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Late-Life Depression is Associated With Increased Levels of GDF-15, a Pro-Aging Mitokine

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SUPPLEMENTARY MATERIALS

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Abstract

Objective: In older adults, major depressive disorder (MDD) is associated with accelerated physiological and cognitive aging, generating interest in uncovering biological pathways that may be targetable by interventions. Growth differentiation factor-15 (GDF-15) plays a significant role in biological aging via multiple biological pathways relevant to age and age-related diseases. Elevated levels of GDF-15 correlate with increasing chronological age, decreased telomerase activity, and increased mortality risk in older adults. We sought to evaluate the circulating levels of GDF-15 in older adults with MDD and its association with depression severity, physical comorbidity burden, age of onset of first depressive episode, and cognitive performance.

Design: This study assayed circulating levels of GDF-15 in 393 older adults (mean ± SD age 70 ± 6.6 years, male:female ratio 1:1.54), 308 with MDD and 85 non-depressed comparison individuals.

Results: After adjusting for confounding variables, depressed older adults had significantly higher GDF-15 serum levels (640.1 ± 501.5 ng/mL) than comparison individuals (431.90 ± 223.35 ng/mL) (t=3.75, d.f.= 391, p=0.0002). Among depressed individuals, those with high GDF-15 had higher levels of comorbid physical illness, lower executive cognitive functioning, and higher likelihood of having late-onset depression.

Conclusion: Our results suggest that depression in late life is associated with GDF-15, a marker of amplified age-related biological changes. GDF-15 is a novel and potentially targetable biological pathway between depression and accelerated aging, including cognitive aging.

Keywords

Late life depression; biological markers; GDF-15; Aging; Geroscience

INTRODUCTION

Many psychiatric conditions are associated with accelerated biological aging processes.[1] Major depressive disorder (MDD) in older adults -a.k.a. late-life depression (LLD)- has been associated with dysregulation of pathways related to biological aging.[2] For example, MDD has been consistently associated with high pro-inflammatory cytokines, contributing to prominent changes in cell senescence, the molecular changes that lead to cell replication arrest, that are observed in this condition.[3] Pro-inflammatory biomarkers have also been associated with increased severity of depressive symptoms in a population of older inpatients with LLD.[4] Telomere attrition, a classic marker of cellular senescence, has also been

reported amongst patients with MDD, including those with LLD, and is a possible marker of depression severity.[5] When damaged, mitochondria elicit a stress response by releasing various proteins and peptides known as mitokines.[6] Mitochondrial dysfunction and the release of mitokines have also been associated with abnormal regulation of apoptosis and increased oxidative stress markers that contribute to accelerated aging associated with MDD.[7] Moreover, mitochondrial dysfunction in skeletal muscle has been associated with an increased likelihood of clinically significant depressive symptoms in individuals with LLD.[8] Similarly, alterations in DNA methylation have been widely shown to be significantly associated with MDD and LLD, with one study demonstrating that the mitokine growth differentiation factor-15 (GDF-15) is associated with different DNA methylation patterns in cardiovascular disease.[9]

There is accumulating evidence that growth differentiation factor 15 (GDF-15) plays a significant role in biological aging and the development of age-related diseases. GDF-15 is involved in biological pathways relevant to aging, such as energy homeostasis, stress response, and inflammatory regulation.[10] GDF-15 is a pleiotropic molecule, and its biological effects are probably dependent on different biological contexts as well as chronological age.[9] GDF-15 is prominently expressed in senescent cells, and its peripheral levels are strongly correlated with chronological age and decreased telomerase activity.[11]

In a previous investigation aimed to identify proteins and genes regulated in aging and frailty, GDF-15 was identified as one of 19 high priority markers that provided considerable evidence supporting its involvement in accelerated aging.[12] There is also evidence that higher levels of GDF-15 are associated with cognitive impairment, particularly in older adults.[13] In animal models, GDF-15 expression is significantly higher in animals with mitochondrial dysfunction and higher oxidative stress markers.[10] Energy impairment in the brain due to mitochondrial dysfunction has been implicated in the pathogenesis of depression in addition to accelerated aging, suggesting that mitokines such as GDF-15 may be a biomarker for LLD.[7] Recent community-based studies have shown that higher GDF-15 levels strongly predicted overall mortality, probably due to its pro-inflammatory effects and negative impact on cardiovascular and renal function.[14]

GDF-15 has been studied in severe mental illness, and some studies have found elevated GDF-15 levels in individuals with bipolar and psychotic disorders.[15,16] Few studies, however, have evaluated GDF-15 levels in older adults with MDD or a major depressive episode, although growing evidence indicates that LLD is associated with markers of accelerated aging.[3] In a study including only older adults, GDF-15 levels were not significantly higher in LLD than in non-depressed comparison participants after controlling for lifestyle factors such as smoking, physical activity, and alcohol use, and were not significantly correlated with depression severity.[17]

The overarching aim of this study was to evaluate the circulating levels of GDF-15 in older adults with MDD. Our primary hypothesis was that males and females with LLD would have higher levels of GDF-15 than age-matched never-depressed comparison participants. We also hypothesized that, in patients with LLD, GDF-15 levels would be associated with

higher severity of depressive symptoms, a higher burden of physical comorbidity, older age of onset of first depressive episode, and poorer cognitive performance.

METHODS

Study Sample

This study included participants from two NIH-funded multi-site studies: Incomplete Response in Late-Life Depression: Getting to Remission (IRL-GRey) (ClinicalTrials.gov Identifier: NCT00892047) and Mindfulness-Based Stress Reduction, Health Education, and Exercise (MEDEX) (ClinicalTrials.gov Identifier: NCT02665481).

Late-life depression participants—A total of 308 older adults diagnosed with an acute episode of a MDD were included in this analysis. They were participants in the IRL-GRey trial conducted at three different sites (Pittsburgh, PA; St Louis, MO; and Toronto, Canada).[32] The diagnosis of MDD was made based on the SCID-IV (Structured Clinical Interview for DSM-IV). Single versus recurrent MDD status, episode duration, history of previous suicide attempts, comorbid anxiety disorders, and age of onset of MDD were collected based on SCID-IV. The severity of depressive symptoms was measured by the 10-item Montgomery-Asberg Depression Rating Scale (MADRS).[18] Physical and clinical data, including blood samples, were also obtained during the baseline visit. Additional details of the baseline assessment and characterization of participants in this study have been reported previously.[19] All participants were not under antidepressant treatment at the time of the baseline assessment and blood draw. We administered a neuropsychological test battery (supervised by a senior neuropsychologist [MAB]) at baseline. The battery included the Repeated Battery for the Assessment of Neuropsychological Status (RBANS), which evaluates the cognitive domains of attention, language, visuospatial abilities, immediate memory, and delayed memory. It also yields a global performance score. Executive function was evaluated using two tests from the Delis-Kaplan Executive Function System: the Color-Word Interference task (measuring response inhibition) and two Trail Making Test tasks (measuring set-shifting).[20] Color-Word Interference condition 3, which measures inhibition, assesses the ability to inhibit an automatic response (i.e., reading words) in favor of producing a response that requires more effort (i.e., naming colors of ink in which words are written). The Trail Making Test condition 4 (also known as the Number-Letter Switching condition) requires that examinees switch back and forth between connecting numbers and letters (i.e., 1, A, 2, B, etc., to 16, P). Condition 5 is a motor speed condition in which examinees trace over a dotted line connecting circles on the page as quickly as possible to gauge their motor drawing speed. Comparing performance on condition 4 (which assesses cognitive flexibility) with performance on condition 5 (which assesses motor speed) removes the motor speed element from the test score to ascertain cognitive flexibility.[21] We used the Delis-Kaplan Executive Function System normed scaled score (with a mean [SD] of 10^3) based on the difference in speeds between condition 4 and condition 5, representing set-shifting performance.[22]

Never-depressed comparison participants—A total of 85 older adults without history of a MDD or major neurocognitive impairment were included as a comparison

group (CG). They were recruited as part of the MEDEX study, a randomized controlled trial that evaluated the effects of mindfulness and multimodal exercise to improve cognitive performance and that was conducted at two sites (San Diego, CA; St. Louis, MO). Only baseline data (pre-intervention) were used in this analysis. MEDEX study participants underwent an assessment including an evaluation of current and past psychiatric history using the MINI 7.0.[23] Additional details of the baseline characterization and assessment of participants in MEDEX have been reported elsewhere.[24]

Additional Variables

Demographic and physical data (chronological age, self-reported sex and race, weight, height, medical history) were collected as part of the baseline assessment of both studies. The body mass index (BMI) was calculated based on the formula: BMI = weight (Kg)/ height^2 (m^2). Physical comorbidity burden was evaluated by the Cumulative Illness Rating Scale – Geriatric (CIRS-G) in both the IRL-Grey and MEDEX studies[25]; higher scores indicate greater levels of overall medical illness summed from all organ systems.

Laboratory Analyses

Blood was collected by venipuncture using serum separator tube. Blood was processed within 3 hours of collection using standard procedures. Serum was separated, aliquoted, and stored at −80°C until laboratory analysis. The GDF-15 serum levels were measured in an assay using a LUMINEX technology and according to the manufacturer's instructions (R&D, Minneapolis, USA). The biomarkers analyses were done in two batches using the same control standards and detection antibody. The intra-assay coefficient of variance was below 10% for each batch.

Upon analysis of potential site and batch effect on the GDF-15 results, we found a significant effect of the study site (Pittsburgh, PA; San Diego, CA; St. Louis, MO; and Toronto, ON) in batch one (d.f, 119, p=0.009). Based on this evidence of the site-by-batch effect, we included both batch and site as random variables in all statistical models.

Statistical Analyses

We carried out t tests or univariate analyses of variance to test the effect of depression diagnosis or specific characteristics of the depressive episode (such as severity or recurrence) on GDF-15 levels and other demographic or clinical, or psychiatric variables. Chisquare analysis evaluated whether categorical variables had different frequency distributions according to diagnosis (MDD versus control). We used Pearson correlation analyses to evaluate the association between GDF-15 levels and demographic, physical, and psychiatric variables. The significance level was set at $\alpha < 5\%$ because the primary hypothesis was a single comparison of GDF-15 levels between LLD and nondepressed comparisons. We used a multilevel mixed-effect linear model to evaluate the potential effects of recruitment sites, laboratory analyses batch, and covariates (age, sex, body mass index, and CIRS-G scores) on the association between diagnosis and serum GDF-15 levels. Recruitment site and laboratory batch were included as random effect variables. We used the restricted maximum likelihood method (REML) to reduce the bias in the variance estimation in the model. Stata v.17.0 software (College Station, TX) was used for all analyses.

RESULTS

LLD participants were younger and had higher BMI values and comorbid physical burden than never-depressed comparison participants (Table 1). There were no significant differences between groups in sex frequency distribution or race distribution (Table 1). Participants with LLD had significantly higher GDF-15 levels than the non-depressed comparison participants ($t=3.75$, d.f.= 389, $p=0.0002$). When examining sex, GDF-15 levels were significantly higher in men than women ($t=2.00$, d.f.=391, $p=0.04$). There were significant but weak correlations between GDF-15 and chronological age ($r=0.11$, $p=0.02$) or CIRS-G score ($r=0.13$, $p\leq0.001$), but not with BMI ($r=-0.005$, $p=0.91$). Mixed model linear analyses showed that the association between LLD and GDF-15 levels remained statistically significant after controlling for the effect of potential confounding variables (i.e., age, sex, BMI, and CIRS-G scores) and the random effect of recruitment site and laboratory batch ($z=2.24$, $p=0.02$).

Since the total CIRS-G scores were correlated with GDF-15 levels, we further explored if organ systems significantly influenced the GDF-15 levels. We divided both depressed and comparison participants based on absent or mild problems in each system (CIRS-G scores 0 and 1) versus those with moderate to very severe problems (CIRS-G scores 2–4) in each system. We found that participants with moderate to very severe problems in the heart, vascular, respiratory, upper gastrointestinal, and renal systems had significantly higher GDF-15 levels (Supplementary Table 1).

We carried out additional analyses including only the participants with LLD (n=308). We found no significant correlation between GDF-15 levels and the severity of depressive symptoms measured by the MADRS ($r=0.13$, $p=0.18$). We also found no significant association between GDF-15 levels and other characteristics of the depressive episode such as recurrence ($t=-1.3$, d. f.=306, $p=0.19$) or duration of the depressive episode ($r=-0.03$, $p=0.67$). There was a significant but weak association between age of first depressive episode and GDF-15 levels ($r=0.12$, $p=0.043$), such that those with later onset depression had higher levels of GDF-15. Individuals with late-onset depression (LOD) (i.e., first depressive episode at age 65 or older) had higher GDF-15 levels than those with early-onset depression (EOD) (i.e., first depressive episode before age 65) ($t=-3.5$, d.f=305, $p<0.001$) (Supplementary Table 3). Presence of comorbid anxiety disorders, a history of previous suicide attempt, or recurrence of depressive episodes were not significantly associated with GDF-15 levels (Supplementary Table 3). Higher GDF-15 levels were significantly associated with worse set shifting (a measure of executive function; $r=-0.147$, $p=0.011$), but not with other cognitive domains (Supplementary Table 4) in the whole LLD group. In participants with LLD, we further examined the relationship between organ systems and GDF-15 (Supplementary Table 2). There was a significant difference in GDF-15 levels in those with absent or mild problems versus moderate to severe problems in the renal and endocrine systems.

DISCUSSION

In this study, we evaluated the association between circulating GDF-15 levels and MDD in older adults. Our main finding was a significantly higher GDF-15 level in LLD than in older adults with no lifetime history of depression. We also found a significant association of GDF-15 with age, BMI, and comorbid physical burden in the whole sample, and with executive function in the LLD group only.

GDF-15 levels were significantly higher in those with LOD than with EOD. This finding suggests that those with LOD may be more affected by age-related biological abnormalities compared to those with early-onset depression. As a result, LOD may represent a prodromal manifestation for several age-related outcomes including cognitive decline and dementia. Individuals with LOD have a higher burden of cardiovascular disease, more cerebrovascular changes, and increased cortical atrophy compared to those with EOD. They also present with worse global cognitive impairment and executive dysfunction.[26,27] Our findings are in line with a large body of literature that indicates that LOD and EOD may have distinct pathophysiological mechanisms and long-term outcomes, despite sharing similar phenomenological presentation.[28]

Our findings that GDF-15 levels were not significantly associated with depression severity or other specific characteristics of a depressive episode in older adults (such as single versus recurrent episode) are congruent with previous studies.[15,17] Interestingly, we found a significant association between LOD and GDF-15 levels, but not among those with EOD. These results points to the high heterogeneity of the biological changes in older adults with major depression and suggest that LOD may represent a different phenotype than EOD. Alternatively, GDF-15 is a versatile mitokine that exhibits variance in biological function and signaling pathways depending on organ system. This may explain the paradoxical lack of significant association with recurrence, as its role in the etiology of recurrent depressive episodes may be different than its role in LOD.[29] Additionally, the difference in GDF-15 levels observed in those with absent or mild problems versus moderate to severe problems in the renal and endocrine systems highlights the need for future investigation to examine these differences due to the small sample size of those with LLD and comorbid system problems

A possible explanation for elevated GDF-15 levels seen in LLD may be mitochondrial injury. When damaged, mitochondria elicit a stress response, releasing various proteins and peptides known as mitokines.[6] GDF-15 is one of the most abundant mitokines, and its higher levels have been previously associated with mitochondrial dysfunction under different conditions[6,30] Neuroprogression, the loss of neurocognitive functioning, is associated with suboptimal mitochondrial functioning and altered biochemical cascades involving GDF-15.[31] Our finding of increased GDF-15 levels is aligned with recent studies pointing to significant mitochondrial dysfunction in LLD as manifested by increased oxidative stress markers in these individuals.[32] Mitochondrial dysfunction, oxidation stress, and pro-inflammatory biomarkers have been implicated in the pathophysiology of LLD. The stronger associations observed in the depressed versus non-depressed participants between GDF-15, demographic and somatic health parameters suggest that the overactivation of these biological cascades processes may have a greater impact among subjects with LLD

compared to never-depressed individuals.[3] Moreover, the pleiotropic effects of GDF-15 may be dependent on different physiological contexts. For example, in younger individuals, conditions that involve acute mitochondrial stress can lead to higher GDF-15 expression,[30] which in turn, can lead to a suppression of pro-inflammatory response through actions such as GFRAL receptor binding and the inhibition of macrophage signaling and T-cell activation.[29,33] However, in older individuals or those under chronic systemic stress conditions (e.g., accumulation of cellular senescence changes, physical multimorbidity, or MDD), the initial beneficial effect of higher GDF-15 expression would be lost, with the higher GDF-15 expression leading to deleterious physiological effects, including the stimulation of pro-inflammatory cytokines.[29,33]

Abnormalities in several biological hallmarks of aging and increasing brain age gap (i.e., the difference between biological brain age and chronological age[34]) have been previously described in LLD.[35] These changes have been linked to common negative health outcomes in older adults, including cognitive impairment, physical multimorbidity, and metabolic dysfunction.[2,36] High levels of GDF-15 in older patients are associated with worse recovery after acute physical illnesses and increased risk of cardiovascular and cancer-specific mortality,[37] Collectively, our findings provide a possible mechanistic link between the diagnosis of LLD, acceleration of different biological aging processes, and risk of adverse health outcomes, including the risk of cognitive decline and mortality observed in this population.[38] This may be particularly relevant to individuals with LOD who have higher GDF-15 since they are those with more severe cerebrovascular burden and are at high risk of accelerated cognitive decline.[27] However, depression can result from and is affected by any combination of influences including environmental, genetic, social, and developmental factors.[39] This inherent complexity emphasizes that a relationship between LLD and accelerated aging may be bidirectional and need to be explored in large studies with longitudinal designs.

Our results should be considered in the context of some limitations of our study. First, this is a cross-sectional analysis of serum GDF-15 levels, precluding causal inferences about the association between elevated GDF-15 and LLD. Also, since the GDF-15 was measured in two different laboratory batches, this could have introduced a batch effect in the analyses. However, our analyses included laboratory batch as a random variable to mitigate the possible bias of batch effects. Individuals with LLD and comparison participants came from two different studies at four different sites, introducing another potential bias. However, sites were also included as random variables in the statistical analyses to mitigate their effect on the study results. Finally, recent studies have demonstrated an association between lifestyle factors (e. g., smoking, physical activity, alcohol consumption) and biomarkers of aging (e.g., telomere length), suggesting further research is needed to investigate why some but not all older adults with LLD have elevated GDF-15 levels.[40]

In conclusion, participants with LLD had higher circulating levels of GDF-15 than non-depressed comparison participants; and in those with LLD, GDF-15 levels were associated with worse burden of comorbid physical illness and executive cognitive dysfunction. These findings provide additional evidence that a major depressive episode in older adults is associated with age-related biological changes and support the hypothesis of accelerated

biological aging in this disease state. Further research is needed to confirm our findings and to assess whether targeting GDF-15 biology could mitigate the risk of adverse health outcomes in LLD (e.g., cognitive decline, worsening physical illness, and premature mortality).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

DISCLOSURE

Dr. Lenze is a consultant for Prodeo, Boehringer-Ingelheim, Pritikin ICR, and IngenioRxDr. Lenze has a patent application for sigma-1 agonists in COVID-19 treatment. He also receives research support from PCORI, the COVID Early Treatment Fund, Emergent Venture FastGrants, and MagStim. Dr. Wu is consultant for Genzyme, Novartis, Roche, and The Department of Justice. Dr. Karp reports receipt of honorarium from Otsuka for preparation and presentation of a webinar (disease-state, not productfocused) and from NightWare for scientific advising and equity from Aifred Health for scientific advising. Dr. Mulsant holds and receives support from the Labatt Family Chair in Biology of Depression in Late-Life Adults at the University of Toronto. He also receives compensation from the Centre for Addiction and Mental Health (CAMH), Toronto, Ontario. He currently receives research support from Brain Canada, the Canadian Institutes of Health Research, the CAMH Foundation, the US National Institute of Health (NIH), Capital Solution Design LLC (software used in a study founded by CAMH Foundation), and HAPPYneuron (software used in a study founded by Brain Canada). Within the past three years, he has received research support from the Patient-Centered Outcomes Research Institute (PCORI) and he has been an unpaid consultant to Myriad Neuroscience. Dr. Blumberger receives research support from CIHR, NIH, Brain Canada and the Temerty Family through the CAMH Foundation and the Campbell Research Institute. He received research support and in-kind equipment support for an investigator-initiated study from Brainsway Ltd. and he is the site principal investigator for one sponsor-initiated study for Brainsway Ltd. He also receives in-kind equipment support from Magventure for investigator-initiated studies. He received medication supplies for an investigator-initiated trial from Indivior. The other co-authors do not have conflict of interest related to this study. This work was funded by NIH grants R01MH118311 (Diniz & Tseng), R01 MH083660 (Reynolds, Lenze, Mulsant), and R01AG049369 (Lenze & Wetherell).

DATA STATEMENT

The data has not been previously presented orally or by poster at scientific meetings

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Highlights

- What is the primary question addressed by this study?— We sought to evaluate the circulating levels of growth differentiation factor-15 (GDF-15) in older adults with major depressive disorder and its association with depression severity, physical comorbidity burden, age of onset of first depressive episode, and cognitive performance.
- What is the main finding of this study?— Depressed older adults had significantly higher GDF-15 serum levels than comparison individuals. Among depressed individuals, those with high GDF-15 had higher levels of comorbid physical illness, lower executive cognitive functioning, and higher likelihood of having late-onset depression.
- What is the meaning of the finding?— GDF-15 is a novel and potentially targetable biological pathway between depression and accelerated aging, including cognitive aging.

TABLE 1.

Demographics, Clinical Variables, and GDF-15 Levels in Controls and LLD Participants

Variables	Controls (n=85)	LLD (n=308)	Statistics	p value
GDF-15 (ng/mL)	431.90 ± 223.35	640.1 ± 501.5	t_{391}=3.72	0.0002
CIRS-G	6.4 ± 2.9	10.0 ± 4.5	T_{391}=7.18	<0.0001
Age	72.2 ±5.04	69 ± 7.1	T_{391}=3.92	0.0001
BMI	27.7 ± 5.0	29.6 ± 6.8	T_{391}=2.32	.02
Age of first depressive episode	-	42.1 ± 21.4	-	-
MADRS	-	26.6 ± 5.6		
Self-Reported Sex				
Female	59	201	Chi^2_1 =0.5	0.4
Male	26	107		
Self-Reported Race				
White	74	274	Chi^2_3=5.02	0.17
Black	10	30		
Asian Pacific	0	4		
More than One Race	1	0		
Comorbid Anxiety Diagnosis	0%	40%		
Depressive Episode Severity				
Mild	-	10%		
Moderate	-	56%		
Severe	-	34%		
Depressive Episode Recurrence				
Recurrent Depressive Episode	-	71%		
Single Depressive Episode	-	29%		
Age of onset				
LOD	-	17%		
EOD	-	83%		
History of suicide attempt				
Yes	-	13%		
No	-	87%		

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Notes: BMI: body mass index; CIRS-G: Cumulative Illness Rating Scale-Geriatrics; EOD: Early onset depression; GDF-15: Growth Differentiation Factor-15; LOD: Late onset depression; LLD: Late-Life Depression; MADRS: Montgomery-Asberg Depression Rating Scale.