RESEARCH PAPER

Association of Cognitive Dysfunction with Inflammatory and Neurodegenerative Biomarkers in Postmenopausal Women with Non Alcoholic Fatty Liver Disease

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ABSTRACT

Objective: The objective of our study was evaluation of relationship between cognitive performance and circulating biomarkers of inflammation, neurodegeneration, and oxidative stress in postmenopausal women with NAFLD in Pakistan. Study Design: This case control study was designed to compare postmenopausal females suffering from non alcoholic fatty liver disease (NAFLD) against age matched controls by using universal and purposive sampling technique.

Place and Duration of study: Present study was conducted at Aziz Fatimah Hospital, Faisalabad (IEC/141-21), in collaboration with Universiti Sains Malaysia (USM), Malaysia (reference no. USM/JEPeM/KK/23010002), between April to October 2023.

Methods: Out of 80 postmenopausal females selected, 42 were diagnosed with NAFLD and 38 served as controls. While those with a history of alcohol use, viral hepatitis, autoimmune liver disease, psychiatric illness, or hepatotoxic medication were excluded. Samples were recruited using a combination of universal and purposive sampling techniques. Data collected comprised demographic characteristics, cognitive performance, anthropometric measurements, biomarker of amyloid-beta homeostasis (Aβ40, Aβ42), pro-inflammatory cytokines (interleukin-1α, interleukin-6), and oxidative stress assessed by total antioxidant capacity (TAC). Montreal Cognitive Assessment (MoCA) was used to assess the cognitive function. Suitable Parametric and non-parametric tests were done for group comparisons and correlation analyses.

Results: Women with NAFLD had significantly lower MoCA scores than controls ($p < 0.001$). Interleukin-6 levels in Serum were markedly elevated in the NAFLD females ($p = 0.006$) with inversely correlated with cognitive performance. IL-1α, Aβ40, Aβ42, or TAC levels showed no significant difference among groups.

Conclusion: NAFLD affected postmenopausal females showed cognitive impairment indicating a relationship with raised IL-6 (systemic inflammation). The results were consistent with the notion that NAFLD is a multi-organ disease involving neurocognitive abnormalities and confirmed the idea that inflammatory pathways might be one of the mechanisms linking the two organs in this high risk population.

Keywords: Cognitive Impairment, IL-1α, IL-6, Inflammation, NAFLD, Post-menopause

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INTRODUCTION

A common chronic disease of liver (Non-alcoholic fatty liver disease, NAFLD) is affecting the world's huge population and healthcare system significantly.[1,2] Earlier considered a liver disease, now has been evolved into a multiple-system disease affecting also to cardiovascular, kidneys, endocrine and nervous systems along with its hepatic effects.[3,4]

Recent studies have shown that it may affect the cognitive function due to inflammatory interaction between multiple body systems. [5,6] In particular, this may be a vulnerable group in this regard, especially postmenopausal women.[7,8] Visceral adiposity, insulin resistance, dyslipidaemia and chronic inflammations due to oestrogen reduction after menopause, may lead to NAFLD development.[9,10] Similarly hormonal disturbance during menopause accelerates cognitive ageing and origin of neural defects.[11,12] Being higher occurance of NAFLD in the South Asian population, [13] its neurocognitive effects have not been well studied.

Certain evidences suggested that the association between hepatic steatosis and cognitive dysfunction may be follow mechanisms like inflammatory pathways where we see raised IL-6 in liver inflammation, insulin resistance, disruption of the blood–brain barrier, and neurodegeneration. [14-16]

Amyloid beta peptides (Aβ40 and Aβ42) may also be associated with the neurodegenerative processes that are linked to cognitive decline and are in addition to inflammatory mediators. The impaired amyloid-beta metabolism has been associated with synapse impairment, changes in Alzheimer and is mechanistically involved with other metabolic and inflammatory changes seen in NAFLD. [17] The other pathogenic mechanism in NAFLD is oxidative stress, which is due to mitochondrial dysfunction and lipid peroxidation, and may lead to liver damage as well as brain damage. [18]

Together these biomarkers offer complementary information on inflammatory, neurodegenerative and oxidative processes that could be involved in liver brain interactions in NAFLD. Nevertheless, very few researchers have combined all these mechanisms in post-menopausal women with the NAFLD. Therefore, in this study, we wanted to investigate the association between cognition and blood levels of inflammatory, neurodegenerative and oxidative stress markers in postmenopausal women with and without NAFLD in a case–control study.

METHODOLOGY

This case–control research was done at Aziz Fatimah Hospital, Faisalabad, Pakistan in collaboration with Universiti Sains Malaysia from April to October 2023. Out of 80 postmenopausal women (45-65 yrs of age) selected, 42 were having NAFLD and 38 were without NAFLD. Participants who had no menstruation for more than 12 months were included with prior consent form signatures. And exclusion criteria included those having a history of alcohol consumption, HBV or HCV infection, any autoimmune or other liver diseases, psychiatric illness or using any medication for such conditions.

An experienced radiologist performed abdominal ultrasonography, which was used to diagnose the NAFLD. Hepatic steatosis was defined by the standard ultrasound hepatic fat evaluation criterion, without taking into account other potential causes of hepatic fat accumulation. Those with NAFLD were defined as having hepatic steatosis and who met all of the exclusion criteria.

A prior approval of study was obtained from the Human Research Ethics Committee, Universiti Sains Malaysia (USM/JEPeM/KK/23010002) and Institutional Ethics Committee, Aziz Fatimah Hospital, Pakistan (IEC/14121) and the guidelines were followed with the ethical principles of Declaration of Helsinki.

Structured interviews and medical record review were used to collect data on demographic and clinical parameters that included duration of menopause, medical history, socioeconomic status and education. Montreal Cognitive Assessment (MoCA), a validated screening instrument for mild cognitive impairment (MCI), was used to assess the cognitive performance and was scored from 0-30, higher scores representing high cognitive performance.

The participants were deprived of food for at least 18 hours and venous blood was collected. Serum was separated by centrifugation and stored at −80°C until analysis. Concentrations of inflammatory biomarkers interleukin-6 (IL-6) and interleukin-1α (IL-1α), neurodegenerative biomarkers amyloid-beta 40 (Aβ40) and amyloid-beta 42 (Aβ42), and the oxidative stress marker total antioxidant capacity (TAC) were quantified using commercially available enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturers' protocols.

Statistical Analysis: The data were analysed by SPSS Ver. 27. Shapiro-Wilk test was used to assess continuous variables for normality. The data were shown as mean ± standard deviation (normally distributed data) and as median (non-normally distributed data) with interquartile range. Categorical variables were reported as frequencies and percentages. Between-group comparisons were conducted using independent-samples t tests or Mann–Whitney U tests for continuous variables, and chi-square tests for categorical variables, as appropriate. Associations between cognitive performance and biomarker levels were examined using Pearson or Spearman correlation analyses depending on data distribution. Logistic regression was applied to evaluate independent associations between biomarker levels and cognitive impairment, adjusting for relevant covariates. A two-tailed p-value <0.05 was considered statistically significant.

RESULTS

A total of 80 postmenopausal women participated in the study, including 42 with NAFLD and 38 controls. The mean age was comparable between groups; however, women with NAFLD had significantly higher body mass index (BMI) and waist circumference values (Table 1).

Table 1

Baseline characteristics of study participants

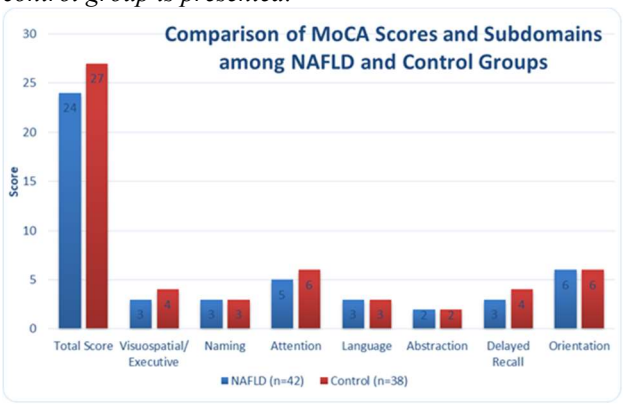
Variable	NAFLD (n = 42) mean ± SD	Control (n = 38) mean ± SD	p-value
Age (years)	56.2 ± 5.8 [a]	55.7 ± 6.1 [a]	0.72 [b]

BMI (kg/m², mean ± SD)	29.4 ± 3.5 [a]	26.1 ± 3.2 [a]	<0.001 [d]
Waist Circumference (cm)	84.00 (6)[b]	74.00 (7)[b]	<0.001[c]
Duration of menopause (years)	10.50 (7) [c]	7.50 (9) [c]	0.091 [d]

[a] Mean (SD), b p value determined by Independent T test, c Median (IQR)
[d] p value determined by Mann-Whitney, P value ≤0.05 is taken as significant., BMI: Body Mass Index

Cognitive performance, assessed by the Montreal Cognitive Assessment (MoCA), was markedly reduced in the NAFLD group compared to controls ($p < 0.001$). Subdomain analysis revealed deficits in executive function and memory, and no significant differences in attention and language (Figure 1).

Figure 1
The distribution of MoCA scores in both NAFLD and control group is presented.



NAFLD females had raised serum interleukin-6 (IL-6) levels ($p = 0.006$), indicating the importance of inflammation in its pathogenesis. Interleukin-1α (IL-1α), on the other hand, showed no significant difference between groups, indicating a smaller role in this group. Likewise, neither amyloid beta peptides (Aβ40 and Aβ42) was found to be significantly associated with cognitive scores, indicating that their role in neurocognitive impairment may differ between populations.
There was no significant difference between groups in terms of measures of oxidative stress as indicated by total antioxidant capacity (TAC), suggesting no significant group-level imbalance in antioxidant defence (Table 2).

Table 2
Biomarker levels in NAFLD and control groups

Biomarker	NAFLD (mean ± SD)	Control (mean ± SD)	p-value
IL-6 (pg/mL)	12.4 ± 3.1	9.8 ± 2.7	0.006
IL-1α (pg/mL)	4.2 ± 1.5	4.0 ± 1.4	0.58
Aβ40 (pg/mL)	145 ± 28	142 ± 30	0.64
Aβ42 (pg/mL)	38 ± 9	37 ± 8	0.71
TAC (mmol/L)	1.2 ± 0.3	1.3 ± 0.4	0.33

IL-6: Interleukin-6, IL-1α: Interleukin-1α, Aβ40: Amyloid Beta 40, Aβ42: Amyloid Beta 42, TAC: Total Antioxidant Capacity

DISCUSSION

In this case–control study, women with NAFLD exhibited higher IL-6 levels, and significantly lower cognitive functioning than controls. The results corroborate the growing understanding of NAFLD as a multisystem disease that can have neurocognitive effects and that systemic inflammation could be a common mechanism through which hepatic steatosis is associated with cognitive impairment.

The association between NAFLD and cognitive dysfunction is consistent with existing evidence indicating that there is a link between steatotic liver disease and cognitive impairments in executive function, memory and brain structural abnormalities despite the presence of traditional cardiometabolic risk factors.[16,17] There is recent experimental and clinical evidence supporting the liver-brain axis hypothesis and a corresponding adverse effect of hepatic metabolic dysfunction on neuroinflammation, endothelial dysfunction, and cerebral metabolic dysfunction. [5,16] Our results add to this evidence as they found these associations in postmenopausal women, who may be at higher risk for NAFLD and cognitive decline during hormonal and metabolic transition.

Of the assessed biomarkers, IL-6 was the only biomarker to significantly correlate with cognitive impairment in patients with NAFLD. A pleiotropic cytokine, IL-6 has been associated with inflammation, insulin resistance and neurodegenerative signalling pathways of the liver. This could be caused by higher levels of IL-6 and lead to a disruption of cognitive function due to higher blood brain barrier permeability, microglial activation, and synapse damage. [14,19] The results of this study corroborate previous studies noting the inverse relationship between IL-6 and cognition in older adults, and that this relationship appears to exist in cognitively unimpaired older adults. [19] The findings suggest that inflammatory activation may play a central role in the vulnerability of neurocognition in NAFLD particularly in women at the age of menopause who are highly vulnerable to inflammation.

The other analytes such as amyloid beta peptides (Aβ 40 and Aβ 42) and total antioxidant capacity did not correlate significantly with any of the other measures. However, the absence of any differences in amyloid beta may be understood to imply that early cognitive impairment in NAFLD may be mostly driven by inflammatory and metabolic mechanisms rather than by true amyloid pathology. Similarly, the absence of any significant difference in the overall antioxidant capacity suggests that the oxidative imbalance may not be large enough to distinguish between NAFLD-related cognitive

impairment in this specific group of patients or that the overall antioxidant capacity may not be a reflection of the complexity of the oxidative stress pathways between liver/brain interaction. [20]

Our results could also be expressions of specific pathophysiological patterns among populations. Most studies conducted to date to evaluate the relationship between NAFLD and neurocognitive biomarkers have been performed in Western populations and differences in expression of these biomarkers and in the disease phenotype may be attributed to ethnic, dietary, genetic and environmental differences. This is especially important in SAs, with lower BMIs associated with central adiposity and insulin resistance, potentially changing the inflammatory profile of NAFLD.

These findings have significant clinical implications. This is an additional example of a postmenopausal woman who was cognitively vulnerable in the setting of liver disease related to NAFLD, and might be an unrecognized extrahepatic manifestation of the disease. Routine cognitive screening should be considered in selected patients with high inflammatory burden, with metabolic risk factors and/or with cognitive screening. In addition, IL-6 could be a useful biomarker to identify those at risk of having neurocognitive complications, but this will need to be validated in prospective studies.

There are some caveats to be noted. The study has small sample size, participants recruited from a hospital environment, and the study has a cross sectional design, which does not allow for causal inference. These associations are constrained by the need for larger, longitudinal studies that test these associations and explore temporal relationships. Despite these limitations, this study is novel in that it is the first to define a novel cognition-NAFLD-secondary-to-systemic-inflammation association in post-menopausal women of a South Asian population. Future longitudinal studies using more complex liver phenotyping, imaging studies of the brain and an expanded inflammatory profile are suggested, to further elucidate the causal pathway and to investigate the effect of inflammatory interventions on reducing neurocognitive risk in NAFLD.

CONCLUSION

Systemic inflammation is suggested to be a possible contributor to neurocognitive dysfunction in women with NAFLD, who have impaired cognitive function and elevated circulating levels of IL-6. The results further support the notion that NAFLD is a multisystem disease with nonhepatic clinical effects that are relevant. The inflammatory pathways could provide a mechanism point that can be investigated further as an opportunity for risk stratification and intervention in liver—brain axis. Larger prospective longitudinal studies are needed to determine whether inflammatory targeted drugs will slow the cognitive decline in this high-risk group and prove to be causative.

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