The Role of Leptin and Inflammatory Related Biomarkers in Individuals with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

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BACKGROUND

Leptin is a member of the cytokine family with at least six isoforms of receptors (LEPR) in tissues, including hypothalamic and brainstem nuclei.[1,2]

Studies have assessed the role of plasma leptin levels regulating the long-term energy status and its relationship with insulin and high-sensitivity c-reactive protein (hsCRP); however, leptin related metabolic dysregulations in individuals with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (MECFS) have not been fully elucidated. [3,4,5]

Hypothesis: we examined the relationship between patients-reported outcomes: [fatigue, generalized pain, sleep disturbance, brain fog, and Post Exertional Malaise (PEM)] and within-individual-variability (WIV) of leptin, insulin, and hsCRP plasma levels in white females diagnosed with MECFS.

METHOD

Prospective analysis of 29 cases from "Birmingham hospital, Alabama, U.S.A", who met the Fukuda/CDC diagnostic criteria of ME/CFS:

- Independent variables:
  - WIV of leptin, insulin, and hsCRP levels were calculated for each individual as standard deviation/sample residuals adjusting for time from once-daily random plasma samples over 10-12 weeks.
  - Leptin, insulin, and hsCRP levels were categorized as "Hypoleptinemia<3.3", and "Hyperleptinemia>18.3" ng/ml, "Hyperinsulinemia>174 µIU/ml" and "residual inflammation risk hsCRP ≥2 and ≤ 26.2 mg/L".
- Patients' primary outcomes were defined using self-reported MECFS symptoms' scores using MFI-20 questionnaire with anchors from 0-100.
  - Repeated measures (score-trends) recorded daily over a matching 12-14 weeks.
  - Dichotomized symptom severity , defined as "severe ≥60/100".
- Multivariable mixed-effect linear regression models, and multivariable fixed-effect alternating logistic regression models, after adjusting for age, were fit using PROC MIXED and PROC GEE consequently to examine our hypothesis.
- Odds Ratios of hyperleptinemia were compared to hypoleptinemia

RESULTS

Baseline Characteristics by quartiles of WIV-leptin

Variable, n(%)	< 0.15 n=639(26)	0.15-<0.25 n=503(21)	0.25-<0.40 n=546(23)	≥0.40 n=730(30)	P-VALUE
Patients' characteristics					
Age in years, median (IQR)	41 (24-47)	42 (40-52)	47 (39-52)	46 (34-54)	<.01
WIN insulin, median (IQR)	0.37 (0.27-0.99)	0.23 (0.16-0.24)	0.56 (0.19-0.90)	0.54 (0.38-0.60)	<.01
WIN hsCRP, median (IQR)	0.37 (0.13-0.65)	0.33 (0.13-0.85)	0.55 (0.33-0.82)	0.37 (0.11-0.85)	<.01
Hyperinsulinemia, n(%)	0(0)	91 (18)	91 (17)	0 (0)	<.01
Hyperleptinemia, n(%)	180 (28)	454 (90)	546 (100)	730 (100)	.002
Hypoleptinemia, n(%)	183 (29)	0 (0)	0 (0)	0 (0)	.002
Residual inflammation risk, n(%)	367 (57)	272 (54)	546 (100)	546 (75)	<.01

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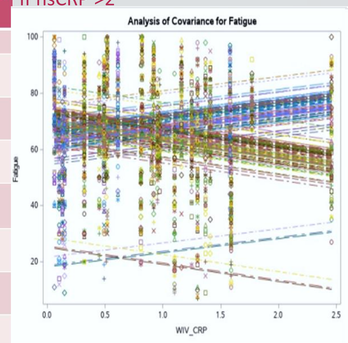
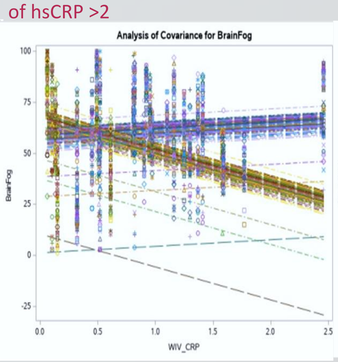
Patients' outcomes					
Severe Fatigue, n(%)	334(52)	231(46)	231(42)	413(57)	<.01
Severe pain, n(%)	237(37)	124(25)	97(18)	210(29)	<.01
Severe sleep disturbance, n(%)	179(28)	122(24)	130(24)	248(34)	.0005
Severe Brian fog, n(%)	199(31)	252(50)	264(48)	321(44)	<.01
Severe PEM, n(%)	274(43)	253(50)	350(64)	476(65)	0.02

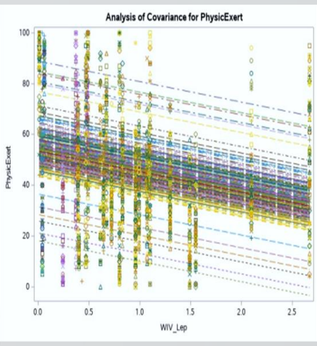
(β, 9.68; SEM, 3.26; p=.007) If hsCRP >2



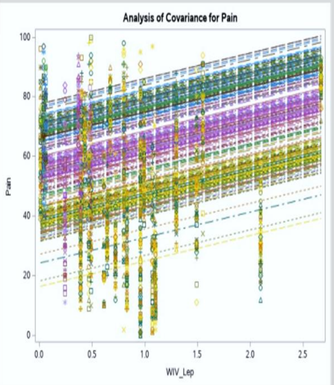
(β, 19.51; SEM, 4.65; p=.0003) of hsCRP >2



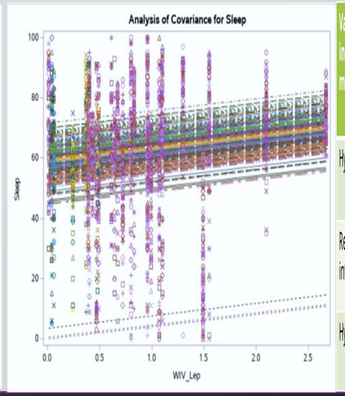
(β, -9.94; SEM, 1.84; p<.01)



(β, 7.17; SEM, 2.30; p=.005)



(β, 3.37; SEM, 1.47; p=.03)



Adjusted odds ratios for severe symptoms

Variable (by individual measures)	OR 95% CI Fatigue	OR 95% CI Pain	OR 95% CI Sleep disturbance	OR 95% CI Brain Fog	OR 95% CI PEM
Hyperleptinemia	1.54 (1.14-2.10)	1.58 (1.20-2.10)	0.38 (0.24-0.59)	1.42 (1.18-1.68)	0.60 (0.45-0.84)
Residual inflammation risk	1.65 (1.22-2.25)	1.75 (1.32-2.32)	0.32 (0.19-0.54)	1.43 (1.16-1.77)	0.57 (0.39-0.84)
Hyperinsulinemia	1.51 (0.91-2.46)	1 (0.68-1.49)	0.43 (0.23-0.82)	1.39 (0.95-2.03)	0.80 (0.33-1.07)

CONCLUSIONS

Fatigue scores trends were significantly worse with higher WIV-insulin and WIV-hsCRP among patients with residual inflammation risk; however, PEM trends were significantly worse with higher WIV-insulin, higher WIV-leptin, and lower WIV-hsCRP among patients with residual inflammation risk.

Generalized pain scores trends were significantly worse with higher WIV-leptin and higher WIV-hsCRP; however, sleep disturbance scores were significantly worse with lower WIV-leptin.

Brain fog trends were significantly worse with higher WIV-insulin, higher WIV-leptin and higher WIV-hsCRP among patients with residual inflammation risk.

Participants with hyperleptinemia were associated with higher odds of severe fatigue, severe pain and severe brain fog, compared to hypoleptinemia.

Participants with residual inflammation risk were associated with higher odds of severe fatigue, severe pain and severe brain fog, compared to participants with hsCRP < 2.

A future longitudinal inception cohort study: gender-based clinical trial to examine and validate a complex predictive index (metabolic biomarkers and epigenetic signatures) in MECFS patients with their symptoms' severity, clinical cardiometabolic outcomes, and coronary risk.

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