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ABSTRACT

trigliceridi significativamente più bassi rispetto ai maschi. Analizzando i valori lipidici nei soggetti suddivisi per classi di età si nota che gli individui più giovani (36-69 aa) hanno livelli più elevati di colesterolo totale, LDL, trigliceridi e livelli più bassi di HDL rispetto a quelli in età più avanzata (70-100 aa). Considerando alterazioni lipidiche dei singoli parametri si evidenzia che LDL ≥160 mg/dl, trigliceridi ≥200 mg/dl e HDL≤35 mg/dl sono presenti rispettivamente nel 9%, nel 12% e nel 34% dei soggetti consider ati. HbA1C≥6.5% è stata ritrovata nel 15% dei soggetti considerati.
Conclusioni. I soggetti con IMA in età più giovanile (36-69 aa) presentano un assetto lipidico più sfavorevole rispetto ai soggetti in età più avanzata (70-100 aa). Bassi valori di HDL (≥35 mg/dl) rappresentano la dislipidemia singola più frequente (34%).
Secondo i criteri del Dutch Lipid Clinic Network, 20 soggetti (3,9%) possono essere considerati possibili/probabili ipercolesterolemici familiari (FH), con indicazione alla misurazione dei valori lipidici nelle famiglie.

EVALUATION OF HDL FUNCTIONALITY IN PEDIATRIC PATIENTS WITH CHOLESTERYL ESTER STORAGE (CESD) DISEASE

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The capacity HDL to act as cholesterol acceptor and to promote cholesterol efflux from cells is the fist step of the reverse cholesterol transport (RCT) process and represents an index of HDL functionality in humans. This process can occurs by multiple pathways, including aqueous diffusion (AD), scavenger receptor B-I (SR-BI) or ATP-binding transporters A1 (ABCA1) and G1 (ABCG1). Cholesteryl ester storage disease (CESD) is a disorder caused by mutations of LIPA gene encoding for lysosomial acid lipase (LAL). CESD subjects display accelerated and premature atherosclerosis associated with dyslipidemia (high total cholesterol [TC] and LDLc, high triglyceride [TG] and low HDLc). Since evidences from retrospective studies indicate that such lipoprotein derangement already occurs in pediatric age the objective of this work is to evaluate the efficiency of cholesterol efflux capacity (CEC) of HDL from serum of CESD subjects compared to control subjects in pediatric age. Methods: pediatric patients with CESD (n=2) and age-matched control subjects (n=5) were testes for their serum HDL capacity to promote efflux via the multiple pathways. HDL were isolated by (PEG) precipitation. Results: in CESD subjects AD-mediated CEC was lower compared to control subjects (5,82%±0,35 vs 5.15%±0.38; p=0.074), with a trend towards statistical significance; SR-BI- and ABCG1-mediated CEC were significantly reduced in CESD compared to control subjects (-60% and -40%, respectively; $p<0.05$); on the contrary, ABCA1-mediated CEC appeared to be significantly increased in CESD subjects (+28%; $p<0.05$). Conclusion: CESD pediatric patients displayed an impaired HDL serum CEC through SR-BI and ABCG1 pathways, that could explain the accelerated atherosclerosis in CESD; on the other hand, the ABCA1-mediated CEC resulted increased in such patients, presumably related to a formation of specific nascent HDL particles able to promote ABCA1-CEC. This can be seen as a sort of compensatory mechanism aimed to counteract foam cell formation and atherosclerosis in these patients.

PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9 DEFICIENT MICE ARE PROTECTED FROM NEOINTIMA FORMATION IN CAROTID ARTERY INJURY MODEL

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Proprotein convertase subtilisin kexin type 9 (PCSK9) is an important regulator of hepatic low-density lipoprotein (LDL)-cholesterol levels. We have previously shown that PCSK9 is expressed in cultured smooth muscle cells (SMCs) and it is detectable in human carotid atherosclerotic plaques. The aim of the present study was to compare the vascular changes induced by periadventitial placement of a non-occlusive constrictive silicone collar for 9 weeks around the common carotid artery of WT and PCSK9 deficient mice. As expected, the plasma cholesterol were mainly in the HDL particles and the PCSK0 KO mice had a significant lower total cholesterol levels (47.1±8.8 mg/dl vs 13.6±3.3 mg/dl *P=0.01). Collared carotids of the PCSK9-/- mice (n=6 per group) showed a less marked intimal thickening compared WT mice (19055±10158 um^2 vs. 34989±12823 um^2; *P=0.05), a decreased intimal media ratio (2.54±1.67 vs. 0.82±0.70 *P=0.05) and higher lumen area (11821±7980 um^2 vs. 18830±8816 um^2). Carotid lesions of WT mice had an elevated content of SMCs (21.0±7.56% vs. 10.7±1.97% P=0.05) and collagen (18.38±7.90% vs 10.45±9.11%; **P=0.01) and no difference in macrophage content was detected between the two groups. Cultured SMCs isolated from WT mice showed lower levels of the contractile markers smooth muscle α-actin (-94±6%; ***P=0.001) and calponin (-74±18%; ***P=0.001), and increased Col1a1 mRNA levels (2.30±0.3 fold ***P=0.001) after stimulation with PDGF-BB. Finally, the proliferation rate of PCSK9-/- SMCs was significantly lower compared to PCSK9-/- SMCs reconstituted with PCSK9 encoding plasmid (doubling time 41.2±1.9 h vs 32.2±3.1 h; ***P=0.01). Taken together, the present results suggest a favorable action of PCSK9 on neointima formation in response to perivascular carotid, probably facilitating the phenotypic switch of medial SMCs and their proliferation. However, the influence of the different plasma cholesterol profile cannot be excluded. Thus, the direct role of PCSK9 on neointima formation will be investigated, in the future, by generating SMC specific PCSK9 KO mice.
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SREBF-1C POLYMORPHISM AFFECTS POSTPRANDIAL LIPID METABOLISM IN NAFLD SUBJECTS

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Background. The prospective data on factors predisposing to NAFLD and associated cardio-metabolic disorders link metabolic syndrome, insulin resistance/hyperinsulinemia and weight gain

to NAFLD; however, not every insulin resistant or obese subject develops NAFLD and NASH, suggesting additional genetic or environmental factors promote liver disease in insulin resistant subjects. A genetic predisposition to NAFLD/NASH is indisputably present. The transcription factor sterol regulatory element-binding protein modulates lipogenesis and insulin sensitivity and has been experimentally connected to NAFLD.
Objective. In population-based studies, SNPs in SREBF-1 gene have been connected to obesity, insulin resistance and T2DM. We aimed at assessing the impact of a common SREBF-1c polymorphism on postprandial lipoprotein metabolism.
Methods. We followed-up 212 nonobese nondiabetic, insulin sensitive participants without NAFLD or metabolic syndrome at baseline, characterized for the common SREBF-1c gene rs11868035 A/G polymorphism, dietary habits, physical activity, adipokine profile, C-reactive protein (CRP), and circulating markers of endothelial dysfunction. A comparable cohort of NAFLD patients underwent liver biopsy, and an oral fat tolerance test with measurement of plasma lipoproteins, adipokines, cytokeratin-18 fragments.
Results. NAFLD patients had a higher postprandial lipemia as compared with healthy controls. In both NAFLD and controls, SREBF-1c GA/AA carriers showed higher IAUC Tg and FFA than GG genotype. SREBF-1c independently predicted postprandial IAUCs of Tg and intestinal and hepatic VLDL1. SREBF-1c GA/AA carriers displayed also a significant increase in IAUC oxLDL and a fall in HDL-C and apoA1 levels.
Conclusions. SREBF1c predisposes to NASH and cardio-metabolic disorders by affecting dietary fat tolerance. SFEBF-1c may promote hepatic synthesis of lipotoxic FFA, which may directly promote hepatocyte apoptosis and necroinflammation. In the absence of detectable differences in nutrient intake and physical activity, we may speculate that in at-risk genotypes SREBP-1c-mediated de novo lipogenesis interacts with age-related decline in basal metabolic rate to promote adipose tissue expansion and weight gain.

MONOCYTE INTERACTION WITH THE ENDOTHELIUM: EFFECTS OF CIGARETTE SMOKE

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Circulating monocytes participate in the atherogenic process by adhering to the endothelium and migrating into the intima where they differentiate to macrophages and contribute to plaque growth. Cigarette smoke is a risk factor for atherosclerosis, but it is not clear how it affects monocyte behavior in atherogenesis. We studied the effects of cigarette smoke condensate (CSC) on human monocytes (HM) chemotaxis and transmigration through an endothelial cell (EC) monolayer. Experiments conducted with the Boyden chamber showed that pre-treatment with CSC (7,5-30 µg/ml) for 24 h caused a concentration dependent decrease in HM chemotaxis and transmigration (-55% and -18% vs Control, p 0.05, respectively), paralleled by a reduced expression of the small signaling G proteins Rac 1 GTPase. On the contrary, direct exposure of both HM and EC to CSC increased (+23% vs control, p 0.05) the transmigration of HM, paralleled by a strong stimulation of VCAM1 and ICAM1 expression on ECs, and by a slight increase in monocyte integrin expression. An even more evident enhancement of monocyte transmigration was obtained after the exposure of both HM and EC to medium conditioned by HM previously incubated with CSC (+265% vs control, p 0.001). Interestingly, incubation with neutralizing antibodies against both MCP1 or IL8 completely abolished the CSC-conditioned medium induced HM transmigration. Finally, treatment with CSC increased the expression of IL8, IL1β, MCP1 and TNFα by HM, and was ablated by pretreatment with PDTC, a well-known NFkB inhibitor. These results indicate that CSC induces HM to release chemotactic factor(s), which may amplify the recruitment and transmigration of inflammatory cells through an EC monolayer; in addition, long-term exposure to CSC reduces HM migratory capacity. Therefore, exposure to CSC affects monocyte behavior and interaction with the endothelium, thus potentially facilitating and/or further aggravating the atherogenic process.
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INFLAMMATION IMPAIRS ENDOTHELIAL NITRIC OXIDE SYNTHASE ACTIVATION BY HDL IN PATIENTS WITH ACUTE CORONARY SYNDROME

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Aims. The aim of the present study was to evaluate the high-density lipoprotein (HDL) structure and endothelial NO synthase (eNOS) activation capacity in ST-elevation myocardial infarction (STEMI) patients with different acute-phase inflammatory response (APR).
Methods and Results. Forty-five STEMI patients were stratified in quartiles according to the delta CRP level, calculated by subtracting the CRP value at admission from the CRP peak value (APR peak). The HDL structure and HDL capacity to stimulate NO production were evaluated at admission and at APRpeak. STEMI patients with a low APR had a completely preserved HDL structure and HDL ability to activate eNOS and promote NO production, which did not change during STEMI. On the contrary, HDL from STEMI patients developing a significant APR had compromised ability to stimulate eNOS and promote NO production, and underwent a significant particle remodelling during STEMI. The defective capacity to stimulate NO production of HDL isolated from STEMI patients with high APR was explained, at least in part, by the reduced PON-1 and S1P content. The HDL ability to promote cell cholesterol efflux through different pathways was preserved in ACS patients independently of the inflammatory response.
Conclusions. The present results extend previous studies reporting an impaired eNOS-activating capacity of HDL from ACS patients, showing that only a subset of patients undergoing STEMI, and in particular those developing an important inflammatory response, have circulating HDL defective in stimulating endothelial eNOS and NO production.