AORTIC TRANSCRIPTOME ANALYSIS REVEALS THE ASSOCIATION BETWEEN ATHEROSCLEROTIC LESIONS AND ALTERED SYMPATHETIC INNERVATION IN GENETICALLY MODIFIED MICE

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Aim. Previous reports have suggested an association between the development of atherosclerosis and alterations in the aortic sympathetic nervous system, located in the adventitial layer. In a recent study, an increased adventitial axon density in proximity to advanced atherosclerotic plaques of Apoe-deficient mice was observed.
Methods. Eight-week-old C57Bl/6J control mice (Bl/6), ApoE knockout mice (EKO), EKO mice overexpressing human apoA-I (EKO/hA-I) and double ApoE/ApoA1 knockout mice (DKO) mice were fed a standard rodent diet or a Western-type diet for 22 weeks. At the end of the dietary treatment the aortic atherosclerosis was quantified, and a high-throughput sequencing approach was used to analyze the aortic transcriptome.
Results. On standard rodent diet no atherosclerosis was detectable in EKO/hA-I aortas and a moderate plaque development was observed in EKO and DKO, whereas Western-type diet increased plasma cholesterol levels, led to atherosclerosis development in EKO/hA-I and worsened that in EKO and DKO. The administration of Western-type diet deeply modified the aortic transcriptome. In the three genetically modified mouse lines, an upregulated expression of genes associated with the immunomodulatory response was observed. This was paralleled by a downregulated expression of genes involved in the activity of the aortic sympathetic nervous system. Functional enrichment analysis indicated that the presence of advanced atherosclerosis was accompanied by reduced neuronal generation, modulation of synapse chemical transmission, and catecholamine biosynthesis.
Conclusions. A relationship exists between atherosclerosis, dyslipidemia, and sympathetic neurotransmission. Advanced lesions are associated with reduced transcriptional activity related to sympathetic innervation of the aorta.

THE SEQUENTIAL USE OF LS MEASUREMENT AND DIRECT BIOMARKERS OF FIBROSIS IS ABLE TO IDENTIFY PATIENTS WITH SEVERE NASH

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Background and Aims. The identification of patients with severe non-alcoholic steatohepatitis (NASH), who are at greater risk of progression to cirrhosis, and who most deserve targeted interventions and recruitment in clinical trials, is a major priority. Several non-invasive tests (NITs) have been developed to detect patients at risk of severe NASH and to reduce the use of liver biopsy. We conducted a prospective single-centre study aimed at evaluating the diagnostic performance of different NITs in the identification of biopsy- confirmed severe NASH. Moreover, we explored if the sequential use of NITs was able to improve their diagnostic accuracy.
Method. 56 consecutive patients (73.2% men; age 52 [22-69] years) performed liver biopsy for the suspicionof severe NASH, defined as the presence of NASH, NAFLD activity score ≥4 and fibrosis stage ≥F3. Simplewet NITs [aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, platelet count, AST/ALT ratio (AAR) and AST to platelet ratio index (APRI)], complex wet NITs, [BARD score, Fibrosis-4 index (FIB-4), NAFLD fibrosis score (NFS), Forns Index and Hepamet fibrosis score (HFS)], direct biomarkers of fibrosis [collagen IV (CIV), laminin (LM), cholylglycine (CG), hyaluronic acid (HA) and procollagen type III amino-terminal peptide (PIIIP)], measurement of liver stiffness (LS) with Fibroscan® , and AGILE 3+ and AGILE 4 scores, were all evaluated at the time of liver biopsy. The area under the receiver operating characteristic curve (AUROC) for the identification of severe NASH of each single NIT was calculated. Finally, we evaluated the diagnostic accuracy of the sequential use of the NITs yielding the best diagnostic performance at AUROC analysis.
Results. Severe NASH was present in 12 (21.4%) patients. Simple wet NITs were not able to significantly detect severe NASH (AUROCs ranging from 0.46, p=0.68 for albumin to 0.67, p=0.08 for GOT, platelet and AAR). Among complex wet NITs, only BARD was able to significantly detect severe NASH (AUROC 0.77, p=0.004), while FIB-4, NFS, Forns Index and HFS were not (AUROCs ranging from 0.45, p=0.71 for Forns Index to 0.65, p=0.12 for NFS). All direct biomarkers of fibrosis significantly detected severe NASH, with PIIIP (AUROC 0.81, p=0.001) and CIV (AUROC 0.80, p=0.002) showing the best diagnostic performance. NITs based on LS with Fibroscan® also significantly detected severe NASH, however AGILE 3+ (AUROC 0.71, p=0.03) and AGILE 4 (AUROC 0.70, p=0.04) scores did not improve the diagnostic performance of LS alone (AUROC 0.76, p=0.007). The sequential use of LS (cut-off 8.5 kPa) and PIIIP (cut- off 22 ng/ml) or CIV (cut-off 16.5 ng/ml) had a diagnostic accuracy of 85.7% and 91.1%, respectively.
Conclusion. The use of FIB 4 and NFS in high risk populations for severe NASH has a diagnostic accuracy lower than the sequential use of LS in association with direct fibrosis The sequential use of LS and direct biomarkers of fibrosis, such as PIIIP and CIV, may be a promising approach to non-invasively identify patients with severe NASH.