to less than 0.5 for aldosterone/MN below the PV was seen in unilateral disease. With regards to the six co-secretors, all had elevated cortisol/MN ratios of more than 2 on the affected side. Three had concordant results but the other three had discrepant results, with MN analysis suggesting unilateral disease and cortisol measurements suggesting bilateral disease. Two had undergone surgery with biopsy confirming unilateral disease that correlated with MN analysis. The third is under medical management. **Conclusion:** This is the first study evaluating the use of MN to determine lateralisation of aldosterone production in PA. Further studies are needed, but using MN may be a more reliable alternative to cortisol in the analysis of AVS before definitive surgery in particular in patients with cortisol co-secretion.

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Visualization of Ca Channel Blocker on Human Adrenal Tissue by Mass Spectrometry Imaging ~Its Predominant Distribution at Aldosterone-Producing Cells ~

Naoki Motomura, Bachelor[1], Yuto Yamazaki, MD, PhD[1], Gao Xin, MD[1], Yuta Tezuka, MD, PhD[1], Kei Omata, MD, PhD[1], Yoshikiyo Ono, MD, PhD[2], Ryo Morimoto, MD, PhD[3], Fumitoshi Satoh, MD, PhD[1], Yasuhiro Nakamura, MD, PhD[4], Hironobu Sasano, MD, PhD[5].
[1]Tohoku University Graduate School of Medicine, Sendai, Japan, [2]Tohoku University, Sendai, Japan, [3]Tohoku University Hospital, Sendai, Japan, [4]Tohoku Medical and Pharmaceutical University, Sendai, Japan, [5]Tohoku University School of Medical, Miyagi, Japan.

Primary aldosteronism (PA) is the main cause of secondary hypertension, accounting for approximately 5–10% of all hypertension. Amlodipine, a third-generation calcium channel blocker, is one of the most frequently administered pharmaceuticals medications of hypertension, binds specifically to Cav1.2, a calcium channel primarily localized in the cardiovascular system, and exerts antihypertensive effects through inhibiting calcium influx into the vascular smooth muscle cells. In addition, calcium influx also plays important roles in aldosterone production and amlodipine was also reported to influence *in vitro* functions of Cav1.3, a calcium channel involved in aldosterone secretion. Ca channel blockers were also reported to reduce plasma aldosterone concentration by some clinical studies although with mild degrees. However, *in vivo* effects of amlodipine to aldosterone secretion has remained virtually unknown. A novel technique "Matrix-Assisted Laser Desorption/Ionization Mass Spectrometry Imaging (MALDI-MSI)" has been recently developed, which did make it possible to visualize non-labeled small molecules on tissue sections. Therefore, in this study, we firstly applied MALDI-MSI to visualize amlodipine on human adrenal glands including aldosterone producing adenoma (APA). We performed selective imaging of amlodipine using MALDI-MSI on the resected adrenal tissues from APA patients. Frozen sections containing whole representative tumor area were coated with a matrix called CHCA (α-Cyano-4-hydroxycinnamic acid) by deposition as a pretreatment. We subsequently analyzed and detected a precursor ion with MS at m/z 407.1 and then an amlodipine-specific ion with MS/MS at m/z 318.1. We also examined the concordance of amlodipine distribution obtained by this method with immunohistochemistry. Human resected adrenal tissues obtained from the patients APAs treated with and without amlodipine before adrenalectomy were examined. Periadrenal adipose tissues were also analyzed as a control tissue of non-aldosterone-producing tissues. Amlodipine was specifically detected and visualized only in the administered cases. Amlodipine was more abundantly detected in adrenal tissues than periadrenal adipose tissues. On the other hand, significant different was not detected between tumors and adjacent adrenal glands by semi-quantification using MALDI-MSI. In this study, we firstly visualized amlodipine directly in human tissue sections using MALDI-MSI. Increased accumulation of amlodipine in APAs treated with amlodipine did indicate direct effects of amlodipine on aldosterone production but further investigations are required for clarification between neoplastic and non-neoplastic aldosterone producing cells.

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Vitamin D Deficiency Induces Macrophage Pro-Inflammatory Phenotype via ER Stress-Mediated Activation of Renin-Angiotensin System

Kevin Thomas Bauerle, MD, PhD[1], Jisu Oh, MS[2], Amy Elizabeth Riek, MD[2], Adriana Dusso, PhD[2], Anabel L. Castro-Grattoni, PhD[2], R Ariel Gomez, MD[3], Maria L. Sequeira-Lopez, MD[3], Carlos Bernal-Mizrachi, MD[1].
[1]Washington University in St Louis School of Medicine, VA Medical Center, St Louis, MO, USA, [2]Washington University in St Louis School of Medicine, St Louis, MO, USA, [3]University of Virginia School of Medicine, Charlottesville, VA, USA.

Chronic inflammation and local activation of the renin-angiotensin-aldosterone system (RAAS) play a pivotal role in the pathogenesis and progression of diabetic complications. In patients with type 2 diabetes (T2DM), the prevalence of vitamin D deficiency is almost twice that of non-diabetics, and vitamin d deficiency nearly doubles the risk of developing hypertension and cardiovascular complications compared to diabetics with normal vitamin D levels. Interestingly, mice lacking the vitamin D receptor (VDR) in macrophages (KODMAC) develop renin-dependent hypertension, insulin resistance, and inflammation via up-regulation of macrophage ER stress. Macrophages also express all major components of the RAAS system. However, little is known about the regulation of macrophage-generated renin and its role in modulating the sequelae of VDR signaling in macrophage function and cytokine production. This study found that KODMAC macrophages and vitamin D-deficient macrophages have increased expression and secretion of renin, angiotensin II, ACE, and AT1 receptor and that adhesion, migration, and cytokine release were also increased. Inhibition of ER stress in KODMAC macrophages and vitamin D-deficient macrophages with 4-Phenylbutyric acid (PBA) reduced RAS gene expression and macrophage pro-inflammatory phenotype. Renin 1c gene deletion decreased macrophage

adhesion, migration, and cytokine release compared to macrophages with disrupted VDR signaling. Notably, disruption of VDR signaling induced peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α) expression in macrophages, and upregulation of renin expression in response to vitamin D deficiency was blunted in PCG1α-deficient macrophages. In conclusion, our findings delineate a mechanism by which impaired VDR signaling induces ER stress to drive PGC1α-dependent expression of renin and RAAS hyperactivation, thereby altering macrophage function and cytokine production. These data implicate RAAS as an essential mediator of VDR-mediated macrophage function and support ongoing investigations of VDR and RAAS modulation as therapeutic approaches in the management of T2DM and its complications.

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Volanesorsen, an Antisense Oligonucleotide to Apolipoprotein-CIII, Decreases Triglycerides and Increases Lipoprotein Lipase Activity in Partial Lipodystrophy

Marissa Lightbourne, MD, MPH[1], Brianna Brite, BS[2], Megan S. Startzell, RN, MPH[2], Bruce Kimberley, PhD[3], Robert Eckel, MD[3], Rebecca J. Brown, MD[2].
[1]National Institute of Child Health and Human Development, Bethesda, MD, USA, [2]National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, USA, [3]University of Colorado Anschutz Medical Campus, Morrison, CO, USA.

Partial lipodystrophy syndromes (PL) involve selective deficiency of adipose tissue, with regional deficiency of fat in the lower extremities and preservation or even excess fat in the face and neck. Clinical features typical of PL include severe insulin resistance, diabetes mellitus, hypertriglyceridemia and non-alcoholic fatty liver disease. Apolipoprotein CIII (Apo-CIII) is elevated in PL, and is thought to contribute to high TG by inhibiting lipoprotein lipase (LPL). However, prior studies of this drug in patients with LPL mutations demonstrated LPL-independent mechanisms of TG-lowering. We hypothesized that Volanesorsen, an antisense oligonucleotide (ASO) to apo-CIII, would decrease apo-CIII, increase LPL activity, and lower TG in PL. We further hypothesized that Volanesorsen would improve insulin resistance and glycemia by directing free fatty acids (FFA) into adipose tissue, rather than ectopic sites (e.g. liver) associated with insulin resistance. Five adults with PL and TG ≥500 mg/dL or TG≥200 with A1c >7.0% were enrolled in a 16-week placebo-controlled, randomized, double blind study of Volanesorsen, 300 mg SC weekly, followed by a 1-year open label extension. Here, we report within-subject effects of Volanesorsen lipids, glycemia and lipolysis, before and after 16 weeks of active drug. From week 0 to week 16, apoC-III decreased from 380 (246, 600) to 75 (26, 232) ng/mL, TG decreased from 503 (330, 1040) to 116 (86, 355) mg/dL; and LPL activity measured in post-heparin plasma utilizing the subject's serum as activator increased from 22.0±3.0 to 35.5±5.9 nEq/ml/min. Free fatty acid turnover (measured by palmitate tracer studies) decreased from 0.41 (0.35, 0.45) to 0.25 (0.23, 0.29) mg/kg/min. There was no change in A1c (8.4±1.2 to 8.3±0.9%), however there was a decrease in HOMA-IR from 26 (20, 54) to 13 (9, 43) and an increase in peripheral insulin sensitivity (glucose infusion rate during euglycemic hyperinsulinemic clamp, 120 mU/m^2/min) from 3.6±2.4 to 4.4±1.5 mg/kgFFM/min and in hepatic insulin sensitivity (% suppression of hepatic glucose production during clamp) from 78±19 to 90±13%. Adverse events include injection site reactions and decreased platelets. Volanesorsen decreased apo-CIII and triglycerides, at least in part through an LPL dependent mechanism, and may improve insulin resistance.

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Why Should We Measure Low-Density Lipoprotein Cholesterol Directly? Comparison of Low-Density Lipoprotein Cholesterol Assessment by Friedewald Estimation, and Direct Measurement

Hofit Cohen, MD.
CHAIM SHEBA MEDICAL CENTER, Ramat gan, Israel.

Intorduction: Plasma levels of low-density lipoprotein cholesterol (LDL-C) are an important biomarker for coronary artery disease. In clinical and research settings worldwide, levels LDL-C are often not measured and are estimated using the Friedewald equation (total cholesterol - HDL cholesterol - triglycerides)/5). Bias of either over or underestimation of LDL-C can be corrected by direct measurement of LDL-C. We assessed the precision of the Friedewald equation in a heterogonous patients population within a wide range of lipid levels. **Methods:** A sample of consecutive fasting lipid profiles was obtained from ambulatory and hospitalized patients at the Chaim Sheba Medical Center, Tel-Hashomer. LDL-C concentrations were directly measured (dir LDL-C) (Olympus, Ireland) and correspondingly calculated at by the Friedewald equation (calc LDL-C). **Results:** 32,245 samples were analyzed. In 93% of the samples, underestimation of plasma levels of LDL-C was observed using the Friedewald equation. In 11,054 patients (34.3%), the difference between dir LDL and calc LDL were over 10mg/dl. In 7,693 patients (23.8%), the difference between dir LDL and calc LDL were over 20mg/dl. The difference between dir LDL and calc LDL correlated with plasma TG levels, including TG levels within the normal range. The difference between cal LDL and dir LDL levels is inversely correlated to cholesterol plasma levels. **Conclusions:** Direct measurement of LDL-C is more precise than Friedewald's formula and overcomes the inaccurateness, due to elevated TG levels or relatively low LDL-C levels, in the setting of a heterogeneous Israeli population. In the era of extremely low LDL-C treatment goals, our findings require consideration due to their clinical importance and direct measurement of plasma LDL-C should be implemented as underestimation of LDL levels may lead to inappropriate therapeutic decisions.

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CARDIOVASCULAR ENDOCRINOLOGY AND LIPIDS DISORDERS CASE REPORT

A Case of Fishy Smell-Fish Malodor Syndrome