Abstract Volume

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ABSTRACTS

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Disclosure: **S.K. Hecquet:** None.

SO 088 Fatty liver in diabetes: pathways and relationships

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Vitamin D_3 in the regulation of autophagy and mitochondrial dynamics in non-alcoholic fatty liver disease induced by type 2 diabetes

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Background and aims: Autophagy disorder, characterized by impaired intracellular self-degradation, has been reportedly implicated in various pathologies, including non-alcoholic fatty liver disease (NAFLD) associated with type 2 diabetes mellitus (T2DM). Vitamin D_3 (D_3) and D_3 receptor (VDR) may play a hepatoprotective role by inhibiting oxidative stress, inflammation and fibrosis. However, whether D_3-VDR pathway regulates abnormal autophagy in NAFLD remains unclear. Herein, our goal was to elucidate the relationship between autophagy disorder and D_3 status, hepatic expression of VDR and D_3-metabolizing enzymes, as well as oxidative stress in T2DM-induced NAFLD.
Materials and methods: We induced T2DM in male Wistar rats using a high-fat diet (3 months) and a low dose of streptozotocin (25 mg/kg of body weight). Diabetic rats were treated with or without D_3 (1000 IU/kg b.w., 30 days). Hepatosteatosis was assayed by staining with Sudan III&Gill's Hematoxylin II and AFOG. ELISA was used to measure 25-hydroxyvitamin D_3 ($25D_3$). Target proteins were determined in liver tissue by Western blotting. Data were analyzed by one-way ANOVA followed by *Tukey's* test and $p<0.05$ was considered to be statistically significant.
Results: Liver examination revealed steatosis without signs of inflammatory tissue destruction and fibrosis in T2DM. Diabetes lowered circulating $25D_3$ (2.8-fold) and downregulated hepatocellular protein levels of vitamin D_3-25-hydroxylase (CYP27A1, CYP2R1), $25OHD_3$-1α-hydroxylase (CYP27B1), and VDR in diabetic vs. control rats. A 2.9- and 1.7-fold elevation of carbonylated and nitrated (3-nitrotyrosin) proteins was shown in diabetic liver vs. control ($p<0.05$). Hepatic levels of ATG7 and the molecular chaperone Hsp70 increased by 1.4 and 4.2 times, respectively, with the simultaneous 3.1-fold decrease in cathepsin B and unchanged levels of cathepsin L and calpain-2 in T2DM vs. control ($p<0.05$), indicative of T2DM-related activation of autophagy. In addition, we detected an increase in molecular markers of both mitochondrial fusion (mitofusins 1 and 2 - by 1.7- and 4.2-fold, respectively) and mitochondrial fission (Fis1 - by 5.0-fold) vs. control ($p<0.05$), suggesting a significant enhancement of mitochondrial dynamics in T2DM. Repletion of $25D_3$ following vitamin D_3 treatment upregulated the expression of VDR and D_3-metabolizing enzymes and diminished the content of carbonylated and nitrated proteins in the liver. D_3 contributed to partial or complete normalization of the content of autophagy proteins except for calpain-2. Notably, D_3 shifted the balance between mitochondrial fission/fusion towards fission, as it inhibited the expression of mitofusins 1 and 2 and significantly stimulated Fis1 synthesis.
Conclusion: We identified an association between T2DM-induced D_3 deficiency, increased oxidative-nitrosative stress, and autophagy in liver tissue that correlated with enhanced mitochondrial dynamics as a possible mechanism of bioenergetic adaptation to the metabolic demands of cells. The therapeutic efficacy of vitamin D_3 in alleviating diabetic NAFLD was demonstrated.

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One-hour plasma glucose concentration during the OGTT is a strong predictor of hepatic steatosis in nondiabetic individuals

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Background and aims: Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD) is intricately linked with Type 2 Diabetes Mellitus (T2DM), transitioning to more severe conditions in a subset of patients. Despite its relatively benign nature, MAFLD can progress to Metabolic Associated Steatohepatitis (MASH) and chronic liver disease. With a notable prevalence among T2DM and prediabetes patients, the predictive capability of 1-hour plasma glucose (1-h PG) levels during an Oral Glucose Tolerance Test (OGTT) for MAFLD risk in nondiabetic individuals is of significant interest. This study aims to investigate the predictive value of 1-h PG for MAFLD amongst individuals without diabetes.
Materials and methods: We conducted a study involving 300 nondiabetic participants who underwent a 75-gram OGTT and liver fat assessment through elastography. Participants were categorized into normal glucose tolerance (NGT), impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and undiagnosed diabetes based on the American Diabetes Association criteria.
Results: The study cohort comprised 148 NGT, 43 IFG, 74 IGT, and 35 undiagnosed diabetes participants. Liver fat, as measured by Controlled Attenuation Parameter (CAP) score, showed a significant increase across the spectrum from NGT (232±4), IFG (253±7), IGT (266±6), to undiagnosed diabetes (292±9; $p<0.0001$). The 1-h PG level was significantly correlated with the CAP score ($r=0.41$, $p<0.01$), demonstrating superior predictive power over traditional indices of hepatic steatosis. A 1-h PG > 155 mg/dl identified NGT and IFG subjects with a high risk of elevated CAP scores, indicative of significant liver fat accumulation comparable to IGT subjects. The proportion of NGT and IFG subjects with advanced steatosis (Stage S3/4) was notably higher in those with 1-h PG > 155 mg/dl compared to their counterparts with lower 1-h PG levels.
Conclusion: The 1-hour plasma glucose level during an OGTT is a significant indicator of liver fat content in nondiabetic individuals, revealing an elevated risk for future T2DM and MAFLD in subjects with 1-h PG > 155 mg/dl. These findings highlight the potential of 1-h PG as an early predictive marker for MAFLD, advocating for its consideration in preventive strategies against the progression of MAFLD and its associated complications.
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Machine learning approach reveals proteome and lipidome profile in patients with metabolic associated fatty liver disease complicated with poly-vascular plaques

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