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Research Article

Sex-Specific Elevated Fasting Glucose in Patients with Major Depressive Disorder

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Abstract

Background: This study aimed to test whether the relationship between Major Depressive Disorder (MDD) and prediabetes is sex-specific and explored potential pathways.

Methods: One hundred sixty-eight participants were enrolled, and 142 completed the study for data analysis. Participants were divided into patients with MDD (n=58) and without MDD, i.e., controls (n=84). The Oral Glucose Tolerance Test (OGTT) was conducted, and the serum cortisol levels of each participant were also measured. Demographic variables were analyzed using t-tests or chi-square tests. Covariance analysis was conducted to test the measures derived from OGTT and cortisol levels between groups.

Results: There was no difference in fasting glucose, 2-hour post-prandial levels, and indices of insulin sensitivity between MDD and control groups. However, in a stratified and sex-comparative analysis, female participants with MDD had higher fasting glucose and cortisol levels than female controls, but this was not seen in males. Also, fasting glucose was positively correlated with the severity of depression in females with MDD.

Conclusion: Females with MDD have the highest risk of developing prediabetes compared to female controls and males, possibly through cortisol. Fasting glucose and cortisol could be biomarkers to recognize prediabetes in females with MDD for early intervention and better outcomes.

Keywords: Major Depressive Disorder; Prediabetes; Fasting Glucose; Cortisol; Sex

Introduction

Major Depressive Disorder (MDD) is a debilitating disease characterized by adverse mood changes, cognitive function impairments, and a worsened quality of life [1]. MDD is associated with high costs in the United States; there is a significant economic burden on adults with MDD – this increased by 37.9%, from $236.6 billion to $326.2 billion between 2010 and 2018 [2]. MDD has a lifetime prevalence of about 12%, almost double in women than in men [3]. In addition, MDD often co-occurs with other chronic diseases. However, this observation has not been well-studied as common among patients with prediabetes [4].

Prediabetes is characterized by impaired fasting glucose levels and/or impaired glucose tolerance (defined as 2-hour glucose levels ≥ 140–199 mg/dl in an Oral Glucose Tolerance Test (OGTT)) [5]. The CDC 2022 National Diabetes Statistics Report estimates that over 96 million adults in the United States have prediabetes [6]. Additional research has shown that males are more likely to develop impaired fasting glucose, while impaired glucose tolerance is more prevalent among females [7]. However, the underlying mechanisms are not entirely understood [8]. Impaired glucose tolerance may be a better predictor of a future diagnosis of diabetes and cardiovascular risk (Kautzky-Willer et al., 2016); this suggests that testing for impaired glucose tolerance should be done

more regularly, especially in females [7].

Insulin resistance can also contribute to prediabetes [9]. Insulin resistance is the body's inadequate biological response to insulin, resulting in the inability to lower glucose levels and hyperinsulinemia [10]. Because of this, extra glucose remains in the bloodstream, which can contribute to impaired glucose tolerance [11].

Both prediabetes and MDD are common and chronic disorders and tend to co-exist. Researchers have found that, in a Finnish population, insulin resistance and the severity of MDD are positively correlated with impaired glucose tolerance [12]. Another study found that individuals with prediabetes have an increased risk of developing MDD compared to those with normal glucose metabolism [13]. Recent research also found that depressive symptoms were significantly more common in women with prediabetes [14]. In contrast, men with depression did not have impaired glucose metabolism [14]. Thus, previous studies have indicated a relationship between MDD, insulin resistance, and impaired glucose metabolism, which might be sex-specific. However, it is not yet clear whether the same associations are present between MDD and fasting glucose levels and what the characterization of their association and potential pathway might be.

Cortisol is a glucocorticoid triggered by stress and could be abnormally higher in patients with MDD [1]. Studies showed that in patients with MDD, the hypothalamic-pituitary-adrenal (HPA) axis, responsible for the stress response, is also altered and over-activated [15]. Additionally, cortisol increases visceral fat [16], which is associated with insulin resistance and impaired glucose tolerance [17]. Increased cortisol levels are also associated with hyperinsulinemia in women, suggesting insulin resistance, a characteristic of prediabetes [18]. Thus, cortisol may act as a potential pathway linking MDD and prediabetes, i.e., impaired glucose tolerance and elevated fasting glucose.

We designed a cross-sectional study to explore the relationship between MDD and prediabetes in an adult population. We hypothesize that: 1) patients with MDD will have higher levels of fasting glucose and/or 2-hour post-prandial glucose than participants without MDD during the OGTT, 2) a sex-specific relationship between prediabetes and MDD exists, in that female patients will have a greater risk for prediabetes, as compared to females without MDD and males in general, and 3) females with MDD will have higher cortisol levels than females without MDD.

Methods

Participants and Groups

The Institutional Review Board at the University of Alabama at Birmingham approved this study. Participants were recruited from Jefferson County, Alabama. Each participant provided written informed consent before the start of the research procedures. Among 168 enrolled participants, 142 completed the study for data analysis, including whites and Blacks, and males and females aged 19 to 60 years. Participants self-reported their age, race, medical history, employment status, and level of education. We measured each participant's body weight and height to calculate Body Mass Index (BMI). The exclusion criteria were endocrine disorders (e.g., Cushing syndrome, Addison's disease, or diabetes), systemic corticosteroids or drugs affecting glucose metabolism, and pregnancy or lactation. All participants were evaluated using the Mini International Neuropsychiatric Interview (MINI) [19] for their psychiatric disorders. They were excluded from the study if they had current psychotic and manic symptoms and had used alcohol or illicit drugs in the last 12 months [19]. The psychiatrist diagnosed participants with MDD using MINI and verified with the DSM-5 diagnostic criteria [20]. The participants completed a short version of a Childhood Trauma Questionnaire for their early life experiences [21]. The participants were stratified into the MDD group and the control group (i.e., the non-MDD group). The Beck Depression Index-II was administered to all participants with MDD to estimate the severity of depression [22,23].

Oral Glucose Tolerance Test and Insulin Sensitivity Assessment

An oral glucose tolerance test was conducted in the morning and usually started at 8 am. All participants underwent a standard 2-hour Oral Glucose Tolerance Test (OGTT) after an overnight fast (10-12 hours) and were administered a 75-gram oral glucose solution [24]. To determine glucose levels, blood samples were collected at 0, 0.5, 1, and 2-hour post-glucose load. Glucose levels were measured using the glucose oxidase method with a glucose analyzer (Beckman Coulter Unicell DxC 800). Insulin was determined using an enzyme-labeled chemiluminescence immunoassay (Siemens).

Both the homeostasis model assessment of insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) were utilized as surrogate estimates of insulin sensitivity [25,26]. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated according to the formula: [fasting insulin (μU/L) x fasting glucose (nmol/L)]/22.5 [26].

Cortisol Measurement

Blood samples (10 milliliters) were drawn from each participant by venepuncture at approximately 1300 to avoid the diurnal variation in cortisol levels. The blood was centrifuged at 3000g for 10 minutes and immediately divided into aliquots. We then stored the samples at -80°C until they were analyzed. Plasma concentrations of cortisol (intra- and inter-assay variability of 4.6% and 8.6%, respectively) were analyzed using the immunoassay. All samples ran in duplicate, and the mean of the duplicate samples was reported and used for data analysis.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences version 26 (SPSS Inc., Chicago, IL). Except for cortisol, the rest of the data were presented as mean ± standard deviation in the text, figures, and tables. Cortisol data were presented as mean ± standard error in the text and figures. P values ≤0.05 were considered significant. Normal distribution and homogeneity of variances were confirmed by Shapiro-Wilk's and Levene's tests, respectively. Variables were log-transformed so that each variable followed an approximately normal distribution. Demographic variables were analyzed using t-tests or chi-square tests. Differences between the MDD and control groups in variables of interest were compared using the analysis of covariance (ANCOVA) with adjustment for age, race, employment status, education level, BMI, and early life stress experiences. A correlation analysis was used to estimate the levels of association between cortisol levels and depression severity in females with MDD after adjusting the covariates stated above.

Results

Participants' characteristics

Table 1 presents the characteristics of participants in the MDD and control groups. There were no significant differences in sex, BMI, and education level between participants in the control and MDD groups. However, there were significant differences in age, race, employment status, and early life stress experiences between the two groups. Thus, these variables were adjusted for data analyses.

	MDD n=58	Control n=84	P
Age, Years (SD)	43.2 (12.9)	35.4 (11.5)	<0.01
Sex, Female/Male, N	34/24	58/26	0.201
Race, Blacks/Whites, N	24/34	49/35	0.047
Body mass index, kg/m^2 (SD)	29.6 (6.6)	30.8 (7.1)	0.317
Education Level			0.057
<10 Years	4	0	
10-12 Years	10	8	
>12 Years	40	72	
Unknown	4	4	
Total ELS Score (SD)	54.1 (20.5)	36.6 (11.3)	<0.001
Employment Status			<0.001
Yes	20	70	
No	37	13	
Unknown	1	1	
Note: MDD: Major Depressive Disorder; ELS: Early Life Stress			

Table 1: Characteristics of Participants.

Glucose and insulin comparisons between groups

We conducted an ANCOVA analysis to compare fasting and 2-hour post-prandial glucose levels between the two groups with early life stress experiences, age, race, employment status, and BMI as covariates. Although BMI was not significantly different between groups, it is related to glucose levels [27]. Thus, BMI was also adjusted for data analyses. Fasting glucose tended to be greater in the MDD group but were not significantly different between the MDD group and the control group (99.4 ± 9.7 vs. 94.9 ± 8.5, p=0.07) (Figure 1A). In addition, 2-hour post-prandial glucose was not significantly different between the two groups (106.3 ± 26.6 vs. 103.5 ± 26.7, p=0.48). 30-minute and 60-minute post-prandial glucose were also not significantly different between the MDD and control groups (148.3 ± 28.9 vs. 134.9 ± 28.5, p=0.54; 141.3 ± 42.6 vs. 125.4 ± 32.6, p=0.32). Insulin levels at the four time points during the OGTT were not different between the MDD and control groups.

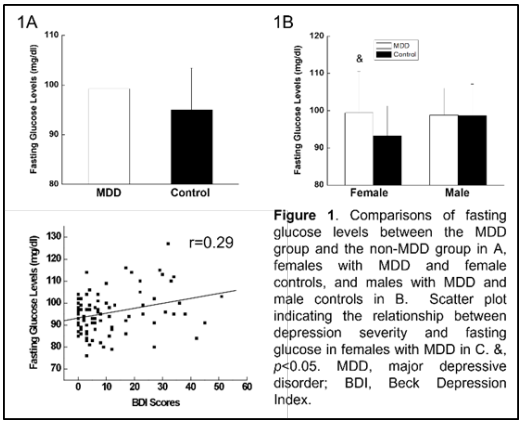

Figure 1. Comparisons of fasting glucose levels between the MDD group and the non-MDD group in A, females with MDD and female controls, and males with MDD and male controls in B. Scatter plot indicating the relationship between depression severity and fasting glucose in females with MDD in C. &, *p*<0.05. MDD, major depressive disorder; BDI, Beck Depression Index.

Figure 1: Comparisons of fasting glucose levels between the MDD group and the non-MDD group in A, females with MDD and female controls, and males with MDD and male controls in B. A scatter plot indicates the relationship between depression severity and fasting glucose in females with MDD in C (correlation coefficient was 0.29). &, *p*<0.05. MDD, major depressive disorder.

Sex-specific elevation in fasting glucose and cortisol levels in females

An ANCOVA analysis was conducted, with the same covariates as stated above, to compare glucose levels by stratifying MDD and control groups by sex. Fasting glucose was significantly elevated in females with MDD compared to female controls (99.4 ± 11.1 vs. 93.2 ± 8.1, p=0.04) (Figure 1B). However, there was no significant difference in the fasting glucose levels between males with MDD and male controls (98.8 ± 7.2 vs. 98.7 ± 8.4, p=0.52). The correlation between fasting glucose and the severity of depression measured by the Beck Depression Index-II in females with MDD was positive and moderately strong (r=0.29, p=0.004) (Figure 1C).

Elevated levels of cortisol were found in participants with MDD compared with controls (Figure 2A). When the two groups were divided further by sex and similar comparisons were conducted, cortisol levels were higher in females with MDD than in female controls (10.9 ± 0.8 vs. 7.9 ± 0.4, p=0.004) (Figure 2B). However, no significant differences in cortisol levels were found between males with MDD and male controls (10.0 ± 0.4 vs. 9.6 ± 0.6, p=0.51). No sex-related differences were found in other OGTT measures, including glucose levels at 30-, 60-, and 120-min and insulin levels at the four time points during the OGTT.

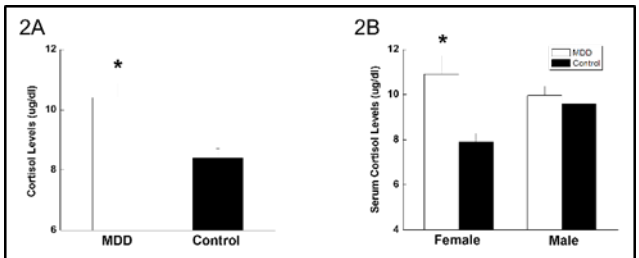

Figure 2. A). Comparison of cortisol levels between the MDD group and the non-MDD group (controls); B). Comparison of cortisol levels between females with MDD and female controls, and between males with MDD and male controls. *p<0.01. MDD, major depressive disorder.

Figure 2A: Comparison of cortisol levels between the MDD group and the non-MDD group (controls); B). Comparison of cortisol levels between females with MDD and female controls and between males with MDD and male controls. *p<0.01. MDD, major depressive disorder.

Indices of insulin sensitivity

HOMA-IR and QUICKI were calculated to be indices of insulin sensitivity. The MDD and control groups did not differ in HOMA and QUICKI scores, and no sex-related differences were found either.

Discussion

In this cross-sectional study, it was found that participants with MDD tended to have higher fasting glucose levels, although they were not significant when compared with participants without MDD. Additionally, 2-hour post-prandial levels and indices for insulin sensitivity, including HOMA-IR and QUICKI, were not different between MDD and control groups. However, our findings indicate a sex-specific relationship between MDD and fasting glucose in which female participants with MDD had higher fasting glucose levels than female controls. This observation did not hold in male participants compared with male controls. Furthermore, fasting glucose was positively correlated with the severity of depression in females. Similarly, serum cortisol levels were only elevated in female participants with MDD compared with female controls.

CDC data have shown that MDD is associated with a 60% increased risk of developing diabetes. Per the CDC report, researchers have studied the relationship between MDD and the subsequent development of incident prediabetes [13,28-30]. The current study, which showed that female participants with MDD had elevated fasting glucose compared to those without MDD, further supports these findings. Several epidemiological studies have evaluated the association between metabolic syndrome and MDD, with most revealing a link. Research has also shown the associations between various components of the metabolic syndrome (elevated fasting glucose in our study) and MDD are affected by sex [31]. For example, several studies found an association between depression and elevated fasting glucose levels in women only [32-34]. We stratified our sample by sex and supported this sex-specific relationship between MDD and fasting glucose. Hence the association between MDD and prediabetes appears to be more pronounced in females.

Evidence of insulin sensitivity is accumulating with the development of MDD [35-37]. For example, a study of adults over a 9-year follow-up period found that insulin resistance, a condition associated with diabetes, positively predicted incident MDD among people who had never had a history of depression before. Also, the development of prediabetes from the time of enrollment in the study and the 2-year study period positively correlated with the risk of developing MDD [38]. Fasting glucose levels and insulin sensitivity are also closely related [39-41]. Interestingly, our study showed no differences in glucose levels and indices for insulin sensitivity between the MDD and non-MDD groups. However, in contrast to male controls, fasting glucose levels were significantly higher in female participants with MDD than in female controls. No sex-specific difference was observed in indices of insulin sensitivity between groups in our study. Thus, future studies with regard to indices of insulin sensitivity are warranted for further determination and clarification.

The underlying pathway remains unclear despite the relationship between MDD and prediabetes, i.e., elevated fasting glucose in females with MDD in the current study. Research has shown that MDD is associated with high levels of the adrenergic nervous system, as measured by adrenaline, norepinephrine, and dopamine in plasma and cerebrospinal fluid [42-44]. Higher levels of the adrenergic-sympathetic system could result in impaired glucose and elevated blood glucose levels [45]. MDD has also been associated with impaired HPA axis [46], leading to elevated cortisol levels, decreased glucose uptake, and increased glucose levels [45]. Other studies have shown that cortisol and metabolic syndrome are related, with higher cortisol levels associated with increased fasting glucose [47-49]. Our findings further support the likelihood of cortisol being a potential pathway linking MDD and prediabetes, i.e., fasting glucose, although this warrants further

studies, especially longitudinal studies.

The current study has critical clinical indications. Women with elevated fasting glucose co-occurring with MDD are likely to practice poorer self-care, have impaired treatment adherence and glycemic control, and have reduced quality of life than women without a depression diagnosis [50-52]. Furthermore, many women with MDD may not be aware that their fasting glucose level is elevated and that this condition poses a risk of developing diabetes. This lack of awareness is unfortunate because early identification of prediabetes can delay the onset of diabetes and its related complications among susceptible individuals, including patients with MDD. Our study and other previous studies provide convincing data supporting prediabetes screening in patients with MDD, especially in females. Our findings also indicate that elevated fasting glucose and cortisol may serve as biomarkers to screen for prediabetes in patients with MDD.

The present study has several limitations, including a cross-sectional design that does not allow for a causal relationship to be established. A longitudinal study is warranted to answer some of the questions regarding the causal link between MDD, prediabetes, and elevated cortisol. Previous studies from cross-sectional and longitudinal designs have produced inconsistent results about antidepressant effects on glucose homeostasis [53, 54]. Due to this, we did not covariate antidepressants. Future research should focus on the role of antidepressants in developing prediabetes and diabetes.

Conclusion

Our study showed that females with MDD were more likely than female controls and males to develop prediabetes. The findings suggest that fasting glucose levels, especially in females with MDD, should be examined to monitor the risk of prediabetes, diabetes, and other complications. An increasing number of people have MDD and unrecognized prediabetes and diabetes, and there is a heightened risk for prediabetes among females with MDD. This suggests that biomarkers such as fasting glucose and cortisol should be included in routine physical examinations. In females with MDD, it is vital to recognize and potentially treat prediabetes earlier to prevent future diabetes and its complications.

Conflict of Interest

The authors declare that the research was conducted without commercial or financial relationships that could be construed as a potential conflict of interest.

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Author contributions

N.P. collected and analyzed the data, drafted, edited, and approved the final manuscript. B.B. drafted, edited, and approved the final manuscript. L.L. conceptualized and designed the study, collected and analyzed the data, and reviewed, edited, and approved the final manuscript.

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