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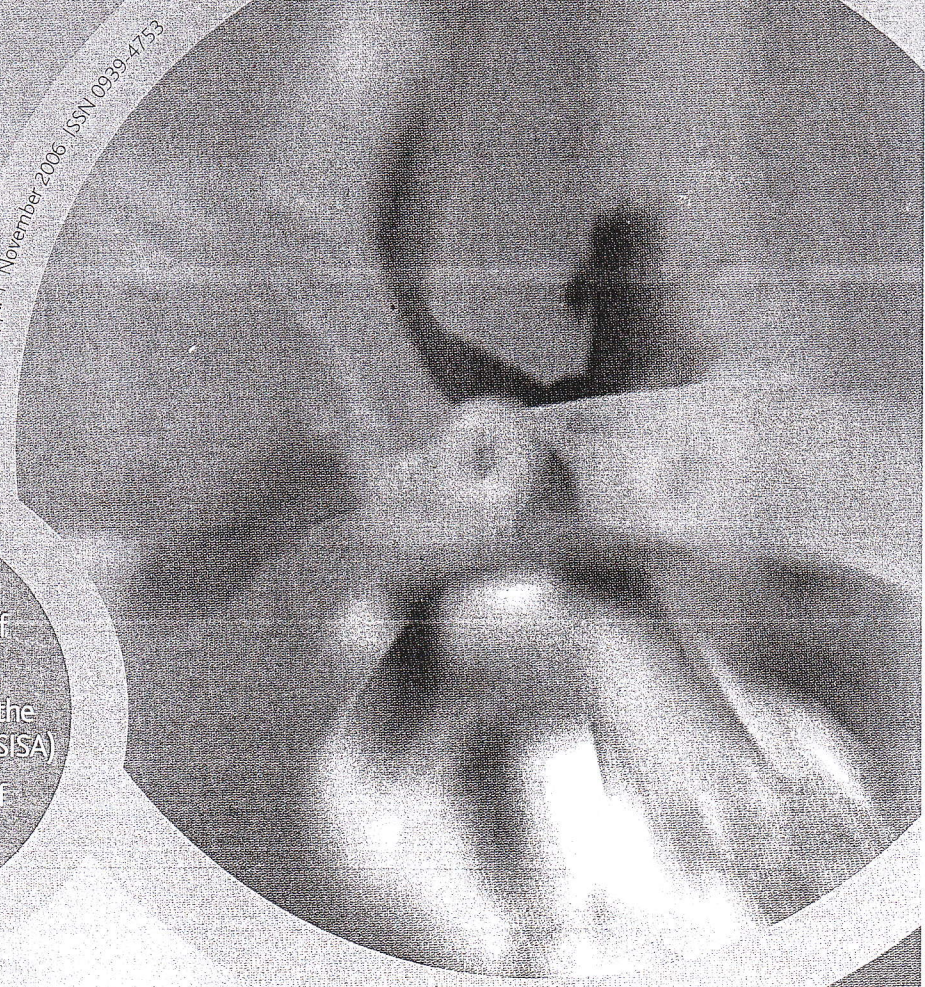

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45 ROLE OF SGK-1 IN THE PREVENTION OF ENDOTHELIAL DYSFUNCTION

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Hyperglycaemia increases Reactive Oxygen Species production and reduces nitric oxide production in endothelial cells, inducing cell damage and endothelial dysfunction. In our experiments we investigated the role of SGK-1 after insulin stimulation and oxide stress induction in HUVEC. We found that SGK is predominantly localized on plasmatic membrane where it's degraded. We found high SGK expression levels after ALLN incubation, but not after ALLM incubation, suggesting that SGK-1 is degraded by 26S proteasome-ubiquitin pathway. HUVEC cells were infected with control vector, SGK1-WT or delta60 SGK1 mutated (Ubiquitin domain deleted). To induce oxidative stress infected cells were incubated with high glucose (30 mM) and Glucosamine 10 mM, for 72 hours. SGK-1 activity was measured by FOXO 3a phosphorylation levels in SGK-1 specific site, demonstrating that SGK-1 delta60 construct is active at basal level. We found a reduction of ROS production, an increased activity of Na-K ATPase and a decrease of NO production in HUVEC infected with SGK-1 delta60 compared with SGK-1 wt infected cells or with control in basal condition and after treatments. Delta60 construct appears protect by apoptosis, annexine analysis demonstrates that this construct protects HUVEC by glucose and glucosamine induced apoptosis. We can hypothesize that increased expression of SGK-1 protects endothelial cell from oxidative stress damage and we can speculate that induction of SGK-1 expression could be a strategy to prevent and/or treat macrovascular disease and atherosclerosis.

46 ASYMMETRIC DIMETHYL-ARGININE IS INDEPENDENTLY RELATED TO FOREARM FLOW-MEDIATED DILATATION IN APPARENTLY HEALTHY VOLUNTEERS AT LOW CARDIOVASCULAR RISK

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Increased plasma concentrations of asymmetric dimethylarginine (ADMA) contribute to impair endothelial function in patients with established cardiovascular disease (CVD) and/or individuals with clinical syndromes known to increase CVD. However, the impact of ADMA on endothelial function in apparently healthy individuals has not been determined. To address this issue, we measured endothelial-dependent vasodilatation in response to forearm ischemia (flow-mediated vasodilatation, FMD) in 111 non-smoking, healthy volunteers with low CVD risk by the Framingham risk equation. Measurements were also made of multiple anthropometric, metabolic, and dynamic variables related to FMD. After adjustment by gender, lower values for FMD were significantly associated with increases in plasma ADMA concentrations (ANOVA linear trend by FMD tertiles, $p < 0.05$) as well as body mass index (BMI, $p < 0.005$), systolic blood pressure ($p < 0.05$), fasting plasma insulin concentration ($p < 0.001$), and high-sensitivity C-reactive protein (hs-CRP, $p < 0.05$) levels. Multiple linear regression analysis indicated that the only statistically significant predictors of FMD were gender ($p < 0.05$), ADMA ($p < 0.05$) and fasting plasma insulin ($p < 0.005$) concentrations.

In conclusion, a significant relationship between increases in plasma ADMA concentration and lower values of FMD is not limited to patients with clinical syndromes related to CVD, but can also be seen in healthy subjects at low global CVD risk.

47 ASSOCIATION OF MICROSOMAL TRIGLYCERIDE TRANSFER PROTEIN 493-T VARIANT WITH RESISTIN LEVELS AND C-REACTIVE PROTEIN

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Background: The microsomal triglyceride transfer protein (MTP) is a heterodimeric lipid transfer protein that consists of a large unique 97 kDA subunit and protein disulfide isomerase. MTP is involved in the assembly of apoB-containing lipoprotein and enables the secretion of VLDLs by the liver and chylomicrons by the intestine. The MTP gene is highly polymorphic. The less-common T variant has been associated with reduction of plasma LDL cholesterol levels and with an increased risk in coronary heart disease. We hypothesized that MTP polymorphism could be associated to pro-inflammatory cytokines, such as resistin.

Methods and Results: The –493G/T MTP gene polymorphism was investigated in 290 subjects. Subjects carrying the TT genotype had lower level of LDL-cholesterol and higher serum resistin levels than individual carrying one or two copies of the –493G allele. After adjustments for age, BMI, waist circumference, alcohol intake and exercise levels, a significant direct association was evident between hs-CRP and resistin levels and presence of the TT genotype in a multiple regression model.

Conclusion: This study supports the notion that the rare MTP-493T/T genotype is associated both with higher levels of inflammatory parameters and to low levels of LDL cholesterol. Prospective data are needed to investigate if the association between CVD and the MTP-493T/T genotype might be due to the increased sub-clinical pro-inflammatory state associated with this mutation.

48 SMALL DENSE LDL PARTICLES AND METABOLIC SYNDROME IN A SAMPLE OF MIDDLE-AGED WOMEN FROM SOUTHERN ITALY. FINDINGS FROM PROGETTO ATENA

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Metabolic Syndrome (MS) is highly prevalent in the general population. Recently, small dense LDL (sd-LDL) particles have been considered as possible new risk marker in MS. We analyzed the relation between sd-LDL and MS in a population based sample of 210 middle-aged Southern Italian women; among them 86 participants had MS (prevalence 40.9%). LDL particle separation was performed by Lipoprint System: seven LDL subfractions were obtained and LDL score (% of sd-LDL particles) calculated. Women with the MS had LDL score significantly higher compared to participants without MS (median 0 vs. 3.6, $p < 0.001$ by Mann Whitney). The univariate analysis showed a positive and significant association between MS and LDL score (OR 4.80, 95% CI: 2.29–10.18, $p < 0.001$ for MS), apo B and insulin levels were also positively related to the presence of sd-LDL (OR 31.56, 95% CI: 5.58–178.29, $p < 0.001$ for apo B; OR 1.07, 95% CI 1.00–1.15, $p < 0.05$ for insulin). After controlling for age and insulin, MS remained related to high LDL score (upper quintile). After including in the model also apo B, MS was still strongly related with LDL score (OR 4.0, 95% CI: 1.76–9.09, $p < 0.001$ for MS). Our results suggest that sd-LDL particles could be, in addition to other risk factors, a valuable marker for diagnosis and severity of the MS. The LDL size measurement could be a useful tool for identification of a subset of patients at relatively high risk of cardiovascular disease (CVD) within the large population with the MS, and who are candidates for intensive lipid-lowering interventions.

49 TISSUE FACTOR A-603G GENOTYPE ASSOCIATES WITH CAROTID INTIMA-MEDIA THICKNESS IN SUBJECTS UNDERGOING CARDIOVASCULAR RISK PREVENTION

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Tissue factor (TF), initiator of coagulation, is also ascribed a non-hemostatic function in atherosclerosis development. Polymorphisms in the TF gene promoter have been shown to modulate the expression of TF, and thus perhaps also its role in atherosclerosis. Hence, this study investigated associations between TF promoter genotype and carotid intima-media thickness (IMT), a well-established marker of atherosclerosis. The TF A-603G polymorphism and carotid IMT was analysed in 324 patients undergoing primary and secondary cardiovascular risk prevention. Subjects were 60.5±8.4 years old, 80% were male, and 77% were undergoing secondary prevention with a history of atherosclerotic disease. Both mean and maximum carotid IMT (measured at the common carotid, bifurcation, and internal carotid) differed significantly according to A-603G genotype, being highest in –603A/A (n = 95), intermediate in A/G (n = 164) and lowest in G/G (n = 65) (mean IMT: A/A 1.31±0.37 mm, A/G 1.28±0.33 mm, G/G 1.22±0.35 mm; max IMT: A/A 2.35±0.91 mm, A/G 2.25±0.84 mm, G/G 2.15±0.97 mm; both $p < 0.05$; tested for trend; adjusted for age, gender, smoking habits, and anti-hypertensive treatment.

In summary, a significant association between TF promoter genotype and carotid IMT was observed, maybe mediated via altered TF expression levels in the circulation or within the carotid vessel wall. These findings support a role of TF in the atherosclerotic process, beyond its role in hemostasis and thrombosis, thus implicating TF not only in thrombotic complications of atherosclerotic disease, but also in plaque progression.