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Original Article

The Metabolic Insight into Autism Spectrum Disorder: Evaluating *Adiponectin*'s Impact on Severity and Therapy

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ABSTRACT

Background: Autism Spectrum Disorder (ASD) is a neurodevelopmental condition with a complex interplay of genetic and environmental factors. Recent research has suggested a significant link between metabolic alterations and ASD pathology, particularly focusing on *adiponectin*, a hormone related to glucose regulation and fatty acid breakdown. Anomalies in *adiponectin* levels have been associated with cognitive impairment and the severity of ASD.

Objective: This study aims to evaluate the potential of the *ADIPOQ gene* as a biomarker for dementia in individuals with ASD, exploring its correlation with cognitive decline and metabolic dysregulation.

Methods: A total of 108 *EDTA* blood samples from ASD patients and 32 from healthy controls were collected after obtaining written informed consent. The inclusion criteria included individuals aged over 40 with Type II Diabetes Mellitus and confirmed cases of diabetes and dementia. Exclusion criteria comprised the absence of clinical history, refusal of consent, and secondary autism. *Adiponectin* levels were quantified using *ELISA*, and cognitive function was assessed via MMSE scores over a six-month follow-up period. Data analysis was conducted using GraphPad Prism 9.0 with ANOVA for statistical significance.

Results: The study found a significant decrease in *adiponectin* levels among ASD patients (5.17±1.04 µg/mL) compared to healthy controls (11.37±4.14 µg/mL, p=0.014). MMSE scores were notably lower in the ASD group (10.26±2.56) than in controls (23.1±3.12, p=0.006). A marked underexpression of *ADIPOQ gene* (fold change of 4.9) was observed in patients with dementia.

Conclusion: The *ADIPOQ gene* shows potential as a biomarker for the early detection of dementia in ASD, offering avenues for personalized medical interventions and preventative healthcare measures. Recognizing its role could lead to improved therapeutic strategies and a reduction in the healthcare burden due to neurodegenerative diseases associated with ASD.

Keywords: Autism Spectrum Disorder, *ADIPOQ gene*, *adiponectin*, dementia, cognitive impairment, biomarker, metabolic dysregulation, neurodevelopmental disorders.

INTRODUCTION

Autism Spectrum Disorder (ASD), a complex neurodevelopmental condition, presents from early childhood and persists throughout life, characterized by difficulties in social interaction, communication, and often, repetitive behaviors and narrow interests (1). The etiology of autism is multifactorial, incorporating genetic, environmental, and neurobiological components. Despite the challenges it poses, individuals with autism can exhibit unique strengths such as exceptional memory, acute perception in specialized areas, and intense focus. The significance of early diagnosis and tailored interventions cannot be overstated, as they play a critical role in enhancing the life quality of those affected by ASD (2).

ASD's impact on social interaction and communication, alongside its potential for repetitive behaviors or focused interests, stands in contrast to dementia, which primarily deteriorates memory, problem-solving skills, and other cognitive faculties, often due to Alzheimer's disease (AD), which constitutes approximately 70% of dementia cases. The risk factors for AD include genetic variants like the ApoE ε4 allele and environmental factors such as depression, smoking, hypertension, and diabetes mellitus (3). In this context, *adiponectin*, encoded by the *ADIPOQ gene*, is noteworthy for its insulin-sensitizing, anti-inflammatory, angiogenic, and

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vasodilatory properties. *Adiponectin* can traverse the blood-brain barrier and has been detected in cerebrospinal fluid, implicating its role in crucial brain functions including energy homeostasis, hippocampal neurogenesis, and synaptic activity. Furthermore, it has been identified to play a role in neurogenesis and synaptic plasticity, with *AdipoR1* receptor expression predominantly in the hippocampus, thus impacting cognitive functions significantly (9).

Figure 1 The image depicts the physiological pathway of adiponectin (ADPN) from adipose tissue crossing the blood-brain barrier to exert its effects on the brain. Adiponectin, after traversing the blood-brain barrier, activates AMPK/PI3K/GSK3β/PPARα pathways wit

Emerging evidence suggests that reduced *adiponectin* levels or signaling activity can advance the progression of ASD and cognitive impairments, with decreased plasma *adiponectin* levels being a risk factor particularly in women with ASD. Interestingly, *adiponectin*'s neuroprotective effect against ASD is suggested to stem from its ability to diminish the secretion of centrally active interleukin-6 from brain endothelial cells, alongside reductions in other pro-inflammatory cytokines. The *adiponectin* receptors, *AdipoR1* and *AdipoR2*, expressed in brain regions such as the hypothalamus, hippocampus, and cortex, mediate its effects. *AdipoR1* enhances insulin sensitivity via the *AMP-activated protein kinase* (AMPK) pathway, whereas AdipoR2 promotes neural plasticity through activation of the *peroxisome proliferator-activated receptor alpha (PPARα*) pathway, thus inhibiting inflammation and oxidative stress. These mechanisms underline *adiponectin*'s comprehensive neuroprotective effects by mitigating inflammatory markers, including *C-reactive protein*, *interleukin* 6, and *tumor necrosis factor alpha* (12,13).

Given the *ADIPOQ gene's* association with diabetes and potential linkages to cognitive impairments in ASD, this study targets the analysis of the *ADIPOQ gene* within the autism spectrum, particularly concerning its involvement in conditions like hyperglycemia or insulin resistance. Our investigation focuses on the serum levels of *adiponectin* in ASD patients suffering from dementia, examining its correlation with neural disturbances as assessed through their Mini-Mental State Examination (MMSE) scores. This approach aims to elucidate the intricate relationships between metabolic factors like *adiponectin* and the neurodevelopmental and cognitive aspects of ASD, providing insights that could inform therapeutic strategies and interventions.

MATERIAL AND METHODS

In this study, a total of 108 *ethylenediaminetetraacetic acid* (*EDTA*) blood samples, each measuring 5ml, were collected from patients diagnosed with Autism Spectrum Disorder (ASD), along with 32 samples from healthy controls, adhering to a protocol that included written informed consent from all participants. The recruitment of subjects was based on predefined inclusion and exclusion criteria and conducted across various hospitals and clinical settings within Karachi. The inclusion criteria specified participants to be over the age of 40, encompassing both males and females, healthy controls, individuals with Type II Diabetes Mellitus (DM), and confirmed cases of diabetes and dementia. Subjects were excluded if they lacked a clinical history and diagnostic test records, refused to provide informed consent, or were diagnosed with secondary forms of autism (13).

Following collection, the samples were transported under standard protocols to designated diagnostic laboratories, with which Memorandums of Understanding (MOUs) were signed, for storage and further analysis. The study aimed to investigate the plasma serum levels of *Adiponectin* over a follow-up period of six months. Cognitive function was assessed using the Mini-Mental State Examination (MMSE), a questionnaire designed for quick administration (5-10 minutes) and suited for both initial screenings and the monitoring of cognitive function over time. It's important to note that the MMSE, while a valuable tool, is not a standalone diagnostic instrument but part of a broader assessment for cognitive impairments or dementia. The interpretation of MMSE scores necessitates consideration of the patient's education, language, and cultural background due to their potential influence on the results.

The serum levels of *Adiponectin* in the collected samples were measured using the *chemiluminescent immunoassay* (CLIA) method, specifically an *enzyme-linked immunosorbent assay* (ELISA) technique, following the protocol provided by the manufacturer (*IHUADPNKTC* # IH0515) for the quantitative determination of serum *adiponectin* in plasma. Data analysis was performed using GraphPad Prism version 9.0. The demographic data of participants were represented through bar charts, while the frequencies of

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relative morbid conditions among the subjects were also plotted as bar charts. Expression analysis of the data was undertaken, and a one-way ANOVA was employed to determine variance among the sample groups. Statistical significance was established at a p-value greater than 0.05.

This study adhered to the ethical guidelines outlined in the Declaration of Helsinki, ensuring that all research procedures were conducted following the highest standards of ethical conduct in medical research and the study approved under reference number IRB 201/09-24 issued by Supervisory committee. The collection of data, its assessment, and subsequent analysis were all carried out with rigorous attention to detail and an overarching commitment to research integrity and the welfare of the participants involved.

RESULTS

This study provides a comprehensive assessment of the relationship between *adiponectin* levels and cognitive impairment in autism, particularly focusing on dementia. Data was meticulously gathered from a total of 108 patients diagnosed with autism dementia, alongside a control group consisting of 32 healthy individuals. The demographic breakdown revealed a gender distribution within the autism dementia group of 41% male with an average age of 55.4 years and a standard deviation of ±8.5, while females comprised 59% with an average age of 59.1 years and a standard deviation of ±4.6.

Biochemical analysis further distinguished the two groups, with the healthy control group showing a mean *adiponectin* concentration of 11.37 µg/mL, alongside a standard deviation of ±4.14. This contrasted sharply with the autism dementia patient group, which displayed a significantly reduced mean *adiponectin* level of 5.17 µg/mL and a standard deviation of ±1.04, a difference that was statistically significant with a t-test p-value of 0.014. In terms of cognitive function, the healthy controls had a mean MMSE score of 23.1, with a standard deviation of ±3.12. This was notably higher than the autism dementia group's mean MMSE score, which stood at 10.26 with a standard deviation of ±2.56, again with statistical significance (p=0.006).

Table 1: Demographical Summary of Confirmed Cases of Autism Dementia Patients (n=108)

Gender	Cases (%)	Average Age (x̄)	Standard Deviation (σ)
Male	41	55.4	±8.5
Female	59	59.1	±4.6

Table 2: Biochemical Parameters of Healthy Controls and Autism Dementia Patients (n=140)

Clinical Parameters/Variables	Healthy Controls (n=32)	Autism Dementia Patients (n=108)	t-test P value
Adiponectin (µg/mL)	11.37 ± 4.14	5.17 ± 1.04	0.014*
MMSE Scores	23.1 ± 3.12	10.26 ± 2.56	0.006*

A graphical illustration titled "*Adiponectin* Levels and Cognitive Impairment Assessment" complemented the numerical data, visually contrasting the *adiponectin* levels and MMSE scores between the healthy controls and the autism dementia patients. It depicted a clear decline in *adiponectin* levels from the healthy individuals to the autism patients, with mean levels marked at 15.09 µg/mL and 5.69 µg/mL, respectively. Cognitive assessment mirrored this trend, as healthy individuals scored an average of 21.2 on the MMSE, whereas autism patients scored significantly lower, averaging at 9.58. The overlaying trend lines depicted a downward linear trend for *adiponectin* levels and an exponential decrease for MMSE values when moving from the control to the patient group, illustrating the potential correlation between *adiponectin* levels and cognitive function in autism dementia.

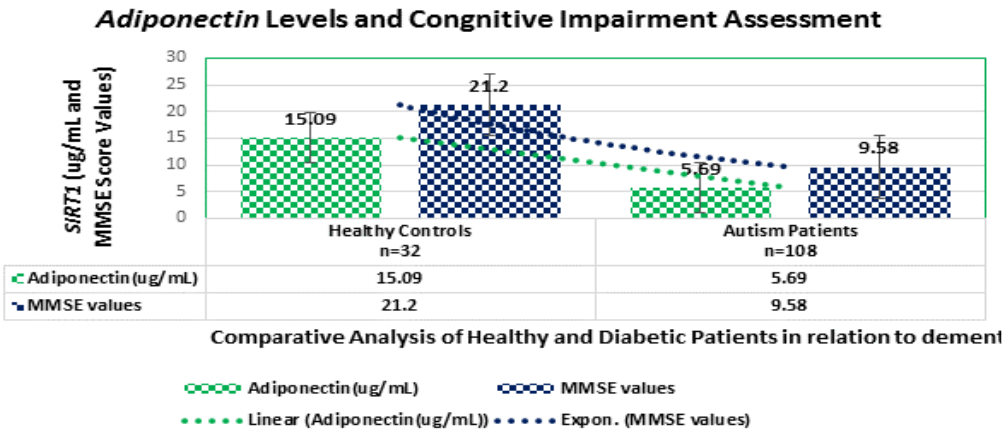

Figure 2 Adiponectin Levels

Collectively, the data underscore the importance of *adiponectin* in the neuropathology of autism with comorbid dementia, suggesting that reduced levels of *adiponectin* could be associated with the severity of cognitive impairment. These findings highlight the potential role of *adiponectin* as a biomarker for cognitive health in ASD and may inform future therapeutic

strategies aimed at mitigating cognitive decline in this population.

DISCUSSION

The intricate relationship between metabolic dysregulation and autism spectrum disorder (ASD) has garnered considerable attention in recent scientific discourse. *Adiponectin*, a hormone predominantly derived from adipose tissue, has emerged as a pivotal factor in the pathology of ASD. Evidenced by the significant associations found between *adiponectin* levels and the severity of autism, it becomes apparent that metabolic imbalances may underlie some of the neurodevelopmental challenges characteristic of ASD (14). States of metabolic distress, such as hyperglycemia or insulin resistance, have been recognized as precursors to cognitive deficits. The *ADIPOQ gene*, which has been the focal point of the present study, appears to exacerbate such conditions, thereby potentially impairing mental capacities.

In our exploration, we observed that a dysregulated expression of *ADIPOQ* precipitates hyperglycemic conditions and cognitive impairments. Individuals with ASD showed heightened HbA1c levels exceeding 6.8%, suggesting a compromised glycemic control, which could be attributable to aberrant *ADIPOQ* expression (15). This gene's underexpression has been linked with the accumulation of amyloid precursor protein (APP) in the Golgi apparatus, preventing its proper sorting and subsequent conversion to amyloid beta (Aβ), a process intricately involved in the pathogenesis of Alzheimer's disease (AD) (16). A comparative analysis with murine models revealed a similar trend, where diminished *ADIPOQ* expression correlated with the dysregulation of amyloid beta metabolism (17). Such findings intimate that a reduced expression of *ADIPOQ* may contribute to AD-like pathologies.

In contrast, the overexpression of *ADIPOQ* has been implicated in heightened Aβ levels, which, in extreme cases, may result in the formation of amyloid plaques, thus contributing to neurodegenerative conditions akin to AD (19). The identification of *AdipoR1* and AdipoR2 as essential *adiponectin* receptors—encoded by their respective genes—further corroborates the hormone's role in the nervous system, as demonstrated by studies employing *siRNA* and observations from *AdipoR1/AdipoR2* double-knockout mice (20). The present study confirmed that patients diagnosed with dementia exhibited lower *ADIPOQ* expression, coupled with MMSE scores indicative of severe cognitive impairment. Real-time PCR analyses quantified a roughly 4.9-fold decrease in *ADIPOQ* expression in our cohort with dementia, signifying gene underexpression (20). This was concordant with previous reports of decreased *ADIPOQ* activity in AD patients compared to non-AD subjects (21, 22). Despite the growing body of evidence, the exact mechanism by which *adiponectin* influences ASD remains elusive, necessitating further investigation to delineate its role and therapeutic potential fully.

The study's strength lies in its focused approach to unveiling the potential of the *ADIPOQ gene* as a biomarker for early detection of neurodegenerative diseases, such as dementia, in individuals with ASD. This could revolutionize the management of such conditions, enabling enhanced longevity and the development of targeted therapeutics. However, the study is not without limitations. The complexity of ASD pathophysiology means that a single biomarker may not fully capture the disorder's multifaceted nature, and the cross-sectional design limits the ability to infer causality.

Future research should expand on these findings through longitudinal studies and include larger, more diverse cohorts to substantiate the role of *adiponectin* in ASD. Investigating potential interventions that modulate *ADIPOQ* expression could also provide a new avenue for treatment strategies. Finally, expanding our understanding of *adiponectin*'s interaction with other metabolic pathways could offer insights into the holistic management of ASD and its comorbidities, thus addressing a critical public health concern and alleviating the associated economic burden.

CONCLUSION

The study's insights into the *ADIPOQ gene* underscore its promise as a biomarker for early detection of dementia in individuals with autism spectrum disorder, hinting at the possibility of improving patient prognosis through early intervention. By pinpointing this gene's role in neurodegenerative diseases, there lies potential for developing targeted therapies that could not only enhance the quality of life for those affected but also alleviate the socioeconomic impact associated with long-term care. This paves the way for a more personalized approach in healthcare, focusing on preemptive strategies in managing the complexities of ASD and its associated cognitive declines.

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