GAVIN PUBLISHERS

Journal of Diabetes and Treatment

Aoki Y. J Diabetes Treat (2016): 110.

Short Communication

High Serum Levels of Amyloid Beta Peptides Decreased and Their Low Levels Increased after 6-Month Treatment with Pioglitazone in Japanese Elderly Patients with Type 2 Diabetes

Yuji Aoki*

Department of Internal Medicine, National Hospital Organization Matsumoto Medical Center Matsumoto Hospital, Matsumoto 399-8701, Japan

***Corresponding author:** Yuji Aoki, Department of Internal Medicine, National Hospital Organization Matsumoto Medical Center Matsumoto Hospital, Matsumoto 399-8701, Japan, Tel: +81 0263 58 4567; Fax: +81 0263 86 3183; E-mail: yaoki55@nifty.com

Citation: Aoki Y (2016) High Serum Levels of Amyloid Beta Peptides Decreased and Their Low Levels Increased after 6-Month Treatment with Pioglitazone in Japanese Elderly Patients with Type 2 Diabetes. J Diabetes Treat (2016): 110.

Received date: December 13, 2016; **Accepted date:** December 16, 2016; **Published date:** December 20, 2016

Abstract

Since the previous study showed that serum levels of amyloid beta peptides (β1-40 and β1-42) tended to increase after the pioglitazone treatment in female diabetic patients, their changes were reassessed by increasing the number of study patients in this report. Forty-three patients (21 males, 22 females) with type 2 diabetes aged ≥ 70 years were studied before and after the 6-month treatment with low-dose pioglitazone (15 mg for males and 7.5 mg for females). At the baseline, serum amyloid β peptides positively correlated with serum high-molecular-weight adiponectin, but the correlations disappeared after the treatment that raised all the adiponectin levels. When classified by serum amyloid β1-40 level of 50 pmol/L or β1-42 level of 3 pmol/L at the baseline, in patients with the higher levels, serum amyloid β1-40 or β1-42 levels significantly ($p<0.01$) decreased after the treatment from 61.1±7.6 to 54.2±6.7pmol/L or from 4.3±1.1 to 3.2±1.4 pmol/L. On the contrary, in patients with the lower levels, the levels significantly ($p<0.005$) increased from 37.3±7.6 to 45.1± 11.9 pmol/L or from 2.2±0.4 to 2.8± 0.9 pmol/L. Such changes were predominant in female patients. In conclusion, there was a positive correlation between serum levels of amyloid beta peptides and adiponectin only at the baseline. High serum levels of amyloid beta peptides decreased and their low levels increased after the 6-month treatment with pioglitazone in Japanese elderly patients with type 2 diabetes. The relevance of such changes would be worthy of further investigation.

Keywords: Amyloid beta peptides; Pioglitazone; High-molecular-weight adiponectin; Type 2 diabetes

Introduction

Amyloid beta peptides in the blood originate not only from the brain but also from almost all peripheral cells, including platelets, vascular wall cells, muscle cells, liver cells and so forth. Despite the low correlation between plasma and brain amyloid beta peptides, the measurement of amyloid beta peptides in plasma or serum (less stable) could be the least invasive and most cost-effective biomarker assay for Alzheimer's disease and also vascular dementia [1,2].

Pioglitazone, a peroxisome proliferator-activated receptor γ agonist, has been suggested to have potential for the treatment of Alzheimer's disease [3-5], and a large phase 3 clinical trial is currently being undertaken to evaluate its safety and efficacy [6]. In the previous report [7], the effects of low-dose pioglitazone on several age-related biomarkers including amyloid beta peptides 1-40 and 1-42 (amyloid β1-40 and β1-42) were assessed in Japanese elderly patients with type 2 diabetes. Since serum amyloid β1-40 level tended to be increased by the add-on treatment with pioglitazone in female patients, changes in serum amyloid beta peptides after the pioglitazone treatment were reassessed by increasing the number of study patients in this report. It was unexpectedly found that high serum levels of amyloid beta peptides decreased and their low levels increased after 6-month treatment with pioglitazone.

Materials and Methods

Study Patients. Forty-three patients (21 males, 22 females) with type 2 diabetes aged ≥ 70 years, who gave their informed consent to the study in accordance with the Declaration of Helsinki, were examined at Matsumoto Medical Center Matsumoto Hospital. The effects of the 6-month treatment with low-dose pio-

glitazone (15 mg for males, 7.5 mg for females) on serum amyloid β levels were assessed. Twenty-four patients (12 males, 12 females) in the previous report [6] were included, and the same data from them were used. Clinical characteristics of all the patients at the baseline are shown in Table 1. Serum creatinine levels were 0.9±0.1 mg/dL in male patients and 0.7±0.2 mg/dL in female patients. Four insulin-treated patients, 5 patients who were started on pioglitazone treatment during hospitalization, and 10 patients whose antidiabetic (other than sulfonylurea) or antihypertensive agents were changed during the 6-month treatment with pioglitazone were newly included. One of the 19 patients newly included had been diagnosed with Alzheimer's disease.

n	Male	Female
	21	22
Age (year)	75.6±4.1	76.7±5.9
Body height (cm)	161.0±7.3	148.4±6.3
Body mass index (kg/m^2)	23.1±2.3	22.7±4.0
Duration of diabetes (year)	11.7±8.8	13.8±11.1
Diabetic therapy (diet/OHA/Insulin)	1/19/1	0 / 19 / 3
OHA, oral hypoglycemic agents		

Table 1: Baseline clinical characteristics of 43 elderly patients with type 2 diabetes.

Blood Collection and Measurements. Before and after the 6-month treatment with pioglitazone, casual blood samples were collected and stored in serum at -20ºC until used. Amyloid β1-40 and β1-42 were measured with Human βAmyloid (1-40) and (1-42) ELISA kits (Wako Pure Chemical Industries, Ltd., Osaka, Japan), and high-molecular-weight (HMW) adiponectin was measured by chemiluminescent enzyme immunoassay (CLEIA). The measurements were performed by a referee laboratory (SRL, Inc., Tokyo, Japan). HbA1c levels were measured at the outpatient clinic by an automated analyzer ADAMS HA-8160 (ARKRAY, Tokyo, Japan).

Statistical analysis. Results are expressed as mean±SD. Differences between data were analyzed by two-sided paired or unpaired t-test and Pearson's correlation coefficient when appropriate, with a significance level at $p<0.05$.

Results

At the baseline, as shown in Figure 1, there were significant correlations ($p<0.02$) between serum HMW adiponectin level and serum amyloid β1-40 level in male and female patients, and between serum HMW adiponectin level and serum amyloid β1-42 level in male patients. After the 6-month treatment with pioglitazone, serum HMW adiponectin levels increased from 4.7±3.1 to 13.5±15.6 μg/mL in male Patients and from 7.0±3.5 to 13.9±6.0 μg/mL in female patients, where the HMW adiponectin levels increased in all the patients. At the 6-month treatment with pioglitazone, no significant correlation was found between HMW adiponectin and amyloid β1-40 (r=0.287, p=0.208) or amyloid β1-42 (r=0.181, p=0.432) in male patients, or between HMW adiponectin and amyloid β1-40 (r=0.174, p=0.439) or amyloid β1-42 (r=0.200, p=0.371) in female patients.

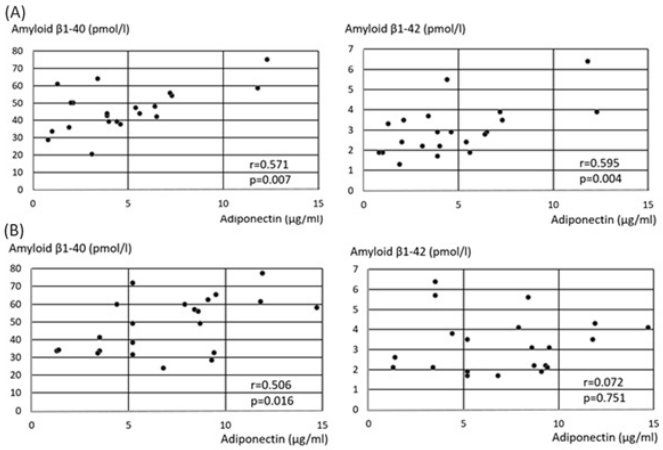

Figure 1: Correlations between serum high-molecular-weight adiponectin levels and serum amyloid β1-40 or β1-42 levels in (A) male and (B) female elderly patients with type 2 diabetes at the baseline are shown. Except between the adiponectin and amyloid β1-42 levels in females, there were significant correlations between them.

Figure 2 shows individual changes in serum amyloid β1-40 or β1-42 levels before and after the pioglitazone treatment in each of male and female patients. There was no significant difference in the mean values of amyloid β1-40 levels (46.4±12.6 vs. 47.1±11.5 pmol/L, p=0.711) or β1-42 levels (3.0±1.2 vs. 2.9±0.9 pmol/L, p=0.687) in male patients, or in those of amyloid β1-40 levels (48.1±15.6 vs. 50.6±10.4 pmol/L, p=0.411) or β1-42 levels (3.2±1.4 vs. 3.0±1.4 pmol/L, p=0.677) in female patients. Interestingly, however, it appeared that higher levels of serum amyloid β1-40 and β1-42 decreased and their lower levels increased after the pioglitazone treatment, as shown in each of panels. In one patient with Alzheimer's disease, serum amyloid β1-40 and β1-42 levels decreased from 55.9 to 43.4 pmol/L and from 3.1 to 1.3pmol/L.

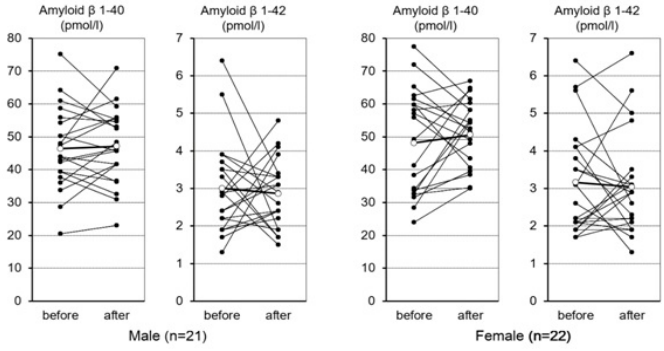

Figure 2: Individual changes in serum amyloid β1-40 or β1-42 levels before and after the pioglitazone treatment in each of male and female elderly patients with type 2 diabetes are shown. There was no significant difference in the mean values (open circles) of amyloid β1-40 levels (46.4±12.6 vs. 47.1±11.5 pmol/L, p=0.711) or β1-42 levels (3.0±1.2 vs. 2.9±0.9 pmol/L, p=0.687) in male patients, or in those of amyloid β1-40 levels (48.1±15.6 vs. 50.6±10.4 pmol/L, p=0.411) or β1-42 levels (3.2±1.4 vs. 3.0±1.4 pmol/L, p=0.677) in female patients. However, it appears that higher levels of serum amyloid β1-40 and β1-42 decrease and their lower levels increase after the pioglitazone treatment in each of panels.

Then, as shown in Tables 2 and 3, data were reassessed when patients were classified by the serum amyloid β1-40 level of 50 pmol/L or β1-42 level of 3 pmol/L at the baseline. Patients with serum amyloid β1-40 levels > 50 pmol/L or β1-42 levels > 3 pmol/L showed a significant decrease in the mean value of amyloid β1-40 or β1-42 levels after the pioglitazone treatment in total patients, being predominant in female patients (Table 2). On the contrary, patients with serum amyloid β1-40 levels < 50 pmol/L or β1-42 levels < 3 pmol/L showed a significant increase in the mean value of amyloid β1-40 or, to a lesser extent, β1-42 levels after the pioglitazone treatment in total patients, being predominant in female patients (Table 3). There was no significant difference in the mean HbA1c values between before and after the pioglitazone treatment, or between patients with higher and lower amyloid β levels (Tables 2 and 3).

	Male			Female			Total		
	Before	**After**	**P value**	**Before**	**After**	**P value**	**Before**	**After**	**P value**
Serum amyloid β1-40 >50 pmol/L									
n	**8**			**10**			**18**		
Age (year)	78.0±4.2[a]			79.1±6.1			78.6±5.2[b]		
HbA1c (%)	7.3±0.7	7.0±0.4	0.151	7.8±2.5	7.0±1.9	0.277	7.6±1.9	7.0±1.4	0.149
HWM adiponectin (μg/mL)	5.9±4.4	21.5±23.4	0.068	9.2±3.1[b]	18.3±4.9[b]	<0.001**	7.7±4.0[b]	19.7±15.5[b]	0.002**
Amyloid β1-40 (pmol/L)	58.7±8.3[b]	54.7±4.7[a]	0.201	62.9±6.9[b]	53.8±8.2	<0.004**	61.1±7.6[b]	54.2±6.7[b]	0.002**
Serum amyloid β1-40 <50 pmol/L									
n	**13**			**12**			**25**		
Age (year)		74.1±3.4			74.8±5.2			74.4±4.3	
HbA1c (%)	6.7±0.8	7.0±1.2	0.516	7.0±1.0	7.3±1.3	0.293	6.9±0.9	7.1±1.3	0.254
HWM adiponectin (μg/mL)	4.0±1.9	8.5±4.3	<0.001**	5.2±2.8	10.3±4.1	<0.001**	4.6±2.4	9.4±4.2	<0.001**
Amyloid β1-40 (pmol/L)	38.8±7.7	42.4±12.0	0.174	35.7±7.6	47.9±11.5	0.001**	37.3±7.6	45.1±11.9	<0.001**

HWM, high-molecular-weight; *p<0.05, **p<0 .01 between before and after the 6-month treatment by two-sided paired t-test; [a]p<0.05, [b]p<0.01 vs. serum amyloid β1-40 <50 pmol/L by two-sided unpaired t-test

Table 2: Relevant data before and after the treatment of low-dose pioglitazone for 6 months (15 mg for males, 7.5 mg for female) in patients with serum amyloid β1-40 levels > or < 50 pmol/L.

	Male			Female			Total		
	Before	**After**	**P value**	**Before**	**After**	**P value**	**Before**	**After**	**P value**
Serum amyloid β1-42 >3pmol/L									
n	**8**			**11**			**19**		
Age (year)	77.1±4.7[a]			76.7±5.8			76.9±5.2		
HbA1c (%)	7.2±1.0	7.3±0.9	0.795	7.9±2.3	7.2±1.8	0.148	7.6±1.9	7.2±1.5	0.441
HWM adiponectin (μg/mL)	6.2±4.2	21.3±23.6	0.079	8.1±3.7	16.7±6.0[a]	<0.001**	7.3±3.9[a]	18.6±15.5[a]	0.002**
Amyloid β1-40 (pmol/L)	4.2±1.1[b]	2.6±0.7	0.527	4.3±1.1[b]	3.6±1.7	0.158	4.3±1.1[b]	3.2±1.4	0.004**
Serum amyloid β1-42 <3pmol/L									
n	**13**			**11**			**24**		
Age (year)		74.6±3.6			76.7±6.2			75.6±5.0	
HbA1c (%)	6.9±0.7	6.8±1.0	0.407	6.8±1.0	7.1±1.3	0.320	6.9±0.8	7.0±1.1	0.569

HWM adiponectin (μg/mL)	3.8±1.9	8.7±4.2	<0.001**	5.9±3.0	11.1±4.6	<0.001**	4.8±2.7	9.8±4.5	<0.001**
Amyloid β1-40 (pmol/L)	2.3±0.5	3.0±1.0	0.025*	2.0±0.3	2.5±0.6	0.064	2.2±0.4	2.8±0.9	0.003**
HWM, high-molecular-weight; *p<0.05, **p<0.01 between before and after the 6-month treatment by two-sided paired t-test; [a]p<0.05, [b]p<0.01 vs. serum amyloid β1-40 <50 pmol/L by two-sided unpaired t-test									

Table 3: Relevant data before and after the treatment of low-dose pioglitazone for 6 months (15 mg for males, 7.5mg for female) in patients with serum amyloid β1-42 levels > or < 3 pmol/L.

Discussion

Firstly, it is of interest that serum HMW adiponectin level was found to significantly correlate with serum amyloid β1-40 and β1-42 levels at the baseline (but not with amyloid β1-42 in female patients). Adiponectin is secreted by adipocytes, and exists in 3 major forms (trimers, hexamers and HMW multimers) in plasma, influencing biological processes including energy metabolism, vascular function and immune responses. HMW adiponectin, which is predominantly upregulated by pioglitazone or caloric restriction, can activate adenosine 5'-monophosphate-activated protein kinase most potently, but does not enter the cerebrospinal fluid [8,9]. Adiponectin has been suggested to have positive effects for the prevention and treatment of Alzheimer's disease and dementia [10,11]. Unexpectedly, however, the Framingham Heart Study demonstrated that increased plasma adiponectin levels were an independent risk factor for the development of both all-cause dementia and Alzheimer's disease in females over a mean follow-up of 13 years [12]. A meta-analysis of plasma amyloid β levels indicated that in longitudinal studies, cognitively normal individuals who converted to Alzheimer's disease had higher baseline amyloid β1-40 and β1-42 levels [13]. Accordingly, it may be conceivable that positive correlations were found between serum HMW adiponectin and amyloid β peptides in the present study. No direct interaction between them should exist, because their significant correlation disappeared after the pioglitazone treatment. In a similar vein, high adiponectin levels have been reported to be associated with increased cardiovascular disease and all-cause mortality in the elderly population, where weight loss and sarcopenia are presumed to be involved in their association [14,15].

Secondly, it is noteworthy that high serum levels of amyloid beta peptides decreased and their low levels increased after the 6-month treatment with low-dose pioglitazone. The relevance of low-dose pioglitazone was discussed in the previous report [7]. When serum amyloid β1-40 or β1-42 levels were divided by the level of 50 pmol/L or 3 pmol/L at the baseline, the mean value of the higher levels significantly decreased and that of the lower levels significantly increased after the pioglitazone treatment in total patients. Although the association between plasma amyloid β peptides and Alzheimer's disease is inconclusive, it is in general thought that plasma amyloid β peptides increase with age (production in the brain) and begin to decrease before the conversion to Alzheimer's disease (deposition in the brain) [1,2,16-18]. Such pathophysiological changes might have been augmented by the pioglitazone treatment in the present study. This presumption is, however, inconsistent with the potential protective effects of pioglitazone for Alzheimer's disease [3-5]. Distinct changes in amyloid β peptides during a short period as demonstrated in the present study have not been described thus far. The patients studied and their treatments were somewhat heterogeneous. If a presumption favoring the pioglitazone treatment would be made, pioglitazone could enhance clearing amyloid β peptides from the brain [18,19] and inhibit amyloid β oversynthesis in the brain [20,21]. In addition, there is a possibility that pioglitazone could modulate the production of amyloid β peptides in the peripheral cells [1].

In conclusion, serum levels of amyloid beta peptides positively correlated with serum HMW adiponectin levels only at the baseline. High serum levels of amyloid beta peptides decreased and their low levels increased after 6-month treatment with pioglitazone in Japanese elderly patients with type 2 diabetes. The relevance of such changes would be worthy of further investigation to use peripheral amyloid β peptides as better biomarkers for Alzheimer's disease and vascular dementia.

Conflict of interest

The author declares that there is no conflict of interest regarding the publication of this paper.

References

1. Toledo JB, Shaw LM, Trojanowski JQ (2013) Plasma amyloid beta measurements– a desired but elusive Alzheimer's disease biomarker. Alzheimers Res Ther 5: 8.
2. Weinstein G and Seshadri S (2014) Circulating biomarkers that predict incident dementia. Alzheimers Res Ther 6: 6.
3. Sato T, Hanyu H, Hirano K, Kanetaka H, Sakurai H, et al. (2011) Efficacy of PPAR-γ agonist pioglitazone in mild Alzheimer disease. Neurobiol Aging 32: 1626-1633.
4. Papadopoulos P, Rosa-Neto P, Rochford J, Hamel E (2013) Pioglitazone improves reversal learning and exerts mixed cerebrovascular effects in a mouse model of Alzheimer's disease with combined amyloid-β and cerebrovascular pathology. PLOS ONE 8: e68612.
5. Chang KL, Pee HN, Yang S, Ho PC (2015) Influence of drug transporters and stereoselectivity on the brain penetration of pioglitazone as a potential medicine against Alzheimer's disease. Sci Rep 5: 9000.

6. Takeda (2013) Biomarker qualification for risk of mild cognitive impairment (MCI) due to Alzheimer's disease (AD) and safety and efficacy evaluation of pioglitazone in delaying its onset (TOMMORROW). ClinicalTrial.gov: Identifier: NCT01931566.

7. Aoki Y (2015) Effects of low-dose pioglitazone on serum levels of adiponectin, dehydroepiandrosterone, amyloid beta peptide, and lipid profile in elderly Japanese people with type 2 diabetes. Adv Endocrinol: 782530

8. Kadowaki T, Yamauchi T, Kubota N (2008) The physiological and pathophysiological role of adiponectin and adiponectin receptors in the peripheral tissues and CNS. FEBS Lett 582: 74-80.

9. Yamauchi T and Kadowaki T (2013) Adiponectin receptor as a key player in healthy longevity and obesity-related diseases. Cell Metab 17: 185-196.

10. Song J and Lee JE (2013) Adiponectin as a new paradigm for approaching Alzheimer's disease. Anat Cell Biol 46: 229-234.

11. Wan Z and Little JP (2014) Adiponectin and Alzheimer's disease: is there a link? Inflamm Cell Signal 1: e154.

12. Van Himbergen TM, Beiser AS, Ai M, Seshadri S, Otokozawa S, et al. (2012) Biomarkers for insulin resistance and inflammation and the risk for all-cause dementia and Alzheimer Disease: results from the Framingham Heart Study. Arch Neurol 69: 594-600.

13. Song F, Poljak A, Valenzuela M, Mayeux R, Smythe GA, Sachdev PS (2011) Meta-analysis of plasma amyloid-β levels in Alzheimer's disease. J Alzheimers Dis 26: 365-375.

14. Laughlin GA, Barrett-Connor E, May S, Langenberg C (2007) Association of adiponectin with coronary heart disease and mortality. The Rancho Bernardo Study. Am J Epidemiol 165: 164-174.

15. Wannamethee SG, Whincup PH, Lennon L, Sattar N (2007) Circulating adiponectin levels and mortality in elderly men with and without cardiovascular disease and heart failure. Arch Intern Med 167: 1510-1517.

16. Schupf N, Tang MX, Fukuyama H, Manly J, Andrews H, et al. (2008) Peripheral Aβ subspecies as risk biomarkers of Alzheimer's disease. Proc Natl Acad Sci USA 105: 14052-14057.

17. Toledo JB, Vanderstichele H, Figurski M, Aisen PS, Petersen RC, et al. (2011) Factors affecting Aβ plasma levels and their utility as biomarkers in ADNI. Acta Neuropathol 122: 401-413.

18. Shah NS, Vidal J-S, Masaki K, Petrovitch H, Ross GW, et al. (2012) Midlife blood pressure, plasma β amyloid and the risk for Alzheimer's disease: the Honolulu Asia Aging Study. Hypertension 59: 780-786.

19. Moon JH, Kim HJ, Yang AH, Kim HM, Lee BW, et al. (2011) The effect of rosiglitazone on LRP1 expression and amyloid β uptake in human brain microvascular endothelial cells: a possible role of a low-dose thiazolidinedione for dementia treatment. Int J Neuropsychopharmacol 15: 135-142.

20. Chen LM, Lin ZY, Zhu YG, Lin N, Zhang J, et al. (2012) Ginsenoside Rg1 attenuates β-amyloid generation via suppressing PPARγ-regulated BACE1 activity in N2a-APP695 cells. Eur J Pharmacol 675: 15-21.

21. Lin N, Chen LM, Pan XD, Zhu YG, Zhang J, et al. (2015) Tripchlorolide attenuates β-amyloid generation via suppressing PPARγ-regulated BACE1 activity in N2a/APP695 cells. Mol Neurobiol 53.