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Adiponectin Possibly has A Potential Role to Protect Postoperative Patients from Delirium

Takamichi Kogure[1], Reo Inoue[2], Kazuhito Mietani[2], Yaeko Yokoshima[2], Yoshika Sudo[2], Toru Ogata[3], Nobutake Shimojo[4], Masahiko Sumitani[1*]

Abstract

Postoperative delirium is a common complication in older patients. Changes in adipokine levels are associated with advanced stages of dementia and aging. However, the role of adipokines in the development of postoperative delirium has not been fully investigated. In this study, we examined the association between delirium and adipokines including, adiponectin, resistin, and leptin after surgery. We conducted a post hoc analysis of 117 patients who participated in a prospective observational study of delirium in patients undergoing cancer surgery. The patients were clinically assessed for delirium within the first 5 days after surgery. Serum levels of adipokines such as adiponectin, resistin, and leptin as well as related inflammatory markers were measured on postoperative day 3. Forty-one patients (35%) were clinically diagnosed with postoperative delirium. Serum levels of adiponectin on postoperative day 3 were significantly decreased in patients with delirium compared with those without delirium (8.615 [8.005–11.306] *vs.* 11.306 [8.465–11.306], $P = 0.0031$) whereas levels of resistin were increased (10.960 [10.742–11.050] *vs.* 10.393 [9.794–11.126], $P = 0.0018$). Serum levels of adiponectin were associated with delirium (adjusted odds ratio [aOR], 0.673; 95% confidence interval [CI], 0.514–0.882; $P = 0.0030$) and the detection of phosphorylated neurofilament heavy subunit (aOR, 0.666; 95% CI, 0.494–0.900; $P = 0.0057$). Serum adiponectin levels were associated with delirium and the presence of phosphorylated neurofilament heavy subunit in serum. Therefore, adiponectin might be one of the useful biomarkers of postoperative delirium.

Abbreviations: Apo: Apolipoprotein; CSF: Cerebrospinal fluid; MRI: Magnetic resonance imaging; CAM: Confusion Assessment Method; pNF-H: Phosphorylated neurofilament heavy subunit

Keywords: Postoperative delirium; Resistin; Adiponectin; Phosphorylated neurofilament heavy subunit

Introduction

With the aging of the population, delirium that occurs during disease progression in cancer patients is becoming an increasingly serious global public health issues [1]. Aging alters adipose tissue composition and function, and induces changes in the secretion of adipose tissue-derived hormones, or adipokines, that promote a chronic state of low-grade systemic inflammation [2]. While adiponectin has anti-inflammatory properties and can directly act on vascular endothelial cells and macrophages [3], other adipocyte-derived factors such as resistin, leptin, and chemokines, including CC chemokine

Affiliation:
[1]Department of Pain and Palliative Medicine, The University of Tokyo Hospital, Tokyo, Japan
[2]Department of Anesthesiology and Pain Relief Center, The University of Tokyo Hospital, Tokyo, Japan
[3]Department of Rehabilitation Medicine, The University of Tokyo Hospital, Tokyo, Japan
[4]Department of Emergency and Critical Care Medicine, Tsukuba University Hospital, Ibaraki, Japan

***Corresponding author:**
Masahiko Sumitani, Department of Pain and Palliative Medicine, The University of Tokyo Hospital, Tokyo, Japan.

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ligands (CCL)2 (also known as macrophage chemoattractant protein-1, MCP-1), and CCL5 (regulated on activation, normal T cell expressed and secreted, RANTES), are highly expressed in the pathogenesis of perivascular adipose dysfunction state such as that involved in atherosclerosis, hypertension, diabetes, and obesity [4]. Both chronic inflammation and critical illness have been associated with lower adiponectin concentrations in intensive care unit (ICU) patients [5]. Furthermore, plasma adiponectin was more strongly correlated with plasma cortisol in the ICU versus non-ICU patients, and an inverse correlation was observed between plasma adiponectin and C-reactive protein.

Systemic perivascular inflammation alters adipose tissue macrophage subsets [6], resulting in an increased susceptibility to age-associated central nervous system (CNS) disorders such as cognitive impairment and dementia [7]. For instance, patients with mild cognitive impairment have been found to have increased serum leptin and resistin, but decreased adiponectin concentrations [8,9]. In terms of ICU-acquired delirium, diagnosed via the Confusion Assessment Method in the Intensive Care Unit (CAM-ICU), adiponectin levels were significantly higher in patients with delirium compared with those without delirium [10]. However, low plasma leptin levels at admission to the ICU were independently associated with the subsequent occurrence of delirium [11]. Additionally, preoperative levels of CCL2 were independently associated with the development of delirium in patients undergoing cardiac surgery [12]. These previous studies suggest that changes in the adipokine profile that accompany aging might influence on the development of delirium in the acute phase of the perioperative period. Although the role of adipokines in postoperative delirium has not been well- investigated, Xie *et al*. reported that serum adiponectin levels were significantly decreased in individuals with postoperative cognitive disorder (COPD), diagnosed via the Montreal Cognitive Assessment scores on day 3 after surgery, compared with non-COPD patients undergoing selective total hip arthroplasty on postoperative days 1, 2, 3, and 7 [13].

We previously reported that CNS-derived axonal protein, pNF-H was highly detected in serum of delirium patients on day 3 after surgery [14]. More recently, we found that apolipoprotein (Apo) A-1 and Apo E were associated with serum phosphorylated neurofilament heavy subunit (pNF-H) levels and this association significantly discriminated delirium from non-delirium with high accuracy in patients undergoing cancer surgery [15]. Taken together, these data indicate that the risk of CNS disruption triggered by surgery might be associated with changes in the adipokine profile of the elderly patients.

To address this, we investigated the relationship between the development of postoperative delirium undergoing cancer surgery and postoperative serum levels of these adipokines, as well as the detection of CNS-derived axonal marker, pNF-H after surgery.

Materials and Methods

Ethics

This study was conducted at The University of Tokyo Hospital, Saitama Red Cross Hospital, and Tsukuba University Hospital. This study was approved by the institutional review board [10051]. Written informed consent was obtained from each patient before participating in the study. This study was registered in the University Medical Information Network (UMIN trial ID: UMIN000010329).

Study population

Patients undergoing cancer surgery were enrolled and followed up between July 23, 2013 and February 28, 2015. The study population was identical to that of our previous study14. Therefore, in the present study, we used serum samples previously collected from the enrolled patients. The study exclusion criteria, patient demographics, and the positivity of pNF-H have previously been published [14].

Patient assessment

Patients were assessed for delirium-associated symptoms using CAM-ICU by nurses and the Intensive Care Delirium Screening Checklist by investigators14. The threshold of pNF-H (enzyme-linked immunosorbent assay; BioVendor, Modrice, Czech Republic) positivity (70.5 ng.ml-1) was determined according to the manufacturer's instructions. Levels of adiponectin, leptin, and resistin were measured using a multiplex immunoassay (MILLIPLEX® MAP Kit Human Adipokine Magnetic Bead Panel 1; Millipore Merck, Burlington, MA, USA), while CCL2 and CCL5 were measured using a multiplex immunoassay (Luminex® Assay Human Premixed Multi-Analyte Kit; R&D Systems, Minneapolis, MN, USA) according to the manufacturer protocol.

Statistical analysis

All analyses were performed based on the log-transformed concentration of the potential candidate variables. Patient biomarker levels were compared using the Wilcoxon signed rank test. To identify biomarkers for postoperative delirium diagnosis or to detect CNS-derived pNF-H in the serum, we performed multiple logistic regression as well as univariate analysis. We conducted multiple regression analysis with a stepwise method using adipokines and pro-inflammatory cytokines as independent variables, and delirium and serum pNF-H levels as the dependent variable.

Analyses were performed using JMP Pro version 15 (SAS Institute, Cary, NC, USA). $P \leq 0.05$ was considered significant.

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Results

Characteristics of patients are shown in Supplementary table 1. Serum levels of adiponectin were significantly lower in patients with delirium compared with those without delirium (P= 0.0031), whereas those of resistin were lower in patients with delirium compared with those without delirium on postoperative day 3 (P = 0.0018, Table 1). Serum levels of either leptin, CCL2, and CCL5 did not differ between the delirium and non-delirium groups. Serum levels of only adiponectin, but not resistin were independently associated with the development of delirium (adjusted odds ratio [aOR], 0.673; 95% confidence interval [CI], 0.514−0.882; P = 0.0030, Table 2). Consistently, only serum adiponectin levels were able to predict the presence of pNF-H (aOR, 0.666; 95% CI, 0.494−0.900; P= 0.0057, Table 3).

Table 1: Comparison of serum adipokine levels between delirium and non-delirium.

	delirium (n = 41)	non-delirium (n = 76)	*P* value
log (adiponectin)	8.615 (8.005−11.306)	11.306 (8.465−11.306)	0.0031
log (resistin)	10.960 (10.742−11.050)	10.393 (9.794−11.126)	0.0018
log (leptin)	7.822 (6.947−8.651)	8.060 (7.229−8.647)	0.4234
log (CCL2)	5.999 (5.593−6.496)	5.955 (5.714−6.370)	0.8842
log (CCL5)	10.166 (10.068−10.265)	10.112 (9.535−10.651)	0.5295

patients.
CCL, C-C motif chemokine ligand. Values are presented as the median (interquartile range).

Table 2: Logistic regression analysis for diagnosing delirium.

	crude OR	95% CI	*P* value	adjusted OR	95% CI	*P* value
log (adiponectin)	0.218	0.075−0.595	0.0027	0.673	0.514−0.882	0.003
log (resistin)	1.43	0.937−2.217	0.0972	1.431	0.920−2.225	0.1083
log (leptin)	0.848	0.593−1.213	0.3638	–	–	–
log (CCL2)	1.092	0.638−1.856	0.7437	–	–	–
log (CCL5)	1.099	0.729−1.653	0.6485	–	–	–

CCL, C-C motif chemokine ligand; OR, odds ratio; CI, confidence interval.

Table 3: Logistic regression analysis for the detection of phosphorylated neurofilament heavy chain in serum.

	crude OR	95% CI	*P* value	adjusted OR	95% CI	*P* value
log (adiponectin)	0.683	0.501−0.909	0.0084	0.666	0.494−0.900	0.0057
log (resistin)	1.326	0.838−2.104	0.2262	–	–	–
log (leptin)	1.276	0.860−1.894	0.2216	–	–	–
log (CCL2)	0.611	0.322−1.160	0.1176	0.568	0.296−1.091	0.0763
log (CCL5)	0.886	0.552−1.382	0.5984	–	–	–

CCL, C-C motif chemokine ligand; OR, odds ratio; CI, confidence interval.

Discussion

Serum levels of adiponectin were significantly lower in patients with delirium compared with those without delirium (Table 1). In addition, the serum adiponectin level was independently associated with both delirium (Table 2) and pNF-H (Table 3). In contrast, other adipokines such as resistin, leptin, CCL2, and CCL5 were not associated with either delirium or pNF-H detection, although serum resistin levels were significantly but slightly higher in patients with delirium compared with those without delirium (Table 1). The results of the present study are consistent with those of our recent report that postoperative serum levels of apolipoproteins were associated with delirium [15]. Adiponectin has been detected in human cerebrospinal fluid [16], suggesting that adiponectin can cross the blood–brain barrier to act on specific neuronal populations. Additionally, adiponectin at a physiological concentration of 10 μg/ml protected the human neuroblastoma cell line, SH-SY5Y, in which the Swedish amyloid precursor protein (Sw-APP) mutant was transfected, leading to an overexpression of Aβ with abnormal intracellular Aβ accumulation, against cytotoxicity under oxidative stress induced by hydrogen peroxide [17]. This suggests that adiponectin has direct protective effects on degenerating neurons. Because only serum adiponectin levels were negatively associated with the detection of pNF-H in the serum (Table 3), adiponectin might have direct protective effects on axonal stability in the inflammatory state during postoperative periods.

The serum level of adiponectin in diabetic patients with mild cognitive impairment was found to be significantly lower than that in diabetic patients without mild cognitive impairment [18]. Furthermore, lower levels of adiponectin were correlated with decreased gray matter volume and reduced cerebral glucose metabolism in temporal regions, even after adjusting for age and the presence of at least one epsilon 4 allele for the apolipoprotein E [19]. These previous reports suggest that the perioperative status of adiponectin and apolipoproteins may influence on the neuronal activity and associated brain atrophy, which has been implicated in delirium, and which may result in the progression of long-term cognitive impairment [20].

Serum adiponectin levels were higher in ICU patients with delirium compared with those without delirium [10]. However, serum adiponectin levels were lower in patients with delirium compared with those without delirium in acute phase of postoperative periods (Table 1). Although the reason for this discrepancy is unclear, it has been reported that adiponectin increased and resistin decreased significantly over time during the course of sepsis [21]. The mechanism of developing delirium might differ depending on septic phase and its severity.

As a limitation of this study, we did not screen for metabolic disorder such as type 2 diabetes mellitus or hyperlipidemia. In addition, we did not investigate preoperative levels of adipokines. Plasma adiponectin levels are inversely associated with the body mass index (BMI) [21], implying that there is a relationship between obesity and delirium. However, as we previously reported, BMI did not differ between patients with delirium versus without delirium14. In this present study, no serum levels of any adipokines on day 3 after surgery were not correlated with BMI (data not shown). However, the possibility that energy expenditure and nutrient status during perioperative periods might be related to the production of adiponectin and the development of postoperative delirium cannot be excluded. Further studies are required to clarify the perioperative transition of adipokine levels.

Conclusion

Serum adiponectin levels during the postoperative period were decreased in delirium patients and were associated with both pNF-H positivity and the development of delirium. Thus, adiponectin may be a useful therapeutic target for the prevention of postoperative cognitive disorder in older patients undergoing cancer surgery.

Data Availability

Anonymized data from this study are available for academic purposes upon reasonable request. All data generated or analyzed during this study are included in this article [and/or] its supplementary material files. Further enquiries can be directed to the corresponding author.

Competing interests

Masahiko Sumitani receives research grant from Japan Agency for Medical Research and Development, Eisai Inc.(Tokyo, Japan), Pfizer Inc.(Tokyo, Japan), Nipro Corporation (Osaka, Japan), and Fureasu Corporation(Tokyo, Japan). Masahiko Sumitani is a board membership of AEON HAPYCOM(Tokyo, Japan)and received speaker honoraria with travel reinbursement from Dai-ichi Sankyo Co. Ltd. (Tokyo, Japan), and GlaxoSmithKline (Tokyo, Japan). Reo Inoue, and Nobutake Shimojo receives a research funding from Japan Society for the Promotion of Science for topics unrelated to the present study. Ogata Toru receives a research funding from Japan Society for the Promotion of Science, Nipro Corporation, and Ministry of Health, Labour and Welfare for topics unrelated to the present study. All do not affect the content of this article.

They do not alter our adherence to the journal policies on sharing data and materials.

Authorship contribution statement

MS contributed to the study concept and design and reviewed the final version of the manuscript. KM, RI and KM

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performed the statistical analyses, interpreted the data, and wrote the initial draft of the manuscript. RI, YY, YS and NS assisted KM with the data acquisition. TO contributed to the study concept and design. MS reviewed the final version of the manuscript. All contributors approved the final version.

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Trial Registration

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Supplementary table 1: Characteristics of patients grouped according to development of postoperative delirium

	delirium (n = 41)	Non-delirium (n = 76)	*P* value
Age ; y	78 (73−81)	67 (58−74)	< 0.0001
Gender ; male	24 (58.5%)	40 (52.6%)	0.54
BMI ; kg/m^2	22.8 (20.2−24.1)	21.8 (19.8−24.1)	0.32
pNF-H positive	23 (56.1%)	7 (9.2%)	< 0.0001

Values are presented as numbers (proportion) or medians (interquartile range). BMI, body mass index; pNF-H, phosphorylated neurofilament heavy subunit. All the data in Table S1 were reported in Ref. 14.