while the expression CDKN1a at mRNA level is increased (NG vs HG P=0.01). In both cases, GLP-1 does not exert its effects after chronic exposure to high glucose concentration (NG vs NG+GLP-1 P=0.02 and P=0.06, BCL-2 and CDKN1A, respectively. And HG vs HG+GLP-1 P=0.30 and P=0.74, BCL-2 and CDKN1A, respectively).

**Conclusion:** Our preliminary findings suggest that endothelial cells, after a long of exposure to high glucose, lose their ability to respond normally to the GLP-1 action, in terms of increasing their antioxidant capacity and regulating ER function and UPR response. This effect is probably due to the development of resistance to GLP-1 during high glucose chronic exposure.

Grant : FIS P110/01256 from Instituto Carlos III

**OP8: Early atherosclerosis in Familial Partial Lipodystrophy of the Dunnigan-type: Endothelial cell dysfunction induced by p.R482W lamin-A**

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**Background:** Some mutations in LMNA, encoding A-type lamins, are responsible for lipodystrophic syndromes, which present features of severe metabolic syndrome. p.R482W substitutions lead to the Dunnigan familial partial lipodystrophy (FPLD2) while the p.L92F mutation gives a phenotype of metabolic laminopathy (ML). FPLD2 has been associated with precocious atherosclerosis.

**Methods and Results:** We analyzed the cardiovascular phenotype of nineteen patients with FPLD2 and a patient with ML (LMNA p.L92F). Despite similar metabolic alterations, FPLD2 patients, but not the ML patient, presented early atherosclerosis.

We then studied the effects of wild-type or mutated p.R482W and p.L92F-prelamin-A overexpression on primary cultured human coronary endothelial cells (HCAECs).

Although both mutations led to defects in prelamin-A maturation, only p.R482W-prelamin-A was predominantly distributed to the nuclear envelope, in favor of its persistent farnesylation. p.R482W but not wild-type or p.L92F-prelamin-A overexpression led to endothelial dysfunction, with decreased expression of endothelial nitric oxide synthase, increased inflammation, and increased endothelial adhesion of peripheral blood mononuclear cells. p.R482W-prelamin-A also induced oxidative stress, increased DNA double-strand breaks and cellular senescence. In vitro pravastatin treatment, which inhibits prelamin-A farnesylation, decreased p.R482W-prelamin-A association to the nuclear envelope, oxidative stress and inflammation. In addition, anti-oxidants decreased inflammation and DNA double-strand breaks occurrence, suggesting that farnesylated p.R482W-prelamin-A induced oxidative stress which resulted in endothelial dysfunction.

**Conclusions:** FPLD2-associated p.R482W but not ML-associated p.L92F lamin-A mutation resulted in farnesylated-prelamin-A accumulation that induced endothelial dysfunction in vitro. These observations suggest that LMNA p.R482W mutations have a direct pro-atherogenic role, contributing to the early occurrence of atherosclerosis in FPLD2.

Grant: Funding sources were from INSERM, the Programme National de Recherche sur le Diabète (PNRD/ARD), the EU FP6 Eurolaminopathies project, and the Société Francophone du Diabète. GB is a recipient of a fellowship from the Ministère Français de l’Enseignement Supérieur et de la Recherche.

**OP9: Diet modulates endogenous thrombin generation, a biological estimate of thrombosis risk, independently of the metabolic status**

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**Background and aims:** The association between obesity and thrombosis might be explained by a hypercoagulable state. In addition, it is still discussed controversially whether obesity, fat diet or metabolic disturbances are the main influence factors of the changes in the coagulation system.

**Methods and Results:** In this study, we investigated the effect of postnatal overfeeding and high fat diet (HFD) on thrombin generation. Endogenous Thrombin potential (ETP) was measured using the Calibrated Automated Thrombogram. Weaning rats exhibited high ETP values that decreased under low-fat diet (LFD) and remained elevated upon HFD. In adult rats, HFD-induced ETP increase was independent of coagulation factors, obesity and insulin resistance and negatively associated with polyunsaturated fatty acid (PUFA) levels. Switching from HFD to LFD reversed the procoagulant phenotype with a slower kinetic than the normalization of hyperinsulinemia. In humans, ETP was independent of body weight while it was negatively associated with nutritional markers such as the percentage of energy provided by proteins, the protein/fat ratio, and circulating phenolic compounds and omega-3 PUFA. A recommended 3-month healthy diet with reduced energy density, including lipids, decreased ETP (- 21%; P<0.0001). ETP changes were not associated with body weight, insulin sensitivity or coagulation factor variations, but correlated negatively with plasma docosahexaenoic acid, a nutritional status sensitive fatty acid, and compounds reflecting vegetable intake.

**Conclusion:** Diet plays a pivotal role in regulating ETP, independently of obesity and insulin resistance. Global nutritional recommendations could be useful in primary prevention of thrombosis.

**OP10: Analysis of the relationship between the presence of metabolic syndrome with the level of oxidized LDL and impaired fibrinolysis in patients with type 2 diabetes**


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**Background and aims:** It is known that in patients with type 2 diabetes (T2D) and the metabolic syndrome (MS) there is a higher risk for atherosclerosis. The aim of this study was to investigate the relationship of non-traditional risk factors for atherosclerosis, biomarkers of lipid peroxidation measured by oxidized LDL levels (oxLDL) and markers of fibrinolysis measured by plasminogen activator inhibitor 1 (PAI-1) in patients with T2D and the MS.
OP12: Association between retinopathy and early echographic markers of cardiomyopathy in type 2 diabetes

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Background and aims: Alterations in cardiac structure and function occur in type 2 diabetes independently of coronary artery disease or hypertension. The underlying mechanisms remain unclear. The aim of our study was to explore the putative involvement of microangiopathy in the determination of cardiac myocardiopathy.

Materials and Methods: 387 patients with type 2 diabetes mellitus (D2) with controlled blood pressure and without overt valvular or coronary heart disease were prospectively enrolled. All subjects underwent comprehensive echocardiography, including evaluation of diastolic and systolic LV function by conventional assessment and use of speckle-tracking imaging. Diastolic dysfunction was defined by left atrium area (adjusted for body surface area) > 11 cm²/m² and/or lateral E' <10 and preclinical systolic dysfunction was defined by longitudinal strain >-18%.

Diabetic retinopathy assessed by ETDRS criteria was graded in 3 stages 0: no retinopathy, 1: mild non proliferative retinopathy, 2: moderate, severe non proliferative and proliferative retinopathy.

Results: 191(57.2%) patients exhibited diastolic dysfunction vs 143 (42.8%) who had no dysfunction. By univariate analysis: diastolic dysfunction was associated with diabetic retinopathy (p =0.01), additionally these patients were more likely to be female (M/F 95/96 vs 88/55, p=0.02), were older (60±8 vs 55±8, p<0.001 with a longer diabetes duration (13±8 vs 10±7, p<0.001) and a lower blood glucose control: Hba1c (7.9±1.5 vs 7.6±1.4, p=0.046) and had higher SPB (systolic blood pressure) (136±15 vs 131±16, p =0.001). Microalbuminuria was not different in both groups, p=0.35.

83 (26%) patients only had systolic dysfunction vs 236 (74%) who had no dysfunction. By univariate analysis: presence of subclinical LV systolic dysfunction in diabetic patients was associated with a higher prevalence of diabetic retinopathy (p =0.04), additionally these patients were more likely to be male (M/F 59/98 vs 88/85, p=0.005), to have obesity BMI (31±5 vs30±4, p=0.02), with higher SPB (138±15 vs 132±16, p =0.001), and lower HDL (1.2±0.3 vs 1.3±0.4, p=0.03). Microalbuminuria was not different in both groups, p=0.3.

By multivariable analysis, factors independently associated with diastolic dysfunction were age (OR95%=1.09 [1.05-1.12 ],p<0.001) and retinopathy stage (OR =1.45 [1.01-2.08], p = .04) whereas factors independently associated with systolic dysfunction were gender (M vs F OR=2.09[1.18-3.71],p=0.01), BMI (OR=1.07[1.07-1.18],p=0.03) and SBP (OR=1.30[1.09-1.54],p=0.004).

Conclusion: In our cohort of type 2 diabetic patients, only retinopathy was found associated with the commonly reported diastolic dysfunction whereas retinopathy was not found independently associated with systolic dysfunction.