Investigation of vascular changes associated with familial combined hypolipidemia

Aim. To evaluate the biochemical determinants of aspirin-resistance in a population of type 2 diabetic men on aspirin therapy.
Methods. In 81 type 2 diabetic men (age: 63.5±0.7 years; diabetes duration: 12.5±2.1 years; BMI: 29.1±0.4 kg/m^2) on chronic aspirin (100 mg/die), defined aspirin-resistant if they presented PFA-100 CEPI closure time <200 seconds, we determined:
1. metabolic parameters: HbA1c, fasting blood glucose, total, HDL and LDL cholesterol, triglycerides and apo B-100;
2. oxidative stress markers: urinary isoprostanes (8-epi-PGF2alpha) and plasma Superoxide Dismutase activity (SOD);
3. markers of platelet activation: sCD-40L, sP-Selectin, serum and urine Thromboxane (TX) B2.

Results. 60 men (74%) were ASA-sensitive and 21 men (26%) ASA-resistant. ASA-resistant vs ASA sensitive patients differed for:
1. total cholesterol (181.0±6.6 vs 159.0±4.1 mg/dl, p=0.007), LDL-cholesterol (117.0±6.5 vs 93.2±3.9 mg/dl, p=0.003), non-HDL cholesterol (142.8±7.1 vs 117.7±3.7 mg/dl, p=0.01), APO-B100 (93.0±4.9 vs 77.2±3.0 mg/dl, p=0.009);
2. plasma SOD activity (0.21.0±0.01 vs 0.24±0.01 U/ml, p=0.05), urinary 8-epi-PGF2alpha isoprostane (1.35±0.11 vs 0.84±0.09 ng/mg creatinine, p=0.003);
3. serum TXB2 (5242±2314 vs 1550±313, p=0.01) and 11-dH-TXB2 (2144.8±306.0 vs 1387.2±66.11 pg/mg creatinine, p=0.0001). PFA-100 CEPI significantly correlated (p=0.05-0.0001) with non-HDL-cholesterol, APO-B100, serum and urinary TXB2, and 8-epi-PGF2alpha. Both HbA1c and non HDL cholesterol significantly contributed to the oxidative stress (measured as isoprostane values) in a linear multivariate analysis.

Conclusions. In type 2 diabetes mellitus determinants of aspirin resistance are parameters of lipid control (non HDL-cholesterol and Apo-B100) and oxidative stress markers. Both HbA1c and non HDL-cholesterol contribute to explain the increased oxidative stress observed in this condition.

MICRO-RNA 143/145 DEFICIENCY IS ASSOCIATED WITH REDUCED ATHEROSCLEROSIS IN LDL-RECEPTOR KNOCK-OUT ANIMALS

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MicroRNAs (miRNAs) have emerged as a novel class of endogenous, small, non-coding RNAs that negatively regulate gene expression via degradation or translational inhibition of their target mRNAs. MicroRNA-143/145 have an important role in the modulation of vascular smooth muscle cell (VSMC) phenotype whose deregulation is associated with vascular disorders such as atherosclerosis. In order to study the influence of these miRNAs on atherosclerosis development we have generated miR-143/145 knock out (KO) mice on atherogenic background (LDL receptor KO). The animals were fed with an high-fat diet for 16 weeks and then blood lipids content and atherosclerosis development were investigated.Cholesterol and triglycerides blood levels were similar among the animal groups. The morphometric analysis at tricuspid valve level showed a 40% decrease in atherosclerotic lesion of double KO animals compared with LDL-R KO. Further characterization of the lesion showed a similar collagen content and necrotic core extension. Gene expression analysis of the atherosclerotic lesions in the arterial wall is on going to identify the genes and the molecular mechanisms associated with these findings.
In summary, miRNA 143-145 deficiency is associated with an atheroprotective effect in LDL-receptor knock-out animals.
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INVESTIGATION OF VASCULAR CHANGES ASSOCIATED WITH FAMILIAL COMBINED HYPOLIPIDEMIA

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Familial combined hypolipidemia (FHBL2, OMIM #605019), due to mutations in ANGPTL3 gene, is a recently described low-cholesterol syndrome characterized by a reduction of both pro-atherogenic (VLDL and LDL) and anti-atherogenic (HDL) lipoproteins. The impact of FHBL2 on the risk of atherosclerosis is not well defined. We assessed in 66 FHBL2 subjects carrying the ANGPTL3 S17X LOF mutation (7 homozygotes and 59 heterozygotes) and 126 age- and sex-matched controls the extent of preclinical atherosclerosis by measuring carotid intima-media thickness (IMT) and flow-mediated dilatation (FMD). Three IMT values on each side were obtained and average (Avg-IMT) and maximum IMT (Max-IMT) were calculated. FMD was measured according to the guidelines of the International Brachial Artery Reactivity Task Force. Plasma concentration of soluble forms of VCAM-1, ICAM-1, and E-selectin were also measured as biomarkers of endothelial function. Finally, the capacity of serum obtained from 15 FHBL2 individuals (7 homozygotes, 8 heterozygotes) and 8 non-carriers to promote cell cholesterol efflux was tested.
Compared with controls, homozygous FHBL2 carriers showed increased avg-IMT (0.81±0.20 vs. 0.59±0.33 mm, p<0.01) and max-IMT (1.57 ± 0.41 vs. 0.82±0.66 mm, p<0.001). Homozygous carriers also showed lower, although not significant, FMD. As a group, FHBL2 showed significantly higher concentration of sE-selectin when compared to non-carriers. In addition, homozygous FHBL2 presented the highest concentration of sE-selectin and sVCAM, even though only the former reached the statistical significance; no difference were observed in sICAM-1 levels. Compared to controls, ApoB-depleted sera from FHBL2 individuals had a reduced capacity to promote cell cholesterol efflux (4.9±1.8% vs. 8.5±1.6%; p<0.01). This was evident with ABCA1-, SR-BI- and ABCG1-mediated pathways and was related to the number of mutated alleles
In summary, homozygous FHBL2 appear to have more advanced preclinical atherosclerosis and this might be related to their impaired HDL function.