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Differential glucose metabolism in weight restored women with anorexia nervosa

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ABSTRACT

Women with anorexia nervosa (AN) develop visceral adiposity associated with insulin resistance after partial weight restoration, but little is known about the glucose homeostasis after full weight restoration. In this investigation, we studied glucose homeostasis in twenty-four women with AN before (AN) and after weight restoration (WR) at a single institution, with both restricting and binge-purge subtypes (> 70% binge-purge), compared to gender-, age- and BMI-matched healthy controls (HC). Participants underwent fasting plasma hormone analysis, oral glucose tolerance test (OGTT), and body composition analysis. Glucose homeostasis was assessed by the homeostasis model assessment (HOMA) and OGTT, and parameters were analyzed for association with body composition. We observed that a subset of the WR patients (21%) had metabolically unhealthy HOMA insulin resistance estimates (HOMA-IR), while this was not seen in the control group. Overall mean HOMA-IR between groups were not significantly different. Mean glucose reactivity was higher in the WR group than HC women ($p = 0.008$, Hedges' $g = 0.811$), and time-adjusted glucose reactivity in the WR group was inversely associated with visceral adiposity ($r = -0.559, p = 0.006$), but not with fat mass ($r = -273, p = 0.208$) or lean mass ($r = -0.002$, $p = 0.994$). Our findings suggest that glucose response during the OGTT in women with AN is altered in association with visceral adiposity acutely after full weight restoration, but that they do not develop overt insulin resistance. Glucometabolic profiling could offer novel insights to energy homeostasis acutely after weight restoration.

1. Introduction

Anorexia nervosa (AN) has the highest mortality among the psychiatric disorders (Eckert et al., 1995). The clinical features of AN are significant weight loss and an extreme fear of weight gain, leading to self-starvation that results in many medical complications including: electrolyte imbalance, amenorrhea, osteoporosis, and cardiac arrhythmias. These medical co-morbidities tend to resolve with weight restoration, which is a primary goal of treatment, but preoccupation with shape and weight and fear of fat often persist past resolution of weight status. Growing evidence suggests that patients' fears of uneven fat deposition during re-feeding may relate to preferential abdominal fat accumulation in the acutely recovered period (Grinspoon et al., 2001; Iketani et al., 1999; Mayer et al., 2009).

Although the central adiposity phenotype seemed inconsequential and harmless as it was shown to normalize after a maintenance period (Dellava et al., 2009; El Ghoch et al., 2014; Mayer et al., 2009), a single study has shown that even a small increase in abdominal fat is associated with the appearance of insulin resistance after partial weight restoration (Prioletta et al., 2011). Both abdominal adiposity and insulin resistance are features of metabolic syndrome (MetS), a cluster of metabolic derangements associated with increased risk of developing diabetes and cardiovascular disorders (Elks and Francis, 2010). This abnormal metabolic profile can be found in a subgroup of normal weight population, termed "metabolically obese normal weight" (MONW) individuals (Ruderman et al., 1981), and has been shown to have 4-fold increase in prevalence of central adiposity, glucose intolerance, and other features of MetS (Oliveros et al., 2014). In relation to this, it is unknown whether there are metabolic derangements other than visceral adiposity in patients with AN after full weight normalization.

Our primary investigative aim was to assess whether abnormalities in glucose homeostasis associated with abdominal fat accumulation persist after full weight restoration. It should be noted that glucose homeostasis in the AN population has been studied since the classical studies of OGTTs in AN in the 1930s (Sheldon, 1937; Sheldon and

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Young, 1938), leaving us with an extensive yet conflicting body of literature. For instance, in the underweight AN, insulin sensitivity has been reported to be increased (Fukushima et al., 1993; Zuniga-Guajardo et al., 1986), normal (Castillo et al., 1985; Prioletta et al., 2011), or decreased (Franssila-Kallunki et al., 1991; Pannacciulli et al., 2003). In the weight restored AN patients, contrary to Prioletta et al. that reports impaired insulin sensitivity with partial weight gain, two other studies report normal insulin sensitivity (Soman and Felig, 1980; Zuniga-Guajardo et al., 1986). However, comparability of these studies is limited, because one study does not specify the post-treatment weights making it unclear whether the patients had fully recovered their weight (Zuniga-Guajardo et al., 1986) and the other study shows data for patients with full recovery of weight without specifying the time point after full weight recovery they were studied (Soman and Felig, 1980). Consequently, we hypothesized a relationship between glucose homeostasis and central adiposity in a well characterized sample of weight restored women with AN consistent with central adiposity phenotype.

To this end, we aimed to provide a characterization of glucose homeostasis in our fully weight-restored AN patients (WR) compared to weight-matched healthy control subjects (HC), along with body composition analysis. We have determined steady-state estimates of insulin resistance and beta cell function using the homeostasis model assessment (HOMA) in AN, WR, and HC groups (Matthews et al., 1985). In addition, we assessed dynamic glucose response using oral glucose tolerance tests (OGTTs) in WR and HC participants. Lastly, we examined the association between parameters of glucose homeostasis with body composition. Our results provide novel insights into an aspect of metabolic health of the weight-restored patients with AN.

2. Materials and methods

2.1. Participants

Twenty-four women with AN and 10 healthy control women between the ages of 22–48 years participated in the study. All individuals were screened via the Structured Clinical Interview for DSM-IV-TR Axis I disorders including amenorrhea criterion. All participants provided informed consent prior to research participation. Data collection and analysis protocols were submitted to, approved by, and carried out in accordance with the institutional review board at the New York State Psychiatric Institute/Columbia University Medical Center (NYSPI/CUMC). This study was posted on ClinicalTrials.gov Identifier NCT00271921.

All subjects underwent semi-structured clinical interview for psychiatric and medical history to rule out significant psychiatric or medical illnesses by self-report. Additional medical stability was assessed by initial routine laboratory work including vital signs, clinical presentation on intake, complete blood counts and chemistries, urine drug screen and pregnancy test, reviewed by a licensed physician. All patients with AN met the DSM-IV-TR criteria for AN at admission. Patients were excluded from the study if they: met the criteria for an additional active Axis I disorder other than Major Depression, were on medications including oral contraceptives, had a history of suicide or injurious behavior within 6 months of the study, or had significant current or past medical histories including diabetes and heart diseases. Because weight restoration may have differential effects on glucose metabolism depending on binge-purge history or absence, we included both restricting (AN-R, N = 7) and binge-purge subtypes (AN-BP, N = 17) of AN, and patient groups were similar in demographic and clinical variables at admission. Controls were healthy, weight-stable, menstruating young women without histories of anorexia nervosa, other eating disorders, other psychiatric history, and significant medical issues including diabetes and heart diseases. They were matched for age, gender, and body mass indexes (BMI) to the weight-restored patients with AN.

Women with AN presented with BMI ranging from 13.1 to 18.5 kg/m^2 upon admission and were at 19.3 to 21.2 kg/m^2 upon weight normalization. Healthy controls had BMI ranging from 18.6 to 21.3 kg/m^2. Of the 24 females with AN, 4 individuals participated in weight-restored testing only and did not complete baseline testing at low weight, but as the focus of this paper is between WR patients and HC subjects, we included data from all 24 WR subjects. As different menstrual cycle is likely to create endocrine variabilities that affect glucometabolic hormones, all control subjects and patients with AN who had resumed menstruation were studied during the first half of their menstrual cycle.

2.2. Clinical treatment

Patients were admitted to the Eating Disorders Service of the General Clinical Research Unit (GCRU) at the NYSPI/CUMC. For the first one-two weeks of hospitalization, patients were weighed daily and prescribed calories in the form of food and liquid nutritional supplement (Ensure or Ensure Plus; Ross Nutritional, Columbus OH) to prevent weight loss. Patients then began the weight gain phase of treatment on the standardized caloric prescription plan with proven clinical utility, outlined in Haynos et al. (2016). Briefly, treatment consisted of structured behavioral program aimed at normalizing weight and eating behaviors with the goal rate of weight gain at around 1 kg per week until the patient reached 90% ideal body weight (IBW) as described in the 1959 Metropolitan Life Tables (approximately BMI of 19.5 kg/m^2) (Harrison, 1985). After attaining at least 90% IBW, patients enter a weight maintenance phase. All patients received standard cognitive-behavioral therapy (CBT) for relapse prevention for one year following discharge.

2.3. Data collection

2.3.1. Timing of data collection

Anthropomorphic measures, body composition assessments and all metabolic measurements were collected from patients with AN after reaching and maintaining 90% IBW for 2–4 weeks (56.2 ± 14.6 days after initiation of treatment, data available for N = 20, range 29–90 days), as well as from control subjects. In addition, patients with AN underwent initial data collection after medical stabilization and before the weight gain phase of treatment, and considering the clinical risk of extensive metabolic testing at this stage, we limited the initial data to a single fasting blood draw and noninvasive height-weight measurements.

2.3.2. Anthropomorphic and body composition measures

Height was measured to the nearest millimeter and weight was measured to the nearest pound on a balanced scale (Detecto, Webb City, MO) and converted to kilograms (kg) using a factor of 2.2. BMI was calculated according to standard formula of body weight in kg divided by height in meters squared. Body composition was assessed with the use of whole-body MRI either at the Program for Imaging in Cognitive Sciences of CUMC or at the St. Luke's-Roosevelt Hospital through the New York Obesity Research Center. In both centers, MRI machines were 1.5 T GE Systems (General Electric, Milwaukee, WI). All MRI images were analyzed for body composition by the Image Analysis Laboratory, affiliated with the New York Obesity Research Center. Cross sectional images were analyzed for total adipose tissue (TAT), visceral adipose tissue (VAT), and fat free mass (FFM) by 3 trained observers with the use of VECT image analysis software (Slice-O-Matic, Montreal, Canada) and volume calculations were conducted as in Mayer et al. (2009). MRI data was not available for one patient, and thus, body composition data from 23 patients and 10 control subjects were available for analysis. Total body fat percentage was calculated as TAT/weight × 100. Percentage visceral fat was calculated as VAT/TAT × 100 (VAT, %TAT) and as VAT/weight × 100 (VAT, %BW).

Table 1
Clinical characteristics of the study cohort.

	AN	WR	HC	p AN v. WR	p AN v. HC	p WR v. HC
N	20	24	10	–	–	–
Subtype, %Restricting	25.0	29.2	–	–	–	–
Age, years	29.5 ± 6.3	29.1 ± 5.8	28.7 ± 3.9	–	0.860	0.791
Height, m	1.64 ± 0.06	1.63 ± 0.06	1.65 ± 0.07	–	0.611	0.432
Weight, kg	43.6 ± 4.8	53.7 ± 4.2	55.2 ± 4.5	< **0.001** [L]	< **0.001** [L]	0.354
BMI, kg/m^2	16.2 ± 1.4	20.1 ± 0.5	20.2 ± 0.9	< **0.001** [L]	< **0.001**[L]	0.827
MRI Body Composition						
TAT, kg	–	13.6 ± 2.6	13.1 ± 2.3	–	–	0.570
Body fat percentage, %	–	25.2 ± 4.0	23.7 ± 3.5	–	–	0.318
FFM, kg	–	40.3 ± 3.4	42.1 ± 3.9	–	–	0.186
VAT, kg	–	0.77 ± 0.23	0.52 ± 0.30	–	–	**0.005** [L]
Visceral adiposity, %TAT	–	5.7 ± 1.5	3.8 ± 1.3	–	–	**0.001** [L]
Fasting Plasma						
Fasting glucose (mg/dL)	77.3 ± 8.3	84.5 ± 6.9	86.7 ± 5.8	< **0.001** [L]	**0.004** [L]	0.405
Fasting insulin (mU/L)	5.1 ± 2.5	5.7 ± 3.5	4.5 ± 2.1	0.674	0.676	0.384
Log(Fasting insulin)	0.66 ± 0.21	0.69 ± 0.22	0.60 ± 0.23	0.997	0.520	0.327
HOMA-B	213 ± 279	123 ± 139	70 ± 32	**0.001** [S]	< **0.001** [M]	0.374
Log(HOMA-B)	2.2 ± 0.3	1.9 ± 0.3	1.8 ± 0.2	< **0.001** [M]	< **0.001** [L]	0.374
HOMA-IR	1.0 ± 0.6	1.2 ± 0.7	1.0 ± 0.5	0.808	0.947	0.416
Log(HOMA-IR)	−0.06 ± 0.25	0.01 ± 0.22	−0.07 ± 0.24	0.480	0.948	0.406
Oral Glucose Tolerance						
1-h glucose	–	126 ± 34	113 ± 24	–	–	0.244
2-h glucose	–	91 ± 25	89 ± 15	–	–	0.791
3-h glucose	–	71 ± 20	76 ± 16	–	–	0.457
OGTT-AUC	–	17.6 ± 3.5	17.0 ± 2.2	–	–	0.536
MGR	–	2.0 ± 0.6	1.6 ± 0.3	–	–	**0.008** [L]
MGR_T	–	1.2 ± 0.3	1.0 ± 0.3	–	–	**0.046** [M]

Values are presented as means ± SD. Statistical comparisons between two sets of samples are shown as *p*-values, using paired (AN vs. WR) or unpaired (AN vs. HC, WR vs. HC) methods. Statistically significant *p*-values are in bold. Effect sizes are denoted for significant comparisons with a superscript by the *p*-value, using the absolute value of Hedges' *g* effect size ($|g|$) as follows: [L], large effect size or $|g| > 0.8$; [M], medium effect size or $0.8 > |g| \geq 0.5$; and [S], small effect size or $0.5 > |g| \geq 0.2$. Sample N values correspond to that shown in the top row, except for body composition values in WR group that have N = 23: body fat percentage, VAT, TAT, and VAT/TAT.

Underweight patients with anorexia nervosa, AN; patients after weight restoration, WR; lean healthy control volunteers, HC; body mass index, BMI; visceral adipose tissue, VAT; total adipose tissue, TAT; fat free mass, FFM; homeostasis model assessment, HOMA; HOMA estimate of beta cell function, HOMA-B; HOMA estimate of insulin resistance, HOMA-IR; oral glucose tolerance test, OGTT; area under the curve of OGTT glucose response curve, OGTT-AUC; glucose reactivity, maximum to minimum glucose ratio, MGR; time-adjusted glucose reactivity, MGR_T.

2.3.3. Blood sampling and OGTT

Metabolic assays were conducted at the Core Laboratory of the Irving Institute for Clinical and Translational Research/CTSA. Fasting blood samples were collected using standard venipuncture techniques from participants after an overnight fast. Samples were collected into polypropylene tubes containing EDTA (1 mg/ml) and aprotinin (500 U/ml) and immediately centrifuged to separate plasma and red blood cells. Plasma was stored at −80 °C until subsequent analysis. Fasting plasma samples were assayed for insulin using the Ultra-Sensitive Human Insulin RIA Kit from EMD Millipore (Specificity – Human Insulin 100%, Human Proinsulin 6%, Des 31,32 HPI 6%, Des 64,65 HPI 78%). Fasting glucose in venous blood was assayed with the Hitachi 912 automatic analyzer.

The oral glucose tolerance test (OGTT) was conducted following standard protocols with minor modifications to time-points as follows: baseline blood draws were conducted after an overnight fast, after which participants consume 75 g of a carbohydrate load in 10 ounces of liquid solution in approximately 2 min (Glucola - Ames Co., Elkhart, Indiana), followed by venous blood sampling for glucose levels at 0, 60, 120, and 180 min. During testing, participants' activity was limited and no eating or drinking was allowed.

2.4. Data analyses

2.4.1. HOMA estimates

The HOMA was used to estimate insulin resistance (HOMA-IR) and beta cell function (HOMA-B) from fasting plasma insulin and glucose. The original HOMA model estimates derived from Matthews et al (Matthews et al., 1985) were calculated as follows: HOMA-IR = fasting glucose (mM) × fasting insulin (mU/L)/22.5 and HOMA-B = 20 × fasting insulin (mU/L)/(fasting glucose (mM) − 3.5) × 100%. All available HOMA-IR and HOMA-B values are reported, but non-physiologic HOMA estimates were excluded when determining association with body composition.

2.4.2. OGTT analysis

The OGTT data were analyzed by comparing the glucose levels at individual time points, the area under the curve (AUC) calculated using the trapezoidal method, maximum to minimum glucose ratio (MGR) calculated as maximum glucose/minimum glucose after oral glucose load (Roslin et al., 2011, 2013), and time-adjusted MGR (MGR_T) calculated by MGR / time (hours) to standardize variable time intervals in our study compared to previous use. For some of the OGTT data (10% of both HC and WR groups), the peak glucose values after oral glucose bolus were smaller than fasting glucose level, and we reasoned that it is possible that we missed a true peak glucose due to our first time-point being 1 h rather than 15 min or 30 min within the first hour, which would yield a lower MGR than its true value, had we captured its true peak glucose value with a shorter time interval. For these data points, fasting glucose was used as maximum glucose value, unless the glucose response was multiphasic, in which case the latest peak glucose was used as the maximum glucose.

2.4.3. Statistical analysis

The significance level was set at 0.05 and tests were two-tailed unless otherwise indicated. Data are described as mean ± SD. Analyses were performed with R for Mac OS X, version 3.3.0 GUI 1.68 (http://www.R-project.org) and Prism 5.0a for Mac OS X (GraphPad Software, Inc.). For samples with $N > 7$, intra-group normality was assessed with D'Agostino & Pearson Omnibus and Shapiro-Wilk normality tests, and if there was any evidence of sampling from a non-Gaussian distribution, nonparametric tests were used to compare the group to other groups. To compare AN or WR data to HC data, the unpaired Student's *t*-test or the nonparametric Mann-Whitney test was used. To compare longitudinal data from AN with WR, the paired *t*-test or the nonparametric Wilcoxon matched paired test was used. To reduce the significant intra- and inter-subject variability in fasting insulin measures (Mather et al., 2001), insulin values and HOMA estimates were analyzed additionally after logarithmic transformation. Effect sizes were calculated using the Hedges' g to account for small sample sizes. Correlations were assessed using the Pearson's correlation method after logarithmic transformation of HOMA estimates.

3. Results

3.1. Body composition

The clinical characteristics of the study subjects are given in Table 1. By design, there were no differences in age and BMI between the WR patients and the controls. In addition, the groups were similar in total adipose tissue mass (TAT), fat free mass (FFM), and body fat percentage. As shown previously (Mayer et al., 2009), the WR patients showed a greater visceral adipose tissue mass (VAT) and percentage of visceral adiposity compared to the HC women.

3.2. Fasting glucose homeostasis

The underweight patients with AN had significantly lower fasting glucose and BMI compared to both WR and HC groups but comparable fasting plasma insulin levels. No differences in mean fasting plasma glucose or insulin were found between WR and HC groups.

We then used the fasting glucose and insulin measures to calculate beta cell function (HOMA-B) and insulin resistance (HOMA-IR) estimates. The mean HOMA-B was significantly higher in the underweight AN compared to both WR and HC groups, and there was no difference between WR and HC groups (Fig. 1A, Table 1). Mean HOMA-IR was not statistically different among the three groups (Fig. 1B, Table 1). However, a large population study of normal weight women has established HOMA-IR cut-off for the metabolically unhealthy MONW subgroup (HOMA-IR of 1.69 from ref. Conus et al., 2004). Using this, five of the 24 WR patients and none of the HC women (21% vs. 0%, Fischer's $p = 0.291$) had metabolically unhealthy estimates of insulin resistance.

3.3. Dynamic glucose response

In Table 1, we show the results of the 3-h OGTT. We found no differences in the average 1-, 2-, and 3-h postload glucose values, and the area under the curve of the response curves between WR and HC groups. Only one of the 24 WR patients and none of the HC group showed impaired glucose tolerance or prediabetes, and there was no overt diabetes, as defined by guidelines (ADA, 2016).

Curiously, we noticed that glucose response curves in many WR patients showed evidence of a rapid rise in glucose level after oral glucose load followed by a large decline (Fig. 2A). Even in the WR patients with peak glucose levels similar to the peaks in HC group, the decline in glucose levels appeared greater than in HC. We quantified this characteristic postload glucose reactivity using the maximum to minimum glucose ratio (MGR) (Roslin et al., 2011), which gives an index of glucose excursion relative to nadir reached. Using this construct, we found that WR patients had significantly higher MGR during the OGTT compared to HC women (Fig. 2B). When divided into high or low MGR groups based on the 90th percentile MGR value of the HC group, we also found a greater proportion of WR women to be with a high MGR (Fisher's $p = 0.024$). The difference in mean time-adjusted MGR (MGR_T) was also significant ($p = 0.046$, Hedges' $g = -0.785$), and the average duration between the maximum to minimum glucose levels were comparable between two groups (WR, 1.8 ± 0.5 h; HC, 1.8 ± 0.6 h; $p = 0.971$).

3.4. Relationship between parameters of glucose homeostasis and body composition

We performed correlation analyses to determine the relationship between glucose homeostasis (HOMA-B, HOMA-IR, MGR, MGR_T) and body composition (BMI, VAT, TAT, FFM) parameters. Given significant differences between groups seen in certain measures of glucose homeostasis and body composition, we performed correlation analyses in WR and HC groups separately, shown in Table 2. We found a significant inverse relationship between MGR_T and VAT in the WR group (Estimate = –0.789 ± 0.255, $p = 0.006$, Fig. 3), which remained significant after adjusting for age and BMI.

Given significant differences between groups seen in certain measures of glucose homeostasis and body composition, we performed correlation analyses in each group separately, shown in Table 2. The only association that we found to be significant was an inverse relationship between MGR_T and VAT in the WR group only, as shown in

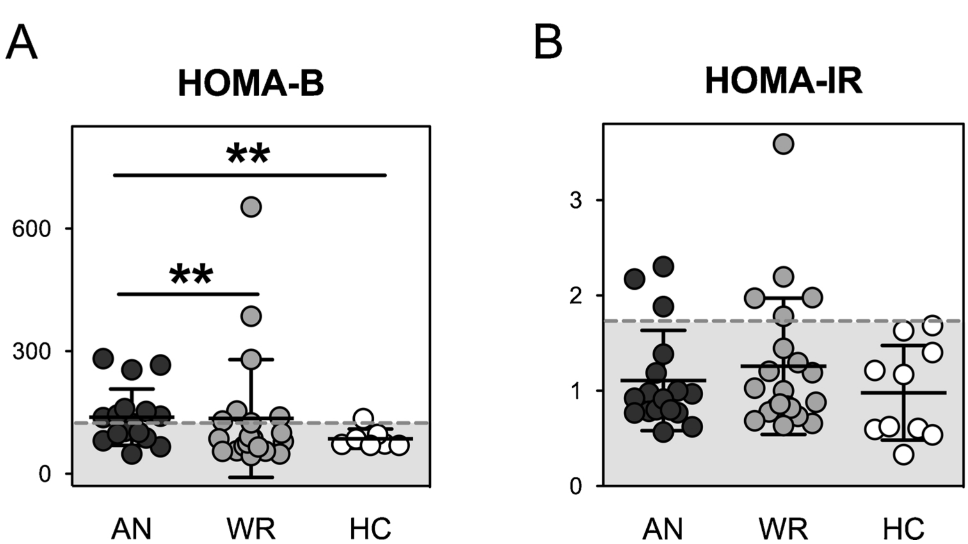

Fig. 1. Homeostasis model assessment estimates of beta cell function (A) and insulin resistance (B). Individual values are shown, as well as means ± SD. (A) Grey dashed line separates the values at the 90th percentile of HC (HOMA-B of 131.1). Statistical differences in pair-wise testing are denoted as follows: **, $P < 0.01$. (B) Grey dashed line separates the values at HOMA-IR of 1.69. None of the pair-wise comparisons were significantly different.

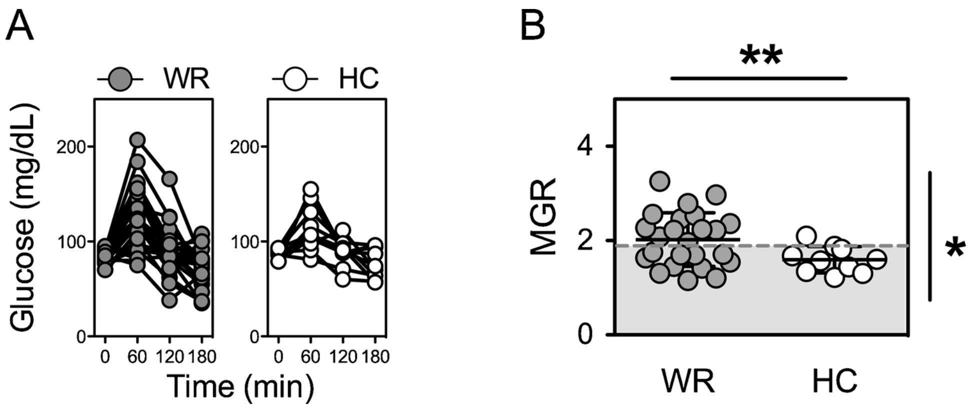

Fig. 2. Oral glucose tolerance test (OGTT). (A) Individual glucose response curves are shown. In (B), individual glucose reactivity (MGR) values are shown, as well as means ± SD. Grey dashed line separates the values at the 90th percentile of HC (MGR of 1.9). Top bar shows t-testing with Welch's correction of MGR values in WR and HC. Bar on the right denotes Fisher's exact test after categorizing each value as above or below the 90th percentile of HC. Statistical differences are as follows: *, $P < 0.05$; **, $P < 0.01$.

Table 2
Correlation analysis between glucose homeostasis and body composition parameters.

	WR		HC	
	r	*p*	*r*	*p*
Log(HOMA-B)				
BMI, kg/m^2	−0.339	0.105	0.014	0.972
FFM, kg	−0.105	0.634	−0.027	0.946
TAT, kg	−0.148	0.500	0.150	0.699
VAT, kg	−0.141	0.521	0.330	0.386
Log(HOMA-IR)				
BMI, kg/m^2	−0.218	0.307	0.052	0.894
FFM, kg	0.158	0.470	−0.037	0.924
TAT, kg	−0.105	0.644	−0.212	0.584
VAT, kg	0.073	0.739	0.019	0.961
MGR				
BMI, kg/m^2	−0.242	0.254	−0.479	0.192
FFM, kg	0.097	0.658	0.265	0.491
TAT, kg	−0.198	0.365	0.414	0.268
VAT, kg	−0.102	0.642	0.458	0.215
MGR$_T$				
BMI, kg/m^2	0.073	0.735	0.237	0.540
FFM, kg	−0.002	0.994	−0.615	0.078
TAT, kg	−0.273	0.208	0.027	0.944
VAT, kg	**−0.559**	**0.006**	−0.159	0.683

Correlation statistics *r* and *p*-values using the Pearson's method are shown. Pairs of individual glucose homeostasis parameters (column 1, bolded subheadings) with each body composition parameters were compared for WR and HC groups separately. The only statistically significant result (MGR$_T$ vs. VAT) is highlighted in bold. Body composition parameters in WR group was not available for one subject, and N = 23 for WR group, and N = 10 for HC.
Patients with anorexia nervosa after weight restoration, WR; lean healthy control volunteers, HC; body mass index, BMI; visceral adipose tissue, VAT; total adipose tissue, TAT; fat free mass, FFM; homeostasis model assessment, HOMA; HOMA estimate of beta cell function with logarithmic transformation, Log(HOMA-B); HOMA estimate of insulin resistance with logarithmic transformation, Log (HOMA-IR); glucose reactivity during oral glucose tolerance test, maximum to minimum glucose ratio, MGR; time-adjusted glucose reactivity, MGR$_T$.

Fig. 3 ($r = –0.559$, $p = 0.006$), which remained significant after adjusting VAT for either body weight ($r = –0.537$, $p = 0.008$) or *TAT* ($r = –0.438$, $p = 0.037$).

4. Discussion

To our knowledge, this study provides the first detailed characterization of fasting and postprandial glucose homeostasis together with body composition analysis in the weight-restored women with AN in relation to that of age- and BMI-matched healthy women. Differences in fasting glucose regulation seen in the underweight AN group seem to normalize with weight recovery, but 21% of WR patients had HOMA-IR estimates in the metabolically unhealthy range contrasting with metabolically healthy HOMA-IR seen in all of the HC women. Furthermore, a tight regulation of postprandial glycemic response was observed in both WR and HC groups with only one WR patient having impaired oral glucose tolerance. Dynamic glucose regulation in the WR patients is markedly different compared to lean healthy women, and we demonstrate an increased glucose reactivity in WR, measured by MGR and time-adjusted MGR$_T$. Thus, both visceral adiposity and MGR$_T$ are greater in the WR patients compared to HC, and within the WR group, these parameters are significantly and inversely associated.

4.1. Glucose homeostasis after weight restoration

Previous studies on insulin resistance in AN have reported variable findings in both underweight and weight restored groups (Castillo et al., 1985; Fukushima et al., 1993; Pannacciulli et al., 2003; Prioletta et al., 2011; Soman and Felig, 1980; Zuniga-Guajardo et al., 1986). In studies utilizing HOMA estimates, HOMA-IR means are reported to be 1–1.3 in underweight patients similar to our study, but contrast with our study in that they report a substantial increase in the mean HOMA-IR from 1.3 to 1.8 after weight recovery (Modan-Moses et al., 2007) or higher HOMA-IR in their healthy cohort (Tagami et al., 2004). Larger studies are needed to address these differences.

In addition to the fasting measures of glucose homeostasis, altered glucose response during the OGTT have been described in underweight patients with AN in relation to altered insulin response and treatment outcomes (Nozaki et al., 1994; Tanaka et al., 2003; Yasuhara et al., 2006, 2005; Yasuhara et al., 2003). Corresponding changes after weight restoration have been reported in two studies in adult patients, which show that the aberrant glucose response in the underweight AN *normalize* after weight gain, but these studies lack data from weight-matched healthy controls (Casper et al., 1977; Kanis et al., 1974). In contrast to this, studies where weight-restored adult patients were compared to healthy adults using methods other than OGTTs, abnormalities in insulin secretion in the underweight AN were found to be *sustained* even after reaching the healthy weight (Kinzig et al., 2007; Kobayashi et al., 1992).

Characterization of glucose reactivity in weight restored patients with AN compared to healthy subjects is lacking in literature to date. In addition, none of the studies reporting glucose homeostasis after full weight restoration mention whether the patients develop central adiposity, and hence, it is unclear whether the metabolic profiles and study findings of their patient cohorts are comparable to study results from patient groups with known visceral adiposity, and we believe that inconsistent findings of glucose metabolism in anorexia literature could be secondary to differing body fat composition in the subjects. As previously reported (Mayer et al., 2009), we show that WR patients have increased visceral adiposity compared to healthy women with similar BMI and body fat percentage, and we add this novel finding of increased glucose reactivity in WR group to our understanding of the metabolic phenotype in this unique patient population.

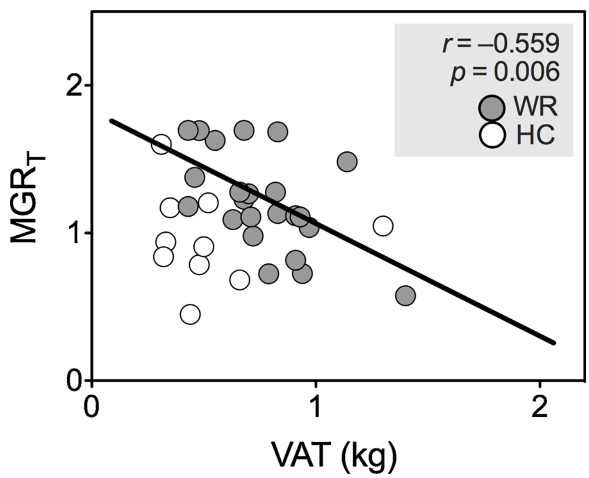

Fig. 3. Inverse relationship between MGR_T and VAT in the WR group. Data points for WR are shown in grey circles, with best-fit line ($y = -0.789x + 1.817$). Correlation statistics and figure legend are shown in light grey box on top right. For comparison, HC data points are shown overlaid with the WR data in white circles.

4.2. Reactive glucose response, insulin sensitivity, and visceral adiposity

Glucose response with a relatively high glycemic peak to a low glucose nadir has many names in literature, most commonly reactive hypoglycemia (RH), and this can present with symptoms of dizziness, fatigue, and hunger, or be asymptomatic (Brun et al., 2000). The optimal criterion for diagnosis and definition of RH in the clinical realm appears to be controversial, but research studies have used various measures to quantify RH during the OGTT either alone or in combination with other methods, including the level of glucose nadir (cutoff ranging from 50 to 70 mg/dL), rate of glucose decline, presence of hypoglycemic symptoms, and hypercortisolemic response (Brun et al., 2000). We chose the maximum to minimum glucose ratio, which incorporates glucose nadir with the rate of glucose decline, utilized in a series of studies in morbidly obese patients following Roux-en-Y gastric bypass (RYGB) patients (Roslin et al., 2011, 2013). These studies report that most of the post-RYGB patients who lose weight followed by weight regain had reactive glucose response patterns with MGR above 3 with several ratios above 4. These results are from a cohort that included both men and women with an older average age 49.5, and they report an MGR range of 1.5–2 as their healthy reference. The MGR range in our HC and WR cohorts were 1.2–2.1 and 1.1–3.3, respectively, but direct comparability with previous studies is unclear due to that lack of data regarding the age, BMI, body composition, and gender of their healthy cohort. It is reasonable that our MGR values were overall lower due to our entire cohort being non-obese and non-diabetic at baseline, with lower degree of abnormality in glucose regulation. Interestingly, most of the post-RYGB patients had rapid increase in serum glucose 1 h post glucose load followed by a rapid decline at 2 h post glucose load (Roslin et al., 2011), whereas in our study, while most WR patients also had a rapid rise in glucose levels by 1 h, the glucose nadirs often reaching hypoglycemic range occurred mostly at 3 h post glucose load. We therefore calculated MGR_T, which would adjust MGR such that a more rapid rise and fall would have a higher ratio than a more temporally restrained rise and fall (i.e. the same MGR would yield a twice as high MGR_T if the glucose excursion happens in 1-h versus 2-h intervals).

Notably, both early stages of insulin resistance with hyperinsulinemia and increased insulin sensitivity even with hyposecretion of insulin have been associated with reactive glucose response (Guiducci et al., 2014). The current study did not include measures of insulin response during the OGTT to be able to elucidate the mechanism of reactive glucose response. However, given the association of visceral adiposity with insulin resistance (Conus et al., 2004; Freedland, 2004), together with the inverse association between MGR_T and VAT in WR seen in our study, we hypothesize that reactive glucose response (i.e. a higher MGR_T) in WR may be secondary to insulin hypersensitivity, which is attenuated with increasing degree of VAT accumulation and presumably associated decrease in insulin sensitivity or clearance.

4.3. Potential clinical implications: behavioral correlates of glucose homeostasis

We observed metabolically unhealthy HOMA-IR levels in 21% of the WR patients and none in the HC women. Conus et al. has reported that lower dietary restraint is a predictor of elevated HOMA-IR in the MONW women (Conus et al., 2004). In relation to this, central body fat deposition has also been associated with higher risk for loss of control eating in normal weight adult women without any eating disorders (Berner et al., 2015), but no study has examined how and whether body fat redistribution after weight restoration is related to eating behavior in the binge-eating/purging subtype. Further research is needed to determine whether there is any predictive power in posttreatment glucose reactivity, insulin sensitivity, or visceral adiposity, either singly or in combination.

With regards to the MGR method, it was particularly attractive because of the association of the characteristic with long-term weight maintenance – Roslin et al. propose that such rapid rise and decrease in blood glucose may lead to increased hunger sensation followed by maladaptive eating behaviors that contribute to eventual weight regain in weight-reduced post-RYGB patients. This is related to one of the classic theories of eating behavior known as the glucostatic theory, proposed by Jean Mayer, which centers around blood glucose changes as the determinant of satiety and feeding behavior (Chaput and Tremblay, 2009; Mayer, 1955). Although it is incompletely understood, relative hypoglycemia perceived by a network of glucose-sensing neurons in the hypothalamus appears to reduce satiety and leads to feeding behaviors (Ogunnowo-Bada et al., 2014), as neural modulation of these glucose-sensing neurons leads to predictable changes in feeding behavior in rodent models (Stanley et al., 2016). Given the elevated MGR in WR patients with AN compared to HC, it may be worthy to consider glucose metabolism as a surrogate measure of a behavioral correlate that may be predictive of long-term weight relapse in WR patients.

Although it should be noted that underweight patients with AN of both subtypes with reactive glucose response during pretreatment OGTT, defined as glycemic nadir less than 70 mg/dL, tended to have higher energy intake and better refeeding progress in the inpatient setting (Yasuhara et al., 2005), this might be an effect of the structured and positively reinforcing environment of the inpatient program. In the outpatient milieu during the maintenance phase, glucose reactivity may differentially affect eating behavior. It is conceivable that glucose fluctuation may confer differential risk of perpetuating maladaptive eating patterns that would contribute to subsequent weight relapse. If our preliminary findings are replicated, future research could be directed to determine whether increased glucose reactivity is associated with long-term weight maintenance, as well as the relationship of eating patterns and eating disorder psychopathology to aberrant glucose response. It would be a powerful step forward to simultaneously assay multiple aspects of metabolic profile acutely after weight restoration, followed by longitudinal assessments of eating disorder psychopathology and weight maintenance, such that we may identify effective biomarkers to improve treatment outcome.

4.4. Strengths and limitations of our study

Our investigation is strengthened by having fasting and dynamic measures of glucose homeostasis together with the MRI-based body composition analysis. Glucose homeostasis in relation to body composition data has never been previously reported for the fully weight-recovered adult patients with AN, and in addition to the novelty, it builds a powerful dimensionality into our understanding of an individual's metabolic phenotype. Other strengths of this study included having age-, BMI-, and gender-matched healthy subjects, as well as including both subtypes of AN.

We recognize, however, a number of limitations to this study. A major limitation of our study is that fasting estimates of HOMA-IR are highly dependent on the fasting insulin measures, which are notoriously variable due to insulin assay variability, subject-to-subject variability, as well as variable plasma insulin levels in the same person from the cyclical nature of insulin secretion, length of fast, stress, and insulin clearance (Matthews et al., 1985; Wallace et al., 2004). The fact that we were able to capture significant novel findings despite variabilities in insulin measures lends further strength to our findings. Secondly, we performed the OGTTs in the WR patients only after weight-recovery, without characterizing longitudinal changes in glucose response curves before and during weight gain. However, because our main objective was to characterize the glucose response in WR compared to weight-matched HC, and because the pretreatment OGTTs in women with AN have been well documented (Casper, 1996; Yasuhara et al., 2005), we sought to focus only on the acutely weight restored state. A related limitation may be that OGTTs are highly variable even in the same individual, but similar to insulin measures, the fact that we captured significant differences despite potential for high variability adds to the strength of our finding. Lastly, we acknowledge that oral glucose challenge without measuring insulin response at various time points after oral glucose load is also a significant limitation. A detailed characterization of insulin dynamics in the WR patients in relation to body composition data would be important, especially if elevated MGR is mediated by hyperinsulinemia, a stepping stone for insulin resistance and diabetes (Goel, 2015), or insulin hypersensitivity, because abnormal glycemic control is prevalent in patients with AN who have relapsed in the long term (Casper et al., 1988).

The classic gold standard of insulin resistance measurement is the hyperinsulinemic euglycemic clamp technique (HEC) (DeFronzo et al., 1979), but the HEC is costly, time intensive, and somewhat invasive and technical, which prevents the general application of this test in clinical practice. In contrast, the HOMA model using only the fasting blood samples allows us to measure both the beta cell function and insulin resistance in a simple and accessible way, and it has been shown that HOMA indices were repeatable and highly correlated with HEC measures despite being less robust in insulin sensitive subjects compared to insulin resistant subjects (Mather et al., 2001). In addition, some authors suggest the more complex HOMA-2 model due to numerous limitations of the HOMA indices (reviewed in Wallace et al., 2004), but there are no existing population studies comparable to WR patients to provide reference values for HOMA indices. Because a previous study of in a large group of young nonobese women in the United States had established a HOMA-IR of 1.69 as the cut-off for the "metabolically obese normal weight" profile, in tandem with the well-correlated HEC measures (Conus et al., 2004; Dvorak et al., 1999), we used the original HOMA model.

5. Conclusion

Despite eight decades of fascination with glucose tolerance in patients with AN (Casper, 1996; Sheldon, 1937) and the simplicity of administering this test in a clinical setting, the glucometabolic profiling is not routinely employed before, during, or after treatment, which suggests a potentially missed opportunity to detect subtle but critical metabolic differences in the WR patients prior to discharge. This study found that glucose reactivity and visceral adiposity can be both elevated in WR, which extends the accumulating evidence that acutely weight restored women with AN can have a differential metabolic profile compared to that of healthy women of similar age and BMI. Furthermore, the two dysregulated parameters are significantly and inversely correlated, offering a novel venue to characterize the complex state of energy balance acutely after weight restoration. Future studies are needed to address the clinical implications of whether and how glucose metabolism and body composition are related to maladaptive eating behaviors and attitudes, as well as to long-term recovery from AN.

Author contributions

The authors contributed as follows: LESM, study design and data collection; YRK, data analysis and interpretation, preparation of all figures, and drafting of the manuscript; TH, critical revision of the manuscript. All authors reviewed and approved the final manuscript.

Declaration of Competing Interest

Authors have no conflicts of interest to disclose.

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