Metabolic outcomes of weight restoration treatment for anorexia nervosa

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Abstract

Objective
Recent advances in genomics highlighted a possible metabolic axis for anorexia nervosa (AN) (1-3). Indeed, following treatment with weight gain to a normal body mass index (BMI), the weight-restored women with AN (WR-AN) develop abnormalities such as central adiposity. This study was aimed to assess the spectrum of metabolic dysfunction in WR-AN as a model of weight gain after sustained starvation.

Methods
A single-arm prospective trial with inpatient weight restoration was conducted in adult women with AN (N=26). Underweight patients with AN were admitted to the hospital and received treatment with our established refeeding protocol. The endpoint in treatment was the successful attainment of 90% ideal body weight, or a BMI of at least 19.5 kg/m^2. Controls were healthy adult women (HC) without eating disorders who were matched to the WR-AN group by age, sex, and endpoint BMI (N=10). Primary outcomes were post-treatment parameters of metabolism including: the metabolic syndrome (MetS) criteria as defined by the NCEP-ATP III, the single most robust biomarker of cardiovascular disease risk through the non-HDL cholesterol, and a panel of inflammatory and endocrine biomarkers associated with impaired metabolic health.

Results
None of the participants met full criteria for MetS, but the WR-AN group had a significantly higher likelihood of meeting at least one MetS criteria compared to matched HC women (RR=2.6, 95% CI=[1.2, 7.5], *Fisher's p*=0.017). Compared to HC, WR-AN had elevated visceral adiposity (*p*=0.004, Hedges' *g*=0.943), differential glucose metabolism (*p*=0.008, Hedges' *g*=1.230), and elevated non-HDL cholesterol (*p*=0.0004, Hedges' *g*=1.419). In addition, WR-AN demonstrated a significant reduction in a subset of metabolism-related biomarkers including free fatty acids (FFA, *p*=0.015, Hedges' *g*=1.167), thyroid-stimulating hormone (TSH, *p*=0.014, Hedges' *g*=0.961), and estradiol (E2, *p*=0.00009, Hedges' *g*=1.158).

Discussion
In this cohort of young normal weight women, these results highlight the existence of substantial metabolic differences between healthy subjects and patients with AN who were recently weight-restored after a sustained period of starvation. The metabolic dysfunction that persists despite weight normalization suggests a need for further investigation into the metabolic axis of AN as a potential mechanism of illness perpetuation in AN, which could enhance our understanding of weight regulatory pathways.

Study design

Participants

AN
26 underweight women with AN studied before weight gain (BMI range 13.0 to 18.5 kg/m^2)

AN-WR
Studied after maintaining weight for 2-4 weeks (BMI range 19.3 to 21.2 kg/m^2)

Inpatient admission to NYS Psychiatric Institute/Columbia General Clinical Research Unit (GCRU) with treatment goal of weight restoration to at least 90% ideal body weight (BMI 19.5 kg/m^2)

HC
10 healthy control women matched to WR patients for age, BMI and gender

- Body composition analysis with whole-body MRI
- Fasting plasma analysis: RIA, ELISA
- 3-hour oral glucose tolerance testing (OGTT) with 75 g liquid glucose bolus

NCEP-ATP III criteria for metabolic syndrome (4)
Presence of any 3 of the 5 criteria:
- Abdominal obesity: WC > 88 cm for women (35 inches)
- Hyperglycemia: Impaired fasting glucose, ≥ 100 mg/dL, or on DM Rx
- Dyslipidemia: Low HDL-c, < 50 mg/dL in women, or on HLD Rx
- Dyslipidemia: High triglycerides, ≥ 150 mg/dL, or on HLD Rx
- HTN: SBP ≥ 130 mm Hg, DBP ≥ 85 mm Hg, or on HTN Rx

Non-HDL-cholesterol – single most robust biomarker of MetS (5)

Hormones and inflammatory markers

Clinical characteristics

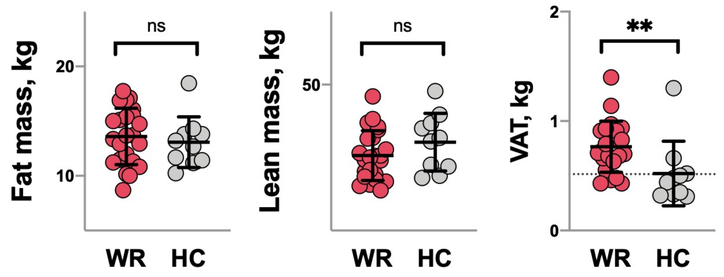
	AN	WR	HC	p AN v. WR	p AN v. HC	p WR v. HC
N	21	26	10	-	-	-
Age, years	26.2 ± 6.2	29.1 ± 5.8	26.3 ± 3.8	-	0.860	0.791
Height, m	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1	-	0.611	0.432
Body weight, kg	42.5 ± 5.3	53.7 ± 4.2	55.4 ± 4.7	**< 0.001**^{L}	**< 0.001**^{L}	0.354
BMI, kg/m^2	15.8 ± 1.6	20.1 ± 0.5	20.1 ± 0.7	**< 0.001**^{L}	**< 0.001**^{L}	0.827
Regular menses, %	-	38	100	-	-	0.536
Hypertensive, %	0	0	0	-	-	-

WR-AN and HC had comparable age, weight, height, and BMI.

Values presented as means ± SD. Statistical comparisons with paired (AN vs. WR) or unpaired (AN vs. HC, WR vs. HC) methods, bold are significant *p*-values. Effect sizes denoted with a superscript, using the absolute value of Hedges' *g* effect size (|*g*|) as: ^{L}, large or |*g*| > 0.8. Body mass index, BMI.

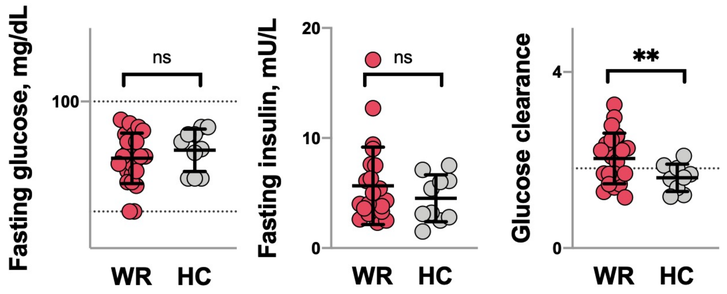
Metabolic syndrome features are elevated in WR-AN vs. HC

Abdominal obesity? In these normal weight, age-matched women, the total adipose tissue mass and lean tissue mass were comparable, but the **visceral adiposity was elevated in WR-AN (6).**



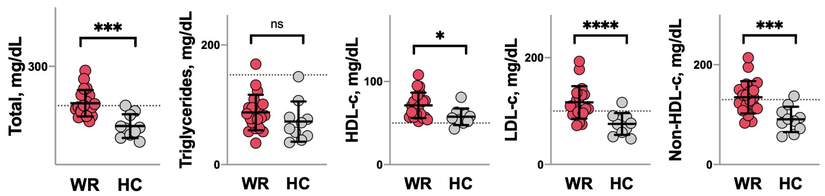
Visceral adipose tissue, VAT. **, *p*<0.01; ns, not significant.
Dotted line in VAT graph indicates 75th percentile for HC data at VAT=0.515 kg.

Dysglycemia? Fasting glucose, fasting insulin, and homeostasis model assessment (HOMA) measures were comparable between WR-AN and HC. **Dynamic glucose clearance was altered in WR-AN with a reactive glucose clearance in OGTT (7).**



Dotted line in fasting glucose graph indicates normal fasting glycemia (70-100 mg/dL).
Dotted line in glucose clearance indicates the 75th percentile for HC at MGR=1.813.

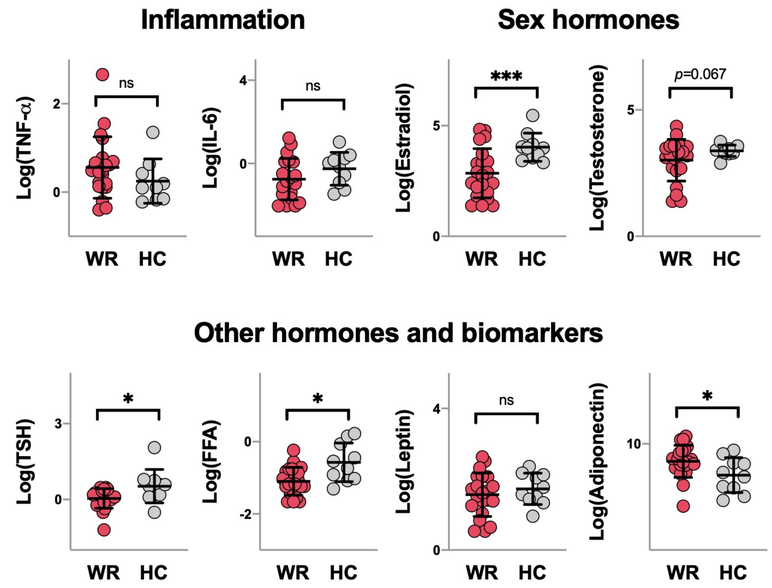
Dyslipidemia? WR-AN had markedly elevated fasting levels of total, high-, and low-density lipoprotein cholesterols, but comparable triglycerides. **Non-HDL-cholesterol was significantly elevated in WR-AN.**



****, *p*<0.0001; ***, *p*<0.001; *, *p*<0.05; ns, not significant. Dotted lines indicate upper or lower (HDL-c only) limits of healthy range, at 200 mg/dL total cholesterol, 150 mg/dL triglycerides, 50 mg/dL HDL-c, 100 mg/dL LDL-c and 130 mg/dL non-HDL-c.

In both WR-AN and HC groups, no single individual met full criteria for metabolic syndrome. However, the risk of meeting at least 1 MetS criterion was elevated by 2.6 fold in WR-AN vs. HC (RR=2.6, 95%-CI=[1.2, 7.5], *p*=0.017), and the average number of MetS abnormalities is significantly elevated in WR-AN vs. HC (*p*=0.015).

Metabolic syndrome-associated biomarkers



***, *p*<0.001; *, *p*<0.05; ns, not significant. Tumor necrosis factor α, TNF-α; interleukin 6, IL-6; thyroid-stimulating hormone, TSH; free fatty acid, FFA.

Inflammatory markers were not elevated in WR-AN. **Sex hormones were significantly lower in WR-AN compared to HC.** Several other metabolic syndrome-associated biomarkers were altered in WR-AN, including TSH, FFA, and adiponectin.

Discussion

Conclusions. Shortly after weight restoration treatment, women with AN have several metabolic abnormalities vs. healthy control women of comparable age and BMI.

Novelty. No previous study has comprehensively examined metabolic syndrome features in WR-AN compared to HC, and even though weight-normalization is assumed to bring about normalization of laboratory abnormalities, our study demonstrates that there are still numerous abnormalities in WR-AN.

Limitations. The assessment of the AN cohort for the full MetS status was limited by the lack of body composition measurements for the underweight patients.

Clinical implications and remaining questions.
- Do abnormalities in metabolic parameters in WR-AN correspond to psychological symptom recovery and/or future risk of cardiovascular disease?
- Lipid metabolism parameters show increase in both HDL and LDL cholesterols. Together with decreased FFA, this could highlight an altered lipid flux in WR-AN.
- The true interaction between metabolism and eating behaviors is likely to be much more complex, but it is conceivable that altered glucose and lipid fluctuations may confer differential risk of perpetuating maladaptive eating patterns that would contribute to subsequent weight relapse.
- Future studies with longitudinal assessments of metabolism and eating disorder symptom recovery may enhance our understanding of weight regulation.

References

1. Duncan L *et al.* Significant locus and metabolic genetic correlations revealed in genome-wide association study of anorexia nervosa. American Journal of Psychiatry (2017) **174:**850-858
2. Hubel C *et al.* Genetic correlations of psychiatric traits with body composition and glycemic traits are sex- and age-dependent. Nature communications (2019) **10:**5765.
3. Watson HJ *et al.* GWAS identifies eight risk loci and implicates metabo-psychiatric origins for anorexia nervosa. Nature genetics (2019) **51:**1207-1214.
4. Alberti KGMM *et al.* Harmonizing the metabolic syndrome: a joint interim statement of the IDF, NHLBI, AHA, WHF, IAS, IASO. Circulation (2009) **16:**1640-1645.
5. Brunner FJ *et al.* Application of non-HDL cholesterol for population-based cardiovascular risk stratification: results from Multinational Cardiovascular Risk Consortium. Lancet (2019) **394:**2173-83.
6. Mayer LES, *et al.* Body fat distribution after weight gain in women with anorexia nervosa. The American Journal of Clinical Nutrition (2005) **81:**1286-1291.
7. Kim Y, Hildebrandt T, and Mayer LES. Differential glucose metabolism in weight-restored women with anorexia nervosa. Psychoneuroendocrinology (2019) **110**.

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