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Advanced Lipoprotein Analysis In Patients With Cushing’s Syndrome

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Introduction: Cushing syndrome (CS) patients have a higher mortality rate due to increased cardiovascular disease (CVD). Analysis of lipoprotein particles with nuclear magnetic resonance (NMR) spectroscopy provides additional insights into CVD risk beyond the standard lipid panel. The goal of the study was to better characterize the lipid abnormalities in patients with CS by using high-resolution separation of lipoprotein particles. Methods: We measured plasma lipids (Cholesterol, TC; calculated low density lipoprotein, LDL; triglycerides, TG; high density lipoprotein, HDL) by the traditional enzymatic assay and lipoprotein...
particles by NMR spectroscopy. Measures of inflammation and insulin resistance were also derived from NMR spectra. Values are shown as mean ± SEM or median [IQR].

**Results:** After initial evaluation, 42 subjects (mean age 47.4 ± 2.5 years; 28 females; weight 85.0 ± 3.1 kg) had Cushing’s disease (n=23), ectopic ACTH secretion (n=17), or adrenal adenoma (n=2). Ten patients were on chronic statin therapy, and 14 subjects had type 2 diabetes mellitus (T2DM). The control group comprised 45 subjects without T2DM [mean age 45.4 ± 2.1 years and weight (83.5 ± 2.7) kg]. None in the control group were on statin therapy. Compared to controls, CS patients had significantly higher systolic (135 ± 2 vs. 119 ± 2 mm Hg, p<0.001) and diastolic blood pressure (79 ± 2 vs. 71 ± 1 mm Hg, p<0.001), HbA1c (6.1 [5.4-7.5] vs. 5.4 [5.0-5.7], p<0.001), plasma glucose (103 [90-137] vs 94 [89-100] mg/dL, p=0.003), and insulin (17[12-26] vs 11[7-15] uU/mL, p=0.01) levels. Compared to controls, patients with CS had significantly higher triglyceride concentration (116 [84 -146] vs 87 [62-120] mg/dL, p=0.02) and lower LDL concentration (90 [69 -113] vs 108 [90 -125] mg/dL, p=0.04). However, total cholesterol and HDL cholesterol concentrations were not different. LDL particle size in CS was smaller (20.5[20.0-21.0] vs 21.0 [20.7-21.2] nm, p=0.01) and VLDL particle size was larger (49.8 ± 0.9 vs 45.7 ± 1.0 nm, p=0.002) than in controls. No difference was noted between groups in HDL particle number or size or in LDL and VLDL particle number. In the group with CS, a marker of inflammation, GlycA (Glycan N-acetylglucosamine) (494.5 ± 18.2 vs. 382.5 ± 9.0 µmol/L, p<0.001) and Lipoprotein Insulin Resistance score (LPIR) (46.4 ± 3.1 vs. 36.2 ± 3.1, p=0.02) were significantly higher. There were no group differences in branch-chained amino acids (BCCA) levels. These differences remained even when patients with type 2 diabetes and those on statin therapy were excluded. **Conclusions:** These data suggest that the higher inflammatory and insulin resistance state, dysglycemia, hypertension, and altered lipoprotein profiles may contribute to the increased CV risk in patients with Cushing’s syndrome. Early detection and treatment for these abnormalities may attenuate CV risk.

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