Association of Up-Regulated Plasma Adiponectin With Risk of Incident Depression in a Community-Dwelling Elderly Population

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ABSTRACT

Objective: Despite robust interest in the association between inflammation and depression, anti-inflammatory markers have been scarcely investigated as predictors of the future risk of depression. The aim of this study is to determine whether up-regulation of plasma adiponectin, an anti-inflammatory adipokine, precedes and predicts the development of depression in the elderly.

Methods: This prospective cohort study was launched in 2005. Among 1,000 participants who were randomly sampled from community-dwelling individuals 65 years or older, 633 euthymic individuals without prior history of depressive disorders were enrolled for a baseline evaluation and follow-up after 5 years. Incident clinically significant depression, including major and minor depressive disorders (by *DSM-IV* criteria), subsyndromal depression (by operational criteria), and euthymia after antidepressant treatment, was assessed by clinical interviews.

Results: Baseline plasma adiponectin values were divided into tertiles (low tertile: ≤ 5.685 μg/mL, middle tertile: 5.686–10.367 μg/mL, high tertile: ≥ 10.368 μg/mL). Among the 261 euthymic individuals who responded to the 5-year follow-up evaluation, 17 developed incident depression (7 from the high tertile, 8 from the middle tertile, and 2 from the low tertile). The risk of incident depression was much higher in the high tertile group than in the low tertile group after adjusting for age, sex, body mass index, burden of chronic medical illnesses, and Mini-Mental State Examination score (odds ratio = 10.64; 95% CI, 1.21–93.84; $P = .033$).

Conclusions: Up-regulation of plasma adiponectin may precede the onset of clinically significant depression in the elderly, and thus plasma adiponectin level is a potential candidate marker for the risk of depression.

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As proposed in the "cytokine hypothesis" of depression,[1] inflammation may play an important part in the biological underpinnings of depression. This hypothesis is founded in robust epidemiologic data revealing increased production of proinflammatory molecules such as interleukin (IL)-1, IL-6, C-reactive protein (CRP), and tumor necrosis factor (TNF)-α in depressed individuals.[2,3] In addition, many prospective studies[4] have reported that high levels of inflammatory markers, CRP and IL-6 in particular, may predict the subsequent development of depression within the next few years. By contrast, research on possible associations of anti-inflammatory cytokine levels with depression is limited, even though the production of proinflammatory and anti-inflammatory cytokines is coregulated through strictly controlled complex feedback mechanisms.[5]

Adiponectin is the most abundant of the human adipose tissue–derived anti-inflammatory adipokines.[6] Adiponectin inhibits the production and action of TNF-α, which in turn leads to the attenuation of endothelial cell activation.[6] Adiponectin also increases the production of anti-inflammatory cytokines[7] and inhibits the activation of macrophages.[8] In our previous work,[9] we found that plasma adiponectin levels of patients with subsyndromal depression (SSD) were higher than those of euthymic controls, while those of patients with major depressive disorder (MDD) patients were comparable. In other previous studies, plasma adiponectin levels in patients with MDD were comparable to[10–14] or even lower than[15–18] those of euthymic controls. Together, these studies suggest that plasma adiponectin may be up-regulated in the subsyndromal stage of depression, possibly to compensate for increased activity of proinflammatory processes, and is then normalized or down-regulated as depression worsens. However, no previous studies except for the aforementioned have assessed plasma adiponectin levels in patients with SSD.

The aim of the research described here was to determine whether up-regulation of adiponectin precedes and predicts the development of depression through a longitudinal study. To accomplish this, we investigated the association of baseline plasma

Clinical Points

- The longitudinal association of adiponectin with depression is not well known.
- Up-regulated plasma adiponectin may predict the risk of incident depression in late life and is a potential candidate biomarker for depression.

adiponectin level with the risk of incident depression in a 5-year prospective cohort study of randomly sampled, community-dwelling, euthymic elderly individuals without previous history of depression.

METHODS

Study Design and Participants

This study was conducted as part of the Korean Longitudinal Study on Health and Aging (KLoSHA).[19] In the KLoSHA, 1,000 community-dwelling elderly Koreans 65 years or older were randomly sampled from the resident roster of Seongnam, the largest satellite city in the metropolitan area of Seoul, Korea. One thousand participants completed the baseline assessment, which was conducted from September 2005 through September 2006. Ultimately, 633 euthymic participants were included in the current study. Participants were excluded based on the following criteria: 301 were diagnosed in our baseline assessment with at least 1 psychiatric disorder according to the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (*DSM-IV*) criteria, 51 had prior history of depressive disorders, 4 were taking antidepressants, and 11 declined laboratory tests. Among the 633 euthymic participants, 261 (41.2%) completed the 5-year follow-up assessment, 258 (40.8%) refused the follow-up assessment, and 114 (18.0%) died during the 5-year interval. All 261 euthymic participants who responded to follow-up assessment were included in the longitudinal analysis of incident depression.

This study protocol was approved by the Institutional Review Board of Seoul National University Bundang Hospital. In all cases, a written statement of informed consent was obtained from either the participants or their legal guardians.

Assessments and Diagnosis

In both baseline and 5-year follow-up evaluations, we administered standardized clinical interviews, neurologic and physical examinations, and laboratory tests. Psychiatric disorders were diagnosed using the Korean version of the Mini International Neuropsychiatric Interview,[20] which assesses Axis I psychiatric disorders. Cognitive disorders were diagnosed using the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Clinical and Neuropsychological Assessment Battery.[21] We also administered the Geriatric Depression Scale (GDS)[22] and 17-item Hamilton Depression Rating Scale (HDRS)[23] to evaluate the severity of depressive symptoms, the Mini-Mental State Examination (MMSE) to evaluate global cognition,[24] and the Cumulative Illness Rating Scale (CIRS)[25] to evaluate the burden of chronic medical illnesses.

We diagnosed MDD according to the *DSM-IV* criteria and minor depressive disorder according to the research criteria proposed in the *DSM-IV*. We diagnosed SSD according to the operational criteria proposed in our previous report.[9] In the analysis of the risk of incident depression after 5 years, we defined incident depression as MDD, minor depressive disorder, SSD, or euthymic after taking antidepressants.

Plasma Adiponectin Level

After overnight fasting, a venous blood sample was drawn from all participants at the baseline survey. Plasma adiponectin level was measured by an enzyme-linked immunosorbent assay kit developed by AdipoGen (AdipoGen; Seoul, Korea).[26] The intraassay and interassay coefficients of variation were 3.3 and 7.4%, respectively.

Statistical Analysis

Participants were grouped into tertiles according to the level of plasma adiponectin. As the levels of plasma adiponectin were positively skewed, the values were logarithmically transformed for all analyses. Baseline demographic and clinical characteristics were compared by Pearson χ^2 test for categorical variables and by 1-way analysis of variance with Tukey post hoc comparison for continuous variables. To determine if there was an association of plasma adiponectin level with the risk of incident depression at the 5-year follow-up evaluation, we performed univariate and multivariate logistic regression analyses. In the multivariate logistic analyses, age, sex, body mass index (BMI), CIRS score, and MMSE score were computed as covariates that have potential effects on plasma adiponectin concentration. We also performed the same multivariate analysis using the plasma adiponectin concentration as a continuous variable. Average marginal effects (AMEs) of plasma adiponectin level on the probability of depression were calculated along with odds ratios (ORs). All statistical analyses were performed using STATA version 12.1 (StataCorp LP; College Station, Texas).

RESULTS

Baseline Characteristics of Participants According to Level of Plasma Adiponectin

The characteristics of the 633 participants who participated in the baseline evaluation are summarized in Table 1. Cutoff points for classifying the tertiles of plasma adiponectin level were 5.685 μg/mL and 10.368 μg/mL. Mean plasma adiponectin levels were 3.538 ± 1.307 μg/mL for the low tertile, 7.951 ± 1.333 μg/mL for the middle tertile, and 16.337 ± 5.283 μg/mL for the high tertile. The mean age was older, the male:female ratio was lower, and BMI and MMSE scores were lower in the high tertile plasma adiponectin group than in the middle or lower tertile plasma adiponectin groups. However, the CIRS scores were comparable across groups. The subjects in the high tertile group showed higher

Table 1. Baseline Characteristics of the Subjects Stratified by Level of Plasma Adiponectin*

Characteristic	Low Tertile (n = 211)	Middle Tertile (n = 211)	High Tertile (n = 211)	Statistics†	
				P	Post Hoc
Age, mean (SD), y	74.51 (7.94)	74.10 (7.52)	79.01 (8.56)	< .001	low, middle < high
Sex, n (%) male	115 (54.5)	99 (46.9)	90 (42.7)	.048	…
BMI, mean (SD), kg/m^2	24.70 (2.85)	24.53 (3.12)	22.77 (3.32)	< .001	low, middle > high
Education, mean (SD), y	8.39 (5.72)	8.15 (5.84)	7.27 (5.94)	.117	…
GDS score, mean (SD)	9.21 (6.41)	9.80 (6.45)	10.35 (6.51)	.203	…
HDRS score, mean (SD)	2.34 (2.24)	2.64 (2.40)	3.11 (2.71)	.006	low < high
MMSE score, mean (SD)	24.26 (3.95)	24.05 (4.56)	22.73 (4.91)	.001	low, middle > high
CIRS score, mean (SD)	3.85 (2.43)	3.66 (2.34)	3.76 (2.39)	.728	…
Adiponectin, mean (SD), μg/mL	3.54 (1.31)	7.95 (1.33)	16.34 (5.28)	< .001	low < middle < high

*Low tertile, ≤ 5.685 μg/mL; middle tertile, 5.686–10.367 μg/mL; high tertile, ≥ 10.368 μg/mL.
†Pearson χ^2 test for categorical variables; analysis of variance for continuous variables.
Abbreviations: BMI = body mass index, CIRS = Cumulative Illness Rating Scale, GDS = Geriatric Depression Scale, HDRS = 17-item Hamilton Depression Rating Scale, MMSE = Mini-Mental State Examination.

HDRS scores than did the other groups (3.11 ± 2.71 [high tertile] vs 2.64 ± 2.40 [middle tertile] and 2.34 ± 2.24 [low tertile], *P* = .006), while the GDS scores were not significantly different across groups (Table 1).

Association of Plasma Adiponectin Level With Incident Depression at 5-Year Follow-Up Evaluation

Among the 633 euthymic participants in the baseline evaluation, 261 completed the 5-year follow-up evaluation, 258 dropped out, and 114 died (Table 2). Compared to the dropouts, the responders were younger (73.10 ± 6.98 vs 75.36 ± 8.04 years, *P* = .002), included more men (52.9% vs 37.6%, *P* < .001), and performed better on the MMSE (24.93 ± 3.45 vs 23.63 ± 4.41, *P* < .001). However, the BMI, GDS, HDRS, and mean plasma adiponectin levels were comparable to those of the dropouts. Compared to the deceased group, the responders were younger (73.10 ± 6.98 vs 83.38 ± 7.18 years, *P* < .001), had higher BMI (24.29 ± 3.03 vs 23.03 ± 3.14 kg/m^2, *P* = .006) and lower CIRS scores (3.62 ± 2.44 vs 4.27 ± 2.38, *P* = .047), and performed better on the MMSE (24.93 ± 3.45 vs 20.94 ± 5.67, *P* < .001). The plasma adiponectin level (8.22 ± 5.60 vs 12.38 ± 7.48 μg/mL, *P* < .001) and GDS score (9.07 ± 6.22 vs 11.76 ± 6.31, *P* = .001) of the responders were also lower than those of the deceased.

Among the 261 responders who were euthymic at baseline, 17 had depression (9 SSD and 8 euthymic after taking antidepressants) at the 5-year follow-up evaluation. Among them, 7 were from the high tertile group (n = 64), 8 were from the middle tertile group (n = 101), and 2 were from the low tertile group (n = 96) at the baseline evaluation. In univariate logistic regression analysis, the risk of incident depression was about 6 times higher in the high tertile than in the low tertile (OR = 5.77; 95% CI, 1.16–28.75; *P* = .032 and AME = 0.089; 95% CI, 0.007–0.170; *P* = .034). In multivariate logistic regression analysis adjusting for age, sex, BMI, CIRS score, and MMSE score, we found an approximately 11 times higher risk of incident depression in the high tertile group (OR = 10.64; 95% CI, 1.21–93.84; *P* = .033 and AME = 0.105; 95% CI, 0.017–0.193; *P* = .019) compared to the low tertile group (Table 3). When we performed the same logistic regression analysis using the plasma adiponectin concentration as a continuous variable, there was also significantly increased risk of incident depression with an increasing log-transformed adiponectin level (OR = 2.82; 95% CI, 1.08–7.41; *P* = .035 and AME = 0.062; 95% CI, 0.001–0.122; *P* = .046).

DISCUSSION

We found that plasma adiponectin level was associated with the risk of incident depression in community-dwelling euthymic elderly individuals; the high tertile group had an approximately 11 times higher risk of incident depression than the low tertile group. To the best of our knowledge, the present study is the first to indicate that up-regulation of circulating adiponectin can predict the risk of incident depression in euthymic individuals.

In keeping with the current study, up-regulation of anti-inflammatory markers was reported to precede incident depression in euthymic elderly individuals in a couple of previous prospective studies. In a prospective study by van den Biggelaar et al[27] of a community-dwelling euthymic elderly cohort, up-regulation of interleukin-1 receptor antagonist (IL-1ra), an anti-inflammatory cytokine that competitively antagonizes the function of IL-1β, preceded incident depression. Moreover, the risk of incident clinically significant depression increased 10% annually in accordance with the 1 standard deviation increase of IL-1ra. In the InCHIANTI study,[28] which is likewise a prospective study of an euthymic elderly population, euthymic elderly individuals in the third and fourth IL-1ra quartiles, respectively, demonstrated a 2.32-fold and 2.78-fold higher risk of developing depressed mood compared with those in the lowest quartile over a 6-year follow-up. In our study, the high tertile group for plasma adiponectin level showed a 10.64-fold risk of incident depression compared with the low tertile group. In addition, the risk of incident depression, although not statistically significant (*P* = .059), was 7.73 times higher than in the middle tertile group. These results suggest that the association of plasma adiponectin level and future risk of depression could be plasma concentration–dependent in the elderly.

Table 2. Baseline Characteristics of the Subjects Stratified by Response to the 5-Year Follow-Up Evaluation

Characteristic	All (n = 261)	Followed (A) Plasma Adiponectin Level* Low Tertile (a) (n = 96)	Middle Tertile (b) (n = 101)	High Tertile (c) (n = 64)	Statistics† P	Statistics† Post Hoc	Dropped Out (B) (n = 258)	Died (C) (n = 114)	Statistics‡ P	Statistics‡ Post Hoc
Age, mean (SD), y	73.10 (6.98)	72.81 (6.79)	72.04 (6.15)	75.20 (8.09)	.015	b < c	75.36 (8.04)	83.38 (7.18)	< .001	A < B < C
Sex, male, n (%)	138 (52.9)	60 (62.5)	50 (49.5)	28 (43.8)	.046	…	97 (37.6)	69 (60.5)	< .001	…
BMI, mean (SD), kg/m^2	24.29 (3.03)	24.81 (2.97)	24.54 (2.88)	23.15 (3.12)	.002	a, b > c	24.09 (3.38)	23.03 (3.14)	.006	A, B > C
Education, mean (SD), y	8.40 (5.64)	8.90 (5.11)	8.37 (5.87)	7.72 (6.04)	.434	…	7.84 (6.03)	7.08 (5.81)	.124	…
GDS score, mean (SD)	9.07 (6.22)	8.81 (5.99)	9.29 (6.24)	9.11 (6.61)	.866	…	9.66 (6.62)	11.76 (6.31)	.001	A, B < C
HDRS score, mean (SD)	2.52 (2.38)	2.35 (2.42)	2.52 (2.33)	2.78 (2.39)	.530	…	2.81 (2.48)	2.85 (2.66)	.330	…
MMSE score, mean (SD)	24.93 (3.45)	25.23 (2.90)	24.86 (3.98)	24.58 (3.30)	.490	…	23.63 (4.41)	20.94 (5.67)	< .001	A > B > C
CIRS score, mean (SD)	3.62 (2.44)	3.77 (2.56)	3.66 (2.30)	3.35 (2.48)	.566	…	3.67 (2.30)	4.27 (2.38)	.047	A < C
Adiponectin, mean (SD), μg/mL	8.22 (5.60)	3.41 (1.25)	7.85 (1.38)	16.04 (5.13)	< .001	a < b < c	8.97 (5.77)	12.38 (7.48)	< .001	A, B < C

*Low tertile, ≤ 5.685 μg/mL; middle tertile, 5.686–10.367 μg/mL; high tertile, ≥ 10.368 μg/mL.
†Comparison between the 3 tertile groups who responded to the 5-year follow-up evaluation.
‡Comparison between the euthymic participants of the baseline evaluation who responded to the 5-year follow-up evaluation, who dropped out, and who died during the follow-up period; Pearson χ^2 test for categorical variables; analysis of variance for continuous variables.
Abbreviations: BMI = body mass index, CIRS = Cumulative Illness Rating Scale, GDS = Geriatric Depression Scale, HDRS = 17-item Hamilton Depression Rating Scale, MMSE = Mini-Mental State Examination.

Table 3. Risks of Incident Depression at the 5-Year Follow-Up Evaluation According to Baseline Plasma Adiponectin Level*

Incident Depression	Low Tertile	Middle Tertile OR (95% CI)	Middle Tertile AME (95% CI)	High Tertile OR (95% CI)	High Tertile AME (95% CI)
No. of cases	2/96	8/101		7/64	
Unadjusted†	Reference	4.04 (0.84–19.55)	0.059 (−0.002–0.118)	5.77 (1.16–28.75)	0.089 (0.007–0.170)
Adjusted‡	Reference	7.73 (0.93–64.53)	0.070 (0.011–0.129)	10.64 (1.21–93.84)	0.105 (0.017–0.193)

*Low tertile, ≤ 5.685 μg/mL; middle tertile, 5.686–10.367 μg/mL; high tertile, ≥ 10.368 μg/mL.
†Univariate logistic regression analysis.
‡Multivariate logistic regression analysis adjusting for age, gender, body mass index, Cumulative Illness Rating Scale score, and Mini-Mental State Examination score.
Abbreviations: AME = average marginal effect, CI = confidence interval, OR = odds ratio.

Our results from baseline evaluation revealed that the high tertile plasma adiponectin group had older age, a higher proportion of women, and lower BMI and MMSE scores than the other groups of euthymic elderly individuals. These findings are consistent with previous observational studies of plasma adiponectin. As plasma adiponectin concentration correlates inversely with body composition of adipose tissue, it normally increases in older and thin adults, as well as with female gender.[29,30] Especially in the elderly population, plasma adiponectin may increase steadily as the chronic low-grade inflammatory state is maintained according to the aging process.[31] A low level of adiponectin, which has anti-inflammatory properties, is known to be associated with the risk of chronic illnesses with underlying inflammation such as metabolic syndrome, diabetes mellitus, and coronary heart disease.[32] There is also emerging evidence that a high level of adiponectin contributes to the risk of cognitive impairment,[16,33,34] in line with our results regarding the association between adiponectin and depression. To control such factors that may influence plasma adiponectin level, we performed multiple logistic regression analyses adjusting for age, sex, BMI, burden of chronic illnesses, and MMSE score. We found that the high tertile of plasma adiponectin increased the risk of incident depression independent of the potential confounders.

Considering the anti-inflammatory nature of adiponectin, plasma adiponectin might be up-regulated in the preclinical or subsyndromal stage of depression as a negative feedback against underlying inflammatory processes. Inhibitory actions on the proinflammatory cytokines may contribute to the protective role of adiponectin against development of depression, at least in part, because adiponectin has been shown to attenuate the production and action of TNF in a dose-dependent manner.[6] Moreover, adiponectin induces the production of anti-inflammatory IL-1ra.[35] Previous research demonstrated that increased production of peripheral inflammatory cytokines can lead to depression by dysregulation of monoamine, glutamate metabolism, and neural plasticity. Induction of p38 mitogen-activated protein kinase (MAPK) by IL-1β and TNF was found to increase the expression and function of the presynaptic serotonin reuptake transporters.[36] IL-1β and TNF were shown to reduce the availability of tetrahydrobiopterin, a key enzyme cofactor in monoamine synthesis,[37] and activated indoleamine 2,3-dioxygenase, leading to decreased levels of tryptophan, a primary precursor of serotonin.[38] Moreover, these cytokines were reported to increase excitotoxicity

in the anterior cingulate cortex by stimulating glutamate release, blocking glutamate reuptake of astrocytes,[39] and reducing levels of brain-derived neurotrophic factor, an important molecule for promoting neural plasticity.[40]

Alternatively, elevated plasma adiponectin in preclinical or subsyndromal stages of depression may be a proxy for down-regulation of adiponectin receptor or dysfunctional adiponectin signaling cascades.[41] Adiponectin receptors such as AdipoR1 and AdipoR2 regulate glucose and lipid metabolism, insulin sensitivity, inflammation, and oxidative stress by activating adenosine monophosphate activated protein kinase, peroxisome proliferator-activated receptor α.[42] However, these adiponectin receptors are also expressed in various brain regions associated with mood regulation, such as medial prefrontal cortex, hippocampus, and amygdala.[43] Although the action of adiponectin in the central nervous system remains poorly understood, activation of AdipoR1 and AdipoR2 by adiponectin may inhibit glycogen synthase kinase 3β (GSK-3β) via mediation of the MAPK signaling pathway.[44] This may in turn lead to inhibition of GSK-3β, which has a known antidepressant effect.[45] In addition, activation of AdipoR/MAPK/GSK-3β cascade has been found to promote hippocampal neurogenesis, which is known to counteract depression-like behaviors in vivo.[44,46] Therefore, we speculate that down-regulation of adiponectin receptors might have the reverse effect of inhibiting antidepressant signaling pathways in mood-regulating brain areas (eg, hippocampus), resulting in increased susceptibility to depression.

Several limitations of this study should be noted. First, the response rate to the follow-up evaluation was low. There were no differences in GDS score and plasma adiponectin level between responders and nonresponders. However, those who died during the follow-up interval had higher GDS scores and plasma adiponectin levels than the responders to the follow-up evaluation, which may have led to an underestimation of the robustness of our findings. Second, we assumed the people who took antidepressants during the follow-up period to be patients with incident depression. However, antidepressants can be prescribed for mental or medical conditions other than depression. Third, we did not measure plasma adiponectin level at the 5-year follow-up evaluation. To clarify whether changes in adiponectin levels correspond to the severity and/or incidence of depression, the longitudinal trajectory of plasma adiponectin level in the context of depression should be investigated.

Despite these limitations, the current study highlights a potential role for adiponectin in depression pathobiology and raises the possibility of using plasma adiponectin as a candidate biomarker of incident depression in euthymic elderly people.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Geriatric Psychiatry section. Please contact Jordan F. Karp, MD, at jkarp@psychiatrist.com, or Gary W. Small, MD, at gsmall@psychiatrist.com.