label, single arm study (NCT03868059); a 12-week study in a high-fat-diet (HFD) induced steatohepatitis and hepatic fibrosis rabbit model. 39% of hypogonadal males (N=210) tested had the elevated key liver injury marker (ALT>30 U/L). LPCN 1144 intervention for 52 weeks in hypogonadal males with elevated ALT levels at baseline resulted in mean decrease about 15%. Moreover, abnormal ALT, AST, ALP, and GGT were normalized in 52%, 50%, 67%, 32% of patients, respectively. In the 4-month study, fatty (>5%) liver disease was present in about 66% of a cohort of hypogonadal males (N=32), more than double the reported rate in the general population (25%). Post LPCN 1144 treatment, the proportion of fatty liver-free subjects increased by 94%. HFD induced substantial suppression of T levels in rabbits accompanied with histologically evidenced hepatic steatosis, inflammation, ballooning, and fibrosis. Upon 12 weeks of LPCN 1144 treatment in conjunction with HFD, histological ballooning, inflammation and fibrosis scores were improved. Importantly, relatively to control, % of hepatic fibrosis in the tissues were significantly reduced with LPCN 1144 treatment. In conclusion, compromised liver health is prevalent in hypogonadal males and may warrant a periodic assessment. Pre-clinical and clinical results with oral T therapy suggest potential beneficial effects on liver health in hypogonadal males. An ongoing study in biopsy-confirmed NASH male patients is expected to shed more light on the potential benefits of LPCN 1144.

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Meal-Related Changes in Apolipoprotein Particles After Treatment With an Antisense Oligonucleotide to Apolipoprotein CIII

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Background: Lipodystrophy (LD) is defined by partial or complete absence of adipose tissue causing metabolic complications such as high triglycerides (TG). Apolipoprotein CIII (ApoCIII) contributes to high TG by inhibiting lipoprotein lipase (LPL). Measurement of lipoprotein particles using NMR can offer insights into lipid metabolism. **Hypothesis:** We hypothesized that during a mixed meal test (MMT), clearance of TG-rich lipoprotein particles (TRLP) measured by NMR would increase in LD patients given an antisense oligonucleotide (ASO) to lower ApoCIII. **Experimental Design:** Five adults with partial LD underwent an MMT (with 18g fat) at week 0 and after 16 weeks (wk) of the ApoCIII ASO. Blood samples were obtained at 0, 30, 60, 120, 180, 240, 300, and 360 minutes (min) and assessed using NMR with the LP4 deconvolution algorithm, which separates TRLPs into 5 size categories: very large (VL), large (L), medium (M), small (S), and very small (VS), all expressed as nmol/L. **Major Results:** At wk 0, patients had high fasting TG (median 523 mg/dL, IQR 335–1060 mg/dL, normal <150), which decreased after 16wk of ASO[BR([1] (196 mg/dL) Mean TRLP over the 360 min of the MMT was lower after ASO (181.6±14.1 at wk 0, 80.4±2.2 at wk 16). At wk 0, mean L_TRLP during the MMT was 26.8 ± 6.9 and decreased to 9.3±1.3 at wk 16. At wk 0, L_TRLP rose during the MMT to a peak at 180min; at wk 16 there was no rise in L_TRLP during the MMT. Mean S_TRLP during the MMT increased from wk 0 (5.4±3.9) to wk 16 (13.4±10.4). At wk 0, S_TRLP increased minimally during the MMT from 5.2±11.7 at 0 min to 10.9±15.2 at 360 min. At wk 16 there was a more notable rise in S_TRLP in the last 3 hrs of the MMT, from 12.2±15.1 at 0 min to 37.6±28.6 at 360 min. **Interpretation of Results and Conclusions:** As expected, an ApoCIII ASO lowered fasting and postprandial TG and TRLP. There was minimal rise or fall in any subclass of TRLP during the MMT, either before or after ASO, likely due to the small fat load, which was chosen due to concern for triggering pancreatitis in this at-risk group. The greater post-prandial fluctuation of L_TRLP prior to ASO may represent appearance and disappearance of chylomicron remnants; at wk 16 this was not seen, perhaps due to more rapid clearance of chylomicron remnants by LPL. The larger increase in S_TRLP at the end of the MMT at wk 16 may reflect more rapid lipolysis of L_TRLP by LPL during ASO treatment, thus generating S_TRLP. Next steps include measuring apoB48 and apoB100 during the MMT to distinguish VLDL from chylomicrons, accruing a larger sample size, and collecting MMT data in healthy controls.

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Menopausal Symptoms and Cardiovascular Disease Risk Indices Among Women With HIV

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Background: Women with HIV (WWH) (vs. women without HIV) have an increased risk of cardiovascular disease (CVD) in relation to heightened systemic immune activation/inflammation. Moreover, WWH show evidence of advanced reproductive aging and unique patterns of hot flash symptomatology. General population studies have revealed that hot flashes may relate to surrogate markers of CVD risk. The relationship between hot flashes and immune activation as well as subclinical cardiac pathology among WWH has not been previously investigated.
Methods: In a prospective, cross-sectional study, 23 WWH on anti-retroviral therapy and 19 women without HIV (ages 40–75), group-matched on age and BMI, were enrolled and completed reproductive health assessments,

immune phenotyping and cardiovascular MRI. Women without prior CVD or diabetes were eligible.
Results: Women were similar in age and BMI (WWH vs. women without HIV: 51 ± 5 vs. 52 ± 6 years, P=0.79 and 32 ± 8 vs. 31 ± 7 kg/m2, P=0.71). There was no significant between-group difference in the percentage of women without menses in the past year (p=0.52) or in the percentage of women with undetectable levels of antimullerian hormone (p=0.71). No women in either group were on estrogen and/or progesterone for treatment of menopausal symptoms. Hot flash frequency (days per week with hot flashes) was higher among WWH versus women without HIV (median [IQR], 7.0 [1.3, 7.0] vs. 0.8 [0.0, 2.1], p=0.01). In sensitivity analyses excluding either women with menses in the past year or with detectable AMH, WWH still reported a significantly higher number of days per week with hot flashes (7.0 [6.3, 7.0] vs. 0.4 [0.0, 2.3], p=0.007, and 7.0 [2.4, 7.0] vs. 0.8 [0.0, 2.1], p=0.01, respectively). Among WWH experiencing (vs. not experiencing) hot flashes in the past year, longer duration of ART use was noted (21.2 [16.0, 22.7] vs. 9.3 [3.3, 16.0] years, p=0.03). Among the entire cohort and among WWH, women with more than one hot flash per day had higher levels of soluble CD14, a marker of monocyte activation, compared to women with one or fewer hot flash per day (p=0.004 and p=0.02, respectively). Among WWH and a history of hot flashes, years since onset of hot flashes related to cardiovascular MRI-derived measures of subclinical pathology. Specifically, years since onset of hot flashes related directly to myocardial steatosis (intramyocardial triglyceride content; ρ=0.80, p=0.02) and inversely to diastolic function (left atrial passive ejection fraction; ρ=−0.70, p=0.03).
Conclusions: WWH experienced a higher frequency of hot flashes compared to women without HIV. Among WWH, hot flash symptomatology related to systemic immune activation and to cardiovascular MRI-derived measures of CVD risk. Additional research is required to improve understanding of mechanisms underlying these relationships and determine if hot flashes are a sex-specific risk factor for CVD in WWH.

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Mild Autonomous Cortisol Secretion in Primary Aldosteronism Enhances Renal and Hemorrhagic Cerebrovascular Complications

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Background: It is well known that primary aldosteronism (PA) is often associated with renal dysfunction and cardiovascular events (CVEs). However, the synergic effect of mild autonomous cortisol secretion (MACS) on the co-morbidities among PA has not been clarified yet. Thus, we retrospectively assessed whether the presence of MACS in PA patients with adrenal tumor, which may have MACS, to enhance the risk of the complications using a large Japanese multicenter database.
Methods: We enrolled patients with both confirmed PA and obvious adrenal tumor (diameter > 1 cm) on computed tomography. The subtype of PA was diagnosed based on the results of adrenal venous sampling with ACTH stimulation. A total of 575 study subjects were stratified into two groups according to 1-mg dexamethasone suppression test (DST) results (cut-off post-DST serum cortisol 1.8 μg/dL): MACS group (N=174, 30.2%) and non-MACS group (N=401, 69.8%). Decreased estimated glomerular filtration rate (eGFR) was defined as <60 ml/min per 1.73m^2.
Results: The percentage of unilateral PA between the MACS and non-MACS group was equivalent (50.0% vs. 48.1%). Prevalence of decreased eGFR in the MACS group was higher than in the non-MACS group [odds ratio (OR) 1.91, 95% confidence interval (95% CI) 1.20–3.04, P=0.006]. Conversely, prevalence of MACS was higher in patients with decreased eGFR than those without decreased eGFR (42.7% vs 28.0%, P=0.008). Proteinuria was deteriorated with the increase in post-DST serum cortisol concentration as well as the basal plasma aldosterone concentration (PAC) (P=0.028 and P<0.001, respectively), although PAC but not the presence of MACS was selected as an independent factor related with decreased eGFR. Prevalence of cerebral hemorrhage in the MACS group was higher than the non-MACS group. (OR 5.35, 95%CI 1.83–15.6, P=0.002). We found that MACS was the only significant factor which increased the odds of developing cerebral hemorrhage (OR 9.13, 95%CI 2.15–38.90, P=0.003). Prevalence of other CVEs between the two groups was similar. Regardless of the PA subtype, complication rate of decreased eGFR and cerebral bleeding in the MACS group were significantly or tend to be higher than non-MACS group.
Conclusion: Our date strongly suggested that co-secretion of cortisol in PA directly and/or indirectly increase renal and cerebrovascular comorbidities. Given that MACS is common in PA, endocrinological testing with DST is recommended in PA patients, especially those with adrenal tumor on imaging. (Supported by Research Grants of AMED:JP17ek0109122, JP20ek0109352; National Center for Global Health and Medicine:27–1402, 30–1008), and Ministry of Health, Labour, and Welfare, Japan (046).

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Modulation of Calcium Signaling by Chemogenetic Tools to Elucidate the Pathogenesis of Primary Aldosteronism