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Late-phase glucose dynamics, insulin sensitivity and body-fat distribution in adults with obesity with and without binge-eating disorder

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Abstract

Binge-eating disorder (BED) is frequently associated with obesity, but its metabolic phenotype beyond body mass index remains incompletely characterized. We examined late-phase oral glucose tolerance test (OGTT) dynamics, insulin sensitivity and regional fat distribution in a retrospective cohort of adults with obesity (BMI ≥ 30 kg/m²) and HbA1c < 6.0%. The primary dynamic measure was the late glucose decline rate (LGDR120–180), the relative fall in glucose between 120 and 180 min. Among 1 034 participants (238 with BED), those with BED had lower 180-min glucose (median 70 vs 74 mg/dL; AUC 0.591) and faster late glucose decline (35.9 vs 30.9%/h; P = 0.020). In the complete-case multivariable model (n = 694; 173 with BED), LGDR remained associated with BED after adjustment for 120-min glucose, sex, BMI and upper/lower fat ratio (OR 1.19 per 10%/h, 95% CI 1.07–1.33), and persisted after participant-level deduplication. Adding LGDR improved model fit (likelihood-ratio P = 0.001) but did not significantly increase discrimination (AUC 0.584 to 0.616; P = 0.099; optimism-corrected AUC 0.598), and did not outperform 180-min glucose alone. Participants with BED also showed lower HOMA-IR (2.90 vs 3.33), a higher Matsuda index (4.42 vs 3.91) and a lower upper/lower fat ratio (1.55 vs 1.69); LGDR remained associated with BED after separate adjustment for either index. Metabolic syndrome, metabolically healthy obesity and menopause did not explain the association. In adults with obesity without diabetes, BED is associated with faster late-phase glucose decline and modestly greater insulin sensitivity. These cross-sectional, hypothesis-generating findings do not support LGDR as a diagnostic biomarker and require prospective validation.

Introduction

Binge-eating disorder (BED) is characterized by recurrent episodes of binge eating accompanied by a sense of loss of control and without the regular compensatory behaviors that define bulimia nervosa.[1] BED is strongly associated with obesity and with metabolic complications, although the relationship is not fully explained by body mass index (BMI) alone.[2–4] The coexistence of BED and obesity is therefore clinically relevant not only because of excess adiposity, but also because behavioral and metabolic mechanisms may interact.[5,6]

One potential mechanism concerns post-load glucose dynamics. Oral nutrient ingestion induces a coordinated sequence involving intestinal nutrient sensing, incretin signaling, pancreatic insulin secretion, hepatic glucose handling and peripheral glucose disposal. An oral glucose tolerance test (OGTT) provides a standardized metabolic perturbation in which the temporal relationship between glucose and insulin can be examined rather than relying solely on fasting measurements or integrated exposure.[7–10]

Our previous work provided the rationale for the present analysis. In 1 166 non-diabetic patients with obesity undergoing a 3-h OGTT and psychological assessment, participants with BED had significantly lower glucose at 180 min and significantly higher insulin at 180 min, whereas glucose and insulin area

under the curve were not significantly different.[11] These observations suggested that the late phase of the OGTT may contain information that is not captured by total glucose or insulin exposure.

Subsequent work has strengthened the biological plausibility of late glycemic disturbances in BED. In a 5-h OGTT study of 200 people with high weight and no diabetes, reactive hypoglycemia was common and severe hypoglycemia was more frequent at the late stage of the OGTT in participants with BED.[12] A recent Translational Psychiatry study further showed that OGTT-derived glucose and insulin-sensitivity features can contribute to BED characterization in individuals with high weight.[13] These observations raise a more specific question: is the metabolic signal in BED simply a lower late glucose value, or does BED involve altered dynamic coupling between glucose and insulin?

Conventional indices such as the homeostasis model assessment of insulin resistance (HOMA-IR) summarize fasting physiology, whereas the Matsuda index integrates glucose and insulin responses during the OGTT.[8] These measures do not directly quantify the shape of the late glucose trajectory. We therefore defined an exploratory Late Glucose Decline Rate (LGDR) to quantify the relative speed of glucose decline during the final hour of the OGTT, while retaining the glucose–insulin coupling indices as secondary mechanistic descriptors.

We hypothesized that BED would be associated with a faster late glucose decline and that LGDR would provide information complementary to the absolute 180-min glucose concentration after accounting for the glucose level at 120 min, sex, overall adiposity and adipose distribution.

Materials and methods

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Policlinico Umberto I–Sapienza University of Rome (protocol CE5475, approved on 24 October 2019, and amendment protocol no. 0513/2024, approved on 6 June 2024). The present secondary retrospective analysis is covered by these approvals. The study was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent to the use of their clinical data for research purposes.

Study design and population

This was a retrospective observational analysis of an existing clinical database of individuals evaluated in an obesity clinical setting. The source dataset included anthropometric, metabolic, OGTT-derived and psychiatric/eating-behavior variables. Participants with HbA1c ≥6.0% were excluded from the present analysis. The primary analysis was restricted to BMI ≥30 kg/m². A broader BMI ≥25 kg/m² population and a BMI ≥35 kg/m² population were retained as sensitivity cohorts. Adults evaluated between 2022 and 2025 were eligible. Exclusion criteria were previous bariatric surgery, pregnancy, use of glucose-lowering drugs or systemic corticosteroids, and severe chronic diseases. The HbA1c threshold of 6.0% was used as an operational criterion to exclude participants in the upper prediabetic range (6.0–6.4%);

participants with HbA1c 5.7–5.9% were therefore retained. The study is reported in accordance with the STROBE guidelines.

The terms “without diabetes” and “non-diabetic” are used operationally to denote this HbA1c-based analytic criterion and do not imply formal clinical adjudication of diabetes status in every participant. The obesity-only primary analysis was selected because only 71 participants in the broader cohort without diabetes had BMI <30 kg/m², while 238 BED cases were retained in the primary cohort.

BED definition

BED was identified using the Binge Eating Scale (BES) (>17), and BED status was recorded in the clinical database as a binary variable (present/absent). Psychiatric diagnostic variables that overlap with the BED classification were not entered as predictors because doing so could introduce circularity or target leakage.

OGTT

After an overnight fast, participants underwent a 3-h OGTT with 75 g glucose. Glucose and insulin were measured at 0, 30, 60, 90, 120 and 180 min. Plasma glucose and insulin concentrations were measured by the hexokinase method and by electrochemiluminescence immunoassay (ECLIA), respectively (Roche Diagnostics GmbH, Mannheim, Germania).

Late glucose decline rate and glucose–insulin coupling indices

Glucose (G) and insulin (I) concentrations are denoted by the sampling time in minutes (for example, G120 is glucose at 120 min). The primary exploratory LGDR120–180 was calculated as: LGDR120–180 = [(G120 − G180) / G120] × 100, expressed per hour because the interval between 120 and 180 min is 60 min. Higher values therefore indicate a faster relative late glucose decline. The absolute slope, (G180−G120)/60, was examined as a secondary measure. Negative values were retained when G180 exceeded G120, indicating a late glucose rise rather than decline; because the measure is normalized by G120, large negative values can occur when G120 is relatively low.

The 0–180-min relative glucose decline was calculated as [(G0−G180)/G0]×100 and was used as a secondary whole-test trajectory measure. LGDR was treated as an exploratory descriptor of glucose dynamics and not as an established clinical biomarker.

The primary late glucose–insulin coupling index (LGICI120–180) was calculated as (I180 − I120) / (G180 − G120).

A relative LGICI was also evaluated as [(I180−I120)/I120] / [(G180−G120)/G120], because absolute coupling can be unstable when the glucose denominator approaches zero.

The broader 0–180-min ΔInsulin/ΔGlucose index was calculated as (I180−I0)/(G180−G0). These coupling measures were treated as secondary exploratory descriptors.

Insulin sensitivity

The Matsuda insulin sensitivity index was calculated as 10 000/√(G0 × I0 × Gmean × Imean), where Gmean and Imean are the means of the 0-, 60-, 120- and 180-min OGTT values, according to the composite formulation described by Matsuda and DeFronzo.[8] Because the corrected Matsuda calculation includes G180, Matsuda was not interpreted as an independent predictor of G180. OGTT-derived insulin-sensitivity indices were interpreted cautiously in light of known confounding by factors other than insulin sensitivity itself.[9]

HOMA-IR was evaluated as a conventional fasting insulin-resistance descriptor (calculated as fasting insulin [μU/mL] × fasting glucose [mg/dL]/405) and was treated as a secondary sensitivity covariate. HOMA-IR and Matsuda were entered in separate models because they summarize different physiological domains and because Matsuda incorporates OGTT glucose values including G180.

Adiposity and body-fat distribution

BMI was used as the global adiposity measure. Body composition was assessed by dual-energy X-ray absorptiometry (DXA; QDR Discovery Acclaim, Hologic Inc., Waltham, MA), and the upper/lower fat ratio was calculated as trunk fat mass/leg fat mass. Upper/lower fat ratio was retained as a prespecified measure of regional adipose distribution because it captures information not provided by BMI alone. Total body-fat percentage, fat mass and trunk fat were considered secondary variables and were not simultaneously forced into the primary model to limit collinearity.[14–18]

Exploratory endocrine variables

Free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH), insulin-like growth factor 1 (IGF-1) and dehydroepiandrosterone sulfate (DHEA-S) were measured as part of the routine clinical evaluation using chemiluminescence immunoassays (LIAISON XL analyser, DiaSorin S.p.A., Saluggia, Italy). These variables were analysed as exploratory correlates, and their association with BED and with the LGDR–BED association was examined in additional adjusted models.

Statistical analysis

Exploratory trajectory clustering. For exploratory validation of OGTT trajectory phenotypes, participants with BMI ≥30 kg/m², without diabetes and complete glucose measurements at 0, 30, 60, 90, 120 and 180 min were included. Glucose trajectories were normalized to baseline glucose and standardized before k-means clustering. Solutions with k=2–4 clusters were compared using silhouette width and within-cluster dispersion. The selected solution was evaluated by 200 bootstrap resamples using the adjusted Rand index. BED prevalence across clusters was assessed descriptively and by logistic regression adjusted for age, sex and BMI. This analysis was considered exploratory and was not used to redefine the primary outcome.

Continuous variables were examined for distributional characteristics and summarized using appropriate descriptive statistics. Between-group comparisons used non-parametric tests where appropriate. Receiver operating characteristic (ROC) curves and the area under the curve (AUC) were computed for G180, LGDR120–180, 0–180-min LGDR and the prespecified secondary metabolic variables.

For each ROC analysis, the exploratory Youden index was calculated as J = sensitivity + specificity − 1. The cut-point maximizing J was retained as the exploratory threshold. These thresholds were not considered clinically validated diagnostic cut-offs.

The primary multivariable logistic regression model included G120, LGDR120–180, sex, BMI and upper/lower fat ratio. G180 was not entered into this model because it is mathematically determined by G120 and the late glucose decline. Associations are reported as odds ratios (ORs) with 95% confidence intervals (CIs).

Missing data were handled by complete-case analysis for models requiring the relevant variables. ROC analyses used all participants with non-missing values for the variable under study. Sensitivity analyses considered BMI ≥25 kg/m², BMI ≥35 kg/m², removal of upper/lower fat, and removal of LGICI from the reference model. Because the source database contained repeated records for a small number of participants, a participant-level sensitivity analysis was also performed by retaining one eligible record per participant, prioritizing a record with complete primary-model variables and then the earliest eligible year. The primary model was evaluated for incremental value of LGDR using a likelihood-ratio test, and discrimination was compared with G180 using DeLong's paired AUC test on the common complete-case cohort. Linearity of the LGDR association was examined using a restricted cubic spline (natural cubic spline, 3 degrees of freedom). Internal optimism was estimated with 2 000 bootstrap resamples, and 10-fold cross-validated AUC was calculated. Statistical analyses were performed using two-sided tests; $P<0.05$ was considered statistically significant for the primary association analyses, while ROC and Youden analyses were interpreted as exploratory. No correction for multiple comparisons was applied to secondary and exploratory analyses. Analyses were performed using Statistica version 14 (StatSoft Inc., Tulsa, OK, USA), IBM SPSS Statistics version 27 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 10 (GraphPad Software, San Diego, CA, USA).

Additional prevalence analysis

As a complementary analysis, we estimated the prevalence of the pre-existing database diagnoses of metabolic syndrome and metabolically healthy obesity (MHO) separately in participants with and without BED among adults with obesity (BMI ≥30 kg/m²) and without diabetes. Wilson 95% confidence intervals were calculated for proportions. Separate logistic regression models used BED status as the exposure and each diagnosis as the outcome, with adjustment for age, sex and BMI. Missing diagnosis values were excluded from the corresponding analysis. Diagnoses were accepted as recorded in the database and were not reconstructed from individual components.

Results

Study population

After applying the HbA1c criterion and restricting the primary analysis to BMI ≥30 kg/m², 1 034 participants with valid BED classification were available; 238 had BED and 796 did not (Table 1). The broader cohort without diabetes (BMI ≥25 kg/m²) contained 1 105 participants and 252 BED cases, while the BMI ≥35 kg/m² sensitivity cohort contained 781 participants and 191 BED cases (Supplementary Table S1).

180-min glucose and late glucose decline

The previously identified late glucose phenotype was confirmed. G180 was lower in participants with BED than in those without BED (median 70.0 vs 74.0 mg/dL; AUC 0.591, $P=8.43\times10^{-5}$). LGDR120–180 was also higher in BED, with median values of 35.9%/h versus 30.9%/h in non-BED participants (P=0.0195). Among 846 participants with complete LGDR data, the ROC AUC was 0.554. The exploratory Youden-optimal threshold was 38.89%/h, with sensitivity 45.8%, specificity 66.6%, and J=0.124 (Figs. 1 and 2; Supplementary Table S5).

Late glucose–insulin coupling

The absolute 120–180-min LGICI showed modest discrimination (AUC 0.543, P=0.0728), whereas relative LGICI showed AUC 0.549 (P=0.0396). The 0–180-min ΔInsulin/ΔGlucose index showed AUC 0.557 (P=0.0187). These indices therefore provided weaker discrimination than the late glucose trajectory measures and were retained as secondary mechanistic descriptors (Supplementary Table S5; Supplementary Fig. S1).

For the 0–180-min ΔInsulin/ΔGlucose index, medians were 0.087 and 0.009 in participants without and with BED, respectively. The Youden-optimal threshold was ≤0.0091, with sensitivity 51.1%, specificity 61.5% and J=0.126. These findings support a modest alteration in the relationship between insulin exposure and the glucose trajectory, but do not establish an independent diagnostic signal.

Robustness, incremental value and sensitivity analyses

On the common complete-case cohort (n=694), G180 had an AUC of 0.585, whereas LGDR120–180 had an AUC of 0.541 (the variable-specific ROC analysis yielded AUC 0.554 in a larger available-case sample); the paired DeLong comparison was not significant (P=0.196). The full model containing G120, LGDR120–180, sex, BMI and upper/lower fat achieved an apparent AUC of 0.616 (95% CI 0.566–0.665). Adding LGDR to the model containing G120 and the prespecified covariates improved model fit (likelihood-ratio P=0.0014), but the AUC increase from 0.584 to 0.616 was not significant by DeLong testing (P=0.099), and the full model did not significantly outperform G180 alone (P=0.114). The linear specification was supported by restricted cubic-spline analysis (non-linearity P=0.951). Internal validation gave an optimism-corrected AUC of 0.598 and a 10-fold cross-validated AUC of 0.594. In the

participant-level deduplicated sensitivity cohort (n=1 023; LGDR available in 841), LGDR remained higher in BED (median 35.86 vs 30.93%/h; P=0.022), with AUC 0.554, and remained associated with BED in the adjusted model (OR per 10%/h 1.185, P=0.003) (Fig. 3; Supplementary Table S4).

Adipose distribution

Upper/lower fat showed AUC 0.572 (P=0.00211), exceeding the discrimination observed for BMI alone (AUC 0.526, P=0.23). Median upper/lower fat was 1.687 in participants without BED and 1.553 in those with BED. The Youden-optimal threshold was ≤1.666, with sensitivity 64.9%, specificity 52.2% and J=0.170, the highest Youden index among the evaluated variables (Supplementary Table S5; Supplementary Fig. S2).

Multivariable analysis

The primary complete-case model included G120, LGDR120–180, sex, BMI and upper/lower fat ratio (n=694; 173 BED cases). LGDR120–180 remained associated with BED after adjustment for G120 and the prespecified covariates (OR per 10%/h increase 1.191, 95% CI 1.066–1.331, P=0.002), whereas G120 was inversely associated with BED (OR per 10 mg/dL 0.890, 95% CI 0.821–0.964, P=0.004). Sex, BMI and upper/lower fat were not independently significant (Table 2).

Unsupervised OGTT trajectory clustering

Unsupervised clustering of normalized 0–180-min glucose trajectories in participants with complete OGTT data (n=829) identified two trajectory phenotypes; the two-cluster solution was optimal and highly stable on bootstrap resampling (200 resamples) (Fig. 4). One phenotype showed a gradual late decline (n=486; median LGDR 25.3%/h), whereas the other showed a rapid late decline (n=343; median LGDR 41.2%/h). The rapid-decline phenotype had substantially higher 120-min glucose but similar 180-min glucose. BED prevalence was numerically lower in the rapid-decline phenotype (20.5% vs 26.2%), but this difference was not statistically significant after adjustment for age, sex and BMI (adjusted OR ≈0.72; P=0.055).

Additional metabolic, menopausal and thyroid sensitivity analyses

Sensitivity analyses further characterized the metabolic phenotype. HOMA-IR was modestly lower in participants with BED than in those without BED (median 2.90 vs 3.33; P=0.043), whereas the Matsuda insulin sensitivity index was modestly higher (4.42 vs 3.91; P=0.036). Importantly, LGDR120–180 remained independently associated with BED after adjustment for HOMA-IR (OR 1.188 per 10%/h, 95% CI 1.060–1.332; P=0.003) and in a separate model including the Matsuda index (OR 1.199 per 10%/h, 95% CI 1.067–1.347; P=0.002). Neither HOMA-IR nor Matsuda was independently associated with BED in these models. These analyses indicate that the LGDR association is not simply explained by conventional estimates of insulin resistance/sensitivity, although Matsuda is mathematically dependent on OGTT glucose values and was therefore retained as a sensitivity analysis rather than a primary covariate.

Neither MHO nor metabolic syndrome was significantly associated with BED (see BED-stratified prevalence analysis below). Formal interaction testing did not support effect modification of the LGDR–BED association by MHO (LGDR×MHO P=0.919) or metabolic syndrome (LGDR×metabolic syndrome P=0.583). Thus, the late glucose trajectory signal was not attributable to either metabolic-health classification.[14,19]

Among women, menopausal status was derived from the recorded age at menopause (417 premenopausal, 367 postmenopausal and 15 with missing status). BED prevalence did not differ between non-menopausal and post-menopausal women (24.7% vs 25.9%; P=0.765). LGDR was higher in women with BED than in those without BED among non-menopausal women (35.65 vs 29.34%/h; P=0.020), whereas the difference was attenuated after menopause (34.77 vs 34.32%/h; P=0.718). However, the formal LGDR×menopausal-status interaction was not significant (P=0.298), so this stratified pattern should be considered exploratory.

Thyroid parameters showed a potentially relevant signal. FT3 was modestly higher in BED than in non-BED participants (median 3.30 vs 3.20 pg/mL; P=0.044), whereas FT4 (1.13 vs 1.16; P=0.066) and TSH (2.23 vs 2.10; P=0.365) were not significantly different. In the adjusted model, FT3 remained independently associated with BED (OR 1.46 per 1-pg/mL increase, 95% CI 1.01–2.10; P=0.043), while LGDR remained significant (OR 1.017 per 1%/h; P=0.012). FT4 and TSH did not show independent associations. The FT3/FT4 ratio was also modestly higher in BED (P=0.009) and remained associated with BED after adjustment (OR 1.45 per unit; P=0.038).

An exploratory LGDR×FT3 interaction was significant in the full cohort (P=0.037), suggesting that the strength of the LGDR–BED association may vary across the FT3 range. However, after restricting the analysis to women and adjusting for menopausal status, the interaction was attenuated and no longer statistically significant (P=0.084), while the main association of LGDR with BED remained significant (P=0.007). Accordingly, FT3 should be regarded as an exploratory metabolic/endocrine correlate rather than an established effect modifier of the late glucose trajectory. LGDR correlated inversely with IGF-1 (rho=−0.118, P=0.0024) and DHEA-S (rho=−0.134, P=0.0033), but these variables did not independently explain the LGDR–BED association.

BED-stratified prevalence of metabolic syndrome and MHO

The database-recorded metabolic-syndrome diagnosis was present in 42.2% of participants with BED (98/232; 95% CI 36.1–48.7) and 47.4% of those without BED (365/770; 95% CI 43.9–50.9). The unadjusted association was not statistically significant (OR 0.81, 95% CI 0.60–1.09; P=0.167); after adjustment for age, sex and BMI, the association remained non-significant (adjusted OR 0.89, 95% CI 0.65–1.22; P=0.479).

The database-recorded MHO classification was present in 22.6% of participants with BED (53/234; 95% CI 17.8–28.4) and 18.7% of those without BED (147/786; 95% CI 16.1–21.6). The unadjusted association

was not statistically significant (OR 1.27, 95% CI 0.89–1.81; P=0.183), and was attenuated after adjustment for age, sex and BMI (adjusted OR 1.21, 95% CI 0.84–1.75; P=0.313).

These BED-stratified prevalence estimates are complementary to earlier models that treated BED as the outcome and metabolic-health classification as a predictor; the conditional percentages answer different questions and should not be interchanged. Neither diagnosis showed a statistically significant prevalence difference by BED status in this HbA1c-defined non-diabetic obesity cohort. Denominators differ because diagnosis data were missing for some participants (Supplementary Table S6).

Discussion

Principal findings

The principal finding of this study is that BED in non-diabetic patients with obesity is associated with a distinct late OGTT glucose trajectory. Lower G180 was confirmed, and the new analysis demonstrates that the final-hour glucose decline is also relatively faster in BED. Importantly, LGDR remained associated with BED after adjustment for the glucose concentration at 120 min, sex, BMI and regional adipose distribution. This supports a trajectory signal beyond the starting late-OGTT glucose concentration, while not establishing superiority over G180 itself. The broader behavioral context of BED, including overlap with addictive-like eating mechanisms and challenges in weight management, is relevant to interpretation but was not directly assessed in this dataset.[20–22]

This distinction is important because G180 is a terminal concentration, whereas LGDR captures the temporal behavior of glucose between 120 and 180 min. Two participants may therefore have a similar G180 but reach that concentration through different trajectories. In the present data, adding LGDR to a model containing G120 and the prespecified covariates improved model fit (likelihood-ratio P=0.0014), although the adjusted model did not show a statistically significant increase in AUC over G180 alone (AUC 0.616 vs 0.585 on the common complete-case cohort; DeLong P=0.114). Thus, LGDR should be viewed as a complementary trajectory descriptor rather than a replacement for G180.

The exploratory clustering analysis did not identify a discrete BED-specific trajectory class; rather, it showed that late glucose decline is a distinct dimension of OGTT dynamics that is separable from the terminal glucose concentration. The numerically lower BED prevalence in the rapid-decline cluster, which was characterized mainly by higher 120-min glucose, is consistent with the inverse association between G120 and BED in the multivariable model and indicates that LGDR is informative only when interpreted conditionally on G120.

Youden analysis and interpretation of discrimination

The ROC analysis provides a useful description of the relative strength of the observed metabolic signals but should not be interpreted as diagnostic validation. In the common complete-case cohort, G180 showed AUC 0.585 and LGDR120–180 AUC 0.541; the paired DeLong comparison was not significant

(P=0.196). The adjusted G120+LGDR model achieved AUC 0.616, but its improvement over G180 alone was not statistically significant (DeLong P=0.114). The exploratory Youden analysis therefore remains hypothesis-generating, and the proposed LGDR threshold should not be considered a clinical cut-off.

Late glucose decline and possible counterregulatory relevance

The present findings raise the hypothesis that an accelerated late glucose decline may be part of the metabolic phenotype accompanying BED. However, the physiological literature does not support interpreting rate of fall alone as a direct trigger of counterregulation. Experimental studies indicate that counterregulatory responses are primarily related to the glucose concentration achieved, although the rate of fall can modify some responses under specific experimental conditions. Accordingly, LGDR should be interpreted as a trajectory descriptor rather than evidence of counterregulatory activation.[23–25]

In the present cohort, the faster relative decline coexisted with lower late glucose concentrations. This combination is biologically more informative than either variable in isolation, but the study does not establish reactive hypoglycemia, impaired counterregulation or symptoms. Late post-load hypoglycemia driven by a mismatch between glucose delivery and insulin secretion is well characterized in other settings, such as after bariatric surgery,[26] but whether a related mechanism operates in BED remains unknown. Future studies should combine serial glucose measurements with insulin, C-peptide, glucagon, catecholamines, cortisol and symptom assessment.

The potential behavioral relevance remains hypothesis-generating. If a subset of individuals with BED develops a rapid late decline together with low glucose concentrations, this could plausibly coincide with hunger or food-seeking signals, but this pathway requires prospective testing rather than inference from the present cross-sectional dataset.

From a clinical perspective, if confirmed, these findings would support strategies aimed at restoring a physiologically coordinated glucose–insulin trajectory, for example through attention to meal composition and to the distribution of rapidly absorbable carbohydrates, within comprehensive nutritional and behavioral management, rather than treatments targeting BED-related hypoglycemia, which was not demonstrated in this study.

Relationship with previous literature

The findings are consistent with the original report by Watanabe et al., which identified lower 180-min glucose and higher 180-min insulin in BED despite no significant difference in overall glucose or insulin exposure.[11] They are also compatible with the subsequent 5-h OGTT study reporting frequent reactive hypoglycemia and more frequent late severe hypoglycemia in BED.[12] The latter study extended sampling beyond 180 min; therefore, its results and the present findings should be considered complementary rather than directly equivalent. Related work from our group has examined dysfunctional eating patterns alongside metabolic parameters and circulating oxytocin in obesity, and has documented associations

between obesity and disordered eating behaviors; these studies provide clinical context but did not evaluate late OGTT glucose trajectories.[5,6,27]

The study by Rania et al. further supports the concept that the temporal structure of glucose responses can contribute to BED characterization in individuals with high weight.[13] Our approach differs by testing a simple, physiologically interpretable late decline-rate descriptor rather than a machine-learning classifier. The present findings should therefore be interpreted as complementary to, rather than superior to, the previously reported multivariable/ML approaches. The modest discrimination and lack of statistically significant AUC superiority over G180 reinforce the need for external validation.

Why the glucose trajectory may be more informative than a single terminal value

LGDR also avoids the instability of the absolute LGICI denominator when G120 and G180 are close or when the glucose trajectory changes direction. Nevertheless, the normalized rate is mathematically related to G120 and G180; this is why the primary regression explicitly adjusts for G120. The persistence of the LGDR association after this adjustment supports the interpretation that the late trajectory contains information not reducible to the starting glucose value alone, but it does not demonstrate incremental diagnostic value beyond G180.

The modest AUCs of the coupling indices indicate that LGICI should not replace G180. Instead, LGICI is best regarded as a mechanistic descriptor of the phenotype identified by G180. This is especially important because the numerator and denominator of LGICI are derived from the same OGTT measurements that generate the late glucose phenotype, creating mathematical dependence.

Adipose distribution

The inclusion of upper/lower fat adds information that BMI cannot provide. Upper/lower fat showed a higher AUC than BMI and the highest Youden index in the exploratory analysis, although it was not independently associated with BED in the multivariable model (P=0.412). The lower ratio in BED, indicating relatively more lower-body fat, is directionally consistent with the modestly greater insulin sensitivity observed in this group. Although the direction and magnitude of this association should not be interpreted causally, the result supports retaining regional adiposity when characterizing metabolic phenotypes within obesity. Differences in adipose distribution may influence insulin sensitivity, fatty-acid flux and glucose handling and could therefore represent part of the metabolic context in which late glucose–insulin abnormalities emerge. Related studies from our group have also examined insulin resistance in relation to metabolic status, body composition and anthropometric indices, including insulin-sensitizing intervention data. These studies provide metabolic context but do not directly test the BED-specific late OGTT phenotype.[14–18,28,29]

Clinical and translational implications

The clinical implication is not that OGTT should be used to diagnose BED. Rather, dynamic metabolic testing may help identify physiological subphenotypes within obesity and may eventually clarify why

some individuals with obesity develop BED while others do not. This is consistent with a precision-medicine framework in which psychiatric phenotype and metabolic phenotype are considered together.

A particularly testable hypothesis emerging from the present work is that the combination of low late glucose, persistent late insulin activity and specific adipose distribution identifies individuals more likely to experience symptomatic late glucose declines or counterregulatory activation. Prospective studies should determine whether such a phenotype predicts hunger, food-seeking, binge episodes or subsequent energy intake and whether interventions that stabilize postprandial glucose trajectories modify these outcomes.

Strengths and limitations

Strengths include the large clinical dataset, direct OGTT measurements of both glucose and insulin, the focus on adults with obesity without diabetes by HbA1c criterion, explicit assessment of adipose distribution, and evaluation of both absolute and normalized dynamic coupling indices. The analysis also incorporates an exploratory Youden framework that makes the discriminatory limitations of the candidate measures explicit.

Several limitations must be acknowledged. First, the retrospective cross-sectional design precludes causal inference and temporal prediction. Second, absence of diabetes was defined operationally by HbA1c rather than by formal clinical adjudication of diabetes status. Third, missingness reduced the sample size for individual ROC analyses and the multivariable model. Fourth, LGICI is mathematically derived from the same OGTT measurements used to define the late phenotype and therefore cannot be considered an independent biomarker. Fifth, the present study does not include serial counterregulatory hormones, symptom ratings or continuous glucose monitoring and therefore cannot establish that late glucose decline leads to hypoglycemia or counterregulatory activation. Sixth, the primary model did not include age as a covariate, and numerous secondary and exploratory analyses were performed without formal correction for multiple comparisons. Finally, the database setting may limit external generalizability, and all cut-points require validation in independent cohorts.

Conclusions

In non-diabetic patients with obesity, binge-eating disorder is associated with an altered late OGTT glucose trajectory characterized by lower 180-min glucose and a faster relative glucose decline during the final hour. LGDR120–180 remained associated with BED after adjustment for G120 and major adiposity covariates. The model incorporating LGDR improved fit over a model without LGDR, but did not significantly outperform G180 alone in discrimination. LGDR should therefore be considered an exploratory physiological descriptor, not a diagnostic biomarker, and its relationship with symptomatic hypoglycemia and counterregulatory physiology requires prospective validation.

Declarations

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Author contributions

Rebecca Rossetti: Investigation, Data curation, Formal analysis, Visualization, Writing – original draft. Chandra Massetti: Investigation, Data curation, Formal analysis, Visualization, Writing – original draft. Davide Masi: Investigation, Methodology, Writing – review & editing. Eleonora Poggiogalle: Investigation, Methodology, Writing – review & editing. Francesco Frigerio: Investigation, Resources, Writing – review & editing. Orietta Gandini: Investigation, Resources, Writing – review & editing. Giorgia Maria Baldazzi: Investigation, Resources, Writing – review & editing. Elena Gangitano: Investigation, Resources, Writing – review & editing. Mariaignazia Curreli: Investigation, Resources, Writing – review & editing. Stefania Mariani: Investigation, Resources, Writing – review & editing. Andrea Marcello Isidori: Writing – review & editing. Daniele Gianfrilli: Investigation, Resources, Writing – review & editing. Carla Lubrano: Conceptualization, Methodology, Supervision, Project administration, Writing – review & editing. All authors have approved the final manuscript and agree to be accountable for their contributions.

Conflict of interest

The authors declare no competing interests.

Data availability

The individual-level clinical data are not publicly available because they contain sensitive clinical information and are subject to institutional and data-protection restrictions. De-identified data may be considered for access from the corresponding author upon reasonable request, subject to institutional authorization, applicable ethics requirements, and data-protection rules.

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Tables

Table 1. Characteristics of participants according to binge-eating disorder status in the primary cohort

Characteristic	Non-BED n	Non-BED, median (IQR) or n (%)	BED n	BED, median (IQR) or n (%)	P value
Age, years	796	45.00 (34.00–54.00)	238	43.00 (32.00–52.00)	0.078
Male sex, n (%)	796	196 (24.6%)	237	38 (16.0%)	0.006
BMI, kg/m²	796	38.84 (34.81–43.75)	238	39.65 (36.33–43.39)	0.230
HbA1c, %	796	5.40 (5.20–5.70)	238	5.40 (5.20–5.60)	0.810
Fasting glucose, mg/dL	795	92.00 (86.00–101.00)	237	90.10 (83.00–97.00)	0.018
120-min glucose, mg/dL	725	110.00 (95.00–131.00)	222	107.00 (92.00–123.75)	0.123
180-min glucose, mg/dL	644	74.00 (65.00–89.25)	207	70.00 (58.50–84.00)	<0.001
LGDR120–180, %/h	643	30.93 (16.40–43.36)	203	35.87 (20.37–46.89)	0.020
HOMA-IR	756	3.33 (2.03–5.55)	226	2.90 (1.86–4.85)	0.043
Matsuda index	624	3.91 (2.33–6.40)	186	4.42 (2.74–6.96)	0.036
Upper/lower fat ratio	650	1.69 (1.41–2.06)	202	1.55 (1.31–1.87)	0.002
Metabolic syndrome, n/N (%)	770	365/770 (47.4%)	232	98/232 (42.2%)	0.167
MHO, n/N (%)	786	147/786 (18.7%)	234	53/234 (22.6%)	0.183
FT3, pg/mL	586	3.20 (2.90–3.51)	161	3.30 (3.00–3.60)	0.044
FT4, ng/dL	616	1.16 (1.05–1.30)	171	1.13 (1.01–1.27)	0.066
TSH, mIU/L	756	2.10 (1.39–3.10)	222	2.23 (1.49–3.15)	0.365

Continuous variables are reported as median (interquartile range [IQR]) and categorical variables as n (%). The variable-specific number of non-missing observations is shown for each group. P values are from Mann–Whitney U tests for continuous variables and unadjusted logistic regression for categorical variables. BED, binge-eating disorder; HOMA-IR, homeostasis model assessment of insulin resistance; LGDR, late glucose decline rate; MHO, metabolically healthy obesity.

Table 2. Complete-case multivariable logistic regression model

Predictor	OR	95% CI	P	Scaling
G120	0.890	0.821–0.964	0.004	per 10 mg/dL
LGDR 120–180	1.191	1.066–1.331	0.002	per 10%/h
Male sex	0.602	0.359–1.011	0.055	per unit
BMI	1.023	0.989–1.059	0.193	per unit
Upper/lower fat	0.861	0.602–1.231	0.412	per unit

Complete-case sample: n=694; BED cases=173. ORs are cross-sectional associations and should not be interpreted as prospective risk estimates. G180 was not included because it is algebraically determined by G120 and the late decline-rate measure.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- BEDSupplementaryInformation.docx