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OC01

ARDIOVASCULAR EFFECTS OF CHRONIC SILDENAFIL TREATMENT IN EN WITH TYPE 2 DIABETES

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ype 2 diabetes (T2DM), cardiomiopathy is characterized by an impairment of diastolic formance resulting in ventricular hypertrophy and dilatation. Heart remodelling leads an increase in its angle of torsion, measurable by an innovative application of cine-gnetic Resonance Imaging (MRI). Cardiomiopathy in T2DM represents an ideal del of endothelial dysfunction. To evaluate the impact of phosphodiesterase 5 ibitors (PDE5i) on cardiovascular performance in T2DM, we designed a randomized, cebo-controlled, double blind (subject/outcome assessor) study on chronic treatment (3 nths) with high dose of Sildenafil (100 mg/in 3 daily doses). The study has been istered at U.S.NIH clinicaltrial.gov (identifier NCT00692237). We have enrolled 50 betic men (35-75 yrs), metabolically controlled; 35 subjects have already ended the dy; 2 patients drop out the study (1 for dyspepsia, 1 for non-compliance). Safety nitoring was taken monthly at follow-up visits. Primary outcome is the analysis of left tricular torsion (cineMRI) thanks to novel HARP software. Secondary outcomes eals: 1) a significant improvement of heart remodelling parameter: end-diastolic ume, ejection fraction and hypokinetic areas. 2) A significant improvement of diovascular risk parameters: reduction of postprandial glycemia from 178±49 to ±48; HbA1c from 7.8±1 to 7.1±0.9; waist to hip ratio and increase of HDL cholesterol n 39±7 to 43±9. 3) A significant reduction of P Selectin on activated platelet-nocytes interaction (cytofluorometry), serum marker of endothelial dysfunction olved in atheromatous process. 4) A significant reduction of systolic (136±12 to ±12) and diastolic blood pressure (78±9 to 76±7) (Holter monitoring 24h). The study ruitment is completed. The present study documents: a) the safety of prolonged onic sildenafil treatment on the adaptative endothelial changes affecting cardiovascular ponse in T2DM; b) an improvement in metabolic parameters and anthropometric asures related to a decrease of cardiovascular risk that underlies an involvement of sphodiesterase type 5 inhibitors on body composition and fat distribution.

OC02

ENDOTHELIAL PROGENITORS CELLS (EPC) WITH IMMUNOPHENOTYPE CD45-/CD34+CD144+ IN PATIENTS WITH ERECTILE DYSFUNCTION AND METABOLIC SYNDROME.

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Introduction and aim. The metabolic syndrome (SM) and erectile dysfunction (ED) of arterial origin share the same risk factors and physiopathological evolution. The EPCs participate to the vascular homeostasis and the endothelial repair phase, with a different capacity according to the various immunophenotypes. The endothelial immunophenotype CD45-/CD34+CD144+ characterizes a pool of advanced EPCs with repairing capability. The presence of the CD144 (VE-cadherin) indicates their capacity to favour endothelial tight junctions. Therefore, this study was undertaken to evaluate the concentration of these type of EPCs in patients with arterial ED and SM on the basis of their erectile response to treatment with iPDE5. **Materials and Methods.** Thirty patients aged 47-58 years, (mean 54) with ED and SM, established according to the ATP III criteria (1999), were treated with tadalafil (Tad, 20 mg) on demand for 3 months. After treatment, all patients underwent the IIEF-5 questionnaire to evaluate their erectile response, and expression of their circulating (CD45-/CD34+ and CD144+) EPCs by 3-color flow cytometry, following incubation with differently labelled antiCD45, antiCD34 and antiCD144 monoclonal antibodies. **Results.** The percentages of EPCs, according to the erectile response to iPDE5, are shown in the table.

IIEF score	22-25 (no ED) (n=3)	17-21 (mild) (n=7)	12-16 (mild / moderate) (n=8)	8-11 (moderate) (n=6)	5-7 (severe) (n=6)
EPCs (%)	0.33±0.15	1.27±0.40	1.88±0.26[a]	4.07±0.63[a,b]	6.05±0.50[a,b,c]

[a]p<0.05 vs. no ED or mild ED; [b]p<0.05 vs. mild-moderate ED; [c]p<0.05 vs. moderate ED (ANOVA followed by the Duncan's multiple range test).

Conclusion. These data suggest the presence of a compensatory mechanism attempting to overcome the endothelial dysfunction present in iPDE5 poor-responder patients. Since, recently it has been reported that the administration of an NO precursor prevents EPC apoptosis in patients with hypercholesterolemia, we speculate that this therapeutic strategy may help poor-responder ED patients with SM.

OC03

STOSTERONE AMELIORATES SEXUAL AND METABOLIC PROFILE IN ANIMAL MODEL OF METABOLIC SYNDROME

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abolic syndrome (MetS) includes abnormalities (hyperglycaemia,hypertension, ipidaemia, visceral obesity) associated to an increased cardiovascular risk.MetS is associated to hypogonadism and erectile dysfunction (ED). ED is a sentinel sign of pient cardiovascular disease.To clarify the pathogenetic relationship among MetS, ogonadism and ED we developed an animal model of MetS. Male adult rabbits fed a -fat diet (HFD) for 12 weeks, with or without testosterone (T) supplementation.They e compared to control rabbits (fed a standard chow). A subgroup of these control nals received also a single injection of Triptorelin pamoate, that has been described to ice a hypogonadotropic hypogonadism. HFD rabbits,showed MetS features nificant increase of glycaemia, cholesterol, triglycerides, visceral fat, and arterial sure). HFD induced a steatohepatites (histological studies),characterized by an ease of inflammatory markers genes (qRT-PCR for TNFα, MCP1, IL6 and COX2) increase of PPARγ and adiponectin and a reduction of PPARα gene expression in . HFD induced also hypogonadotropic hypogonadism, with significant reduction of FSH, LH plasma level, testis and seminal vesicle weights. HFD reduced gene ression of steroidogenic enzymes (3beta-HSD,StAR,CYP17A1) in testis. HFD ced corpora cavernosa (CC) hypo-responsiveness to acetylcholine and a hyper-onsiveness to the nitric oxide (NO) donor SNP respect to controls. These effects were parable to those observed in CC from Triptorelin-induced hypogonadal rabbits, while prevented by T. HFD determined a net reduction of electrical field (EF)-relaxation in CC.The relaxant response to sildenafil and vardenafil was abolished in rabbit CC and restored by T. These results suggest that HFD impair the cGMP/PDE5 activity due to androgen deprivation. Indeed HFD, as well as torelin, significantly reduced PDE5 and eNOS gene penile expression (qRT-PCR), was restored by T. In HFD animals T restored sex accessory gland weight, and natically reduced the HFD-induced visceral obesity, partially ameliorating also the abolic profile. We next evaluated GnRH immunostaining in hypothalamic section. We d that HFD dramatically reduced GnRH immunopositivity respect to control and, that d not restore it. In conclusion, we developed an animal model of MetS associated to gonadotropic hypogonadism, ED, and unresponsiveness to PDE5 inhibitors.We d that T supplementation is able to partially revert this phenotype.

OC04

OXIDATIVE SPERM DNA DAMAGE AND SPERM DNA FRAGMENTATION: IS THERE ANY RELATIONSHIP WITH DIFFERENT SEMEN LEUKOCYTES POPULATIONS IN EJACULATES FROM SUBFERTILE COUPLES?

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Phagocytosis of foreign infectious agents by polymorphonuclear (PMN) granulocytes in the accessory glands and by activated macrophages (MΦ) in the epididymis is suggested to lead to generation of reactive oxygen species (ROS) with a detrimental effect on sperm functions. We analysed the association among the number of seminal PMN, MΦ and activated MΦ, levels of DNA 8-hydroxyguanosine (8-OHdG), a sensitive biomarker of oxidative DNA damage, the number of sperm with fragmented DNA, and routine sperm parameters. Flow cytometric analysis of round cells expressing CD14 (marker of MΦ) and HLA-DR (marker of activated MΦ), and of sperm with DNA fragmentation (TUNEL assay) was applied to 100 ejaculates from the male partner of subfertile couples. The level of 8-OHdG in sperm DNA was determined by an ELISA commercial kit and data were compared with routine semen parameters and number of peroxidase-positive cells (PMN). We found a significant correlation between the peroxidase positive PMN and both the CD14+ ($r=0.66$; $p<.0001$) and the HLA-DR+ ($r=0.63$; $p<.0001$) cells. Moreover, CD14 and HLA-DR expressing cells were strongly correlated to each other ($r=0.86$; $p<.0001$). No differences neither in the routine semen parameters nor in the 8-OHdG levels were found out between samples with a lower ($<0.5\times10^6$/mL) and those with a higher ($>0.5\times10^6$/mL) round cells number but in the latter the percentage of sperm with fragmented DNA was significantly higher. Interestingly, the correlation analysis showed also a significant association of Tunel test with the peroxidase + ($r=0.33$; $p=0.03$), CD14+ ($r=0.33$; $p=0.03$) and HLA-DR+ ($r=0.38$; $p=0.0007$) cells. Our results showed that activated MΦ are detectable in same ejaculates without overt leukocytospermia, confirming our previous observations and they correlate with sperm DNA fragmentation. A prolonged interaction between sperm and activated MΦ in the epididymis, probably triggered by a chronic inflammation, might result in a nuclear damage. Most intriguing, this study demonstrated that apparently normal ejaculates can actually have a damaged DNA, a condition which might reduce the fertility potential.