

mente verificata in studi longitudinali. Abbiamo, pertanto, valutato se esiste una relazione tra la NAFLD e l'incidenza di CVD nei pazienti con T1DM.

**Metodi.** Sono stati studiati 286 pazienti con T1DM (età media  $43 \pm 14$  anni; maschi 42.3%) esenti da epatopatia cronica da causa nota e seguiti per un periodo medio di  $5.3 \pm 2.1$  anni per lo sviluppo di CVD (definita come riscontro di cardiopatia ischemica non fatale, ictus ischemico non fatale o rivascolarizzazione coronarica/periferica). La diagnosi di NAFLD è stata formulata mediante ecografia epatica.

**Risultati.** Complessivamente, al baseline, 150 (52.4%) pazienti avevano la NAFLD. Durante il follow-up sono stati osservati 28 casi di CVD. L'incidenza cumulativa di CVD era maggiore nei pazienti con NAFLD rispetto a quelli senza (17.3% vs. 1.5%,  $P < 0.001$ , rispettivamente). Nella regressione di Cox la NAFLD si associava ad un aumentato rischio di incidenza di CVD (Hazard Ratio [HR] 8.16, 95% CI 1.9-35.1,  $P = 0.005$ ). Dopo aggiustamento per età, sesso, BMI, fumo, durata di diabete, HbA1c, ipertensione, dislipidemia, nefropatia, storia di cardiopatia ischemica e valori di GGT, l'associazione rimaneva significativa e non si attenuava (adjusted-HR 6.73, 95% CI 1.2-38.1,  $P = 0.031$ ).

**Conclusioni.** Questo è il primo studio longitudinale che dimostra l'esistenza di un'associazione significativa tra la NAFLD e l'incidenza di CVD nei pazienti con T1DM, indipendentemente dalla coesistenza di molteplici fattori di rischio.

## SYMPATHETIC NEUROTRANSMISSION DURING ATHEROSCLEROSIS DEVELOPMENT: AN UNRECOGNIZED TARGET OF DYSLIPIDEMIA?

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**Aim.** With the aim of discovering new genes/pathways involved in dyslipidemia-driven atherosclerosis, transcriptomic analysis was performed on aortas of several transgenic mouse lines, with different lipid/lipoprotein profiles and different susceptibility to atherosclerosis.

**Methods.** C57Bl/6, apoE-deficient (EKO), apoE/apoA-I-deficient (EKO/A-IKO) and apoE/apoA-I-deficient mice overexpressing human apoA-I (EKO/A-IKO/hA-I) were studied. Mice were fed chow or Western diet, starting from 8 weeks of age. After 22 weeks of diet, plasma lipoprotein distribution was profiled by FPLC and aortic atherosclerosis evaluated by en-face analysis. The entire gene expression profile of murine aortas was investigated by a high-throughput sequencing approach (Illumina).

**Results.** On chow diet, plaques could only be detected in the aortic arch of EKO (high VLDL-LDL, low HDL) and EKO/A-IKO mice (high VLDL-LDL, absent HDL). Western diet worsened hyperlipidemia and plaque formation in the aortic arch of EKO and EKO/A-IKO mice, but only led to modest atherosclerosis development in EKO/A-IKO/hA-I mice, characterized by elevated VLDL-LDL cholesterol levels and displaying a large HDL cholesterol peak.

Out of a total of 23,000 genes, about 2,300 genes were identified as differentially expressed in at least one condition (dietary or genetically determined). In the athero-prone genotypes, Western diet, with respect to chow diet, dramatically lowered the expression of genes coding for key enzymes of catecholamine synthesis and synaptic

vesicular structure. Interestingly, a similar down-regulation was found in EKO/A-IKO mice (low HDL) compared to EKO/A-IKO/hA-I mice (high HDL), when fed the same diet (chow or Western).

**Conclusions.** Our data suggest that dyslipidemic conditions, predisposing to atherosclerosis development (i.e. hyperlipidemia; low HDL levels), may interfere with the arterial sympathetic innervation by down-regulating the expression of genes involved in catecholamine biosynthesis, as well as in synaptic plasticity and transmission.

## VITAMIN D STATUS AND HDL FUNCTIONALITY IN HEALTHY PRE-MENOPAUSAL WOMEN

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**Background.** Low vitamin D (vitD) status has been linked to increased cardiovascular (CV) risk. Serum HDL cholesterol efflux capacity (CEC) is a metric of HDL functionality that is inversely correlated to CV risk, independently of HDL-cholesterol (HDL-C) plasma levels. At present, there is no data on the possible correlation between HDL CEC and vitD levels. We evaluated whether impaired HDL functionality occurs in otherwise healthy vitD deficient pre-menopausal women. In addition, we evaluated in macrophages the serum capacity to promote cholesterol loading (serum cholesterol loading capacity, CLC), index of its pro-atherogenic potential. We finally evaluated the effect of a vitD integration.

**Material and Methods.** Flow-mediated dilatation (FMD) and pulse wave velocity (PWV) were measured by standard techniques as markers of subclinical atherosclerosis. HDL CEC was assessed by radioisotopic technique while serum CLC was measured by a fluorimetric assay.

**Results.** Healthy pre-menopausal women (n=43) were stratified in two groups according to their vitD levels:  $\leq 10$  ng/mL (very low group, VL), status defined as severe hypovitaminosis and over 10 ng/mL (low/normal group, LN). No differences were found between the two groups in total cholesterol, HDL cholesterol, LDL cholesterol and triglyceride levels. FMD was significantly lower in VL group in comparison with LN group ( $9.90\% \pm 0.26$  compared to  $10.81 \pm 0.31$ ;  $p = 0.03$ ); PWV was higher in VL vitD group ( $6.094$  m/s  $\pm 0.26$  compared to  $5.25$  m/s  $\pm 0.09$ ;  $p = 0.01$ ). HDL CEC through aqueous diffusion and SR-BI was similar between groups. ABCA1-mediated CEC was increased in VL group compared to LN group ( $3.079\% \pm 0.31$  compared to  $2.042\% \pm 0.19$ ;  $p = 0.005$ ). ABCG1-mediated CEC was lower in the VL group compared to LN group ( $2.48\% \pm 0.18$  compared to  $3.30\% \pm 0.22$ ;  $p = 0.01$ ). Finally, VL group serum CLC was significantly increased ( $+1.21$  fold  $p = 0.049$ ). After integration ABCG1-mediated CEC in the VL increased reaching the values of control group at baseline ( $4.09\% \pm 0.12$  compared to  $4.08\% \pm 0.25$ ;  $p = 0.97$ ), while the LN group after supplementation did not improve compared to baseline.

**Conclusions.** VitD status influences circulating lipoprotein functions relevant for atherosclerosis in healthy pre-menopausal women which may be, involved in the association between severe vitD deficiency and increased cardiovascular risk.