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Metabolic Burden and Response to Repeated Intranasal Esketamine in Treatment-Resistant Depression: A Longitudinal Multidomain Biomarker Study

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Abstract

Metabolic, inflammatory, and neurotrophic measures may provide complementary insight into biological heterogeneity underlying treatment-resistant depression and response to ketamine-based treatments. However, biomarker studies of ketamine treatment have focused on individual markers or biological domains, most commonly inflammatory or neurotrophic, while metabolic measures remain comparatively understudied. All three domains were examined in 30 individuals with treatment-resistant depression receiving eight intranasal esketamine treatments in a real-world clinical setting. Depressive symptoms, metabolic, inflammatory, and neurotrophic biomarkers were assessed before and after treatment. Esketamine treatment was associated with a reduction in Montgomery Åsberg Depression Rating Scale scores (mean decrease 7.7 points, $p < 0.001$; Cohen's $d = -0.90$). Greater metabolic burden, quantified using a composite based on metabolic syndrome criteria and comprising waist circumference, triglycerides, HDL cholesterol, blood pressure, and fasting glucose, was associated with greater reductions in depressive symptoms following treatment, after adjustment for baseline depressive symptom severity ($p = 0.032$). Fasting glucose decreased following esketamine treatment (mean decrease 1.58 mmol/L, $p_{FDR} < 0.001$; Cohen's $d = -1.61$), without significant changes in body weight. In contrast, baseline inflammatory and neurotrophic composites were not associated with changes in depressive symptoms, and no inflammatory or neurotrophic biomarkers showed significant longitudinal changes. In sensitivity analyses excluding participants with diabetes or prescribed glucose-altering medications, higher baseline serum vascular endothelial growth factor (VEGF) was associated with greater reductions in depressive symptoms ($p_{FDR} = 0.043$). These findings highlight the value of a multidomain approach and identify metabolic measures as an important domain for understanding heterogeneity in response to esketamine.

Introduction

There is an urgent need to better understand the mechanisms underlying depression. Worldwide, major depressive disorder (MDD) represents the leading cause of disease burden among mental, neurological, and substance-use disorders [1]. Major depressive episodes are also seen in bipolar disorder, which is characterised by more time spent in depressive episodes relative to hypomanic or manic episodes [2,3]. Although there are effective treatments for depression, a significant proportion of patients do not respond to existing pharmacotherapies and may meet criteria for treatment-resistant depression [4]. Often defined as failure to respond to at least two adequate pharmacological treatments for depression [5], treatment-resistant depression is associated with higher prevalence of comorbid psychiatric disorders, elevated suicide risk, more frequent hospitalizations, and reduced quality of life [6].

The discovery of the rapid antidepressant effects of subanaesthetic doses of racemic ketamine has been hailed as a paradigm shift in the treatment of depression [7]. While single intravenous (IV) ketamine infusions elicit rapid yet transient antidepressant effects in both MDD and bipolar disorder [8], repeated infusions produce cumulative and sustained reductions in depressive symptoms and suicidal ideation with response rates exceeding those observed with conventional pharmacotherapies [9]. Sustained antidepressant effects and longer-term relapse prevention have also been demonstrated with esketamine, the S-enantiomer of ketamine [10,11]. While racemic ketamine for depression largely remains an off-label intervention, the intranasal formulation of esketamine received multiple regulatory approvals beginning in 2019, facilitating its broader clinical adoption internationally. Nevertheless, not all individuals with treatment-resistant depression respond to ketamine-based interventions, highlighting the need for biomarkers to

predict treatment response and improve understanding of the biological mechanisms underlying treatment resistance.

Depression commonly co-occurs with a range of other medical conditions, including obesity, metabolic syndrome, cardiovascular disease, and inflammatory disorders [12-14]. Additionally, many of the psychotropic medications prescribed for mood disorders are themselves associated with adverse cardiometabolic side effects [15,16]. Emerging evidence suggests that metabolic dysfunction, systemic inflammation, and impaired neuroplasticity are interconnected processes that contribute to depression pathophysiology and treatment resistance [17,18]. In this context, peripheral biomarkers may provide accessible indicators of these biological processes. Ketamine and esketamine are thought to influence synaptic plasticity, immune signalling, and metabolic function [19,20]; however, biomarker research in ketamine-treated populations has largely remained fragmented across domains.

To date, studies of peripheral biomarkers in ketamine-treated individuals have focused primarily on inflammatory markers, most commonly interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF- α), C-reactive protein (CRP), or neurotrophic factors including brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF). While several individual studies have observed longitudinal reductions in pro-inflammatory markers following ketamine treatment, findings have remained mixed [21]. A recent comprehensive meta-analysis found that increases in BDNF following ketamine treatment were observed only among ketamine responders, while pre-treatment blood-based inflammatory and neurotrophic marker levels were not consistently associated with antidepressant response to IV ketamine [22]. Studies of

peripheral biomarkers during esketamine treatment have been much more limited. Recent small studies have examined individual inflammatory markers alongside esketamine treatment [23-26], though no consistent biomarker association has emerged.

In contrast, metabolic biomarkers remain comparatively understudied. Prior work has largely relied on body mass index (BMI) as a proxy for metabolic health. Several studies have suggested that higher BMI is associated with greater antidepressant response to IV ketamine [27-29], yet a pooled patient-level meta-analysis found that BMI was not a significant predictor of treatment response to single IV ketamine infusions [30]. However, BMI is an incomplete measure of metabolic health and does not capture the broader spectrum of metabolic dysfunction implicated in mood disorders. Dale et al. [31] reported poorer response to an acute series of 3-6 ketamine infusions among participants with highly resistant depression (electroconvulsive therapy non-responders) who presented with at least one of three metabolic conditions: hypertension, hyperglycemia, or hyperlipidemia. To our knowledge, no studies have examined individual components of metabolic syndrome or assessed cumulative metabolic burden as predictors of response in individuals receiving repeated ketamine or esketamine treatment. Furthermore, simultaneous assessment of metabolic, inflammatory, and neurotrophic measures may better characterize biological heterogeneity underlying antidepressant response.

Accordingly, this study used a comprehensive multidomain biomarker approach in individuals receiving repeated intranasal esketamine in a real-world clinical setting. The aims were to: 1) determine whether baseline metabolic, inflammatory, and neurotrophic biomarkers predict changes in depressive symptoms following repeated esketamine treatment; 2) characterize

longitudinal changes in these biomarkers following repeated esketamine treatment; and 3) examine whether longitudinal biomarker changes are associated with changes in depressive symptoms.

Methods

Participants

This single-site longitudinal study included individuals aged 18-65 years receiving repeated intranasal esketamine hydrochloride (Spravato®) as an outpatient clinical treatment at the BMO Innovative Clinic for Depression, a hospital-based ketamine clinic at The Royal (Ottawa, ON, Canada). Data were collected between September 2021 and March 2026. Clinical indication for this treatment is moderate-to-severe treatment-resistant major depressive episode in the context of major depressive disorder or bipolar disorder (type I or II), with diagnoses established by psychiatric consultation according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria [32]. Treatment resistance was defined as failure to respond to at least two mechanistically distinct pharmacological treatments for depression at adequate dosages for a minimum of 6 weeks each during the current depressive episode, as documented using the Antidepressant Treatment History Form [33]. In accordance with Health Canada-approved use of intranasal esketamine [34], patients were required to be receiving a stable oral monoaminergic antidepressant at the time of treatment. Further eligibility criteria for treatment included completion of psychiatric and medical assessments and confirmation through the Janssen Journey patient support program [35] of private insurance coverage for esketamine or the ability to self-fund treatment. All participants in the present study had private insurance coverage; none self-funded treatment. Medical assessment included review of medical history, physical

examination, vital sign measurement, electrocardiography, standard blood test, pregnancy test, and urine toxicology screen. The treatment protocol specified that concomitant medication doses remain stable throughout esketamine treatment. Exclusion criteria for treatment included presence of psychotic disorder, alcohol or other substance use disorder within the past 12 months (excluding nicotine and caffeine) as defined by the DSM-5, a positive urine toxicology screen for non-prescribed substances, or inability to abstain from using prohibited substances or medications (e.g., cannabis, benzodiazepines) during esketamine treatment, unstable or severe medical illness (including uncontrolled hypertension, seizure disorder, renal or hepatic impairment, and significant cardiovascular risk factors), prior intolerance or hypersensitivity to ketamine, and pregnancy or lactation. The study was approved by The Royal's Research Ethics Board. All participants provided written informed consent. Participants received CAD \$40 in compensation for study procedures.

Study Design and Treatment Administration

Baseline clinical assessment, metabolic assessment, and blood collection occurred at the medical assessment appointment scheduled prior to initiation of esketamine treatment. Participants received a series of eight intranasal esketamine treatments administered twice-weekly during a 4-week induction phase [35]. Esketamine was administered at standard doses of 56 mg or 84 mg, with dosing determined according to approved guidelines and treating physician judgment. Participants self-administered esketamine under the medical supervision of physicians and nursing staff with cardiorespiratory monitoring. Vital signs, including blood pressure and heart rate, were monitored at 15-minute intervals throughout the 2-hour post-administration observation period. Pre-treatment protocols required participants to avoid nasal medications and

to fast from food (2 hours) and liquids (30 minutes) prior to treatment.³⁵ On treatment days, participants were required to abstain from medications that may attenuate ketamine/esketamine response, including benzodiazepines [36] (held from the night before), naltrexone, antiseizure agents (such as lamotrigine), and stimulants [37]. At physician discretion and if medically appropriate, participants prescribed glucagon-like peptide-1 (GLP-1) receptor agonists were advised to withhold these medications throughout the esketamine treatment course [38]. Post-treatment clinical assessment, metabolic assessment, and blood collection were scheduled within one week following the eighth esketamine treatment.

Clinical Outcome Measures

The primary clinical outcome measure was the Montgomery Åsberg Depression Rating Scale (MADRS) [39] administered by trained clinical raters. Assessments used the Structured Interview Guide for the MADRS (SIGMA) [40], with the same rater conducting pre- and post-treatment interviews for each participant whenever feasible. Participants also completed the Patient Health Questionnaire-9 (PHQ-9) [41] to assess self-reported depressive symptom severity. Additional clinical scales were collected and will be reported elsewhere.

Metabolic Assessment

Metabolic assessments were completed at the same timepoints as clinical assessment and blood collection. At each metabolic assessment (pre- and post-treatment), measurements of weight, waist and hip circumference, and vital signs (systolic and diastolic blood pressure, heart rate, and respiratory rate) were obtained by a nurse. Height was measured at pre-treatment only. Blood

pressure was measured in triplicate, with 5-minute intervals between readings, and averages were calculated for both systolic and diastolic values.

Blood Collection and Processing

Fasting venous blood samples were collected from the antecubital fossa into chilled, EDTA-coated or serum separator (SST) vacutainer tubes by a registered phlebotomist. Samples were collected within a 2.5-hour morning window (between 9:30 a.m. and 12:00 p.m.) following an overnight fasting period. A portion of samples was processed and shipped to an external commercial laboratory (Dynacare Inc., Brampton, ON, Canada) to obtain standard clinical laboratory tests including triglycerides, a lipid profile (high-density lipoprotein [HDL], low-density lipoprotein [LDL], and total cholesterol), fasting glucose, complete blood count, high-sensitivity CRP, and hemoglobin A1C (HbA1c, pre-treatment only). Remaining samples were processed for on-site analysis. For plasma and serum isolation, EDTA tubes were immediately placed in an ice bath upon collection, whereas SST tubes were maintained at ambient temperature and allowed to clot for 30 minutes. EDTA and SST tubes were centrifuged at 4 °C (1000 x g), for 15 minutes, and 10 minutes, respectively. Plasma and serum were aliquoted into microtubes on ice and stored at -80 °C until batch analysis.

Metabolic Biomarkers

Primary metabolic measures corresponded to the diagnostic criteria for metabolic syndrome defined by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III; 2005 revision) [42,43] (**Supplementary Table 1**). As described above, these measures were derived from metabolic assessments (waist circumference, systolic and diastolic blood pressure)

and blood draws (serum triglycerides, HDL cholesterol, fasting glucose). BMI was examined as an exploratory metabolic marker to align with prior literature. Fasting insulin and homeostatic model assessment of insulin resistance (HOMA-IR) [44] were examined descriptively as additional indices of insulin resistance.

Inflammatory and Neurotrophic Biomarkers

Concentrations of seven inflammatory and neurotrophic biomarkers were quantified from plasma using the EllaTM microfluid immunoassay platform (ProteinSimple; Bio-Techne, Toronto, ON, Canada); these included IL-6, TNF- α , BDNF, VEGF, anti-inflammatory cytokine IL-10, C-C motif chemokine ligand 2/monocyte chemoattractant protein-1 (CCL2/MCP-1), and interferon-gamma (IFN- γ). BDNF and VEGF were also measured in serum using the EllaTM platform. Fasting insulin was quantified from plasma using the EllaTM platform as an exploratory metabolic marker. Samples were assayed in duplicate for multiplex analyses and in triplicate for single-analyte assays (IL-6 and insulin) and for serum BDNF and VEGF, according to the manufacturer's instructions. Inter-assay coefficients of variation (CV) values were <15% for all assays. CRP was measured via standard automated assay in the commercial laboratory, while neutrophil to lymphocyte ratio (NLR) and systemic immune-inflammation index (SII) were calculated using absolute white blood cell and platelet counts obtained during routine clinical laboratory testing.

Statistics

Statistical analyses were organized according to three predefined aims: 1) baseline predictors of esketamine response, 2) changes in metabolic, inflammatory, and neurotrophic markers following treatment, and 3) associations between biomarker change and symptom change. Continuous variables were assessed for normality. CRP, inflammatory and neurotrophic markers, NLR, SII, fasting insulin and HOMA-IR were natural log-transformed to address non-normal distributions (denoted as $\ln[\text{variable}]$), while metabolic measures (waist circumference, triglycerides, HDL cholesterol, blood pressure, fasting glucose, and BMI) were analysed using raw units. No alternative transformations were tested. Raw means and SDs are presented for interpretability. Primary analyses focused on a priori-defined composite scores to limit multiple testing and preserve statistical power. Baseline metabolic burden was quantified as a composite score (range 0-5) for each participant by summing the number of primary metabolic measures exceeding NCEP ATP III criteria clinical thresholds (see Supplementary Table 1). The metabolic burden composite was treated as a baseline index of cardiometabolic risk and was not examined longitudinally. Pro-inflammatory (plasma CRP, IL-6, and TNF- α) and neurotrophic (serum BDNF and VEGF) composites were calculated by averaging the standardized z-scores of their respective natural log-transformed components. No other composites were calculated or tested. Exploratory inflammatory indices were derived from absolute peripheral blood counts; NLR was calculated as neutrophil-to-lymphocyte count ratio, and the SII was calculated as the product of the absolute platelet and neutrophil counts divided by absolute lymphocyte count. HOMA-IR was calculated as: $\text{fasting insulin } (\mu\text{U/mL}) \times \text{fasting glucose (mmol/L)} / 22.5$.

Linear regression models tested whether the metabolic burden, pro-inflammatory, and neurotrophic composites predicted changes in depressive symptom severity following

esketamine treatment, adjusting for baseline MADRS. Secondary analyses examined the individual components of the metabolic, pro-inflammatory, and neurotrophic composites with false discovery rate (FDR) correction applied within each biological domain. Uncorrected exploratory models examined additional markers including IL-10, CCL2/MCP-1, IFN- γ , NLR, SII, plasma BDNF, plasma VEGF, and BMI as baseline predictors. Due to small sample size and non-normal distribution of residuals, bootstrapping (5000 samples) with bias-corrected and accelerated (BCa) confidence intervals (CIs) (BCa 95% CI) was employed for regression analyses.

Changes in clinical scores (MADRS and PHQ-9) and biomarker values were assessed using paired *t*-tests. Change scores for all clinical and biological variables were defined as post-treatment minus baseline values. Pearson or Spearman correlations tested associations between biomarker changes and changes in MADRS scores. Sensitivity analyses excluded participants with a diagnosis of diabetes or those prescribed glucose-altering medications (e.g., GLP-1 receptor agonists, insulin, or metformin, *n* = 9 excluded). Effect sizes were reported as Cohen's *d* for paired comparisons and adjusted *R*² for regression models, with 95% CIs provided for all primary outcomes (bootstrapped BCa 95% CI for regression analyses). Statistical analyses were conducted using Python, with significance set at $\alpha = 0.05$ throughout.

Results

Sample Characteristics

A total of 36 individuals consented and were screened for eligibility at their esketamine medical assessment appointment (**Supplementary Figure 1**). Thirty-three participants were deemed

eligible to initiate treatment and all completed the full course of eight esketamine treatments (100% treatment completion). Three participants withdrew from research procedures prior to post-treatment assessment and did not complete follow-up clinical or biomarker data collection. The final analytic sample included $N = 30$ participants; $n = 29$ had complete clinical outcome data, and $n = 28$ had available pre- and post-treatment biomarker data. Two additional participants were excluded from longitudinal inflammatory analyses due to self-reported acute viral illness at time of follow-up blood collection, supported by elevated CRP (>7 mg/L), and data from one participant was excluded from follow-up blood-derived measures due to non-adherence with fasting requirements. Baseline demographic and clinical characteristics are summarized in **Table 1**.

Participant mean age was 45.8 years (± 12.4 ; 43% were female). Most participants had a diagnosis of MDD ($n = 25$), while five participants had bipolar disorder (bipolar I disorder, $n = 3$; bipolar II disorder, $n = 2$). The severity of baseline depressive symptoms was moderate to severe (mean MADRS 29.8 ± 5.1 ; range 24-42). Scores on baseline rater- and self-assessed depressive symptom scales (MADRS and PHQ-9) were moderately correlated ($r = 0.483$; $p = 0.007$). Concomitant medications used during the treatment period are summarized in **Supplementary Table 2**. Participants had an average of $3.9 (\pm 1.3)$ prior antidepressant treatment failures in the current major depressive episode. The mean interval between baseline assessment and treatment initiation was 21.0 ± 7.9 days (range 8-42 days). Follow-up assessments were obtained 6.6 ± 3.1 days (range 1-14 days) after the eighth esketamine treatment.

Clinical Outcomes

Participants received eight intranasal esketamine treatments (mean dose 76.5 ± 6.9 mg, range 57.8-80.5 mg) over an average of 25.1 ± 4.0 days (range 24-45 days). Esketamine treatment was associated with a significant reduction in depressive symptom severity on both rater-administered and self-report scales (MADRS, mean decrease 7.7 points, $p < 0.001$, Cohen's $d = -0.90$; PHQ-9, mean decrease 5.8 points, $p < 0.001$, Cohen's $d = -0.91$; **Figure 1**). Among participants with complete post-treatment MADRS data, 17.2% of participants met classical antidepressant response criteria ($\geq 50\%$ reduction in MADRS total scores from pre-treatment to post-treatment); 31.0% were partial responders ($\geq 25\%$ to $< 50\%$ reduction) [49]; and 51.8% were non-responders ($< 25\%$ reduction). Remission (MADRS score < 10 at post-treatment) [50] occurred in 3 participants (10.3% of the sample).

Baseline Metabolic Burden and Its Relationship to Antidepressant Response

Metabolic abnormalities were common among participants. At baseline, 9 participants (30%) met diagnostic criteria for metabolic syndrome, while 3 participants had type 2 diabetes (**Table 1**). Overall, 16 participants (53%) had two or more metabolic abnormalities, with increased waist circumference (50%), and elevated blood pressure (47%) being the most common. HbA1c ranged from 4.8-6.6% (mean $5.3 \pm 0.4\%$) and was positively correlated with baseline fasting glucose ($r = 0.629$, $p < 0.001$). The baseline metabolic burden composite, defined as the total number of metabolic abnormalities exceeding NCEP ATP III clinical thresholds, was not significantly correlated with baseline depressive symptom severity (MADRS total scores, $r = -0.148$, $p = 0.419$).

Higher baseline metabolic burden composite scores were associated with greater reductions in MADRS scores following repeated esketamine treatment after adjusting for baseline MADRS scores ($B = -1.88$, $\beta = -0.28$, $p = 0.032$, 95% BCa CI [-4.24, -0.237], adjusted $R^2 = 0.014$; **Figure 2**). Secondary analyses examining individual metabolic components did not identify any significant predictors that survived FDR correction, although waist circumference was significant prior to correction (**Supplementary Table 3**). In exploratory analyses, BMI was not a significant predictor of changes in MADRS scores ($p = 0.107$).

In sensitivity analyses excluding participants with a diagnosis of diabetes or those prescribed glucose-altering treatments ($n = 9$ excluded; see **Supplementary Table 2**), the association between the baseline metabolic burden composite and improvement in MADRS scores remained significant ($p = 0.028$, 95% BCa CI [-8.364, -0.241], adjusted $R^2 = 0.085$).

Baseline Inflammatory and Neurotrophic Biomarkers and Their Relationship to Antidepressant Response

Linear regression analyses revealed that the pro-inflammatory and neurotrophic composites did not significantly predict changes in MADRS scores in the full sample (inflammatory composite: $p = 0.225$, 95% BCa CI [-6.676, 1.145], adjusted $R^2 = -0.018$; neurotrophic composite: $p = 0.247$, 95% BCa CI [-7.873, 1.120], adjusted $R^2 = -0.028$). Secondary and exploratory analyses of individual biomarkers revealed no significant associations as summarized in **Supplementary Table 3**.

In sensitivity analyses, the neurotrophic composite showed a non-significant association with change in MADRS scores ($p = 0.058$, 95% BCa CI [-14.121, -0.772], adjusted $R^2 = 0.056$). Secondary analyses of individual neurotrophic biomarkers identified an association between higher baseline serum lnVEGF and greater reductions in MADRS scores after FDR correction ($p_{\text{FDR}} = 0.043$, 95% BCa CI [-13.579, -0.994], adjusted $R^2 = 0.171$) (**Supplementary Figure 2; Supplementary Table 3**). In exploratory analyses, higher baseline plasma lnVEGF was also associated with greater reductions in MADRS scores in uncorrected analyses ($p = 0.018$, 95% BCa CI [-28.744, -6.846], adjusted $R^2 = 0.183$). Baseline plasma lnVEGF also showed a positive correlation with baseline metabolic burden composite scores within this sample ($\rho = 0.408$, $p = 0.025$). No other individual inflammatory or neurotrophic markers were associated with change in MADRS scores in secondary or exploratory analyses.

Changes in Metabolic Biomarkers Following Esketamine Treatment

Changes in metabolic measures after esketamine treatment are summarized in **Table 2**. Fasting glucose was significantly lower at post-treatment (mean decrease 1.58 mmol/L; $p_{\text{FDR}} < 0.001$, Cohen's $d = -1.61$), with reductions observed in 92% of participants (**Figure 3**). Post-treatment, ten participants (43%) exhibited fasting glucose values below the laboratory-defined hypoglycemia threshold (<3.6 mmol/L), without reported hypoglycemic symptoms at the time of follow-up assessment. Fasting glucose reductions occurred without changes in body weight (pre: 85.8 ± 22.8 kg; post: 86.5 ± 24.1 kg; $p = 0.341$, Cohen's $d = 0.21$) or self-reported exercise frequency (pre: 3.0 ± 2.8 hrs/week; post: 3.1 ± 3.4 hrs/week; $p = 0.891$, Cohen's $d = 0.03$). Changes in fasting glucose were not significantly correlated with cumulative esketamine dose ($\rho = -0.382$, $p = 0.072$); however, the restricted dose range may have limited the ability to

detect a dose-response relationship. To further characterize glucose regulation, fasting insulin and HOMA-IR were also examined. Log transformed fasting insulin (lnInsulin) did not change significantly after esketamine treatment (fasting insulin, pre: 10.5 ± 8.9 μ IU/mL, post: 11.0 ± 10.2 μ IU/mL; $p = 0.949$, Cohen's $d = 0.014$). The log transformed HOMA-IR (lnHOMA-IR) decreased significantly (HOMA-IR: pre: 2.6 ± 2.5 , post: 1.6 ± 1.5 ; $p = 0.003$, Cohen's $d = -0.945$).

Systolic blood pressure also decreased following esketamine treatment (mean decrease 4.31 mmHg); however, this did not remain significant after FDR correction ($p_{FDR} = 0.062$, Cohen's $d = -0.45$). No other metabolic markers showed significant changes following treatment in the full sample after FDR correction ($p > 0.05$).

Sensitivity analyses yielded similar findings as the full sample for fasting glucose ($p_{FDR} < 0.001$, Cohen's $d = -1.60$) (**Supplementary Table 4**). Within this reduced sample, lnInsulin remained unchanged from baseline to post-treatment ($p = 0.996$; Cohen's $d = 0.019$), and the decrease in lnHOMA-IR remained significant ($p = 0.001$, Cohen's $d = -0.797$).

Changes in Inflammatory and Neurotrophic Biomarkers Following Esketamine Treatment

Following repeated esketamine treatment, no changes were observed in the pro-inflammatory or neurotrophic composites in the full sample (**Table 2**) or in sensitivity analyses (**Supplementary Table 4**). Furthermore, no individual inflammatory or neurotrophic marker showed a significant longitudinal change following repeated esketamine treatment (all $p > 0.05$; **Supplementary Table 4**).

Associations Between Biomarker Changes and Clinical Response

Longitudinal changes in metabolic, inflammatory, or neurotrophic markers were not significantly correlated with changes in MADRS total scores in the full sample or in sensitivity analyses (all $p > 0.05$). Full results are provided in **Supplementary Table 5**.

Discussion

In this multidomain biomarker study of individuals with treatment-resistant depression undergoing repeated intranasal esketamine treatment, metabolic measures demonstrated the most consistent associations with antidepressant outcome and longitudinal metabolic changes. Greater baseline metabolic burden, defined according to established metabolic syndrome criteria, was associated with larger reductions in depressive symptom severity following treatment. In addition, repeated esketamine administration was associated with significant reductions in fasting glucose, independent of changes in body weight or self-reported exercise frequency. In contrast, within the full sample, baseline inflammatory and neurotrophic composite measures were not associated with antidepressant outcome and did not significantly change following treatment. Sensitivity analyses excluding participants with diabetes or prescribed glucose-altering medications identified an association between higher baseline VEGF concentrations and greater clinical improvement. Collectively, these findings suggest that metabolic measures may be associated with differences in esketamine response among individuals with treatment-resistant depression.

The observation that greater baseline metabolic burden was associated with greater reductions in depressive symptom severity following repeated esketamine treatment contrasts with prior

literature linking metabolic abnormalities to poorer response to medications targeting monoaminergic systems. Prior studies have associated inflammatory and metabolic dysregulation with greater illness chronicity [51] and reduced response to selective serotonin reuptake inhibitors [52]. However, evidence in ketamine-treated populations is limited. While Dale et al. [31] reported poorer response to IV ketamine in participants classified as having metabolic dysregulation based on the presence of hypertension, hyperglycemia, or hyperlipidemia, this categorical metabolic index did not capture cumulative metabolic burden across multiple domains, as assessed in the present study.

These findings add to prior IV ketamine literature in which BMI has been used as a proxy measure of metabolic status, with several studies reporting greater clinical improvement following ketamine treatment in individuals with higher BMI [27-29]. In contrast, in the present study BMI was not associated with change in depressive symptom severity. More recent evidence in esketamine-treated individuals suggests a potentially non-linear relationship between BMI and antidepressant response, with greater response observed among individuals with obesity despite no significant association when BMI was examined as a continuous measure [53]. A proposed hypothesis for the association between BMI and IV ketamine response is that increased adiposity may alter exposure to lipid-soluble ketamine [53]. In the case of intranasal esketamine, where dosing is not weight-based, it is possible that the relationship between adiposity and drug exposure differs from that observed with IV ketamine. BMI is a limited surrogate for adiposity and metabolic health. The association between metabolic burden and response, observed using a composite measure that did not include BMI, suggests that BMI alone

may not fully capture the metabolic factors associated with antidepressant response to esketamine.

Repeated intranasal esketamine treatment was associated with a significant reduction in fasting glucose values, observed in nearly all participants, independent of changes in weight or self-reported exercise frequency, and accompanied by reductions in HOMA-IR. While large clinical trials have provided evidence supporting the overall metabolic safety of repeated ketamine/esketamine treatment [54,55], longitudinal changes in metabolic markers such as fasting glucose have not been systematically evaluated in individuals receiving ketamine or esketamine treatment [56]. Instead, prior studies have primarily examined metabolic measures as predictors of treatment response or as part of safety monitoring, rather than as outcomes following treatment. Although a recent case report described recurrent hypoglycemia following IV ketamine administration in an individual with type 1 diabetes [57], further published evidence linking ketamine and glucose is limited. Potential mechanisms underlying metabolic changes following repeated subanaesthetic-dose esketamine remain unclear. Given the limited evidence regarding longitudinal metabolic changes during repeated esketamine treatment, these results should be considered preliminary and hypothesis-generating and require replication and mechanistic follow-up studies.

Although inflammatory and neurotrophic composite measures were not associated with treatment outcome in the full sample, sensitivity analyses excluding participants with diabetes or glucose-altering medications identified baseline VEGF as a potential marker associated with response to repeated intranasal esketamine. Higher baseline serum VEGF levels were associated with greater

reductions in depressive symptoms following repeated esketamine treatment, while plasma VEGF showed a similar association in uncorrected exploratory analyses. Preclinical animal data indicate that both BDNF and VEGF signaling are required to elicit the antidepressant-like effects of ketamine [58]. In humans, higher pre-treatment serum VEGF has been associated with better antidepressant response to a single ketamine infusion [59] and to electroconvulsive therapy [60]. However, evidence supporting baseline VEGF as a predictor of ketamine or esketamine response remains limited, with a recent meta-analysis finding no consistent association between pre-treatment neurotrophic marker levels and antidepressant outcomes [22]. Although preliminary, these findings support further investigation of VEGF as a potential biomarker of repeated intranasal esketamine treatment response.

Strengths and Limitations

This study included a longitudinal, real-world clinical cohort of individuals with treatment-resistant depression undergoing a standardized course of repeated intranasal esketamine treatment. A key strength was the simultaneous assessment of metabolic, inflammatory, and neurotrophic systems, allowing evaluation of multiple biological domains rather than focusing on a single biomarker system. Metabolic burden was defined using a metabolic syndrome-based composite measure, aligning the analysis with established, clinically recognized metabolic features. The use of composite measures reduced the number of statistical comparisons. Sensitivity analyses excluding participants with diabetes or prescribed glucose-altering medications strengthened the robustness of the metabolic findings by reducing potential confounding.

Despite these strengths, several limitations should be considered. The sample size was small, limiting statistical power and increasing the risk of Type II error. The treatment was open-label and conducted without a placebo control, limiting the ability to attribute observed changes specifically to esketamine treatment. However, the real-world clinical design reflects a hospital-based treatment setting. The inclusion of individuals with both major depressive disorder and bipolar disorder may have introduced additional heterogeneity, although this reflects the complexity of treatment-resistant depression in clinical practice. Potential residual confounding from concomitant medications cannot be excluded. Biomarker assessments were restricted to peripheral measures, which may not directly reflect central processes relevant to antidepressant response. In addition, the study design included only a single post-treatment timepoint, limiting evaluation of temporal trajectories and longer-term outcomes. Finally, despite the composite approach and FDR correction of secondary analyses, several secondary and exploratory analyses were conducted, and exploratory findings should be interpreted cautiously as hypothesis generating. Future studies should replicate these findings in larger, independent cohorts with additional longitudinal assessments to clarify the relationship between metabolic biomarkers and esketamine response.

Conclusion

In summary, greater baseline metabolic burden was associated with greater reductions in depressive symptoms following repeated intranasal esketamine treatment. These findings raise the possibility that metabolic burden may not necessarily be associated with reduced treatment responsiveness and that individuals with metabolic abnormalities may represent a subgroup with differential response to esketamine. Repeated esketamine treatment was also associated with

reductions in fasting glucose, highlighting a potential metabolic effect of treatment that warrants further investigation. Together, these findings suggest that metabolic measures may represent an important biological domain for understanding response to esketamine. Further studies are needed to determine whether metabolic biomarkers can help identify individuals most likely to benefit from esketamine.

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Author Contributions

JLP contributed to conceptualization, methodology, supervision, project administration, and funding acquisition. IFO, AA, SW, EH, JC, RK, KM, ST, JT, and JLP contributed to investigation, including treatment administration, clinical assessments, and/or data collection. IFO, AA, and RJM contributed to biospecimen collection and processing methodology and implementation and biomarker assays. PB medically assessed all participants. IFO, AA, and JLP contributed to data curation and statistical analysis. JGF reviewed the statistical approach. AA prepared the figures. JLP wrote the original draft of the manuscript. All authors contributed to writing, review, and editing of the manuscript and approved the final version.

548 **Conflict of Interest**

549 PB received grant funding and/or honoraria for lectures, expert testimony, and/or participation in
550 advisory boards for AbbVie, Eisai, Idorsia, Janssen, Lundbeck, Otsuka, Pfizer, Canadian
551 Medical Protective Association, Intracellular Therapeutics, and Merck. All other authors declare
552 no conflict of interest.

553

554 **Supplementary Information**

555 Supplementary information is available at Molecular Psychiatry's website.

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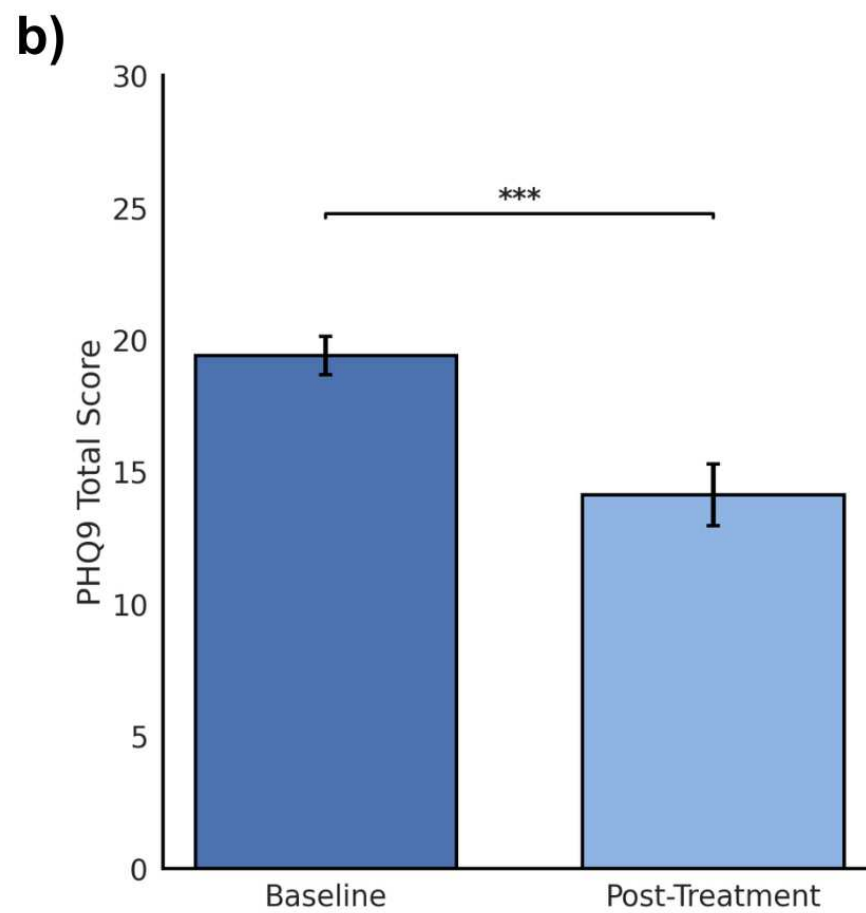
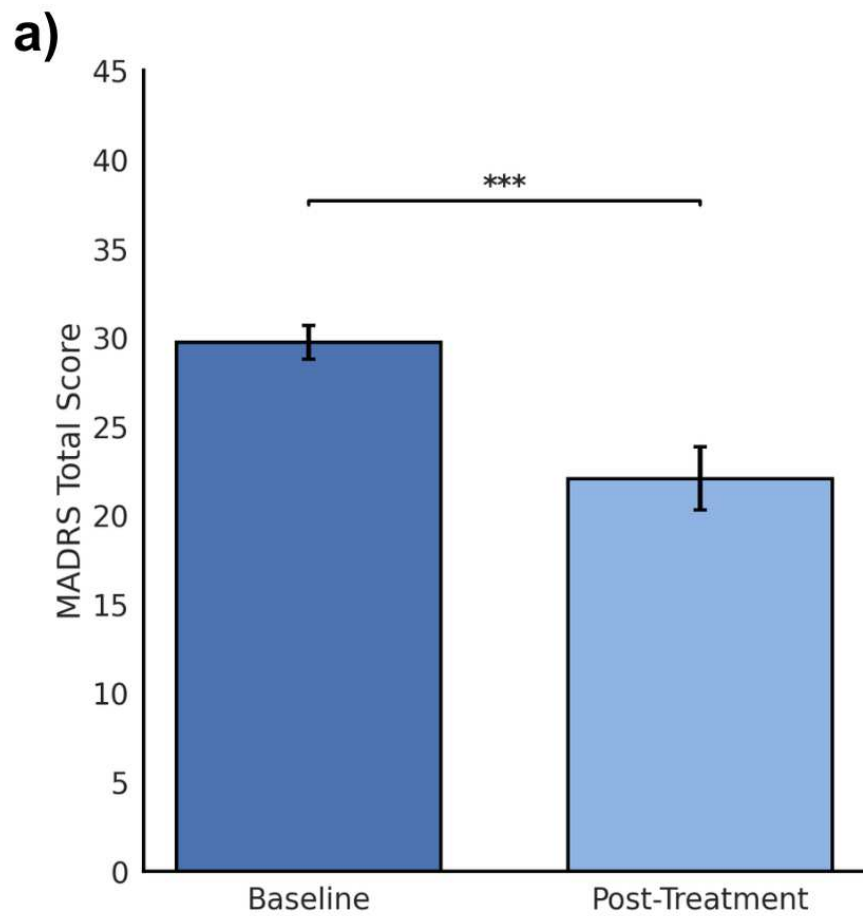
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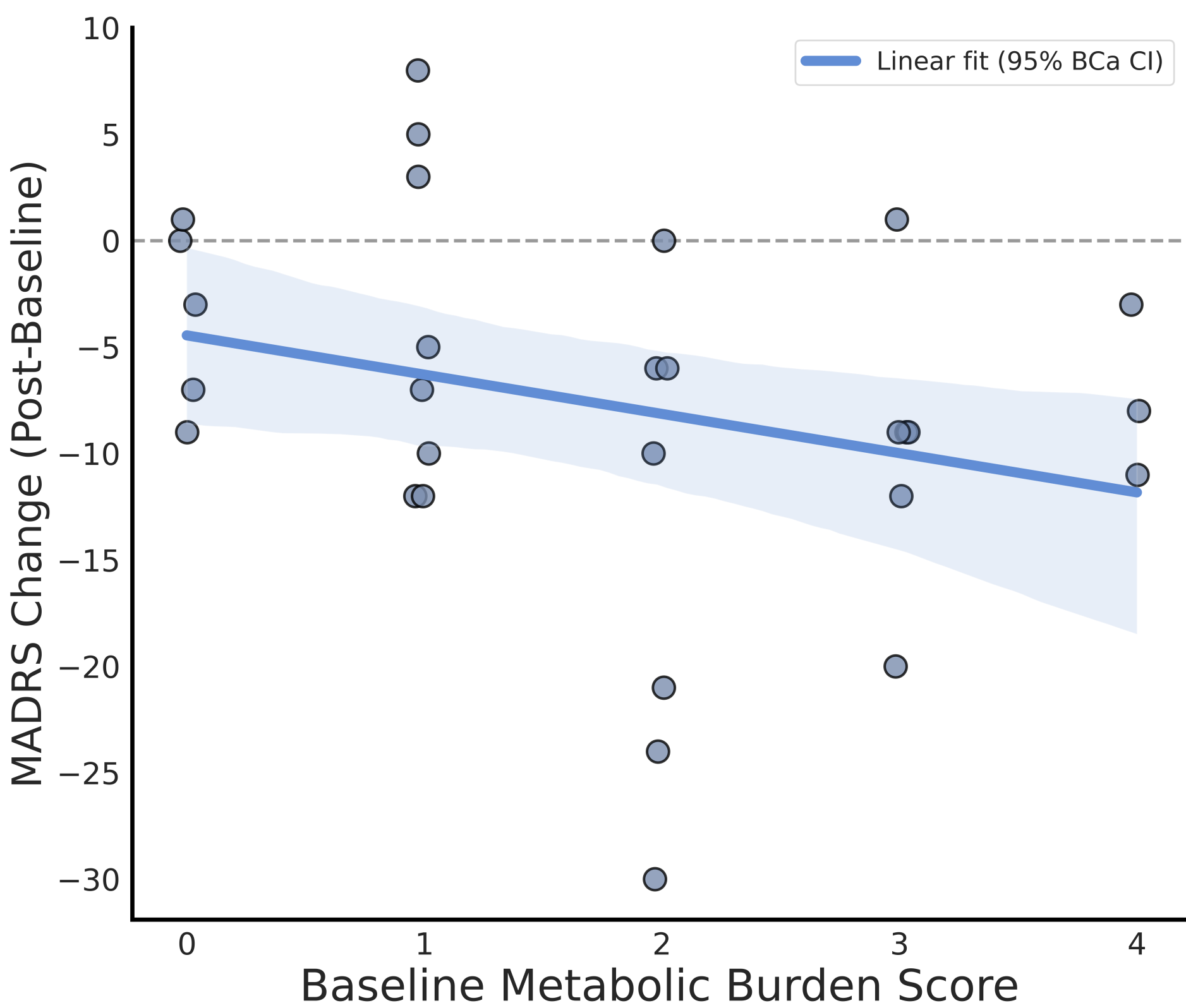
Figure Legends

Figure 1. Changes in depressive symptom severity following repeated intranasal esketamine treatment. Changes in a) Montgomery-Åsberg Depression Rating Scale (MADRS) scores (n=29) and b) Patient Health Questionnaire-9 (PHQ-9) scores (n=30) from baseline to post-treatment. *** $p < 0.001$.

Figure 2. Association between baseline metabolic burden composite score and change in Montgomery-Åsberg Depression Rating Scale (MADRS) scores following repeated intranasal esketamine treatment (n=29).

Figure 3. Change in fasting glucose following repeated intranasal esketamine treatment. Fasting glucose was significantly decreased following repeated intranasal esketamine treatment ($p_{\text{FDR}} < 0.001$, n=23). Each grey line represents an individual participant's change from baseline to post-treatment. The blue line represents the group mean.





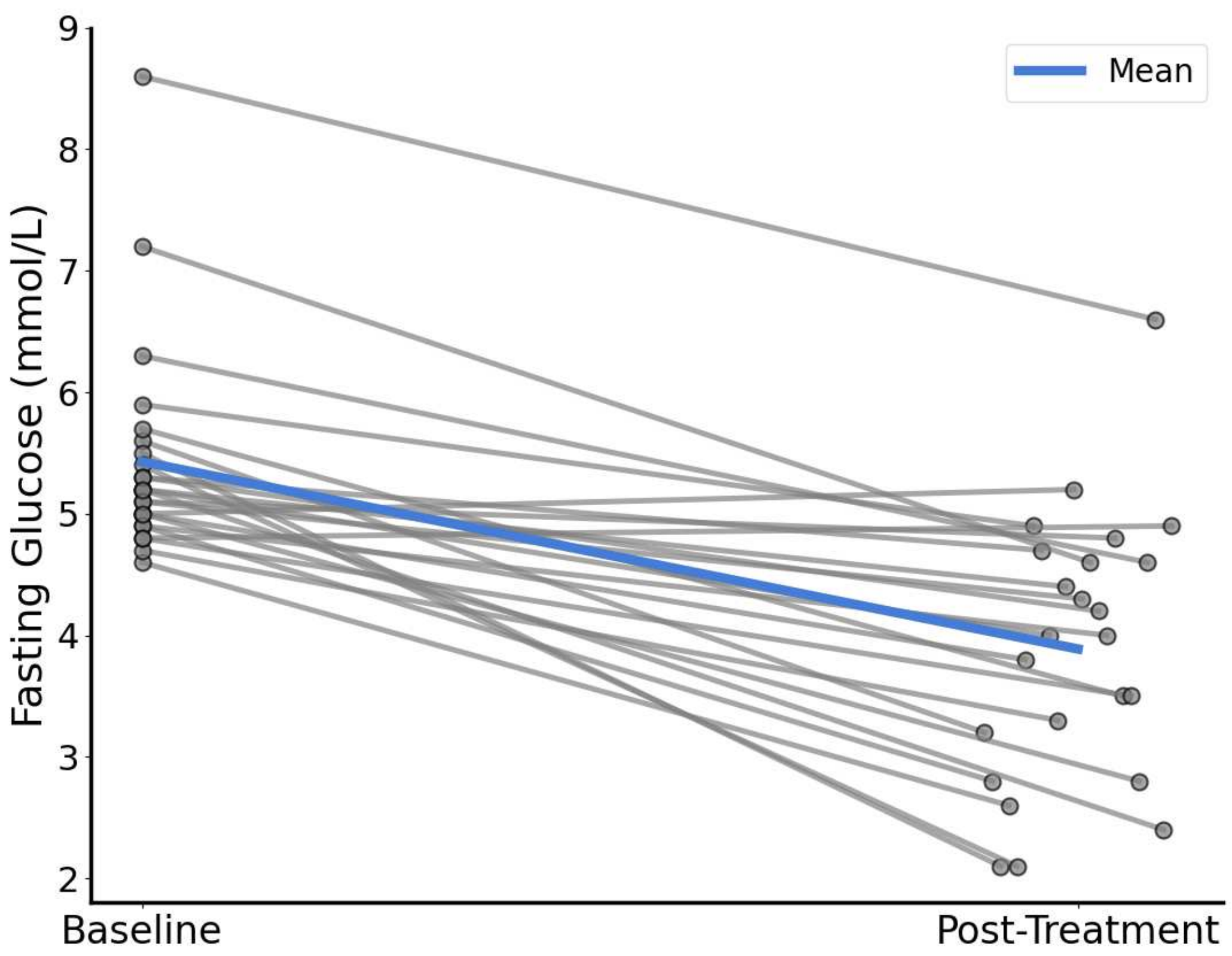


Table 1. Baseline demographic and clinical characteristics of participants (N=30).

Demographics and Characteristics	Value
Age, Years, Mean (SD)	45.8 (12.4)
Sex, Female/Male, n (%)	13 (43)/17 (57)
Race, White, n %	26 (87)
Primary Diagnosis	
Major Depressive Disorder, n (%)	25 (83)
Bipolar I Disorder, n (%)	3 (10)
Bipolar II Disorder, n (%)	2 (7)
Current Comorbid Diagnoses	
Generalized Anxiety Disorder, n (%)	21 (70)
Persistent Depressive Disorder, n (%)	13 (43)
Attention Deficit Hyperactivity Disorder, n (%)	7 (23)
Post-Traumatic Stress Disorder, n (%)	5 (17)
MADRS Total Score, Mean (SD)	29.8 (5.1)
Lifetime History of Suicide Attempt, ¹ n (%)	14 (47)
Past 6 Month Suicidal Ideation Severity (C-SSRS), Mean (SD)	2.7 (1.5)
Failed Antidepressant Trials, ² Mean (SD)	3.9 (1.3)
Metabolic Syndrome, ³ n (%)	9 (30)
Obesity, ⁴ n (%)	7 (24)
Type 2 Diabetes, ⁵ n (%)	3 (10)
Obstructive Sleep Apnea, ⁶ n (%)	11 (37)
Elevated CRP ⁷ n (%)	9 (31)
Smoking Status, Current/Former/Never, n (%)	0 (0)/8 (27)/22 (73)

¹Actual suicide attempt as defined by C-SSRS criteria [45].

²Number of failed antidepressant trials during current episode according to the Antidepressant Treatment History Form [33].

³Defined as presence of ≥ 3 of 5 metabolic abnormalities according to National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria [42,43].

⁴Defined as body mass index ≥ 30 kg/m² [46].

⁵Diagnosis documented in medical records.

⁶Identified through medical records, self-report, or Stop-Bang Questionnaire score ≥ 3 [47].

⁷Defined as CRP values ≥ 3 mg/L [48].

Obesity and CRP values are based on available data (n = 29).

CRP, C-reactive protein; C-SSRS, Columbia Suicide Severity Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale

Table 2. Changes in metabolic, inflammatory, and neurotrophic biomarkers following repeated intranasal esketamine treatment (n=28).

	Baseline	Post-treatment	Mean Change	95% CI	<i>p</i>	<i>p</i> _{FDR}	Cohen's <i>d</i>	<i>n</i>
Metabolic Biomarkers								
Waist circumference (cm)	101.21 (18.75)	101.43 (20.53)	0.22	(-5.12, 2.25)	0.859	0.949	0.03	28
Triglycerides (mmol/L)	1.28 (.40)	1.33 (0.54)	0.05	(-0.09, 0.19)	0.460	0.737	0.15	26
HDL cholesterol (mmol/L)	1.43 (0.39)	1.45 (0.70)	0.02	(-0.17, 0.21)	0.810	0.949	0.05	26
Systolic blood pressure (mmHg)	125.8 (18.0)	121.45 (15.51)	-4.31	(-10.48, -1.22)	0.024	0.062	-0.45	28
Diastolic blood pressure (mmHg)	77.15 (9.24)	75.57 (9.20)	-1.58	(-4.03, 0.86)	0.195	0.390	-0.25	28
Fasting glucose (mmol/L)	5.43 (0.90)	3.85 (1.11)	-1.58	(-2.01, -1.16)	0.001	0.001	-1.61	23
Inflammatory and Neurotrophic Composites¹								
Pro-inflammatory composite	-0.013	0.049	0.062	(-0.069, 0.237)	0.448	-	0.18	25
Neurotrophic composite	-0.030	-0.041	-0.011	(-0.166, 0.145)	0.900	-	-0.03	27

¹Pro-inflammatory composite included CRP, IL-6, and TNF- α ; neurotrophic composite included serum BDNF and VEGF.

BDNF, brain derived neurotrophic factor; CRP, C-reactive protein, FDR, false discovery rate, HDL, high-density lipoprotein, IL-6, interleukin-6; TNF- α , tumour necrosis factor alpha; VEGF, vascular endothelial growth factor

Sample size varies across biomarkers due to assay quality control exclusions and unusable samples due to sample quality (e.g., hemolysis). Biomarker-specific sample sizes are indicated in the table.

Supplementary Files

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