Cardiovascular Endocrinology

CARDIOVASCULAR ENDOCRINOLOGY AND LIPIDS DISORDERS CASE REPORT

Two Cases of Statin Induced Necrotizing Autoimmune Myopathy

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Case 1: Six months ago, patient 1 presented with rhabdomyolysis with a CK of 17,622 Units/L. The statin was discontinued at that time, after which the patient noted substantial improvement in muscle symptoms. Two months later the patient was readmitted for complaints related to continued rhabdomyolysis. CK was elevated at 9800 Units/L, raising suspicion for SINAM. Physical exam findings on readmission were pertinent for 4/5 strength in proximal flexion and extension of the upper extremities bilaterally and 4/5 strength in hip flexion. Pertinent lab values on readmission include increased ALT of 122 Units/L, AST of 103 Units/L, TSH of 7.4 mIU/L, HbA1c of 6.6%, and BUN of 14.5 mg/dL. Urinalysis is positive 3+ for glucose, 1+ for ketones, and 2+ for blood. Brain MRI without contrast negative for any brain malignancies or abnormalities. **Case 2:** Patient 2 presented with gradual proximal muscle weakness while taking a statin for the past six months. Physical exam was notable for 4/5 strength in the biceps and triceps and 3/5 deltoid strength bilaterally. There was 4/5 strength in the knee flexors and extensors with 3/5 strength in the hip flexors bilaterally. Notable lab values include CK of 10,449 Units/L, CK-MB of 492ng/mL, fasting glucose of 160 mg/dL, ALT of 229 Units/L, and HgbA1C of 7.3%. Urinalysis was positive 3+ for glucose, 1+ for ketones, and 2+ for blood. **Discussion:** Statin induced necrotizing autoimmune myopathy (SINAM) is a rare complication of statin therapy in which subjects develop an immune response to 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR). SINAM's pathophysiology remains poorly understood. Studies have shown that statins upregulate expression of HMGCR which serve as antibody targets in SINAM (Mohassel & Mammen, 2013). The HMGCR protein is upregulated in regenerating muscle fibers thus preferentially allowing autoantibodies to bind (Mammen et al, 2011). Additionally, complement is implicated in pathogenicity of SINAM with a study showing that C3 deficient mice had less pronounced deficiency in muscle strength (Bergua et al, 2019). This is further reinforced with a muscle biopsy in another SINAM confirmed patient showed C5b-9 sarcolemmal deposits (Sharma et al, 2019). This implicates the formation of antigen-antibody-complement complexes typical of a type III hypersensitivity reaction. Additionally, genetic risk factors for autoimmunity are important to consider. There is an association of SINAM occurrence in individuals with single nucleotide polymorphism in the SLCO1B1 that regulates hepatic uptake of drugs such as statins (SEARCH, 2008). HLA- DRB1*11:01 is associated with the formation of autoantibodies in SINAM (Mammen, 2016). Recent studies show the triple induction therapy of steroids, IVIG, and a steroid sparing immunosuppressant has been very effective (Meyer et al, 2020).

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Tyhroid Storm-Induced Worsening Acute Myocardial Infarction: A Case Report

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Background: As a true endocrine emergency, thyroid storm is rarely associated with acute myocardial infarction. However Graves' disease is the most common underlying cause of thyroid storm. **Clinical Case:** A 47-year women experienced typical chest pain since 30 minutes before visited emergency room. The patient had type two diabetes as a cardiovascular risk factor and regularly took metformin thrice daily. The electrocardiogram showed non-ST segment elevation in leads I, V4-V6. Coronary arteriography showed stenosis in the three and left main vessels (70% stenosis of right coronary, 80% stenosis of left circumflex, 90% stenosis of left anterior descendent, and 90% stenosis of mid distal, in left main stem) then the patient was planned to do bypass surgery. At day 6 of hospitalization, the typical chest pain was worsening, epigastric pain became more painful, had 5 times diarrhea per day, high grade fever (>38.5°C), severe nausea and vomiting, then generalized tonic clonic seizure and respiratory failure was occurred. The patient was intubated in intensive care unit. Through a detail physical examination, a diffuse palpable thyroid enlargement and class I ophthalmopathy were found. Laboratory findings of free T4 was 2.23 ng/dL and Thyroid Stimulating Hormone (TSH) was 0.003 μIU/mL. The patient was assessed as thyroid storm then immediately, treated with three times of 100 mg hydrocortisone, two times of 20 mg of propranolol, and three times of 400 mg propylthiourasil. The patient's clinical appearance was gradually recovered. After 3 days of treatment, she was extubated from ventilator. Two weeks later, no complaint of chest pain or epigastric pain in observation. **Conclusion:** Our case highlight the possibility that hyperthyroidism may be involved in the development of acute myocardial infarction.

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Both Elafibranor and Liraglutide Improve NAFLD / NASH but Affect Differentially the Hepatic Lipidome and Metabolome in a Diet-Induced Obese and Biopsy-Confirmed Mouse Model of NASH

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Treatment of Nonalcoholic fatty liver disease (NAFLD) constitutes an unmet clinical need owing to the relatively limited efficacy of both novel and readily available metabolic medications, thus warranting pathobiological investigations on the mechanisms of single or combination regimens. In this context, our study aimed to assess and compare whether and how liraglutide, a glucagon-like peptide-1 receptor agonist, and elafibranor, a dual peroxisome proliferator-activated receptor alpha-delta agonist, may affect hepatic histology and metabolipidomic fingerprints in a model of advanced NAFLD. Male C57BL/6JRj mice with biopsy-confirmed hepatosteatosis and fibrosis induced by AMLN diet (40% fat with 20% trans-fat, 2% cholesterol and 22% fructose) were randomized to receive for 12 weeks: a) Liraglutide (0.4 mg/kg/d s.c.), b) Elafibranor (30 mg/kg/d p.o.), c) vehicle. Metabolic indices, liver function markers, liver pathology, and metabolomics/lipidomics were assessed at study completion. Both drugs markedly reduced body weight and fat percentage (p-value <0.001), and improved glucose tolerance and insulin sensitivity, as indicated by oral glucose and intraperitoneal insulin tolerance tests. Hepatic lipid content was downregulated under both treatments (p-value <0.001), especially under elafibranor, which also elevated liver weight in contrast with liraglutide (p-value vs liraglutide <0.001). NAFLD activity score (pre-to-post) and its histological components were substantially improved (mean difference ± standard error of mean: -1.4 ± 0.3 for liraglutide; -2.0 ± 0.2 for elafibranor), with elafibranor demonstrating a more robust anti-steatotic effect vs liralgutide (p-value <0.01) as well as anti-fibrotic effects (-0.5 ± 0.1). Liraglutide also limited the immunohistochemical expression of pro-inflammatory markers of Kupffer and hepatic stellate cell function (Galectin-3, Collagen type I alpha 1, and alpha-smooth muscle actin). In the omics analysis, elafibranor profoundly ameliorated the hepatic lipidome by diminishing the concentrations of glyceride species, increasing phospholipids and carnitine metabolites, and modifying key regulators of fatty acid oxidation, inflammation, and oxidative stress, including metabolites of methionine, glutathione, and pantothenate. Liraglutide significantly affected bile acid and carbohydrate metabolism by restoring the concentrations of metabolically beneficial primary and secondary bile acids, glycogen metabolism by-products, and pentoses, thus probably driving glycogen utilization-turnover and nucleic acid synthesis. Thus, liraglutide and elafibranor diverge in their mechanistic treatment of advanced NAFLD pathology, indicated by their robust but differential regulation of the hepatic metabolipidome. These findings support their combinatory therapeutic evaluation in future studies.

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Genome-Wide Meta-Analysis and Mendelian Randomization Identify Early Biomarkers of Non-Alcoholic Fatty Liver Disease

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Background: The diagnosis of non-alcoholic fatty liver disease (NAFLD) is often challenging. Blood-based biomarkers which are causally influenced by NAFLD and that are not modulated by secondary non-causal pathways, are promising candidates for the identification of patients with NAFLD. **Objectives:** To identify blood metabolites and blood proteins that are causally impacted by the presence of NAFLD using Mendelian randomization (MR). **Methods:** We created a NAFLD genetic instrument through the identification of independent single-nucleotide polymorphisms associated with NAFLD in a meta-analysis of genome-wide association studies (GWAS) (6715 cases and 682,748 controls). Using inverse-variance weighted MR, we investigated the impact of NAFLD on 123 blood metabolites (in 24,925 participants from 10 European cohorts) and 3283 blood proteins (in 3301 participants from the INTERVAL cohort). **Results:** Our genetic instrument for genetically predicted NAFLD included 12 SNPs at the *MTARC1*, *GCKR*, *LPL*, *TRIB1*, *LMO3*, *FTO*, *TM6SF2*, *APOE* and *PNPLA3* loci. After correction for false-discovery rate, we found a positive effect of NAFLD on blood tyrosine levels and on blood levels of eight proteins (encoded by the *IDUA*, *ADH4*, *HMGCS1*, *GSTA1*, *ASL*, *POR*, *FBP1* and *CTSZ* genes). These association were robust to outliers and we found to evidence of horizontal pleiotropy. **Conclusions:** We report the existence of a potentially causal impact of the presence of NAFLD on tyrosine metabolism as well as on eight circulating proteins, which could potentially represent early biomarkers of NAFLD.

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Leptin Improves Cardiac Structure and Function in Patients With Generalized Lipodystrophy

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Lipodystrophy (LD) syndromes are rare disorders of deficient adipose tissue and severe metabolic disease, including insulin resistance, diabetes, and hypertriglyceridemia. LD may affect all adipose depots (generalized LD, GLD) or only some depots (partial LD, PLD). Low adipose mass leads to very low leptin in GLD, and variable leptin in PL. Treatment with exogenous leptin (metreleptin) improves metabolic disease in LD, particularly GLD. Left ventricular (LV) hypertrophy is frequent in LD, especially GLD. The mechanism for hypertrophy in LD is not known and may relate to glucose or lipotoxicity. We hypothesized that metreleptin would improve cardiac abnormalities in LD, and that this would be mediated by improvements in glucose and triglycerides (TG). We analyzed echocardiograms (echo), blood pressure (BP), heart rate (HR), and metabolic