P474 / #707, Poster Topic: *AS04 CLINICAL VASCULAR DISEASE / AS04.03 MAFLD, NASH and other ectopic lipid diseases*

MODULATION OF ENDOGLIN AND SOLUBLE ENDOGLIN IN NASH: COMPUTATIONAL MODELING AND MONOCLONAL ANTIBODY THERAPEUTIC BENEFITS

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Background and Aims: NASH,a growing liver disease worldwide,requires an understanding of its molecular progression for effective treatment.Endoglin,a TGFβ-superfamily coreceptor,has two forms:membrane endoglin (ENG)and soluble endoglin (sENG).While ENG is associated with liver sinusoidal endothelial dysfunction (LSED)and liver fibrosis, its direct involvement in the progression of NASH remains unclear.Our aim was to investigate the relationship between NASH-progression,ENG expression,and LSED development.We hypothesized that the anti-endoglin monoclonal antibody M1043 would affect LSED development by directly affecting ENG expression and signaling with respect to NASH development.
Methods: NASH was induced in two separated groups of male C57BL/6 mice using the CDAA-HFD diet(n=7),while two control groups(n=7)were fed a standard diet.Mice were sacrificed after four and eight weeks to evaluate ENG protein changes during NASH. Then,24 mice were grouped into the control group(-n=8),CDAA + rat IgG(n=8),and CDAA + M1043 group (n=8).After four weeks,CDAA + IgG and CDAA + M1043 groups received intraperitoneal injections of rat IgG (10 mg/kg)and M1043(10 mg/kg) twice a week.The experiment lasted eight weeks,with blood and liver samples collected for analysis.To better understand the role of ENG antibody and its cleavage,a computational model of ENG modulation of TGFβ signaling was developed.
Results: Liver injury was confirmed by elevated liver enzymes,increased fibrosis,and inflammatory biomarkers in both CDAA-HFD groups.LSEC development was confirmed by increased ENG,VCAM-1,and ICAM-1 expression in endothelial cells.We showed increased expression of MMP-14 and higher levels of sENG levels in 8 weeks fed mice.M1043 treatment significantly prevented the increase in ENG,VCAM-1,and ICAM-1 protein expression in liver sinusoidal endothelial cells when compared to non-treated mice.Computational modeling simulations showed the ENG-dependent switch between Smad2/3 and Smad1/5/8 signaling,along with changes in sENG levels,which was reversed by ENG antibodies.
Conclusions: Our findings indicate that NASH development is associated with LSED development,increased ENG and MMP-14 expression,and elevated sENG levels,suggesting ENG role in LSED progression.Blocking of ENG expression and signaling might be a potential target to affect LSED development and possibly prevent NASH aggravation.

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THE ROLE OF ATHEROGENIC DYSLIPIDEMIA AND DISORDERS OF THYROID GLAND FUNCTION IN THE DEVELOPMENT OF VASCULAR COMPLICATIONS IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

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Background and Aims: MASLD is closely related to obesity, insulin resistance, and cardiovascular disease. To date, it is relevant to find out the pathogenetic chains of the formation of MASLD. Many studies in recent years consider hypothyroidism as a condition specifically associated with MASLD. The purpose of the study was to evaluate the relationship between atherogenic dyslipidemia, thyroid gland function and the level of adipokines, the degree of obesity and insulin resistance in patients with MASLD.
Methods: 178 MASLD patients and 32 healthy persons were examined. The age of the examinees ranged from 28 to 67 years, with a median of 55 years (interquartile range Q1-Q3 40 to 61 years). We determined the level of inflammatory mediators (TNF-α, IL-1, IL-6), markers (high-sensitivity C-reactive protein, fibrinogen), and index HOMA-IR. An anthropometric examination was carried out, the levels of AST, ALT, GGT, and the degree of liver fibrosis using elastography (FibroScan), ECG and echocardiography were determined.
Results: Correlation analysis revealed a direct correlation between HOMA-IR and leptin concentration (r=0.8,p=0.0017) and an inverse correlation between HOMA-IR and adiponectin concentration (r=-0.66, p=0.0033) and logarithmic index A/L (r=-0.71, p<0.0001). The decrease in adiponectin concentration with a parallel increase in leptin content increased IR. A comparative analysis of the level of the inflammatory marker hs[1]CRP in obese patients showed a direct relationship with HOMA-IR (r=0.58, p=0.05), glucose (r=0.44,p=0.0045) and insulin (r=0.66, p=0.0001) in the blood. Positive correlations were found between alanine aminotransferase (ALT) and FT3 (r=0.333, p=0.008), and negative correlations were noted between TSH and BMR (r=-0.731, p<0.010). After adjusting for all factors, insulin, FT4, and TSH were identified as significant independent risk factors for MASLD in univariate analysis.
Conclusions: Presence of atherogenic dyslipidemia, hypothyroidism, and hyperinsulinemia were associated with increased body mass index, insulin resistance, elevated hs-CRP, and increased cardiovascular disease in MASLD patients.

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ASSOCIATION OF TRIGLYCERIDES-GLUCOSE (TYG) INDEX WITH MECHANICAL VASCULAR IMPAIRMENT IN SUBJECTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE

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Background and Aims: Non-Alcoholic Fatty Liver Disease (NAFLD) is the most common cause of chronic liver disease. Increasing evidences showed that NAFLD is a multisystem disease associated with insulin resistance, type II diabetes mellitus, dyslipidemia and cardiovascular diseases (CVDs). Recent studies showed that the Triglyceride and Glucose index (TyG) - a marker of insulin resistance – was associated with CVDs risk. In this study we aimed to investigate the potential role of TyG on mechanical vascular impairment, evaluated by pulse wave velocity (PWV) in patients with NAFLD.
Methods: In this observational study we evaluated 80 middle-aged (40–70 years) NAFLD subjects without secondary causes of fatty liver or history of major adverse cardiovascular events (MACE). Fatty liver was diagnosed by ultrasonography. PWV was measured by SphygmoCor CvMS (AtCor Medical, Sydney, Australia). The study population was divided into two groups according to the median value of TyG (high TyG group, TyG $\geq$ 8.58, n=40; low TyG group, TyG < 8.58, n=40). To test differences of clinical and biochemical characteristics between the two groups, we used Student's t test. Simple linear regression analysis was performed to assess the relationship between TyG and PWV.
Results: High TyG group exhibited a significant higher PWV compared to the low TyG group (10.11 $\pm$ 3.28 vs 8.58 $\pm$ 2.22 cm/s, $p < 0.05$) (Figure 1). A simple linear regression analysis showed that PWV was significantly associated to TyG (β=0.324, $p < 0.01$), indicating that higher TyG values were associated with increased arterial stiffness (Figure 2).