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

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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

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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

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Introduction: Primary trimethylaminuria (TMAU), also known as fish malodor syndrome is a rare condition that is characterized by trimethylamine excess. The hallmark of this condition is a body malodor similar to decaying fish. As this metabolic disorder is uncommon, this case highlights the management options for an endocrinologist.
Case presentation: A 56-year-old man was referred to the endocrine clinic for TMAU. Starting in puberty, the patient's family and friends noted a malodor that he has never been able to detect. After several decades, the patient was diagnosed clinically by a dermatologist. Since then, the patient's management had included avoiding cholines in his diet, which included egg yolks and salt-water fish. Additionally, for severe episodes occurring once to twice a year, he took a cup of charcoal daily plus Metronidazole 500 mg twice a day for ten days. The patient was the only member of his family with this condition. Physical exam was unremarkable expect for a faint malodor. Metronidazole, charcoal, and a genetics consult were ordered.
Discussion: TMAU is a rare metabolic disorder in which an individual is not able to convert trimethylamine into trimethylamine N-oxide due to a defect in the hepatic oxidase system. It results from a mutation in the flavin-containing monooxygenase 3 gene (FMO3) that is inherited via autosomal recessive pattern. An excess excretion of trimethylamine in the urine, breath, sweat, and reproductive fluids results in a body malodor similar to that of decaying fish. The odor may be exacerbated by increase in body temperature, emotional changes, puberty, and prior to and during menstruation in women and often results in distressing psychosocial difficulties. Thus, early institution of dietary and pharmacological measures will likely have a major impact on quality of life.
Treatment options are limited and include topical, dietary, and medications. Topical approaches include antiperspirants, deodorants, and pH-balanced soap. A diet low in choline-containing foods such as dairy, beans, and marine fish is beneficial as choline is metabolized to trimethylamine by the intestinal bacteria. For severe cases, antibiotics such as Metronidazole, Rifaximin, and Neomycin sulfate are helpful to reduce the intestinal bacterial load. Other therapeutic strategies consist of activated charcoal (750 mg twice a day for ten days) and copper chlorphyllin (60 mg three times a day for three weeks); both reduce urinary free trimethylamine and increase the concentration of trimethylamine N-oxide.

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CARDIOVASCULAR ENDOCRINOLOGY AND LIPIDS DISORDERS CASE REPORT

A Case of Hypolipidemia and Hypocholesterolemia; Cause and Consequences

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Background: Hypolipidemia and hypocholesterolemia are uncommon and because of the established risk of hypercholesterolemia for cardiovascular disease, reduced lipids and total cholesterol levels are often clinically desired and/or deemed clinically inconsequential. A finding of persistently low lipid levels and total cholesterol may however not be innocuous nor desirable. We describe the case of a 46 yr old man with persistently low total cholesterol levels <70mg/dl and the associated complications and comorbidities identified. **Clinical Case:** A 46 yr old Hispanic man with non-alcoholic fatty liver disease (NAFLD) was referred for evaluation of hyperhidrosis in the setting of persistent hypolipidemia and hypocholesterolemia. Review of the patient's clinical and biochemical history showed persistently low total cholesterol (mean 58mg/dl), hypotriglyceridemia, and low LDL-C (mean 13.4mg/dl) over the prior 7 yrs in addition to undetectable serum lipoprotein A. Evaluation for secondary causes of hypolipidemia, such as multiple myeloma, was unremarkable. He was found to have low carotene, borderline vitamin A and low vitamin E levels while the rest of his serum fat-soluble vitamins were normal. His mother who had presumed Alzheimer's dementia also had a history of very low cholesterol levels. The degree and persistence of his hypolipidemia and hypocholesterolemia raised the possibility of a genetic etiology of his hypolipidemia. Genetic testing confirmed that the patient was heterozygous for a pathogenic variant in the APOB gene, consistent with familial hypobetalipoproteinemia (FHBL) which is autosomal recessive linked. Subsequent close review of his clinical history revealed other potential complications and comorbidities of FHBL including NAFLD with prediabetes, hypogonadism, progressive cognitive and memory decline, peripheral neuropathy and multiple neuropsychiatric syndromes including adult ADHD, borderline personality disorder, bipolar disorder and chronic anxiety. He is presently on vitamin E and A supplementation and being followed by neurology and psychiatry in addition to ongoing endocrine and metabolic clinical surveillance. In addition, in view of his maternal history and several biologic children he has undergone formal genetic and family counselling. **Conclusions:** While lipid panels are ubiquitous in clinical care, clinicians need to be vigilant in settings of severe persistent hypolipidemia and/or hypocholesterolemia to evaluate for possible genetic basis for this and to also screen for possible associated complications and comorbidities.

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CARDIOVASCULAR ENDOCRINOLOGY AND LIPIDS DISORDERS CASE REPORT

A Case of Primary Hyperaldosteronism Presenting as Hemorrhagic Stroke

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Background: Primary aldosteronism (PA) is the most common form of secondary hypertension. Patients with PA are more likely to suffer from end-organ damage compared to matched controls with essential hypertension. We present a case of PA identified in a patient who presented with hypertensive emergency and hemorrhagic stroke.
Clinical Case: A 52-year-old man with hypertension and chronic kidney disease presented with sudden onset