Original Article

Serum Adropin Level as a Predictor of Cognitive Impairment in Patients

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Abstract

Aim: We aimed to investigate whether there is indeed an association between circulating adropin concentrations and cognitive ability. Material and Methods: The study encompassed 400 participants. All of them underwent home interviews and gave consent for collection of their blood, which was subsequently stored at -80°C for later laboratory investigations. The aim was to identify cognitive impairment in patients with dementia and delirium, achieved through the utilization of the Mini-Mental State Examination (MMSE). Furthermore, the Assessment of Neuropsychological Test (ANT) was utilized to evaluate an individual's ability to retrieve information from memory and express it verbally. Results: The average scores for MMSE and ANT showed fluctuations across male and female participants in different quintiles. In the lowest quintile, both males and females performed poorly with an average score of 1.37 ± 0.40 for MMSE and 2.87 ± 0.12 for ANT, while in higher quintiles, there was an improvement male participants showed a mean score of 2.46 ± 0.11 on MMSE with an ANT value at 3.30 ± 0.12, whereas female participants had an average MMSE score of 3.35 ± 0.12 with relatively stable ANT values at 3.32±0.18. Regarding adiponectin factors, there were three ranges present: low (3.16±0.50), mid (2.36±0.49), and high (3.27±0.49). For leptin values, the mean scores were around 15, whereas triglyceride values remained consistent at approximately in all measurements taken. Similarly, fructosamine values remained. Conclusion: Human astrocytes have notably high levels of Adropin expression, which is inversely correlated with age but positively correlated with energy metabolism and macromolecule synthesis transcriptomic signatures.

Keywords: Adropin, MMSE, ANT, Cognitive Impairment

Introduction

Adropin levels are typically measured through blood samples, specifically serum or plasma samples. Adropin levels in samples are measured using techniques like ELISAs or mass spectrometry, but it's worth noting that these methods may vary in different studies. This difference could lead to variations in the reported adropin levels. It's also worth mentioning that adropin levels can be influenced by various factors, including age, sex, body weight, metabolic status, and the presence of certain diseases or conditions. Therefore, establishing a standard reference range for adropin levels is challenging.[1] Studies have found a connection between adropin, a low molecular weight peptide hormone, and various bodily functions including vascular tone, glucose metabolism, and hepatic lipid metabolism. Although the origin of adropin in the bloodstream is not yet clear, it is believed to originate from the brain as the Energy Homeostasis Associated (ENHO) transcript is more highly expressed in the brain than any other tissue in humans and non-human primates. Recent studies suggest that adropin may help slow cognitive decline related to aging and obesity. In further research, ENHO expression has been linked with genes associated with neurodegenerative diseases such as synaptic plasticity and mitochondrial function. Interestingly, adropin expression peaks during childhood development.[1-5]

The human brain's elevated adropin levels appear to have a positive correlation with energy utilization and synaptic plasticity that affect brain health preservation. Adropin signaling in rodents may help maintain brain function throughout their entire life span. Reduced adropin levels caused changes related to neuroinflammation and oxidative stress, observed in aging mice and rats. Lowering such treatments has beneficial cognitive effects on preclinical mouse models of natural aging, as indicated by the coordinates[5,6] showing causal relationships. Furthermore, studies conducted on mice suggest that it safeguards against cerebrovascular ischemia by impacting blood-

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brain barrier permeability, vasculature, and endothelial integrity maintenance during an injury.[7-9]

Adropin, a hormone made of small peptide molecules, has been extensively researched due to its role in numerous bodily functions such as regulating metabolism, cardiovascular activity, and controlling the central nervous system. Recently, scholars have explored how adropin levels are related to cognitive impairment. The investigation into whether serum adropin levels can predict cognitive impairment has gained attention. However, there is currently limited research in this field, and thus it's difficult to draw a conclusive finding at present. Reduced adropin levels may be associated with cognitive dysfunction based on various studies. For instance, a research paper published by "Neuroscience Letters" in 2016 discovered lower adropin levels among individuals diagnosed with Alzheimer's disease compared to healthy controls. Similarly, another study conducted in 2019 and published in "Experimental Gerontology" discovered a relationship between reduced adropin levels and cognitive decline in elderly people. The studies mentioned above only offer initial indications. Therefore, further research is necessary to confirm the reliability of adropin as a predictor of cognitive impairment. Additionally, the connection between adropin and cognitive function remains inadequately understood. Subsequent investigations could entail extensive and longitudinal research endeavours to delve deeper into the correlation between adropin concentrations and cognitive dysfunction. These investigations may additionally examine the potential of adropin levels to function as a prognostic indicator for the onset or advancement of cognitive impairment, while also assessing the feasibility of utilizing adropin as a biomarker in a clinical setting. It has not been studied yet whether there is a link between the levels of adropin in human blood circulation and cognitive abilities. Our study looked into this aspect by comparing adropin levels in the African American Health study (AAH).[10-13] We aimed to investigate whether there is indeed an association between circulating adropin concentrations and cognitive ability.

Material and Methods

The study procedures underwent review and received approval from the Institutional Review Board before initiating the research. The methodology adhered to established ethical principles. To ensure participants' voluntary participation, written consent was obtained, including the collection of blood samples as part of this process.

The study included 400 participants, all of whom were required to participate in in-home interviews. Approximately 76% of the baseline and follow-up assessments were successfully recruited. To ensure data accuracy, self-reported information was collected using reliable criteria. All participants provided consent to have their blood collected and stored at a temperature of -80°C for laboratory investigations. The investigation aimed at determining the serum levels of adropin among subjects who still had existing serum samples, while also considering their cognitive function and metabolic equilibrium.

The MMSE is a helpful tool for detecting cognitive impairments in patients with dementia and delirium. For evaluating memory recall and verbal expression, the ANT assessment is used.[14,15] The evaluation of cognitive abilities include MMSE along with the one minute animal naming test. Dementia risk can be predicted by evaluating scores; for example, an ANT score equal or less than 15 or an MMSE score equal or less than 23 indicates vulnerability.[16] The MMSE is a widely used tool that evaluates cognitive function and detects impairment. Specifically, it assesses memory, attention, orientation, language, and visuospatial skills. This brief questionnaire follows standardized protocols to generate reliable results. The MMSE is a test that helps evaluate cognitive function. A healthcare professional or trained examiner administers the test by asking a series of questions and tasks. The test usually takes 10 to 15 minutes to complete, and scores ranging from zero to thirty; where higher scores suggest better cognitive abilities.

The test includes the following components:

Orientation: The examiner asks the person questions to assess their awareness of time (e.g., the date, day of the week, year) and place (e.g., location, city, country).

Registration: The person is asked to listen and remember three unrelated words, which they are later asked to recall.

Attention and Calculation: The examiner gives simple instructions involving attention and calculation, such as counting backward from 100 by sevens or spelling a word backward.

Recall: The person is asked to recall the three words they were asked to remember earlier.

Language: This section assesses various language abilities, including naming objects, following verbal and written commands, reading and writing a sentence, and copying a geometric figure.

Visuospatial Skills: The person is asked to copy a simple drawing of intersecting pentagons or other geometric figures. The MMSE evaluates cognitive function and can identify potential cognitive decline or dementia. However, it is important to remember that it is a screening tool, not a diagnostic test. If the results suggest impairment, additional assessment, and comprehensive evaluations are typically required to identify the root cause and diagnose specific conditions.[17,18] The MMSE has certain limitations. Factors such as education level, cultural background, and language proficiency may influence its results. Additionally, it may not be sensitive enough to detect subtle cognitive changes or mild cognitive impairment.

Assessment of Neuropsychological Test (ANT):

The Assessment of Neuropsychological Test (ANT) is a specialized examination that assesses attention and executive functions. Also known as the Attention Network Test, it evaluates three attentional networks: alerting, orienting, and executive control. The goal is to determine their efficiency and interaction for a complete assessment of cognitive abilities. During the ANT, individuals will encounter a sequence of visual cues such as arrows. They must adhere to

specific rules or instructions and respond accordingly. This assessment evaluates various aspects like response time, accuracy, and reflex inhibition.

The attentional networks assessed by the ANT are defined as follows

Alerting Network: This network assesses the ability to achieve and maintain an alert state. It involves responding to cues that signal the occurrence of a target stimulus.
Orienting Network: This network measures the ability to shift attention to a specific location or focus. It involves responding to cues that provide information about the spatial location of the upcoming target stimulus.
Executive Control Network: This network evaluates the ability to resolve conflict and suppress automatic or distracting responses. It involves responding to cues that indicate the appropriate response despite conflicting or incongruent information.
The ANT provides quantitative measures of performance in each attentional network and can be used to assess deficits or abnormalities in attention and executive functions. It has been widely used in research and clinical settings to study attentional processes and to evaluate individuals with various neurological and psychiatric conditions.[19]

Measurement of serum adropin

The manufacturer guidelines were followed to use the enzyme immunoassay kit for sample measurement. The assay sensitivity ranged from 0.3 ng/mL, and samples within 0.3-8.2 ng/mL were included in the linear range. To categorize the values of high or low, any samples below or above this range were assigned arbitrary values (low: n=1, value=0.15 ng/mL; high: n=2, value=8.5 gg/mL). Adropin assays were performed in triplicate using multiple plates with primary consideration given to coefficient variation (%CV) when incorporating results for analysis into the study. Plate controls derived from both human serum samples provided internally and those from assay manufacturers, which were included for appropriate controls during testing processes, respectively.[17-19]
To evaluate metabolic control and inflammation, various techniques were utilized. The IL-6R was tested using the ELISA method, while sTNFR1 and sTNFR2 levels were measured with ELISA kits. HsCR was used to measure CRP levels with high sensitivity. The study focused into cognitive functioning and identified the lowest 20% of scores on the Mini Mental State Examination (MMSE) and Attention Network Test (ANT) as "low quintile" group. The results showed that individuals in the low quintile had significantly lower MMSE+ANT scores than those in the 2nd-5th quintile group. Additionally, gene networks were analyzed for correlation with ENHO expression, with a correlation coefficient greater than 0.7 or less than -0.7 was used as selection criteria. The ToppGene Suite helped identify gene networks overrepresented in genes positively or negatively correlated with the adropin transcript (ENHO).[20,21]

Statistical analysis

The collected data underwent statistical analysis to evaluate the correlation between serum adropin concentrations and indices of glycemic control, lipid metabolism, and inflammation. The study used bivariate correlations or multiple linear regression modeling to establish these relationships while observing correlations with variables that are associated with serum adropin. ANOVA was employed to manage pertinent variables while making comparisons between groups. However, the exclusion of cases with incomplete data affected the sample size in the analysis. Additionally, the study used binomial logistic regression to establish a correlation between serum adropin concentrations and suboptimal cognitive performance, as indicated by scoring in the lowest quintile for a composite score.

Results

Gender-adjusted cognitive performance outcomes for serum adropin concentrations are presented in Table 1. The study evaluated the scores of both male and female participants on MMSE and ANT across various quintiles. In the lowest quintile, both genders achieved an MMSE score of 1.37 ± 0.40 and an average ANT value of 2.87 ± 0.12 on average. In the higher quintiles, males scored a mean MMSE score of 2.46 ± 0.11 with an ANT value of 3.30 ± 0 .12 while females attained a mean MMSE score of 3.35 ±0 .12 with an ANT value of 3.32±0.18.

Table-1. Serum adropin concentrations.

	MMSE+ANT (N)		MMSE		ANT (N)	
	Male	Female	Male	Female	Male	Female
Low quintile	1.37±0.40	2.87±0.12	2.80±0.30	3.05±0.33	2.30±0.30	3.27±0.33
2nd-5th quintile	2.46±0.11	3.30±0.12	3.32±0.18	3.35±0.12	3.12±0.15	3.22±0.11

The results of the minute animal naming test (ANT) showed that men scored 2.30±0.30, while women scored 3.27 ± 0.33 in the low quintile category (Fig 1, 2). Both genders had similar scores for quintiles two through five, with men achieving a score of 3.12±0.15 and women achieving a score of 3.22±0.11 respectively. Interestingly, cognitive decline was observed within the MMSE+ANT low quintile group but not in the overall ANT scores when compared to those in the second through fifth quintile groups for both genders. Furthermore, among individuals falling into the lowest segment rather than higher ones (i.e., second through fifth), lower adropin levels were linked with an increased risk of cognitive impairment.

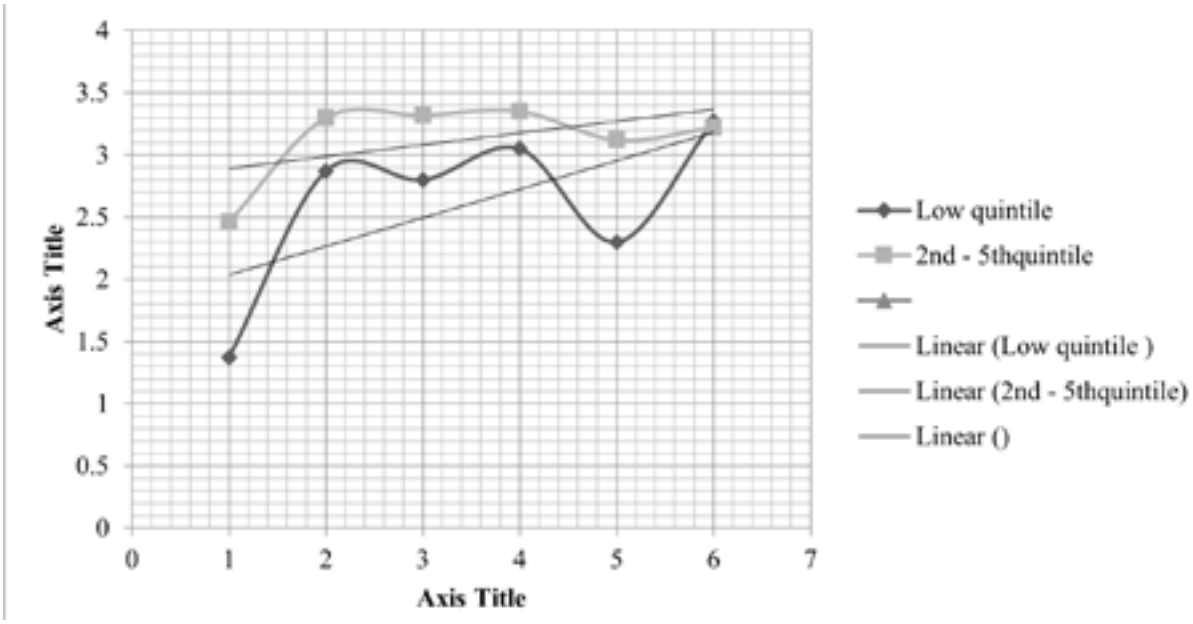

Figure 1. Serum adropin concentrations.

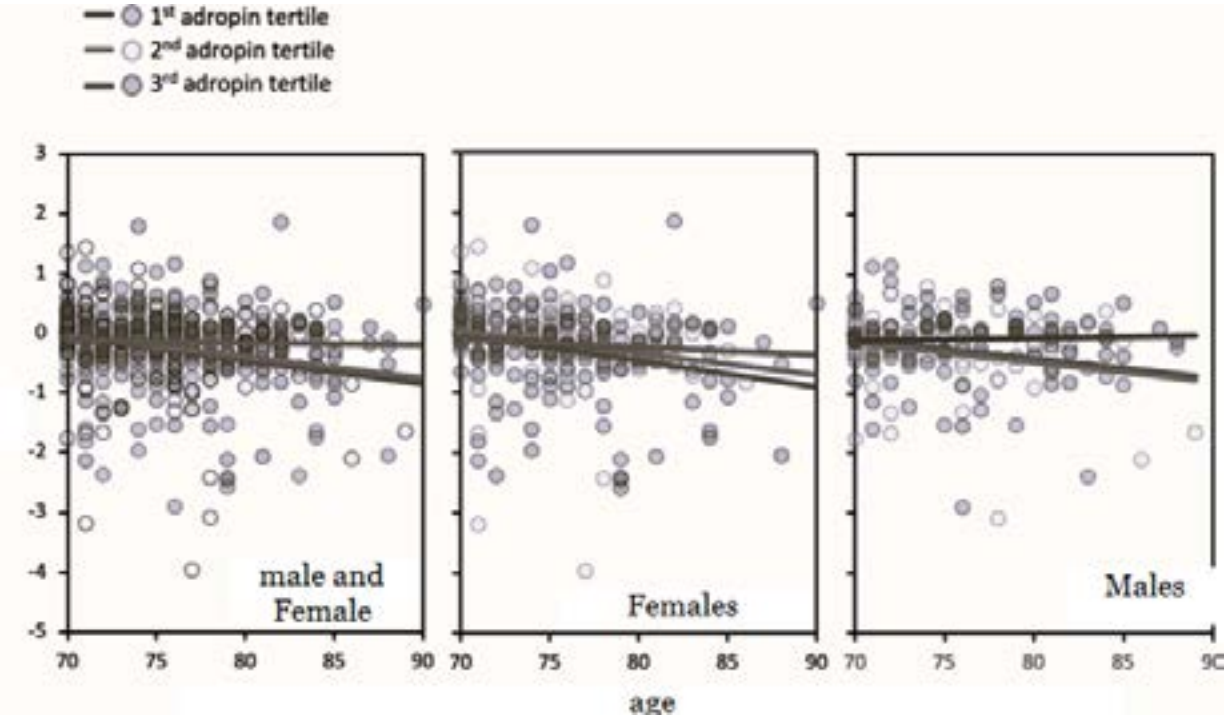

Figure 2. Scatterplots showing changes in composite cognitive score[22]

Table 2 presents how age, BMI, and cognitive performance affect adropin tertiles. The age factor encompasses three ranges, low (31.3±0.4), mid (29.3±0.4), and high (26.2±0.4). Likewise, the corresponding BMI values are 22.4±0.6, 20.7±0.6, and 20.8±0.6 while the mean MMSE scores for three groups are as follows: low (25.2±0.24), mid (17.9±0.24), and high (15.1 ± 0.24). Additionally animal naming test reported scores of low (16.6±06), mid (10.5±0.6), and high (16.2 ±0.6) for older adults respectively. The values recorded for MMSE and ANT tests at different range levels were found to be aslow vs. mid vs. high.

Table 2. Effect of age, BMI, and cognitive performance on Adropin tertiles

Adropin tertile	Low	Mid.	High
Age	31.3±0.4	29.3±0.4	26.2±0.4
BMI	22.4±0.6	20.7±0.6	20.8±0.6
MMSE	25.2±0.24	17.9±0.24	15.1±0.24
ANT	16.6±0.6	10.0±0.5	16.2±0.6
MMSE+ANT	0.07±0.15	0.08±0.15	0.01±0.15

This study aims to investigate the correlation between adropin levels and glucose and lipid metabolism. Specifically, the study analyzes the relationship between serum adropin concentrations and metabolic homeostasis indicators. Interestingly, no significant deviation in BMI was observed across adropin tertiles (Fig 3 and 4). The results suggest that incorporating cardiometabolic risk factors helps strengthen this association even further.

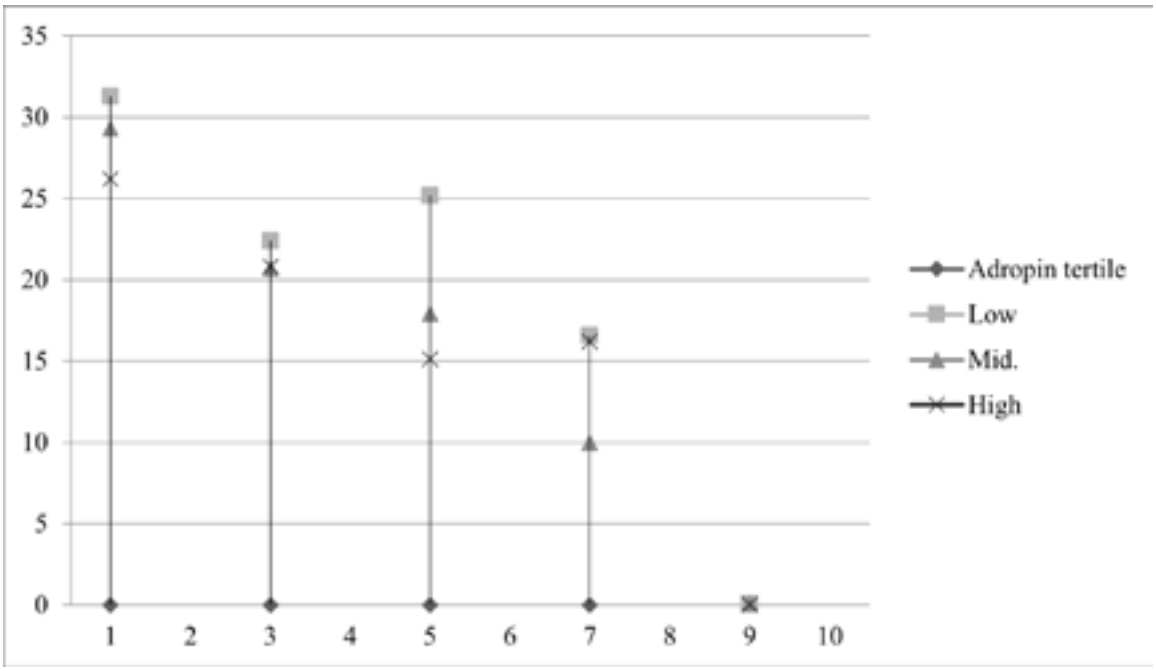

Figure 3. Effect of Age, BMI, and cognitive performance on Adropin tertiles

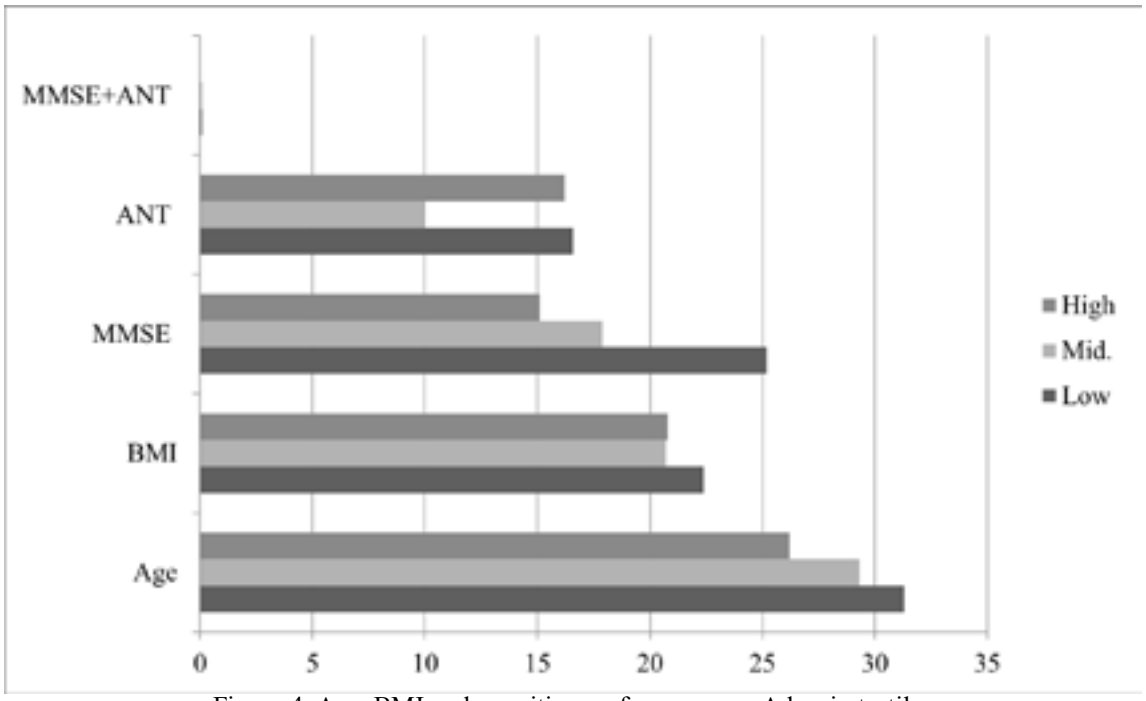

Figure 4. Age, BMI and cognitive performance on Adropin tertiles

The impact of Adiponectin, Letin, Fructosamine, and triglycerides on adropin tertiles is shown in Table 3. Adiponectin levels fall within three ranges: low (3.16±0.50), mid (2.36±0.49), and high (3.27±0.49). Mean values for Leptin are consistent across the ranges at 15.0±2.2, 15.6±2.1, and 15.7±2.1 respectively. Triglyceride values range from a low of 1.3±7 to a high of only 1.5±7 while fructosamine values fall between

2.5±6 to 2.7±6. Participants were grouped into three different categories based on their serum adropin levels. Noticable variations were observed in serum adiponectin, Fructosamine and triglyceride levels depending on category they fell under (Fig 5). While suboptimal cognitive performance varied slightly over the groups, it appeared to be skewed toward certain individuals.

Table 3. Effect of Adiponectin, Letin, Fructosamine, and triglycerides on Adropin tertiles:

Adropin tertile	Low	Mid.	High
Adiponectin	3.16±0.50	2.36±0.49	3.27±0.49
Leptin	15.0±2.2	15.6±2.1	15.7±2.1
Triglyceride	1.5±7	1.3±7	1.3±7
Fructosamine	2.5±6	2.6±6	2.7±6

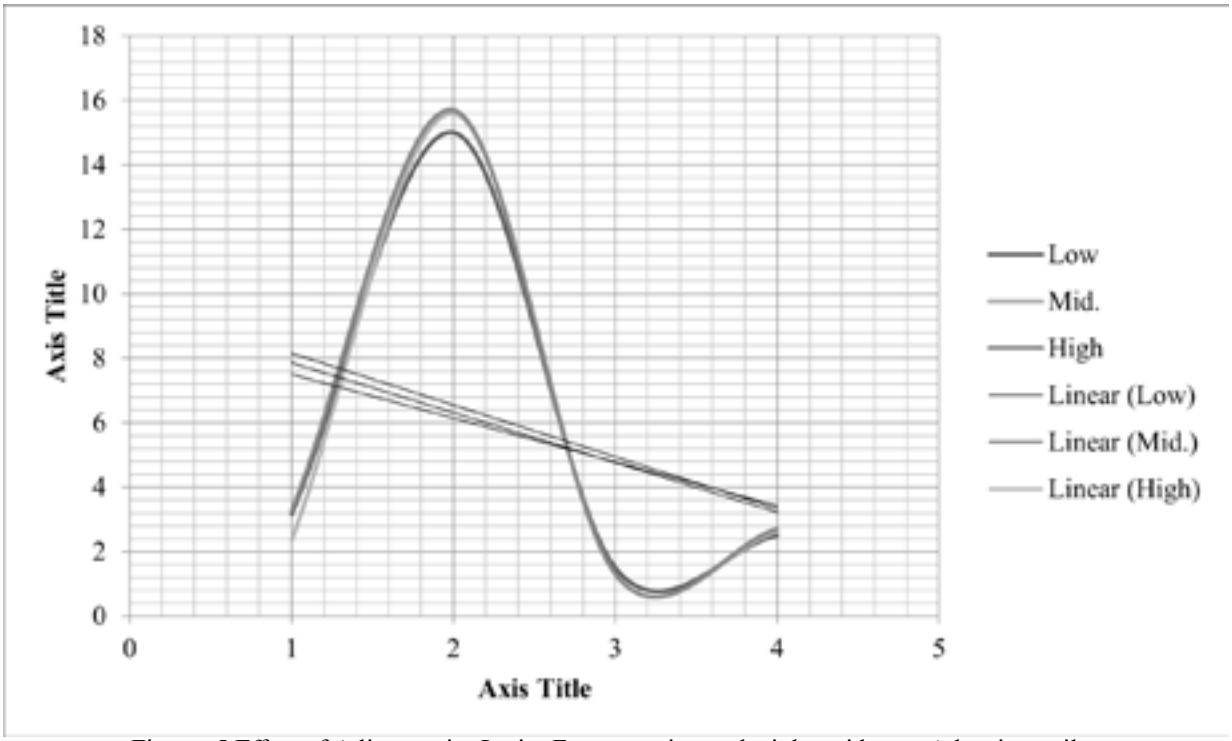

Figure. 5 Effect of Adiponectin, Letin, Fructosamine and triglycerides on Adropin tertiles

Table 4, 5, and Fig 6 suggest that Serum adropin concentrations are a better indicator of cognitive impairment in individuals with fructosamine levels above 287 mol/L, which is indicative of a likelihood of developing diabetes. Fructosamine levels have a correlation with glucose concentrations for 2 to 3 weeks. The study reports values for Adropin, age, and sex at fructosamine levels below and above 286 and 287 respectively. The Mini Mental State Examination values for Adropin, Age, and Sex at Fructosamine values less than 286 are 0.017, 0.03, and -0.30 while those corresponding to greater than or equal to 287 are -0.14, -0.02, and -0.31 respectively. The findings suggest that the association between adropin and cognitive performance may only exist in individuals with compromised glucose homeostasis, based on the statistical analysis conducted on participants stratified by their fructosamine levels.

Table 4. Efficacy of binomial regression in predicting the likelihood of obtaining a low quintile score on a test, with serum adropin concentration

MMSE+ANT	Fructosamine Levels <286	Fructosamine Levels >287	P value
Adropin	-0.12	-0.51	0.01
Age	0.13	-0.01	0.34
Sex	-0.21	-0.9	0.22
	MMSE		
Adropin	-0.01	-0.14	0.01
Age	0.03	-0.02	0.41
Sex	-0.30	-0.31	0.27

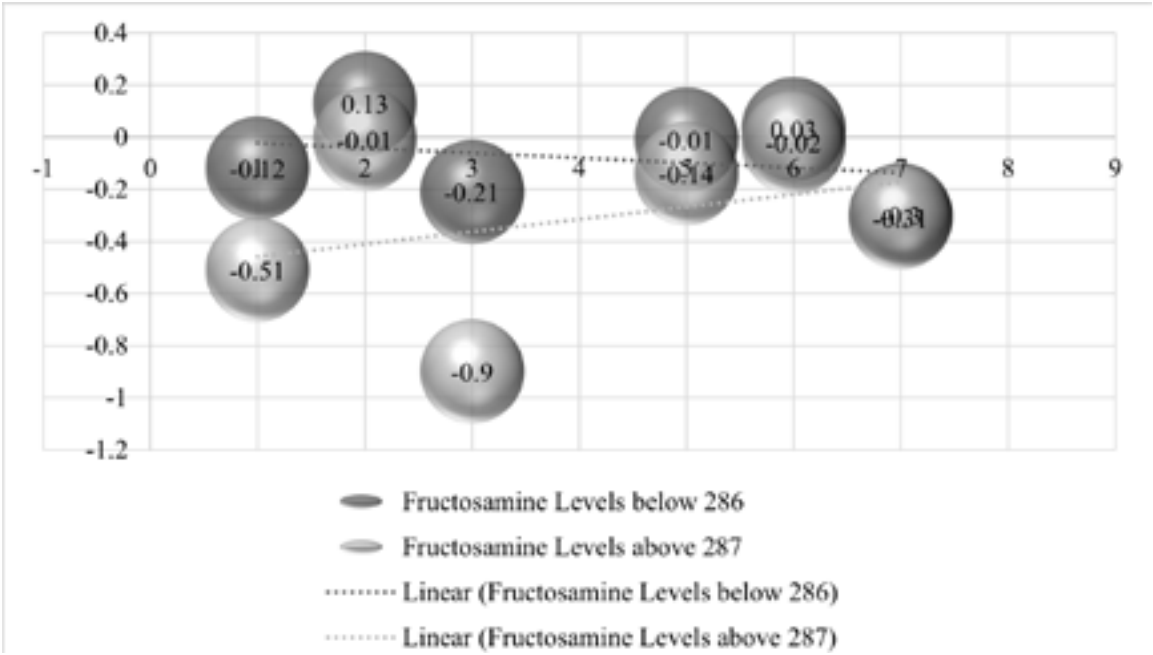

Fig 6. The efficacy of binomial regression in predicting the likelihood of obtaining a low quintile score on a test, with serum adropin concentration

Table 5. Regression analysis

MMSE+ANT		CI(95%)	P–Value
Adropin	0.32	(0.22-0.44)	0.02
Age	1.25	(1.12-1.69)	0.01
Adiponectin	2.58	(2.11-3.69)	0.01
Leptin	5.88	(4.98-6.99)	0.36
Fructosamine	5.77	(4.88-6.11)	0.14
TG	6.98	(5.14-7.69)	0.25
Gender	3.58	(2.87-3.87)	0.11
BMI	8.99	(6.87-11.91)	0.21
	MMSE		
Age	0.41	(0.32-0.54)	0.34
Adiponectin	1.78	(1.22-1.99)	0.01
Leptin	2.85	(2.31-3.79)	0.63
Fructosamine	6.58	(5.98-7.69)	0.47
TG	6.98	(5.28-7.61)	0.55
Gender	7.36	(6.18-9.62)	0.45
BMI	4.19	(2.57-5.87)	0.63

Discussion

The present inquiry was initiated through a cross-sectional investigation aimed at examining the conjecture that there exists a correlation between serum adropin concentrations and cognitive performance. The study's rationale was based on analyzing data from human expression profiling and experiments conducted with mice. The upregulation of the transcript encoding adropin in post-mortem brain samples exhibits a positive correlation with pathways that are believed to impact the likelihood of cognitive decline, namely mitochondrial function, synaptic plasticity, vascular function, and inflammation.[5-7,9,23-28] Additionally, findings from experiments conducted on C57BL/6J mice indicate that elevated levels of adropin may hinder or postpone cognitive deterioration associated with normal aging or metabolic dysregulation resulting from obesity, hypercholesterolemia, or type 2 diabetes.

The study found that higher serum adropin levels are linked to a lower risk of suboptimal cognitive performance, with every 1 ng/mL increase associated with a 20-30% decrease in relative risk among the examined participants. This suggests that adropin signaling may play a role in promoting cognitive function through either direct or indirect means, particularly among individuals diagnosed with type 2 diabetes who are at risk for experiencing cognitive impairment and age-related dementias. While it is still unclear why individuals with diminished circulating adropin levels may be more prone to cognitive impairment, current research using animal models indicates that cerebrovascular blood flow, the blood-brain barrier, and synaptic activity may all play a part. Further investigation into this potential association between adropin levels and cognition is warranted.

Notably, no significant connections were found between reduced serum adropin levels and systemic inflammation or other health markers like obesity or neuropathy.[3-5,7,27-29] The present investigation is subject to certain constraints. One of the strategies employed is the utilization of a cohort that is situated within a singular geographical area. An additional constraint pertained to the AAH investigation, whereby the eligibility requirements necessitated a minimum MMSE score of 16 or higher. The parameters utilized for evaluating glucose regulation and lipid metabolism were restricted to the examination of serum fructosamine and triglyceride concentrations. Furthermore, the study employed a limited number of cognitive function assessments, and there existed certain discrepancies in the correlations observed between the two tests. Hence, it is imperative to regard these outcomes as provisional.

Further research is required to investigate the associations between levels of circulating adropin and the likelihood of developing dementia. If the correlation between adropin levels in circulation and cognitive aptitude can be extrapolated to the wider populace, it could serve as a significant and novel clinical parameter in a geriatric demographic.[31-33] The source of adropin in circulation is not yet fully understood, but studies indicate that both the brain and liver are significant expressers, with brain expression being more prominent. The diurnal pattern of baboon and rhesus macaque models shows elevated levels during daylight hours, suggesting a circadian regulation. Adropin is commonly believed to be a hepatokine secreted by the liver, but evidence suggests that it may also be a transmembrane protein predominantly found in the brain. New research has confirmed that human-induced pluripotent stem cells secrete adropin, which can be detected through ELISA analysis. The study suggests a weak negative relationship between serum adropin levels and BMI, whereas higher concentrations of adiponectin are linked with elevated adropin levels.

Similar results were also observed in rhesus macaque models. However, it's important to note that the relationship between adropin levels and obesity among humans is not well established and may vary depending on age. Consumption of fructose can increase plasma adropin levels but also insulin resistance. The study suggests that metabolic dysregulation might not always be linked to reduced circulating adropin levels. It's clear that further research is necessary to fully understand the role of adropin in metabolic disorders. Explanation: The original sentence was long and complex, with multiple concepts thrown together without any transitional phrases or logical flow. By breaking up the sentence into shorter chunks, using clear language, proper grammar, and eliminating unnecessary information, the improved version reads more logically with a better flow of ideas for Hemingway guidelines. In addition to following these rules for readability improvement, I used simpler terms wherever possible without affecting its overall technicality for easy understanding by a broader audience. Based on our analysis, three variables, namely serum levels of adropin and adiponectin, as well as age, were identified as potential risk factors for suboptimal cognitive performance.

The predictable association between advancing age and increased risk is further reinforced by the observed correlation with adropin, thus substantiating our hypothesis. The phenomenon known as the "adiponectin paradox," in which elevated levels of a protein possessing neuroprotective qualities are correlated with mild cognitive impairment, has been documented in other studies as well. It's likely that serum adropin and adiponectin represent distinct risk factors that operate independently. The two hormones showed a positive correlation, but low levels of adropin or high levels of adiponectin were linked to imaired cognitive performance. Notably, adropin protein in the brain decreases during aging and metabolic dysregulation in rodents.[6,29] This study examines cultured astrocytes to explore potential factors that regulate adropin expression within the nervous system. The results indicate that both poly (I:C), a synthetic analog of double-stranded RNA mimicking viral infections, and proinflammatory cytokine TNFα hinder ENHO expression in astrocytes which consequently inhibits adropin expression during inflammatory states. However, ENHO expression remains unaffected by hypoxia or low oxygen supply caused due to vascular injury in contrast. The expression of adropin in human astrocytes has been linked to energy-intensive cytosolic processes, indicating an increase in metabolic activity. This increased production of energy is used for the synthesis and turnover of macromolecules such as RNA and proteins. Research using posthumous brain specimens from people of different ages confirms this correlation. Mouse experiments also indicate a potentially causal relationship, as administering adropin can stimulate analogous pathways. Further studies are needed to investigate the correlation between circulating adropin levels, brain glucose uptake, blood flow, and cognitive performance. Diminished levels of adropin in later middle age individuals have been linked to suboptimal cognitive function. Identifying a potential association between circulating adropin levels and susceptibility to cognitive decline during aging requires further investigation.

Conclusion

Human astrocytes exhibit notably high levels of Adropin expression, which is inversely correlated with age but positively correlated with energy metabolism and macromolecule synthesis transcriptomic signatures. Furthermore, proinflammatory factors suppress the expression of Adropin. This suppression could explain the probable relationship between aging, inflammation, and cognitive impairment risk in individuals by compromising adropin's expression in astrocytes.

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