Glycerophospholipids as Potential Serum Biomarkers for Traumatic Brain Injuries

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Abstract

Background: Traumatic brain injuries (TBI) have become a significant healthcare issue in the United States of America. Despite the existence of some neuroimaging techniques, a sensitive and reliable serum biomarker is desirable regarding to diagnosis, prognosis and therapeutic evaluation of patients with a history of TBI.

Methods: Using data collected from participants of the Alzheimer's Disease Neuroimaging Initiative, different analysis of covariance (ANCOVA) models were used to determine if glycerophospholipids could be potential serum biomarkers for patients with TBI.

Results: Three phosphatidylcholines: PC.aa.C30.0, PC.aa.C38.5, and PC.aa.C40.5 as well as one lysophosphatidylcholine (LysoPC.a.C18.1) were identified to be potential serum biomarkers for TBI. The PC.aa.C30.0 serum level was higher in the TBI group than the non-TBI group. By contrast, the serum levels of PC.aa.C38.5 and PC.aa.C40.5 were lower in the TBI group than the non-TBI group. The LysoPC.a.C18.1 serum level was mainly determined by the cognitive status at baseline (a worse baseline cognition status associates with a lower level of LysoPC.a.C18.1). In participants with normal cognition, a significantly higher LysoPC.a.C18.1 serum level was seen in participants with than those without a history of TBI.

Conclusions: Four glycerophospholipids are suggested to be potential TBI serum biomarkers. Among them, the LysoPC.a.C18.1 could function as a TBI serum biomarker for those without an abnormal cognition.

Background

Traumatic brain injuries (TBI) have been a common and significant healthcare issue in the United States of America as each year there are more than two million TBI related emergency department visits, hospitalizations or deaths [1]. A sensitive and reliable serum biomarker for TBI is desirable for purposes of diagnosis, prognosis and therapeutic evaluation. For example, diagnosis of TBI remains a challenge with the costly, conventional imaging technologies especially when no obvious clinical symptoms are presented. Biomarkers that correlate well with clinical symptoms and long-term outcome of TBI are needed for optimizing the individualized care for patients with TBI [2]. Glycerophospholipids are the main component of cell membranes, and membrane phospholipid degradations occur after TBI [3]. The highest concentrations of lysophosphatidylcholine and phosphatidylcholine appeared in cerebrospinal fluid within one week after TBI [4, 5]. Traumatic injuries with or without local hypoxemia could disrupt the blood-brain barrier, then phosphatidylcholines are released into blood circulation. The goal of the current study was to determine if glycerophospholipids could function as sensitive and reliable serum biomarkers for TBI using data from participants of the Alzheimer's Disease Neuroimaging Initiative (ADNI).

Methods

Alzheimer's Disease Neuroimaging Initiative (ADNI)

ADNI was launched in 2003 and has been sponsored by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies, and non-profit organizations. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), biomarkers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. During its different phases (ADNI-1, GO, 2, and 3), ADNI has recruited more than 1,800 participants from over 60 sites across the U.S. and Canada. These participants consisted of cognitively normal (CN) older individuals, people with MCI, and people with AD. Further information can be found at http://www.adni-info.org/ and in previous reports [6-11].

Selection of Participants with a Medical History of TBI

Participants with a TBI history were identified from the ADNI (1/GO/2) by screening medical history records of all participants using keywords: post-traumatic stress disorder (PTSD), TBI, trauma, wound, concussion and head injury. In total, 204 records were found, including 5 for PTSD, 16 for TBI, 39 for trauma, 9 for wound, 60 for concussion, and 75 for head injury. After removing duplicates and excluding non-TBI trauma or injuries, 86 participants with a history of TBI were available for further analyses. 5 participants with a diagnosis of PTSD were excluded from the analyses, as their traumas could be either physical or psychological, which could not be determined from the available medical history records. Therefore, the final sample included 81 participants with a medical history of TBI [12, 13].

Data on Serum Metabolites

The serum metabolite raw data were downloaded from the LONI ADNI site (http://adni.loni.usc.edu). The p180 kit of Biocrates Life Sciences AG (Innsbruck, Austria) was used for quantifying 186 serum metabolites, including free carnitine, 40 acylcarnitines (Cx:y), 21 amino acids, 19 biogenic amines, hexoses, 90 glycerophospholipids (14 lysophosphatidylcholines (lysoPC) and 76 phosphatidylcholines (PC), and 15 sphingolipids (SMx:y). The abbreviations Cx:y are used to describe the total number of carbons and double bonds of all chains, respectively. The assay procedures of the Absolute*IDQ*™ p180 kit as well as the metabolite nomenclature were described previously [14, 15]. Data from non-fasting participants were excluded from the analyses.

Statistical Analysis, Tables and Figures

SPSS (version 24.0) was used to conduct all statistical analyses. A two-way analysis of covariance (ANCOVA) model was used to analyze the effects of baseline diagnostic classification (CN, MCI, AD) and a history of TBI (yes, no) on serum phosphatidylcholine levels with age, gender, and *APOE* ε4 carrier status being controlled as possible confounding factors. Then a multivariate analysis of covariance (MANCOVA) was performed to check if the phosphatidylcholines identified from the two-way ANCOVA as possible TBI serum biomarkers were having significantly different serum concentrations between the TBI and non-TBI groups. For the lysophosphatidylcholine acyl C18.1 (LysoPC.a.C18.1), a post hoc analysis was performed to examine how TBI is related to its serum levels among the following six groups: CN with no TBI (CN); MCI with no TBI (MCI); AD with no TBI (AD); CN with TBI (TBI); MCI with TBI (MCI+TBI); AD with TBI (AD+TBI).

Data were shown in the form of mean ± standard error, and a p value of 0.05 was used as the cutoff for significance. In addition, Bonferroni corrections were done for p values in analyses with multiple comparisons. Figures were created using Sigmaplot (version 10.0).

Results

The serum levels of phosphatidylcholines were compared between the TBI group and the non-TBI group. Six phosphatidylcholines were shown to be possible TBI serum biomarkers from the two-way ANCOVA: PC.aa.C30.0, PC.aa.C32.1, PC.aa.C34.3, PC.aa.C38.5, PC.aa.C40.5, and PC.aa.C40.6 (Table 1). Then a MANCOVA was performed using the history of TBI as the independent variable and the six phosphatidylcholines identified from the two-way ANCOVA as the dependent variables. Only PC.aa.C30.0, PC.aa.C38.5, and PC.aa.C40.5 survived from the MANCOVA (Table 2). The PC.aa.C30.0 serum level was significantly higher in the TBI group than the counterpart measurement in the non-TBI group. By contrast, the serum levels of PC.aa.C38.5 and PC.aa.C40.5 were significantly lower in the TBI group than the non-TBI group (Table 2).

Table 1

Six phosphatidylcholines had significantly different serum levels between participants in the TBI and non-TBI groups. The serum levels of phosphatidylcholines were presented in the format of mean ± standard error (μM). PC.aa.C30.0: phosphatidylcholine diacyl C30:0; PC.aa.C32.1: phosphatidylcholine diacyl C32:1; PC.aa.C34.3: phosphatidylcholine diacyl C34:3; PC.aa.C38.5: phosphatidylcholine diacyl C38:5; PC.aa.C40.5: phosphatidylcholine diacyl C40:5; PC.aa.C40.6: phosphatidylcholine diacyl C40:6; *: Phosphatidylcholine serum levels were significantly different between the TBI and non-TBI groups.

Metabolites	Non-TBI	95% CI	N	TBI	95% CI	N	P
PC.aa.C30.0	3.94 ± 0.05	3.84–4.03	710	4.61 ± 0.28	4.07–5.16	26	0.017 *
PC.aa.C32.1	13.95 ± 0.25	13.46–14.44	710	17.64 ± 1.50	14.68–20.59	26	0.016 *
PC.aa.C34.3	20.51 ± 0.19	20.15–20.88	710	23.08 ± 1.13	20.87–25.29	26	0.025 *
PC.aa.C38.5	74.80 ± 0.63	73.56–76.03	710	63.64 ± 3.81	56.16–71.11	26	0.004 *
PC.aa.C40.5	13.45 ± 0.12	13.21–13.69	710	11.74 ± 0.73	10.31–13.17	26	0.021 *
PC.aa.C40.6	24.12 ± 0.39	23.35-24.892	710	19.02 ± 2.38	14.34–23.70	26	0.035 *

Table 2

Three phosphatidylcholines survived from the multivariate analysis of covariance. The serum levels of phosphatidylcholines were presented in the format of mean ± standard error (μM). PC.aa.C30.0: phosphatidylcholine diacyl C30:0; PC.aa.C32.1: phosphatidylcholine diacyl C32:1; PC.aa.C34.3: phosphatidylcholine diacyl C34:3; PC.aa.C38.5: phosphatidylcholine diacyl C38:5; PC.aa.C40.5: phosphatidylcholine diacyl C40:5; PC.aa.C40.6: phosphatidylcholine diacyl C40:6; *: Phosphatidylcholine serum levels were significantly different between the TBI and non-TBI groups.

Metabolites	Non-TBI	95% CI	N	TBI	95% CI	N	P
PC.aa.C30.0	3.96 ± 0.04	3.87–4.05	710	4.52 ± 0.23	4.07–4.97	26	0.016 *
PC.aa.C32.1	13.97 ± 0.24	13.50-14.43	710	16.27 ± 1.24	13.83–18.70	26	0.069
PC.aa.C34.3	20.55 ± 0.18	20.20–20.90	710	21.92 ± 0.93	20.09–23.75	26	0.149
PC.aa.C38.5	74.88 ± 0.60	73.71–76.06	710	64.16 ± 3.13	58.01–70.31	26	0.001 *
PC.aa.C40.5	13.46 ± 0.11	13.23–13.68	710	11.83 ± 0.60	10.65-13.0	26	0.008 *
PC.aa.C40.6	24.19 ± 0.38	23.45–24.92	710	20.49 ± 1.96	16.63–24.34	26	0.065

In light of baseline cognition diagnosis, LysoPC.a.C18.1 had significantly different serum levels among the groups of CN, MCI and AD (Fig. 1) ($p = 0.004$). For the CN group, the serum LysoPC.a.C18.1 level was 37.46 ± 1.34 μM (95% confidence interval (CI): 34.84–40.09 μM, n = 203) (Fig. 1). For the MCI group, the LysoPC.a.C18.1 serum level was 32.72 ± 1.16 μM (95% CI: 30.45–34.99 μM, n = 358), which was

significantly lower than the same measure for the CN group (p = 0.022) (Fig. 1). The LysoPC.a.C18.1 serum level for the AD group was 29.76 ± 2.38 μM (95% CI: 25.08–34.44 μM, n = 175), which was significantly lower than the same measure for the CN group (p = 0.015) (Fig. 1). However, the serum LysoPC.a.C18.1 levels were not significantly different between the MCI group and the AD group (p = 0.794).

Since baseline diagnosis group significantly interacted with the TBI status for their effects on serum LysoPC.a.C18.1 (p = 0.001), a post hoc analysis was done to compare the LysoPC.a.C18.1 serum levels among the six groups: CN, TBI, MCI, TBI + MCI, AD, and TBI + AD. The LysoPC.a.C18.1 serum levels were significantly different between the CN group and the TBI group (Fig. 2). The LysoPC.a.C18.1 serum level for the TBI group was 42.6 ± 2.59 μM (95% CI: 37.52–47.67 μM, n = 10), which is significantly higher than the same measure for the CN group of 32.06 ± 0.59 μM (95% CI: 30.9-33.21 μM, n = 193; p = 0.001). However, the effects of TBI on LysoPC.a.C18.1 levels were not observed in participants with a baseline diagnosis of either MCI or AD (Fig. 2).

Conclusions

Glycerophospholipids as potential serum biomarkers for TBI were examined by comparing their levels between participants with and without a history of TBI. A cascade of reactions initiated with TBI degrade the membrane lipid in both neurons and neuroglia [5]. On a cellular level, stretch-induced injury activates several enzymes, which are involved in either hydrolysis (phospholipase A2 and phospholipase C) or biosynthesis (phosphocholine cytidylyltransferase) of phosphotidylcholine [16]. Prior studies reported that changes in biomarkers as long-term effects of TBI were related to alterations in metabolic and vascular functions, cell adhesion, as well as structural damages in neurons [17]. For example, total tau and its hyperphosphorylated form (pTau) increase their serum levels acutely (within one week) and are still detectable 6 months post to severe TBI [18]. In the current study, four glycerophospholipids were shown to be potential TBI biomarkers in the post-TBI chronic phase. Three phosphatidylcholines showed different serum levels between the TBI group and the non-TBI group (Table 2). The LysoPC.a.C18.1 was the only biomarker that was significantly associated with the baseline cognition diagnosis (the worse the cognition diagnosis the lower its serum level) (Fig. 1). However, the serum level of LysoPC.a.C18.1 was significantly affected by a positive TBI history in participants without abnormal cognition at the baseline. These findings suggest that cognitive status has a more significant role than a history of TBI in terms of their effects on serum level of the LysoPC.a.C18.1.

In a rat model, serum levels of neurofilament heavy chain and Tau, as well as S100B and myelin basic protein (MBP) increased significantly in the acute phase (within two weeks) after TBI [19, 20]. Compared to controls, injured mice with sensorimotor and learning deficits had decreased levels of cortical and cerebellar phosphatidylcholine three months post TBI [21]. The damage caused by TBI disrupts the blood brain barrier, injures the neurons and neuroglial cells, and leads to increased catabolism of phospholipids [22]. These pathological changes can be reflected by serum level changes of breakdown products from membrane phospholipids. TBI was shown to activate phospholipase C after experimental brain injury in

rats or cats [23–25], which catalyzes the release of arachidonic acid from two major membrane phospholipids: phosphatidylinositol and phosphatidylcholine. The lower serum levels of PC.aa.C38.5 and PC.aa.C40.5 in the TBI group than in the control group might be related the increased phospholipase C activities.

Compared with the control group, the TBI group had higher serum levels of PC.aa.C30.0 and LysoPC.a.C18.1, which might be related to an increased production of these glycerophospholipids [16]. For example, monounsaturated fatty acid containing phosphatidylcholines and phosphatidylinositols were reported to be lower in TBI subjects than the controls [26]. However, details on how these glycerophospholipids respond to the impact of TBI need further investigations.

The goal of this study was to determine if glycerophospholipids could be potential biomarkers for subjects with a history of TBI by measuring their serum levels during the post-TBI chronic phase. The study has both limitations and strengths. One limitation is that ascertaining TBI cases from the medical history records of participants might bring some inaccuracy. Another limitation is the cross-sectional design, which only used the baseline data for the serum glycerophospholipid measurements. The lag time between age at injury and blood sample drawing is 36.71 ± 23.63 years (n = 81). While it is a limitation that we are unable to study TBI in the acute phase, a major strength is the length of a long follow-up in our current study. Another strength of this study is that APOE ε4 carrier status, age and gender were controlled as potential confounding factors for all performed analyses. APOE ε4 carrier status was shown to play a role in influencing phospholipid levels after TBI [26]. In addition, both age and lag time can affect the levels of measured biomarkers [27]. However, no significant correlation has been found between the measured glycerophospholipid levels and the lag time in the current study. Replication and prospective validation studies are warranted to evaluate the four glycerophospholipids as potential TBI biomarkers.

Abbreviations

Alzheimer's Disease (AD), Alzheimer's Disease Neuroimaging Initiative (ADNI), confidence interval (CI), cognitively normal (CN), Food and Drug Administration (FDA), magnetic resonance imaging (MRI), mild cognitive impairment (MCI), multivariate analysis of covariance (MANCOVA), myelin basic protein (MBP), National Institute on Aging (NIA), National Institute of Biomedical Imaging and Bioengineering (NIBIB), phosphatidylcholines (PC), positron emission tomography (PET), post-traumatic stress disorder (PTSD), Traumatic brain injuries (TBI)

Declarations

Ethics Approval and Consent to Participate*:* Written informed consent was obtained from all participants (or guardians of participants) participating in the study according to the Declaration of Helsinki (consent for research). For this specific study, the data use was approved by the University of Washington Ethics Committee.

Consent for Publication: Not applicable

Availability of Data and Materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests: The authors declare that they have no competing interests.

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Authors' Contributions: WL conceived the study design, acquired data and drafted the manuscript. DL, AS and WL contributed to data input, analysis and interpretation as well as critical revision of the manuscript for important intellectual content.

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Figures

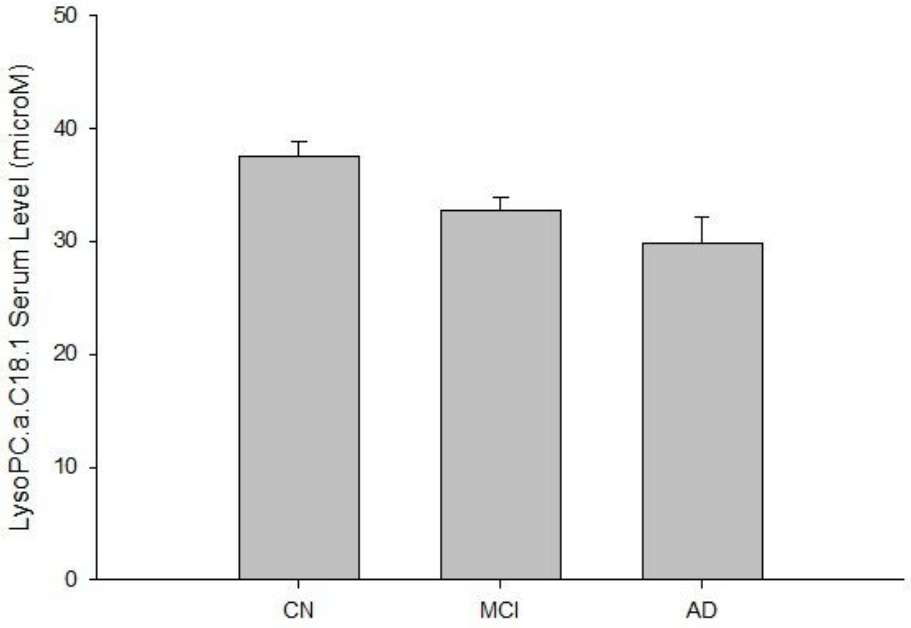

Figure 1

The levels of LysoPC.a.C18.1 were significantly different among baseline cognition diagnosis groups. LysoPC.a.C18.1 stands for lysophosphatidylcholine acyl C18.1, and its serum level was presented in the format of mean ± standard error (μM). CN: cognitively normal; MCI: mild cognitive impairment; AD: Alzheimer's disease

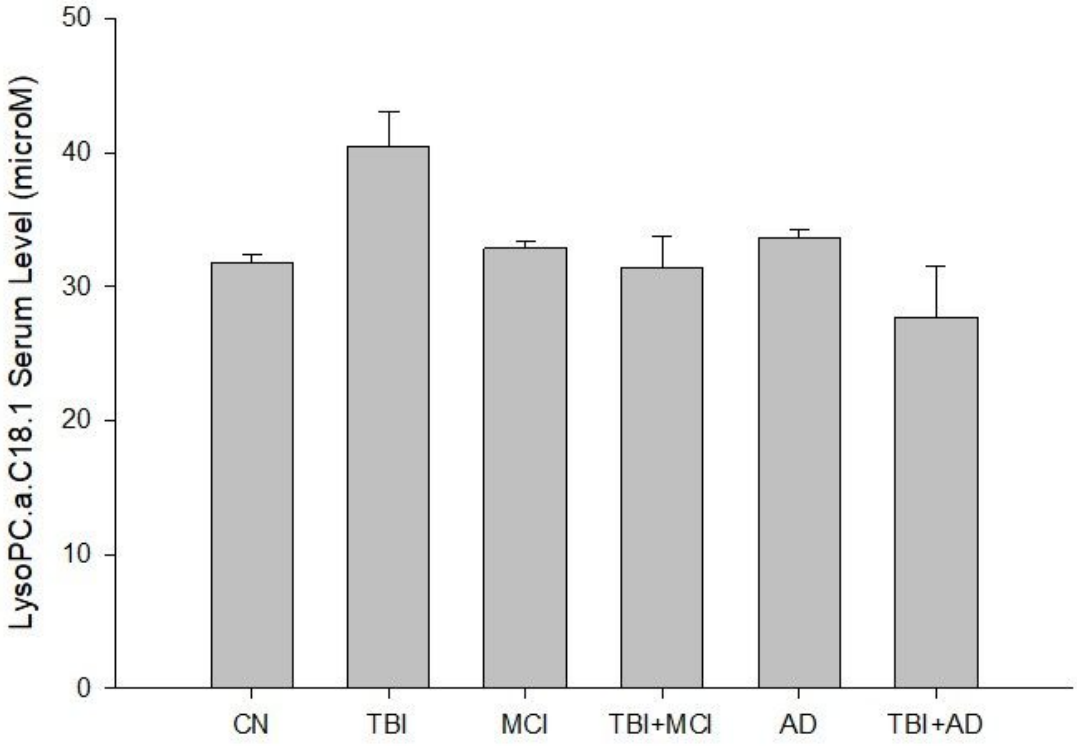

Figure 2

The serum level of LysoPC.a.C18.1 was significantly higher in the TBI group than the same measure for the CN group (p=0.001). LysoPC.a.C18.1 stands for lysophosphatidylcholine acyl C18.1, and its serum level was presented in the format of mean ± standard error (μM); CN: cognitively normal; MCI: mild cognitive impairment; AD: Alzheimer's disease; TBI: Traumatic brain injuries