rho=-0.366).
Conclusion. These results suggest the involvement of PCSK9 in the metabolism of TGRLs, also confirmed in some experimental in vivo and in vitro models. Whether this decrease of TG is due to the lowering of LDL only still remains to be addressed.

PCSK9 DEFICIENCY RESULTS IN ALTERED POST-PRANDIAL LIPEMIA AND INFLAMMATORY RESPONSE IN HUMANS

V. Zampoleri[1,2], A. Baragetti[1,2], F. Bonacina[2], P. Uboldi[1], K. Garlaschelli[2], L. Grigore[2,3], F. Pellegatta[2,3], G.D. Norata[1,4], A.L. Catapano[1,3]
[1]Department of Pharmacological and Biomolecular Sciences, Università degli Studi di Milano;
[2]SISA Center for the Study of Atherosclerosis, Bassini Hospital, Cinisello Balsamo, Milan;
[3]IRCCS MultiMedica Hospital, Sesto San Giovanni, Milan;
[4]School of Biomedical Sciences, Curtin Health Innovation Research Institute, Curtin University, Perth, Western Australia

Aims. PCSK9 targets not only hepatic LDL receptor (thus controlling cholesterol levels), but also other receptors, like VLDL-R and CD36, proteins involved in modulating the metabolism of triglyceride rich lipoproteins (TGRLs). These observation raise the question if in *vivo* PCSK9 reduction, modifyes these interactions. Whether this is translated into increased inflammatory pattern is also unknown.
Methods. A general population was genotyped for the Loss-of-Function (LoF) *PCSK9* R46L human variant, which determines a reduction of circulating PCSK9. Lipid and lipoprotein profiles were evaluated fasting and after an oral fat load (OFL). Changes in the expression of genes coding for mediators of lipid metabolism and inflammatory cytokines in circulating lympho-monocytes were characterized in fasting conditions and during the post-prandial phase. The expression of the protein was quantified as well, via flow cytometry.
Results. Post-prandial lipemia was increased in LoF carriers vs non-carriers. This difference was concurrent with an increased expression of genes involved in lipid metabolism (*LDLR*, *VLDLR*, *FAS*) and coding for pro-inflammatory cytokines (*MCP-1*, *IL-6*). Interestingly, membrane expression of CD36 in circulating cells increased significantly during post-prandial challenge in LoF.
Conclusions. PCSK9 deficiency is associated with increased post-prandial lipemia, as well as with increased expression of genes and proteins related to the metabolism of TGRLs and inflammatory response.

TREATMENT WITH FIBRATES IS ASSOCIATED WITH HIGHER LAL ACTIVITY IN DYSLIPIDEMIC PATIENTS

C. Pavanello[1], A. Branchi[2], G. Franceschini[1], L. Calabresi[1], M. Gomaraschi[1]
[1]Centro Enrica Grossi Paoletti, Dipartimento di Scienze Farmacologiche e Biomolecolari, Università degli Studi di Milano;
[2]Centro per lo studio e la prevenzione dell'Aterosclerosi, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano

Aim. Lysosomal acid lipase (LAL) is responsible for the hydrolysis of cholesteryl esters (CE) and triglycerides (TG) within the lysosomes; generated cholesterol and free fatty acids (FFA) are released in the cytosol where they can regulate their own synthesis and metabolism. When LAL is not active, as in case of genetic mutations, CE and TG accumulate in the lysosomal compartment, while the lack of release of cholesterol and FFA in the cytosol leads to an upregulation of their synthesis and VLDL secretion. Thus, LAL plays a central role in the intracellular homeostasis of lipids. Since there are no indications about the effect of different lipid-lowering agents on LAL activity, aim of the study was to address the relationship between LAL activity and the type of lipid-lowering therapy in a cohort of dyslipidemic patients.
Methods. LAL activity was measured on DBS from 120 patients with hypercholesterolemia or mixed dyslipidemia.
Results. Among collected variables, LAL activity negatively correlated with LDL-cholesterol levels. When patients were divided according to the type of lipid-lowering treatment, three main treatment categories were identified on the base of similar LAL activity: patients untreated or taking only omega-3, patients taking statins with or without ezetimibe or omega-3 and patients taking fibrates with or without statins or omega-3. LAL activity was significantly different between the three groups, with patients taking fibrates showing the highest average activity, also when adjusted for sex, age, BMI, lipid parameters, liver function and statin use. In a small subset of patients, LAL activity was measured before and after 3 months treatment with fibrates, showing a significant increase.
Conclusions. The use of fibrates is independently associated with higher LAL activity in dyslipidemic patients, suggesting that the positive effects of PPAR-a activation on cellular lipid homeostasis can also include an improved LAL activity.

RELATIONSHIP BETWEEN HIGH SODIUM AND LOW PUFA INTAKE AND CAROTID ATHEROSCLEROSIS IN ELDERLY WOMEN

E. Santariga[1], Y. Ferro[1], G. Gorgone[1], E. Mazza[1], M.A. Salvati[1], T. Montalcini[2], Arturo Pujia[1]
[1]Department of Medical and Surgical Science, Nutrition Unit, Magna Grecia University, Catanzaro;
[2]Department of Clinical and Experimental Medicine, Nutrition Unit, Magna Grecia University, Catanzaro

Background and Aims. Several biologically active molecules including nutrients can affect the vascular endothelium which becomes dysfunctional and, as a consequence, predisposes to atherosclerosis. However, the impact of the intake of sodium and polyunsaturated fatty acids on carotid atherosclerosis in a population of elderly women has scarcely been studied. Our aim was to investigate the association between carotid intima-media thickness and atherosclerotic plaque and nutrient intake in asymptomatic elderly women.
Methods. Carotid atherosclerosis was determined by duplex ultrasound in 108 elderly women. Dietary intake was assessed by a combination of a 24 hour recall and a 7 day food record. A physical examination and laboratory tests were performed.
Results. We found an association between the C-IMT and polyunsaturated fatty acid (negative, B=-0.014; p=0.03; CI -0.027/-0.001) and sodium (positive, r=0.16; p=0.09) intake. When linoleic acid was added to the multivariable regression analysis instead of polyunsaturated fatty acids, C-IMT was associated with linoleic acid (B=-0.017; p=0.02; CI -0.032/-0.003). In normotensive women we found a positive association between the C-IMT and sodium intake. The atherosclerotic plaque prevalence increased with the increase in sodium intake (66% *vs* 90% Tertile I *vs* Tertile III; p=0.02) and decreses in PUFA (92% *vs* 75% Tertile I *vs* Tertile III; p=0.05) (***Figure***).
Conclusion. A low salt diet to a level of about 1.5 g/d and a polyunsaturated fatty acid intake of more than 9 g/d were found to be associate with a low atherosclerotic plaque prevalence in an elderly female population. Sodium and polyunsaturated fatty acids-mediated functional changes of the carotid endothelium may be implicated in atherosclerosis development.

CRITICAL ISSUES IN THE APPLICATION OF THE DUTCH CLINIC LIPID NETWORK SCORE IN FH DIAGNOSIS. AN ANALYSIS OF THE LIPIGEN POPULATION

M. Casula[1], M. Arca*, M. Averna*, S. Bertolini*, S. Calandra*, A.L. Catapano*, P. Tarugi* on behalf of the LIPIGEN Group
[1]Epidemiology and Preventive Pharmacology Centre (SEFAP), Department of Pharmacological and Biomolecular Sciences, University of Milan;
**LIPIGEN Steering Committee*

Familial hypercholesterolemia (FH) is a common inherited disorder that leads to aggressive and premature cardiovascular disease. The availability of a tool that guides diagnosis in the setting of general medicine is fundamental to improve FH patient identification. This study aimed to evaluate the performance of the Dutch Clinic Lipid Network (DCLN) score in adult patients enrolled in the Lipigen study.
The DCLN score was applied to all the adult population included in Lipigen so far. The analysis was conducted on 1292 adult patients (mean age 42.7 SD 14.3) with genetic diagnosis of FH. Regarding the DUTCH criteria, 43.2% had at least one missing data out of 8, and 11.1% had 5 missing data or more. In particular, 34.7% did not have information on presence of tendon xanthoma and/or corneal arcus in first-degree relative and about 15% did not have information on positive history of premature coronary heart disease (CHD) or hypercholesterolemia in first-degree relative. The information on premature CHD or on cerebral/peripheral vascular disease was missing in 12.4% and 13.6% respectively. In this sample, diagnosis with DCLN score was probable for 27.8%, and definite for 37.8%. In the subsample with no missing information, the diagnosis was unlikely for 4.5%, possible for 28.9%, probable for 30.5% and definite for 36.1%. In the subjects under18 (on which the algorithm has not been validated), missing information rate was higher; moreover, in 189 patients with no missing information, the diagnosis was unlikely for 15.3% and possible for 50,3%.
Although the DCLN score is undoubtedly a very useful tool for the physician in the diagnosis of FH, it is limited by difficulty in finding information; moreover, it failed to identify a third of the subjects with genetic diagnosis of FH. An update of this tool and its validation in individual national contexts are warranted.

DETECTION OF FAMILIAL HYPERCOLESTEROLEMIA IN A CLINICAL SETTING: A SINGLE CENTER 4-YEAR EXPERIENCE IN THE LIPIGEN STUDY

I. Minicocci, L. D'Erasmo, A. Montali, G. Pigna, M. Maranghi, M. Arca
Department of Internal Medicine and Allied Sciences, Sapienza University of Rome

Introduction. Familial hypercholesterolemia (FH) is a genetic disorder of lipid metabolism characterized by high levels of LDL-C and increased risk of premature atherosclerosis. This condition is largely undiagnosed in the routine clinical setting. Within the LIPIGEN Project, since 2013 our Center performed genetic investigation in subjects with clinical diagnosis of FH. The aim of this report is to describe the spectrum of mutations identified.
Materials and Methods. We enrolled 339 patients with clinically suspected FH (DLCN score ≥3). Patients underwent complete clinical evaluation and blood sampling for searching FH-associated mutations. Next Generation Sequencing method was used to genotyping candidate genes (*LDLR, APOB, PCSK9, LDLRAP1, STAP1* and *APOE*).
Results. We identified FH causative mutations in 248 patients (73.2%). 85.1% were heterozygous carriers of one LDLR variant. We identified 3 heterozygous and one homozygote carriers of mutation in LDLRAP1. Nine heterozygous patients have been identified for variants in PCSK9 and APOB genes. Furthermore, we identified 7 compound heterozygous carriers of mutations in LDLR gene, 15 double heterozygous in 2 candidate genes and 2 triple heterozygotes for candidate genes. Carriers of causative mutations in FH patients with DLCN≥8, 6-7and 3-5 were 92.5%, 82,2 and 52.7 respectively.
Conclusion. This analysis demonstrated that the detection rate of FH-causing mutations in our population is comparable to that reported in previous investigations. In addition, it confirmed that also in our cohort mutations in the *LDLR* were the most frequent cause of FH. Moreover, even though DLCN score >8 is highly predictive of the presence of molecularly confirmed FH, the molecular screening is of crucial importance for the confirmation of this condition also for lower DLCN score values.

SPECTRUM OF RARE VARIANTS IN LPL, APOA5, APOC2, LMF1 AND GPIHBP1 GENES IN PATIENTS AFFECTED BY SEVERE HYPERTRIGLYCERIDEMIA

C. Giacobbe[1,2], M.D. Di Taranto[2], D. Palma[1,2], C. Pagano[3], I. Calcaterra[3], M. Tripaldella[3], M. Gentile[3], P. Rubba[3], G. Fortunato[1,2]
[1]CEINGE S.C.a r.l. Biotecnologie Avanzate, Napoli;
[2]Dipartimento di Medicina Molecolare e Biotecnologie Mediche, Università degli Studi di Napoli Federico II, Napoli;
[3]Dipartimento di Medicina Clinica e Chirurgia, Università degli Studi di Napoli Federico II, Napoli

Aim. Severe Hypertriglyceridemia (HTG) is a rare disease characterized by triglyceride levels (TG) higher than 10mmol/L (890 mg/dL), eruptive xanthomas, lipaemia retinalis and recurrent pancreatitis. HTG is caused by mutations in five different genes: Lipoprotein lipase (*LPL*), Apolipoprotein A-V (*APOA5*), Apolipoprotein C-II (*APOC2*), Glycosyl-phosphatidyl-inositol-anchored HDL-binding protein (*GPIHBP1*), and Lipase maturation factor-1 (*LMF1*). We aim to screen a 22 unrelated patients with clinical suspicion of HTG.
Methods. After genomic DNA extraction from peripheral blood samples, the 5 genes associated with HTG, were amplified by PCR and directly sequenced. SALSA MLPA kit (MRC-Holland) was used to identify large rearrangements in the LPL gene.
Results. We identified 17 rare variants (with MAF <1%) in 12 patients. The pathogenicity of rare variants were evaluated based on ACMG criteria and variants were classified like pathogenic, probably pathogenic and uncertain significance variants (USV); considering only the pathogenic and probably pathogenic variants, we found 6 homozygotes or compound heterozygotes patients for rare variants in *LPL* gene, 4 simple heterozygotes for rare variants in *LPL* gene and 2 simple heterozygotes for rare variants in *APOA5* gene. No statistical differences of lipid levels were observed between patients carrying 2, 1 or none pathogenic /probably pathogenic variants with the exception of total cholesterol levels that are higher in heterozygote patients than in patients with 2 variants (p=0.028).
Conclusions. Our genetic screening allowed to make a definite diagnosis of HTG in 6 patients. It is important to evaluated the pathogenicity of USVs by functional tests. Finally we can't exclude that other genes involved in HTG, patients with 1 rare variant or without rare variants will be investigated by NGS.

CLINICAL PREDICTORS OF A POSITIVE GENETIC TEST IN PATIENTS WITH FAMILIAL HYPERCHOLESTEROLEMIA

S. Lugari, F. Nascimbeni, S. Cagnacci, A. Dalla Salda, M. Dolci, M. Milazzo, A. Mondelli, F. Carubbi
Università degli Studi di Modena e Reggio Emilia, U.O. di Medicina Interna ad Indirizzo Metabolico-Nutrizionistico, Ospedale Civile di Baggiovara, A.O.U. di Modena

Background. There is no consensus on which are the best clinical predictors to refer patients with clinical suspicion of familial hypercholesterolemia (FH) for genetic testing. We aimed to identify clinical-laboratory parameters associated with the detection of an FH-causing mutation and to assess the performance of Dutch Lipid Clinic Network (DLCN) score and other parameters in detecting FH-causing mutations.
Patients and Methods. We enrolled 101 consecutive patients with clinical suspicion of FH, in which clinical and laboratory parameters and a conclusive result of genetic testing were available.
Results. 61 patients were mutation positive. Mutation positive patients more frequently had a familial history of LDL-hypercholesterolemia and familial cases of corneal arcus/xanthomas than mutation negative patients. There were no significant differences with respect to personal history of early cardio-cerebrovascular disease and clinically-detected corneal arcus/xanthomas between mutation positive and negative patients. Conversely, mutation positive patients showed significantly higher baseline LDL cholesterol (LDL-C) levels and DLCN score than mutation negative patients. AUROC of baseline LDL-C for predicting a positive genetic test was 0.754, IC95% 0.660-0.848. The Youden index allowed to identify LDL-C levels >225 mg/dl as the best cut-off value with sensitivity of 64%, specificity of 90%, positive predictive value (PPV) of 91% and negative predictive value (NPV) of 62%. DLCN score showed similar performance to LDL-C as predictor of FH-causing mutations (0.719, IC95% 0.619-0.819). DLCN score >5 and >8 showed sensitivity of 74% and 49%, specificity of 63% and 80%, PPV of 75% and 79%, NPV of 61% and 51%, respectively.
Conclusions. DLCN score seem to be feasible for the identification of mutation positive patients. However, LDL-C levels >225 mg/dl also show good performance in detecting FH-causing mutations, and may be used as a sole criterion to refer patients for genetic testing, when all the clinical variables required for DLCN score are unavailable.

DETECTION OF FAMILIAL CHYLOMICRONEMIA SYNDROME IN A COHORT OF PATIENTS WITH SEVERE HYPERTRIGLYCERIDEMIA THROUGH A NEXT GENERATION SEQUENCING APPROACH

A. Di Costanzo[1*], L. D'Erasmo[1*], F. Cassandra[1], I. Minicocci[1], L. Polito[1], M. Arca[1]
[*]Equal contribution
[1]Department Internal Medicine and Medical Specialties, Policlinico Umberto, Sapienza University

Aims. Familial Chylomicronemia syndrome (FCS) is a rare recessive disease caused by mutations in *LPL, APOC2, APOA5, LMF1* and *GPIHBP1* genes. It is characterized by very severe hypertriglyceridemia (HTG) with or without episodes of abdominal pain and recurrent acute pancreatitis. FCS diagnosis is often difficult due to its phenotypic similarity with other forms of severe hypertriglyceridemia. The aim of our study was to detect pathogenic mutations in candidate genes in patients with suspected FCS based on specific clinical criteria and evaluate clinical differences between genotypes.
Methods. By examining 3000 clinical records, 31 patients were classified as suspected FCS on the following criteria:
a) plasma trigliceridemia (TG) levels >1000 mg/dl in multiple determinations;
b) resistance to pharmacological therapy;
c) history of acute pancreatitis.
All patients underwent fully clinical examination and their information were collected retrospectively. Candidate genes were sequenced using Next generation sequencing (NGS) technique.
Results. 51.6% subjects were carriers of FCS causing mutations, the majority in *LPL* gene (56.2%). Compared to non-carriers, FCS patients showed higher prevalence of history of acute pancreatitis (P=0.04) and early onset of HTG (P=0.0008). Comparing homozygous carriers of mutations in other genes with *LPL* homozygotes, the latter group showed higher TG levels (P<0.001) and lower TG reduction during treatment (P_{adj}=0.03).
Conclusions. Our data suggests that the proposed diagnostic criteria are highly predictive of FCS diagnosis in severe HTG patients. Mutations in *LPL* gene are the most common cause of FCS and homozygous carriers of mutations in *LPL* gene have the more severe clinical phenotype.

DOUBLE HETEROZYGOUS MUTATIONS IN APOAV AND LPL IDENTIFIED BY EXOME SEQUENCING COSEGREGATE WITH AUTOSOMAL DOMINANT HYPERTRIGLYCERIDEMIA AND PANCREATITIS

R. Spina[1], V. Ingrassia[1], A.B. Cefalù[1], V. Valenti[2], G.I. Altieri[1], D. Noto[1], C. Scrimali[1], F. Brucato[1], G. Misiano[2], A. Giammanco[1], C.M. Barbagallo[1], A. Ganci[1], F. Fayer[1], M.R. Averna[1]
[1]Dipartimento Biomedico di Medicina Interna e Specialistica (DIBIMIS), University of Palermo;
[2]Molecular Biology Diagnostic Laboratory, Central Laboratory of Advanced Diagnosis and Biomedical Research (CLADIBIOR), Department of Diagnostic Laboratory, AOUP "Paolo Giaccone", Palermo

Aim. According to a recent definition of the hypertriglyceridemic states, fasting TG plasma levels <2 mmol/l (175 mg/dl) can be considered normal while TG levels between 2 to 10 mmol/l (175 mg/dl - 885 mg/dl) and >10 mmol/l (885 mg/dl) identify subjects with mild to moderate and severe hypertriglyceridemia respectively.
Methods. The proband was a 40 year-old male with moderate HTG (418 mg/dl) and he has suffered an episode of pancreatitis. Moderately high plasma levels of triglycerides were observed in 3 more family members. The father of the proband also suffered an episode of acute pancreatitis. A 6 year old girl who is one of the proband's daughters showed TG levels of 198 mg/dl. To identify the causal mutation in this family, we performed exome sequencing in three participants with moderate hypertriglyceridemia and pancreatitis with an apparently autosomal dominant pattern of inheritance.
Results. Approximately 45,000 single nucleotide variants were identified in each sample. After variant filtering, 40 novel shared variants remained. Among these a heterozygous frameshift variant of APOAV gene (c.427delC; p.R143fs) and a missense mutation in LPL gene (c.953A>G; p.Asn318Ser) were identified and confirmed by Sanger sequencing in all 3 studied subjects.
Conclusion. We used exome sequencing to search for pathogenic mutations responsible for dominant moderate hypertriglyceridemia and pancreatitis in this kindred, and we identified three carriers of double heterozygous mutations in APOAV and LPL genes. If additional genetic defects are responsible of acute pancreatitis in this family, need to be established.

ACHILLES TENDON ULTRASONOGRAPHY MAY PREDICT A POSITIVE GENETIC TEST IN PATIENTS WITH FAMILIAL HYPERCHOLESTEROLEMIA

F. Nascimbeni, S. Cagnacci, M. Dolci, A. Mondelli, M. Bertoldi, A. Dalla Salda, M. Milazzo, S. Lugari, F. Carubbi
Università degli Studi di Modena e Reggio Emilia;
U.O. di Medicina Interna ad Indirizzo Metabolico-Nutrizionistico, Ospedale Civile di Baggiovara, A.O.U. di Modena

Aim. Achilles tendon (AT) xanthomas, specific for familial hypercholesterolemia (FH), may be clinically undetectable. We aimed to evaluate the usefulness of AT ultrasonography in the identification of individuals with an FH-causing mutation.
Methods. 65 consecutive patients with clinical suspicion of FH, in which clinical and laboratory parameters and a conclusive result of genetic testing were available, were submitted to bilateral AT ultrasonography with measurements of thickness and evaluation of tendon structure (abnormal structure and xanthomas).
Results. 39 patients (60%) were mutation positive. AT thickness was significantly and positively associated with age, male gender, weight, LDL cholesterol (LDL-C), Dutch Lipid Clinic Network (DLCN) score and FH severity. However, AT thickness was not significantly correlated with the result of genetic testing. 36 patients showed a pathologic finding at AT ultrasonography: 6 patients had abnormal structure, 9 patients had xanthomas and 21 patients had both abnormal structure and xanthomas. A pathologic finding at AT ultrasonography was significantly and positively associated with AT thickness, LDL-C and DLCN score, but not with gender and weight. Moreover, patients with a pathologic finding at AT ultrasonography were more frequently detected with an FH-causing mutation (37.9% *vs* 77.8%, p=0.001). Among pathologic findings at AT ultrasonography, only xanthomas (40% *vs* 83.3%, p<0.001) but not abnormal structure (52.6% *vs* 70.4%, p=0.150) were significantly associated with the result of genetic testing. The performance of DLCN score calculated after inclusion of ultrasonography-diagnosed AT xanthomas was significantly better than the performance of standard DLCN calculated with clinically-diagnosed AT xanthomas in detecting FH-causing mutations (AUROCs 0.782, 0.667-0.896 *vs* 0.686, 0.557-0.815).
Conclusions. AT ultrasonography may be a useful tool for the evaluation of patients with suspected FH. The sonographic visualization of tendon xanthomas, rather than tendon abnormal structure or tendon enlargement, may significantly improve the detection rate of FH-causing mutations.

GENETIC DIAGNOSIS, ACHILLES TENDON ULTRASONOGRAPHY AND DUTCH LIPID CLINIC NETWORK SCORE OF FAMILIAL HYPERCHOLESTEROLAEMIA: PRELIMINARY DATA FROM THE UNIVERSITY OF PADUA OUTPATIENT LIPID CLINIC

P. Bigolin, M. Moro, P. Scarinzi, M. Biolo, L. Benvegnù, C. Panzavolta, R. Marin, D. Vianello, S. Bertocco, L. Previato, F. Fabris, E. Manzato, A. Zambon, S. Zambon
Department of Medicine - DIMED, University of Padua

Aims. Ultrasonography (US) is used to detect Achilles tendon (AT) xanthomas in patients (pts) with Familial Hypercholesterolaemia (FH). Our study focused on potential associations between FH genotype, clinical phenotype and ultrasonographic (US) AT findings, evaluating the contribution of AT US to identify individuals with an FH-causing mutation.
Subjects and Methods: Genetic screening, clinical and biochemical parameters were analysed in 116 pts with possible, probable or definite clinical diagnosis of FH according to the Dutch Lipid Clinic Criteria (DLCNS); 71 pts underwent bilateral AT US; ultrasonographic xanthomas (USX) were defined as the presence of AT thickness >6.15 mm in at least one of the AT and/or presence of hypoechogenic formations.
Results.
1) 85 pts were positive for LDL gene receptor mutation (35 carriers of null allele (NA) and 50 of defective (DEF) allele) and 31 with no known mutations (NM) for FH. Presence of xanthomas and gerontoxon, total and LDL-cholesterol (NA vs DEF vs NM: 326.5±97.7 mg/dl, 316.9±93.9 mg/dl, 211.1±76.3 mg/dl, p<0.000) at diagnosis were significantly higher in NA pts than other subgroups. AT thickness was significantly different among the three groups (p<0,005)-and 78.2%, 72.4% and 31.6% had USX in NA, DEF and NM carriers respectively (p=0.002).
2) Among the 52 pts positive for FH-causing mutations: 36 pts had definite clinical diagnosis of FH by the DLCNS, while in 16 pts the diagnosis was either possible (5%) or probable (23%). Among these 16 pts, one had clinically evident xanthomas while 10 had USX. Thus, in nine pts the presence of USX was clinically undetected and thereby not considered for DLCNS calculation.
Conclusions.
1) Genotypic functional characterization is associated with different phenotypic clinical features, AT thickness and presence of US xanthomas.
2) AT ultrasonography may help reclassifying as definite FH, patients with DLCN score of possible/probable FH.

EPICARDIAL FAT THICKNESS IN PATIENTS WITH AUTOSOMAL DOMINANT POLYCISTIC KIDNEY DISEASE

A. Concistrè[1], L. Petramala[1], G. Scoccia[1], S. Sciomer[2], V. Bisogni[1], V. Saracino[1], G. Iannucci[1], S. Lai[3], D. Mastroluca[4], G. Iacobellis[5], C. Letizia[1]
[1]Unit of Secondary Hypertension, Department of Internal Medicine and Medical Specialties, University of Rome, "Sapienza";
[2]Department of Cardiovascular and Respiratory Sciences, University of Rome, "Sapienza";
[3]Department of Clinical Medicine, University of Rome, "Sapienza";
[4]Nephrology and Dialysis Unit, Hospital ICOT Latina, University of Rome, "Sapienza";
[5]Division of Diabetes, Endocrinology and Metabolism, Department of Medicine, University of Miami, Miller School of Medicine, Miami, FL, USA

Aim. Autosomal dominant polycystic kidney disease (ADPKD) is associated with early organ damage such as left ventricular hypertrophy (LVH) and higher cardiovascular risk when compared to essential hypertension (EH). Epicardial adipose tissue (EAT) is a new cardiovascular risk factor, but its correlation with LVH in ADPKD is unknown. We sought to evaluate the correlation of ultrasound measured EAT and LVH in a well-studied group of hypertensive patients with ADPKD in comparison with essential hypertension (EH) subjects.
Methods. We performed ultrasound measurement of the EAT and other echocardiographic parameters, such as left ventricular mass (LVM), left ventricular mass indexed by body surface area (LVMi), and left atrium size in 41 consecutive hypertensive patients with ADPKD, compared to 89 EH patients.
Results. EAT was significantly higher in ADPKD group respect to EH subjects (9.2±2.9 mm *vs* 7.8±1.6 mm, p<0.001), and significantly correlated with LVM, LVMi and left atrium size in the ADPKD group (r=0.56, p=0.005; r=0.424, p=0.022; and r=0.48, p=<0.001, respectively). Comparing EAT against body mass index (BMI), waist circumference (WC), systolic blood pressure (SBP), diastolic blood pressure (DBP) and age, we found that EAT is the strongest predictor of LVMi (B=0.59, p=0.036).
Conclusions. Our data shows that EAT is higher in ADPKD patients than in EH subjects and independently correlates with LVMi. EAT measurement can be as useful marker in the cardiovascular risk stratification in ADPKD.

RETINAL ARTERIOLAR WALL-TO-LUMEN RATIO IS USEFUL IN THE MANAGEMENT OF MASKED TREATED HYPERTENSIVE PATIENTS

A. Gallo, A. Mattina, D. Rosenbaum, X. Girerd
Sorbonne Université, Paris, France

Background. The management of masked arterial hypertension (AH) in treated hypertensive patients is challenging. Masked AH is associated to retinal microvascular changes, which may take place at different timings. We have recently observed an increased Wall-to-Lumen Ratio (WLR) in retinal arterioles of patients with masked AH.
Our aim was to evaluate retinal arteriolar remodeling changes before and after Blood Pressure (BP) control improvement in patients with masked AH.
Design and methods: 30 treated hypertensive patients (15 with masked AH, 15 with controlled AH) were consecutively enrolled and evaluated at baseline and after 6 months. Assessment included office and home BP measurements as well as Adaptive Optics RTX1® Camera imaging (ImagineEye, Orsay, France) that was used to measure Wall Thickness (WT), Internal Diameter (ID), Wall Cross Sectional Area (WCSA) and Wall-to-Lumen Ratio (WLR). Controlled AH was defined as office BP <140/90 and home BP <135/85 mmHg, whereas masked AH was defined as office BP <140/90 and home BP ≥135/85 mmHg. In patients diagnosed with masked AH, antihypertensive treatment was increased after the baseline visit.
Results. At baseline mean office Systolic BP (SBP) and Diastolic BP (DBP) were normal in both groups but resulted higher in masked AH compared to controls; home BP in masked AH patients was expectedly increased (Table 1). WLR in masked AH patients was higher than controls (0.339±0.07 vs 0.288±0.04, p=0.03) while other retinal arteriolar parameters did not differ.
In masked AH, at 6 months follow-up we observed a significant decrease in both office BP (SBP - 43% and DBP -8%, respectively) and home BP (SBP -14% and DBP -23%). In this group, while WT and WCSA remained stable, a significant reduction in WLR (-8.6%, p=0.034) was observed due to lumen dilatation (+6.3%, p=0.007).
No changes in BP or in retinal arteriole anatomical indexes were found in the control group.
Conclusions. WLR is increased in masked AH. The increase of antihypertensive therapy that led to an improved home BP control was associated to a decrease in WLR. Retinal arteriolar remodeling with Adaptive Optics may be useful in the management of masked AH.

INCIDENT CARDIOVASCULAR DISEASE AMONG HYPERTENSIVE PATIENTS WITH BLOOD PRESSURE <140/90MMHG

G. De Stefano, C. Mancusi, G. Albano, G. Canciello, N. de Luca, M. Losi, G. de Simone
Hypertension Research Center; Federico II Univeristy, Napoli

Aim. Data from last decade indicate that the majority of incident cardiovascular disease (CVD) events occur among individuals with systolic and diastolic blood pressure (SBP/DBP) ≥140/90 mm Hg. Over the past several decades, BP has declined and hypertension control has improved. We aim to identify clinical characteristics of hypertensive patients with controlled BP (<140/90 mmHg) during follow-up (FU) and incident CV events.
Methods. From the Campania Salute Network we selected 3933 with controlled BP during FU and available information on cardiac and carotid ultrasound as marker of target organ damage (TOD). During a mean FU of 68 months 161 incident composite major and minor CV events occurred.
Results. Among patients with controlled BP during FU those who experience CV events were more frequently older men, with higher prevalence of left ventricular hypertrophy and carotid plaque (all p<0.05). Patient who experience CV events had lower diastolic BP, heart rate and higher LDL cholesterol. In Cox regression analysis older age and male sex confers higher risk of CV events (HR 1.05 95CI 1.03-1.07 and HR 1.7 95CI 1.20-2.42, p>0.01), while both higher diastolic BP at baseline and during FU seems to have a protective role (HR 0.98 95CI 0.96-0.99 and HR 0.96 95CI 0.98-0.99, p<0.05). No effect of common TOD such as LV hypertrophy and carotid plaque was found.
Conclusions. In hypertensive patients with controlled BP during FU CV prognosis seems to be associated with older age and male sex, with no impact of baseline TOD. Diastolic BP close to 90 mmHg seems to have a protective role.

NURSE-OBP: A NURSING STANDARDISED METHOD FOR MEASURING BLOOD PRESSURE

M. Pappaccogli[1], F. Rabbia[1], S. Di Monaco[1], E. Perlo[1], C. Maldarizzi[1], E. Eula[1], C. Fulcheri[1], A. Milan[1], P. Mulatero[1], F. Veglio[1]
University of Turin, Italy

Aim. The role of the nurse in both diagnostic and therapeutic management of hypertensive patient is becoming more and more important; nevertheless, until now there is not a nursing standardised method of blood pressure (BP) measurement. The aim of this study was to standardise a nursing method for measuring blood pressure (Nurse-OBP) and to compare it with the Ambulatory Office Blood Pressure (AOBP).
Method. 118 hypertensives were included in the study. All underwent an AOBP measurement with Omron HEM-907XL and a Nurse-OBP measurement, methodologically identical to the classical AOBP, which takes place with the nurse staying in the same patient's room during the BP measurement. Subjects were randomized into two distinct groups, according to the different order in which the two methods of measurement were performed to avoid eventual reduction of "white coat-effect". All patients underwent a traditional OBP measurement during medical examination. Participants signed an informed consent and the study was approved by local ethical committee (CEI 652).
Results. Mean Nurse-OBP values (132.8±19.4/73.3±12.9 mmHg) were significantly lower than OBP ones (141.3±18.8/84.7±10.7 mmHg). When AOBP and Nurse-OBP were compared, no statistically significant differences between the two methods were found. The Bland - Altman analysis showed how the presence of the nurse could cause a minimum rise of BP values which was found to be not statistically significant, therefore the two modalities, AOBP and Nurse-OBP, can be considered as comparable. Furthermore, no differences in term of Nurse-OBP values were found when the two groups were compared.
Conclusions. Our study proposes a standardised nursing method for measuring BP, comparable to AOBP technique, that could be widely used in clinical practice when it is not possible to perform a classic AOBP measurement.

CHARACTERISTICS AND OUTCOMES OF PATIENTS PRESENTING WITH HYPERTENSIVE URGENCY IN THE OFFICE SETTING

G. Albano, G. De Stefano, M.I. Arnone, A. D'Amato, F. De Pisapia, A. Gaspardini, C. Mancusi
Hypertension Research Center, Federico II University Hospital of Naples

Aim. The prevalence and outcomes of hypertensive urgency are unknown. The aim of this analysis is describing the prevalence of hypertensive urgency, characteristics and outcomes of these patients.
Methods. This retrospective cohort study analyzed patients presenting to an office visit with hypertensive urgency (HypUrg) (systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥110 mmHg) in the Campania Salute Network Registry. Patients were older than 18 years old, with available follow-up (FU), cardiac and carotid ultrasound data, without prevalent cardiovascular disease and no more than stage III Chronic Kidney Disease.
Results. From 6929 patients, 469 presented with HypUrg at first visit. Compared to patients without hypertensive urgency at baseline, HypUrg were more likely to be women, obese, with diabetes (all $p<0.05$), exhibited greater prevalence of left ventricular hypertrophy and carotid plaque and received more antihypertensive medications (all $p<0.005$).
During FU, patients presenting with HypUrg had 5 times increased risk of uncontrolled BP (OR 5.3 95%CI 4.1-6.8, $p<0.0001$). During a mean FU of 62 months the total study population experienced 311 combined major and minor CV events. In Cox regression analysis presenting with HypUrg was not associated with increased CV risk after adjusting for significant covariates (HR 1.42 95%CI 0.96-1.54, $p=0.08$)
Conclusions. Hypertensive urgencies are common in the office setting of treated hypertensive patients from Southern Italy. Despite high CV risk profile, presenting with HypUrg per se is not associated with increased risk of CV events.

BIGLYCAN-INDUCED INFLAMMATORY RESPONSE IN HUMAN MONOCYTE: EX VIVO EXPERIMENTAL MODEL

M. Scuruchi, G.M. Campo, A. Saitta, G. Mandraffino
University of Messina, Clinical and Experimental Medicine

Background. Monocytes are critically involved in the pathogenesis of atherosclerosis, capable of secreting many factors such as chemokines, cytokines, growth factors, and reactive oxygen species, thus contributing to wall lesion development. Biglycan (BGN), a small leucine rich proteoglycan, plays a pivotal role in initiating lipid deposition in the arterial subintimal space, by its ability to bind and retain apoB- containing lipoprotein, including LDL, VLDL and IDL. Furthermore BGN, in its soluble form, acts as an endogenous ligand for Toll-Like receptors (TLR2, TLR4), mediating innate immunity and inflammation.
Methods. We studied the role of BGN in an experimental model of biglycan-induced inflammatory response in human monocytes isolated ex vivo from ten healthy subjects. Monocytes were cultured in six-well culture plates at a density of 1*106 cells/well and treated with BGN (1.25 µg/ml). A separate set of monocytes receiving BGN plus a TLR-2 and/or TLR-4 siRNAs were treated 48h before BGN addiction in order to block their activity. TLR-2, TLR-4, IL-1β and IL-6 mRNA expression was assessed by qPCR and expressed by n-fold increase with respect to baseline and unexposed controls; TLR-2, TLR-4, IL-1β and IL-6 proteins were evaluated by commercially available ELISA kits. NF-kB activation was assessed by a colorimetric commercial kit.
Results. The addition of BGN (1.25 µg/ml) to monocytes induced a high mRNA expression and protein production of pro-inflammatory mediators such as IL-1β and IL-6, as well as NF-kB, TLR-2 and TLR-4 activation. The involvement of TLR-2 and TLR-4 in the mediation of BGN action was confirmed by using the specific siRNAs.
Conclusion. In light of these finding we can suggest further studies in order to evaluate the effects of soluble BGN also in other cells involved in the onset and progression of atherosclerosis, including endothelial cells and endothelial progenitor cells, to deepen to current knowledge of atherogenesis, and also to provide the rationale of novel therapeutic approaches.

IS BLOOD PRESSURE MEASUREMENT AT FOREARM AND UPPER ARM INFLUENCED BY ARM CIRCUMFERENCE?

M. Camilli[1], M. D'Abbondanza[1], G. Pucci[2], G. Lupattelli[1]
[1]Department of Medicine, University of Perugia, Unit of Internal Medicine, Perugia;
[2]Department of Medicine, University of Perugia, Unit of Internal Medicine, S. Maria Hospital, Terni

Aim. accurate measurement of blood pressure (BP) is essential to classify and treat appropriately hypertensive patients and, in this regard, placement and size of the cuff are crucial (1). The increasing prevalence of morbidly obesity and the inaccessibility of upper arm determine the necessity to investigate alternative sites of measurement (2).
In our study, we aimed to determine agreement between BPs measurement at upper arm (UA) and forearm (FA) using auscultatory and oscillometric method in relationship with arm circumference (a.circ.).
Methods. the study enrolled 14 hypertensive and obese subjects with a.circ. larger than 36 cm (group 1) and 7 healthy control patients with a.circ. smaller than 36 cm (group 2).
We measured BP simultaneously at UA and contralateral forearm by:
Auscultatory method by a validated mercury sphygmomanometer in triplicate in supine position by an appropriate cuff and by a downsized cuff ("miscuffing").
Ambulatory BP monitoring (SpaceLab 90207). During cuffing, patients placed FA by the side and not at heart level, in order to estimate the magnitude of error of misplacement.
Results. both auscultatory and oscillometric method overestimated SBP (4 mmHg, nss and 13 mmHg respectively, $p<0.05$) and DBP (5 and 6.5 mmHg respectively, $p<0.05$) at FA rather than UA. The entity of overestimation was higher in group 2 patients rather than group 1 (e.g., for DBP 8 vs 3 mmHg respectively, $p<0.05$) and inferior for nighttime BP rather than daytime. No correction formula was found.
"Miscuffing" at UA determined an overestimation of about 4 mmHg for SBP (nss) and of 5 mmHg for DBP ($p<0.05$).
Conclusions. even if the entity of BP overestimation seems to be related to a.circ., forearm cannot currently replace UA for BP measurement, both in normoweight and obese patients, independently from a correction formula. Further studies are needed to elaborate specific algorithm for oscillometric method use at FA.

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SILENT ADRENAL PHEOCHROMOCYTOMA COEXISTENT WITH CORTICOMEDULLARY HYPERPLASIA: A CASE INCIDENTALLY DISCOVERED

F. Olmati, L. Petramala, V. Saracino, A. Concistré, V. Bisogni, L. Zinnamosca, G. Iannucci, G. De Toma, A. Ciardi, C. Letizia
Unit of Secondary Hypertension, Department of Internal Medicine and Medical Specialties, University of Rome, "Sapienza"

Introduction. Pheochromocytoma (PHEO) is a rare catecholamine-producing tumour arising from chromaffin cells in the sympatho-adrenal system, and can present as asymptomatic adrenal incidentaloma (AI).
Case report. A 61 year old woman was referred to our centre for evaluation of an incidental right adrenal mass (diameter 44 mm) and arterial hypertension. Hormonal evaluation was performed and a diagnosis of subclinical hypercortisolism (SH) was made. Considering the increasing diameter of the adrenal mass, the patient underwent a laparoscopic adrenalectomy.
At the pathological examination, macroscopically, the right adrenal gland showed haemorrhagic and focal pseudocystic appearance. Histology revealed a lesion with tumour cells arranged in well-defined nests. Immunohistochemistry using antibody against chromogranin, synaptophysin and neuron-specific enolase showed positive results. Immunohistochemical studies using antibody against ACTH were positive in the adrenal cortex and medulla.
Results. A final diagnosis was made of adrenal PHEO accompanied by micronodular cortico-medullary hyperplasia.
Conclusions. This report describes a rare case of incidental non-functioning PHEO coexisting with corticomedullary hyperplasia and SH. It's rare to find in literature a rappresentation of coexisting common (adrenal incidentaloma and SH) and uncommon (PHEO) endocrinological conditions.

EVALUATION OF BLOOD PRESSURE HOME MONITORING BY SELF-MEASUREMENT EDUCATION

L. Petramala, F. Olmati, V. Saracino, A. Concistré, V. Bisogni, G. Iannucci, C. Letizia
Unit of Secondary Hypertension, Department of Internal Medicine and Medical Specialties, University of Rome, "Sapienza"

Introduction. Arterial hypertension is responsible for worldwide burden due to high cardiovascular morbidity and mortality (~30%). It is crucial to manage an optimal control of blood pressure (BP) values during pharmacological therapy. Aim of the study is to evaluate in hypertensive patients the hypertension control rate assessment, by making a comparison between home BP home monitoring (HBPM), office BP, and ambulatory blood pressure monitoring (ABPM). We also investigated eventual advantages and limitations of HBPM in BP control and compliance.
Material and Methods. From March to September 2016 we enrolled 150 hypertensive patients (45% M, 55% F; age 53±15.9 yrs). All the subjects were trained in HBPM under medical supervision. Training included information regarding hypertension, BP variability, conditions and procedure for self-monitoring.
Results. 54% of patients [35 M, 46 F], has completed the study by bringing back the HBPM questionary (Group A), while the other 46 % didn't complete the task [31 M, 38 F] (Group B). All subjects were divided and stratified by age, number of medications needed, and arterial hypertension grade. Statistically significant data concerned young compliant subjects in the 30-year age group with a prevalence of 64.8% [total 52; 35 M, 17 F] against 35.71% [total 25; 18 M, 7 F] of non-compliant subjects. Group A subjects showed a wider prevalence of stage III hypertension [total 6; 3 M, 3 F], than Group B subjects (4,93% vs 0,5%; $p<0.05$). Analysis of BP values showed how BP values obtained by HBPM tend, by time, to be similar to ABPM values.
Conclusions. HBPM, during pharmacological therapy, is a fundamental instrument to confirm the real treatment efficacy.

AUTONOMIC DYSFUNCTION AND CARDIOVASCULAR RISK IN PATIENTS WITH ATHEROSCLEROTIC RENAL ARTERY STENOSIS: A PILOT STUDY

V. Zingaretti[1], A. Gigante[1], B. Barbano[1], E. Rosato[1], M. Proietti[2,3], M. Liberatori[1], A. Mazzarella[1], L. Tubani[1], R. Cianci[1]
[1]Department of Clinical Medicine, Sapienza-University of Rome, Rome, Italy;
[2]IRCCS, Istituto di Ricerche Farmacologiche Mario Negri, Milano;
[3]Department of Internal Medicine and Medical Specialties

Atherosclerotic renal artery stenosis (ARAS) is a secondary cause of hypertension and is associated with ischemic nephropathy, congestive heart failure and accelerated cardiovascular disease (CVD). Autonomic dysfunction is a renowned risk factor for cardiovascular disease.
The Aim. Of the study is to evaluate if markers of increased cardiovascular risk, as autonomic dysfunction and QTc interval prolongation can be detected in ARAS patients.
Methods. We performed an observational study on 27 patients with ARAS compared to healty controls (HC). All patients underwent clinical evaluation, renal Doppler ultrasound, electrocardiography, 24 h Holter monitoring and echocardiogram. Autonomic nervous activity was evaluated by heart rate variability (HRV).
Results. Global autonomic activity was significantly lower in ARAS patients than HC ($p<0.0001$), while parasympathetic activity significantly higher in ARAS patients than HC ($p<0.0001$). In the frequency domain, low frequencies modulated mainly by sympathetic system were significantly lower in ARAS patients than HC ($p<0.0001$). In addition, QTc was found significantly higher in ARAS patients than HC ($p<0.0001$).
Conclusion. Patients with ARAS present autonomic dysfunction and QTc interval prolongation. Analysis of HRV is a non-invasive tool to monitor autonomic control of the heart and should be included in the study of patients with ARAS to better stratify cardiovascular risk.

ANALYSIS OF AORTIC REMODELING AND STIFFNESS IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA SYNDROME (OSAS): PRELIMINARY RESULTS

S. Cicco[1], M. Guarascio[1], G. Castellana[2], L. Marra[2], S. Dragonieri[2], P. Carratù[2], G. Ranieri[1], O. Resta[2], A. Vacca[1]
[1]Department of Internal Medicine and Clinical Oncology;
[2]Department of Cardiac, Thoracic, and Vascular Science, Institute of Respiratory Disease, University of Bari Aldo Moro Medical School

Background. Obstructive Sleep Apnea (OSA) is a well-known risk factor for cardiovascular diseases. Several studies have shown that OSA is associated with vessel remodeling. Few studies have examined aorta in OSA.
Aim. To analyze the link between aortic root diameter (ARD) and severity of OSA or diurnal value of PaO2 and PaCO2.
Methods. We studied 30 consecutive OSA patients (22 M/8 F, aged 58.5±13.2 years). All patients underwent to a morning blood gas analysis, a full cardiorespiratory evaluation, including nocturnal polygraphy and echocardiography, with measurement of ARD and aortic stiffness index (ASI). Patients were grouped as follows: Group 1, non-severe OSA (Apnea-Hypopnea Index - AHI - <30, 14 pts) and Group 2, severe OSA (AHI ≥30, 16 pts). Statistical significance: $P\leq0.05$.
Results. No difference has been found between groups in ARD as absolute value (Group 1, 33.64±0.91 mm; Group 2, 33.64±1.02, P=ns) and normalized value for the body surface area - Aoi (Group 1, 16.72±0.63 mm/m^2; Group 2, 16.09±0.44, P=ns). Moreover, no difference has been found in ASI (Group 1, 3.62±0.183; Group 2, 3.51±0.19, P=ns).
Considering all OSA patients, AHI gave an inverse correlation with Aoi (P=0.018) and ASI (P=0.0449). Moreover ASI was directly correlated with Aoi (P=0.01) and morning pO2 (P=0.0349) as well as inversely correlated with oxygen desaturation index (ODI, P=0.031) and total time of apnea and hypopnea (P=0.039).
Conclusions. No differences have been found between severe and not-severe OSA in ARD. Surprisingly, data have shown that severity of OSA correlates inversely with ASI and Aoi. The relation between pO2 and stiffness should be explained with a feedback mechanism that tried to overcome the reduction of aortic elasticity due to night desaturation. These findings need to be investigated in further studies on a larger series of patients.

RELATIONSHIP BETWEEN RENAL HEMODYNAMICS AND CORONARY ATHEROSCLEROTIC BURDEN IN PATIENTS WITH HYPERTENSION

G. Geraci[1], C. Pugliares[1], G. Mulè[1], D. Buccheri[2], K. Di Natale[2], S. Cottone[1]
[1]Dipartimento Biomedico di Medicina Interna e Specialistica, Unità di Nefrologia;
[2]Dipartimento Biomedico di Medicina Interna e Specialistica, Unità di Cardiologia, Università degli Studi di Palermo

Objective. Cardiovascular diseases recognize ischemia as the main pathogenetic prime mover and represent the final step of morphofunctional vascular changes that develop over a long period of time, mostly asymptomatically. Recent studies detected the role of intrarenal hemodynamic changes as independent predictors of cardiovascular events in different populations. No data exist about the relationship between renal hemodynamics and coronary atherosclerotic damage. The purpose of our investigation is to study the relationship between intrarenal vascular changes and coronary atherosclerotic burden in hypertensive patients.
Design and Method. We enrolled 130 hypertensive subjects (30-80 years) who received indication for elective coronary angiography. Duplex ultrasound of intrarenal vasculature was performed to evaluate renal resistive index (RI), renal pulsatility index (PI) and renal acceleration time (AT). Subsequently, a coronary angiography was performed to assess atherosclerotic burden through Gensini Score (GS). Carotid intima-media thickness (cIMT) was also assessed as a model of vascular damage well related with renal parameters. The population was divided into quintiles based on the GS (I quintile: GS <9; II quintile: GS >9 and <17; III quintile: GS >17 and <30.8; IV quintile: GS >30.8 and <44; V quintile: GS >44). Statistical analysis was also performed in the population divided in 2 groups:
1) subjects with mild coronary disease (GS <30);
2) subjects with severe coronary disease (GS >30).
Results. Subjects in higher quintiles had greater values of PI, RI and lower values of AT compared to the ones in lower quintiles. The correlation between GS and PI, RI or AT was not statistically significant at the univariate analysis in overall population, whereas GS, IR and IP were significantly associated with cIMT (all $p<0.01$). IP and IR, but not AT, were associated to GS in the group with GS<30, whereas did not correlate in subjects with GS>30. These correlations held after adjustment for multiple confounders.
Conclusions. Renal vascular changes are not significantly related to coronary atherosclerotic burden in all hypertensive patients. Nevertheless, within the complex mathematical relationship between PI (or RI) and GS, the relationship becomes linear and significant in patients with mild coronary disease.

THE BURDEN OF CARDIOVASCULAR DISEASES ON ADMISSION AND FINAL DIAGNOSES IN AN ACADEMIC DIVISION OF INTERNAL MEDICINE IN SOUTHERN ITALY

M. Nuzzo, M. Capurso, A. Belfiore, P. Buonamico, F. Minerva, V.O. Palmieri, S. Pugliese, V. Di Ceglie, P. Portincasa
Clinica Medica "A. Murri", Department of Biomedical Sciences and Human Oncology, University of Bari "Aldo Moro" Medical School, Bari

Aim. The burden of cardiovascular diseases (CVD, heart and blood vessels disorders) is increasing due to aging and diffused metabolic risk factors worldwide. We report on the CVD burden on admission and final diagnoses observed at a Unit of Internal Medicine in a large 3rd regional Hospital, Southern Italy.
Methods. In 2016, 983 patients were admitted (467M; 516F, mean age 68±SD17 yrs). Results: Referrals were from Bari city, 325.000 inhabitants (57.1%), Bari province (30.3%), Apulia region 4.1M inhabitants (10.4%), other Italian regions (1.63%), extra-EU (0.4%), and EU (0.3%). Admissions from emergency unit (ER) were 67.7% with patients older than elective patients (71±1 vs 62±1 yrs, P=0.0001) in both sexes. Age was similar between men and women for both emergency and elective admission patients. Mean hospital stay was 7.2±0.2 days (range 1-88). The length of hospital stay (days) correlated positively with age (yr) of patients (r=0.2; P=0.0000). Final diagnoses were CVD (23.2%), infective (8.8%), gastrointestinal (17.8%), respiratory (5.6%), tumors (16.9%) and nonCVD miscellanea (27.7%). The majority of CVD patients were from ER (86.0%; 29.5% of total ER admissions). Sex prevalence in the CVD group was M 40.8%, F 59.2% (P=0.0001). Mean age was comparable between sexes within the CVD group, but higher in CVD than non-CVD patients (73±1 vs. 66±1 yrs, P=0.0000). Estimated costs (DRG) were greater (2,773 vs 2,375 €, p=0.0046) and Hospital stay longer (8.5 vs 6.8 days; p=0.0017) for CVD patients than non-CVD patients, respectively.
Conclusions. In a typical 3rd referral centre of Internal Medicine at a large regional hospital in Southern Italy, CVD patients account for 23% of total admissions, are older and require greater clinical and economic effort. We confirm that the burden of CVD in Internal Medicine is partly explained by the aging population and increased prevalence of metabolic disorders.