Exercise as an Adjunctive Treatment Modality for Major Depressive Disorder: A Multi-Omics Perspective

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Major Depressive Disorder (MDD) is characterized by genetic and environmental factors. Current interventions, including selective serotonin reuptake inhibitors and cognitive-behavioural therapy, are often effective yet prone to the development of treatment resistance. A major mechanism for MDD pathogenesis involves dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis, which results in chronic elevation of cortisol. Cortisol has been linked to MDD symptomology through downstream cellular effects, which can be elucidated through multi-omics analyses such as genomics (NR3C1, FKBP5), proteomics (pro-inflammatory cytokines), and metabolomics (shifted kynurenine pathway). A systematic literature search of OVID Medline and similar databases was conducted using literature from the past 10 years to identify studies investigating exercise interventions targeting multi-omics markers in MDD. Inclusion criteria required independent MDD cohorts and included a minimum of two omics levels and their relationship to exercise as an intervention. Existing literature demonstrates that aerobic exercise can regulate cortisol levels: increasing NR3C1 and FKBP5 gene expression, reducing proinflammatory cytokines, and shifting tryptophan metabolism towards the neuroprotective kynurenic acid and away from neurotoxic metabolites. A change in these biomarkers suggests that regular physical activity can exert widespread biological and neurological effects by regulating molecular dysfunctions at a multi-omics level in MDD. Exercise, when prescribed as an adjunct to conventional MDD therapies, may improve clinical outcomes by modulating stress-responsive and inflammatory pathways at multiple omics levels. Further large-scale and longer-term randomized trials are required to validate specific biomarkers for personalized medicine, and additional work should investigate sex-based differences in exercise efficacy. Exercise offers significant promise for optimizing MDD management and promotes greater physiological resistance to depressive symptoms.

Introduction

Major depressive disorder (MDD) is a multifaceted mood disorder arising from a combination of genetic, biological, and psychological factors.[1] Manifestations include explicit changes in mood, pleasure, and cognition; the specific diagnostic criteria are outlined by the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition Text Revision and International Classification of Diseases 11th Revision.[1,2] MDD is defined as an individual showing at least five depressive symptoms almost every day within a 2-week period; individuals must present a change from previous functioning, including depressed mood, anhedonia, sudden mood and sleep fluctuations, or fatigue.[3,4]

Globally, 5% of adults experience depression, with women at a nearly two-fold higher risk of developing MDD.[2,5] The economic burden of MDD is significant, with an estimated $210.5 billion USD in 2010, and a reported increase of 37.9% between 2010 and 2018 – which encompasses direct, workplace, and suicide-related costs.[6] Despite the rising burden, the Association of British Pharmaceutical Industry asserts that only 7% of global research and development is invested in central nervous system diseases – indicating an unmet need for more effective treatments for MDD.[7]

MDD is a highly prevalent psychiatric illness that can be managed, to some extent, through an integrated approach involving psychotherapy, pharmacotherapy, and somatic interventions. Selective serotonin reuptake inhibitors (SSRIs) are commonly used as first-line treatments due to their relatively favourable safety profile. For more resistant or severe cases, other options

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include serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, or even ketamine-based therapies.[8,9] Cognitive-behavioural therapy (CBT) and interpersonal therapy are also effective in reducing depressive symptoms and preventing relapse.[8] In refractory situations, electroconvulsive therapy and repetitive transcranial magnetic stimulation are considered[8,9] Additionally, emerging research suggests lifestyle modifications – such as improved sleep habits, dietary adjustments, exercise, and social support – as promising strategies to prevent and mitigate MDD.[9] Noetel et al. predict that various exercise modalities outperform independent SSRI use compared to active controls, and that exercise alone and in conjunction with standard treatments is significantly more efficacious in reducing depressive symptoms.[10]

Various hypotheses have been proposed to explain MDD pathogenesis, with many arising from chronic cortisol elevation due to hypothalamic-pituitary-adrenal (HPA) axis dysfunction.[1,8] Increased cortisol results in homeostatic deviations within multiple molecular pathways, contributing to disease progression and symptom severity (Figure 1).[11]

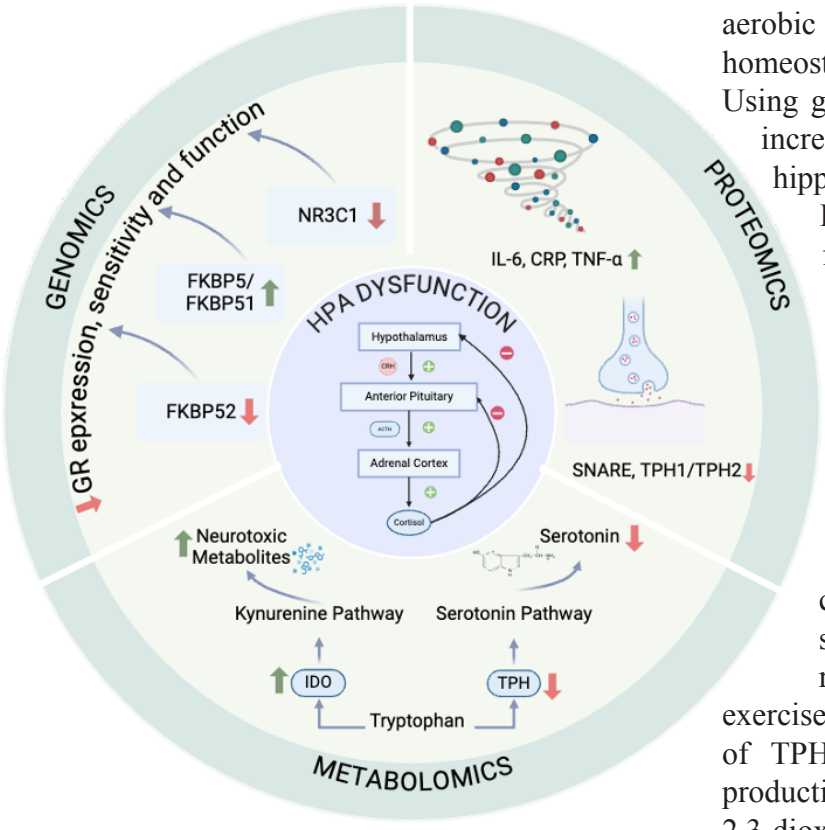

Figure 1. Endocrine and Multi-Omics Insights into Molecular Changes in MDD Patients.

At the genomic level, irregular DNA methylation and decreased expression of genes FKBP5 and NR3C1 reduce downstream glucocorticoid receptor (GR) protein expression, impairing the negative feedback system and subsequent HPA hyperactivity.[12,13] Dysfunctions at the proteomic level include increased expression of pro-inflammatory cytokines – such as interleukin-6 (IL-6) and C-reactive protein (CRP) – and downregulation of enzymes involved in serotonin synthesis–like tryptophan hydroxylase (TPH).[13,14] Metabolomic studies reveal a shift in tryptophan metabolism, favouring the kynurenine (KYN) pathway over serotonin production. In MDD patients, KYN metabolism yields increased neurotoxic metabolites – such as quinolinic acid – and decreased neuroprotective metabolites – such as kynurenic acid (KYNA).[15,16] Through a multi-omics analysis of MDD, it is evident that although standard therapeutic interventions—such as SSRIs, SNRIs, and CBT – target specific omics levels, they do not adequately address the relevance of cortisol dysfunction.[8]

Exercise presents a potential non-pharmacological intervention for MDD, with extensive literature supporting its regulatory effects on the HPA axis and widespread downstream signalling.[12-16] Chronic aerobic exercise has been shown to restore HPA axis homeostasis, regulating cortisol levels in MDD patients.[17] Using genomics analysis, exercise has been shown to increase NR3C1 and FKBP5 gene expression in the hippocampus and prefrontal cortex. Exercise reduces DNA methylation and activates transcription factors, which allows NR3C1 to effectively co-repress GR activity and FKBP5 to increase GR sensitivity.[18,19] Regarding proteomics, exercise has been shown to mitigate neuroinflammation by downregulating IL-6, tumour necrosis factor-alpha (TNF-α), and CRP.[20,21] Dysregulated immune function in chronic stress conditions leads to the upregulation of these pro-inflammatory cytokines. Exercise helps restore microglial structure and regulate its activation, ultimately reducing neuroinflammation.[22] Concurrently, exercise has been shown to increase the expression of TPH – the rate-limiting enzyme for serotonin production – and decrease the expression of indoleamine 2,3-dioxygenase – the rate-limiting enzyme for KYN production. At the metabolomic level, increases in the neuroprotective ratio following exercise indicate a

shift towards kynurenic acid production during KYN metabolism.[23,24] Collectively, these findings substantiate exercise as a systemic regulator to mediate multi-omics disruptions observed in MDD; given its accessibility and widespread benefits, exercise should be prescribed as an adjunctive first-line treatment for depression.

This paper proposes that structured exercise interventions can modulate multiple biological systems implicated in MDD, as captured through multi-omics analysis. By targeting shared pathways underlying depression, exercise offers a potent complementary approach alongside standard pharmacotherapies, while providing additional metabolic benefits.

Methods

A literary search was conducted in OVID Medline to examine the relationship between multi-omics biomarkers, MDD, and exercise modulations of cellular pathways. Studies that were published within the last 10 years in PubMed, ScienceDirect, and ResearchGate were included. Omics studies must have included either MDD patients as a subgroup or the distinct study population or included exercise and control groups. Exercise studies must have investigated MDD patients independently ofhealthy controls. Exclusion criteria included papers that did not examine the relationship between at least two of MDD, exercise, and omics analysis. Randomized-controlled trials and systematic reviews using in vivo models were prioritized in data extraction; however, some observational and narrative studies were used to supplement background information on the topic.[25]

The Role of Omics in the Development of Therapies Targeting MDD

Traditional healthcare has historically focused on disease treatment over prevention, often leading to high costs and limited effectiveness due to a 'one-size-fits-all' approach that ignores individual genetic, environmental, and lifestyle differences.[26] Omics technologies have revolutionized medicine by providing a more nuanced understanding of diseases through the integration of genomics, transcriptomics, proteomics, and metabolomics, enabling personalized treatment and early detection. MDD has a polygenic basis, with approximately 50% of cases linked to genes involved in the serotonergic system and HPA axis.[27] These genes serve as potential diagnostic markers and drug targets, but genetic risk alone insufficiently predicts MDD, underscoring the need for multi-omics integration. Biomarkers such as cortisol, serotonin, CRP and IL-6, and metabolic disruptions in tryptophan metabolism contribute to MDD pathophysiology.[28] In metabolomics, pro-inflammatory cytokines elevate kynurenine levels, which exacerbates symptoms.[29] This integrated omics approach enables the development of biomarker-driven therapies, including anti-inflammatory agents, metabolic modulators, and exercise, thus offering alternatives for patients unresponsive to SSRIs.[30] Exercise, which impacts inflammation and neuroplasticity, emerges as a key non-pharmacological therapy.[31] However, data complexity and validation remain a challenge when translating omics findings into clinical practice.[32]

Omics-Level Alterations in MDD and Their Modulation Through Exercise

MDD risk can be analyzed at the levels of the genome and transcriptome. The NR3C1 gene encodes GRs, which binds cortisol and regulates stress response through negative feedback on the HPA axis.[14] The gene FKBP5 modulates GR sensitivity, reducing its activity to prevent excessive stress responses.[33]

Thus, decreased expression of NR3C1 and FKBP5 influences HPA axis hyperactivity by reducing GR response to cortisol. The transcription of NR3C1 can be modulated on levels of decreased transcription through DNA methylation and modulation of mRNA expression by RNA silencing or translational repression by microRNAs (miRNAs).[34] NR3C1 is located on chromosome five and consists of 9 non-coding first exons, which are hypothesized to act as promoters. Many of these first exons occur on CpG islands, and thus DNA methylation of these areas significantly reduces the transcription of GRs. Consequently, higher levels of DNA methylation are observed in MDD patients, implicating it in MDD risk.[28] Micro-RNA (miR)-124, a small non-coding RNA molecule which downregulates GR activity in vivo, is highly expressed in the brain.[34-36] Zeng et al. found that all CpG islands were significantly hypomethylated in MDD when compared with healthy controls, thus implicating miR-124 dysregulation in MDD.[37] Specifically, the 1F promoter region methylation of the gene is associated with transcriptional silencing of GR and RNA via miR-124.[11,34-37]

Patients with FKBP5 polymorphisms also show higher MDD risk. The presence of the T-risk allele in single nucleotide polymorphism rs1360780 leads to elevated FKBP5 mRNA transcription and translation.[38-40] The T allele specifically forms the transcription start site on intron 2 and is associated with chromatin conformation that increases glucocorticoid response element binding.[40] However, due to the limitations of genetic research, there is significant heterogeneity in research for the rs1360780 T allele. Menke et al. found that depressed patients with the T allele showed reduced FKBP5 mRNA induction, and less cortisol and ACTH suppression post-dexamethasone stimulation compared to healthy T carriers because of GR resistance in MDD risk.[12] These results are in opposition to the research claiming that increased FKBP5 expression is associated with reduced GR sensitivity. Furthermore, Young et al. showed that across various brain regions – including the medial prefrontal cortex, hippocampus, and insular cortex – an increase in NR3C1 and FKBP5 was observed in rats that underwent exercise compared to the non-exercise groups.[41] Increased expression of these genes recalibrates the brain to adjust for stress resilience. Elevated GR enhances the HPA negative feedback loop, while FKBP5 modulates GR activity, preventing excessive cortisol effects. Thus, the discrepancies in the research indicate further need for investigation into the genetic influence on HPA axis regulation and MDD.

Proteomic changes in MDD provide insights into mood regulation. Key proteins play crucial roles: including neurotransmitter transporters, synaptic proteins, and inflammatory cytokines. MDD is characterized by significant changes in proteins including TPH and soluble NSF attachment protein receptors (SNARE); these are essential to neurotransmitter release and synaptic plasticity.[14,42] Elevated levels of inflammatory markers such as IL-6, TNF-α, and CRP have been observed in both brain and serum, establishing a link between inflammation and mood dysregulation.[28]

Exercise demonstrates therapeutic potential for modulating cortisol and pro-inflammatory cytokines.[43-45] After 4 weeks of aerobic training, Liu et al. observed that exercising mice had decreased hippocampal IL-6 and TNF-α expression.[22] A randomized control trial study conducted by Lavratti et al. demonstrated decreased serum IL-6 in patients with psychological disorders after exercise treatment.[20] Additionally, Kasapis et al. showed consistent decreases in CRP levels between various patient profiles after exercise treatment.[46] As these cytokines are linked to depressive symptoms like anhedonia, poor sleep, and poor appetite, exercise serves as a viable holistic supplement for MDD treatment.[13] However, chronic aerobic overtraining may elevate pro-inflammatory cytokine levels, emphasizing the need for individualized treatment plans.[47]

Preclinical and clinical omics data further support resistance training as an effective intervention. In rodents, ladder climbing reversed stress-induced depressive behavior by normalizing TRKB-Akt-mTOR signaling and dampening NLRP3-mediated neuroinflammation.[48] In older men, 12 weeks of high-load training upregulated PGC-1α/PPAR pathways and kynurenine-aminotransferase expression, promoting neuroprotective KYN metabolism.[49]

At the metabolomic level, MDD involves disruptions in amino acid, lipid, and energy metabolic pathways, including tryptophan metabolism which favours KYN over serotonin production. Acute exercise promotes beneficial shifts in tryptophan metabolism, favouring a neuroprotective profile.[23] Extending these findings, Javelle et al. showed that eight weeks of high-intensity interval training decreased neurotoxic quinolinic acid and increased KYNA levels, suggesting a sustained protective phenotype.50 In rodent models, Kim et al. reported that aerobic exercise reversed stress-induced deficits in dorsal raphe TPH expression, highlighting its capacity to restore serotonergic function.[24] Monitoring shifts in KYN–KYNA ratios, quinolinic acid levels, and TPH expression can guide personalized exercise interventions to optimize therapeutic outcomes. Alongside pharmacotherapies, these biomarker-driven interventions – including exercise – may improve remission rates in MDD minimizing adverse effects.[23,24,50]

Understanding the importance of exercise at multi-omics levels – including genomics, transcriptomics, proteomics, and metabolomics – provides a detailed analysis of specific biomarkers which exert an effect on exercise. Deciphering the connection between these levels and their relation to exercise elucidates how physical activity optimizes molecular pathways and promotes greater physiological resistance to depressive symptoms.

Conclusion

Undoubtedly, identifying biomarkers which enhance stress resilience is crucial for regulating mood in MDD patients. Future research should prioritize large-scale studies to validate multi-omics-based biomarkers as a tool for guiding personalized interventions. This underscores the necessity for precision medicine recognizing that patient care for mental disorders must be tailored to individual needs. Future studies would also investigate sex-related disparities in MDD and differences in treatment. Research should focus on strategies for integrating exercise as a therapeutic or adjunct intervention, while considering some individuals may face physical or mental barriers to exercise. Such advancements hold significant promise for improving mental health through specific, evidence-based approaches.

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