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# Plasma adiponectin array in women with Alzheimer's disease

## Osoczowe stężenia frakcji adiponektyny u kobiet z chorobą Alzheimera

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## Abstract

**Introduction:** Alzheimer's disease (AD) is a progressive and irreversible neurodegenerative disease. Typical features of AD include memory loss, social dysfunction, and physical impairment. Although the pathological findings in the central nervous system are well established, the aetiological factors are poorly known. Recent studies suggested the role of metabolic disturbances in the development of AD neurodegeneration. Adiponectin, an anti-inflammatory and metabolism regulating factor, was linked to AD.

**The aim** was to examine whether adiponectin fractions combined with insulin/insulin resistance-associated metabolic parameters correlate with AD progression.

**Material and methods:** The study comprised 98 women: 27 with moderate to severe AD, 31 with AD at early stage, and 40 healthy controls, matched for age and BMI. To evaluate memory impairment, the *Mini-Mental State Examination* (MMSE) was performed. Plasma total adiponectin and its high, medium, and low molecular weights were measured with ELISA. Anthropometric, clinical, and metabolic parameters were assessed. Correlations between adiponectin array and measured parameters were evaluated.

**Results:** In comparison to the controls, enhanced levels of total and medium molecular weight adiponectin characterised AD individuals. In AD, we found correlations between adiponectin array, and anthropometric and biochemical parameters. After adjustment to BMI, a significant increase of the total adiponectin and high and medium molecular weight fractions was observed. A negative correlation between low molecular weight adiponectin and MMSE was found.

**Conclusions:** Our results indicate a possible link between adiponectin variations and AD. We hypothesise that changes in adiponectin profile observed in AD result from compensatory mechanisms against neuropathological processes, as well as from adiponectin homeostasis impairment. **(Endokrynol Pol 2018; 69 (5): 550–559)**

**Key words:** *adiponectin, adiponectin fractions, Alzheimer's disease*

## Streszczenie

**Wstęp:** Choroba Alzheimera (AD) to postępujące, nieodwracalne schorzenie neurodegeneracyjne. Typowe cechy AD to zaburzenia pamięci, dysfunkcje społeczne oraz niepełnosprawność fizyczna. Mimo że zmiany patologiczne w centralnym układzie nerwowym są dobrze poznane, nadal nie przedstawiono wszystkich czynników etiologicznych. Ostatnie badania wskazują na role zaburzeń metabolicznych w rozwoju procesów neurodegeneracyjnych w AD. Adiponektyna, będąca czynnikiem przeciwzapalnym i regulującym metabolizm, została powiązana z AD.

**Celem** pracy było określenie, czy frakcje adiponektyny w powiązaniu z insuliną i parametrami metabolicznymi zależnymi od insulinooporności korelują z progresją choroby Alzheimera.

**Materiał i metody:** Badaniem objęto 98 kobiet: 27 z AD w stadium co najmniej średnio zaawansowanym, 31 w początkowym stadium choroby i 40 zdrowych, dobranych pod względem wieku i BMI. Do oceny zaburzeń funkcji poznawczych użyto badania *Mini-Mental State Examination* (MMSE). W osoczu metodą ELISA określano stężenie adiponektyny całkowitej i jej frakcji. Badano także wybrane parametry antropometryczne, kliniczne i metaboliczne. Oceniano korelacje między profilem adiponektyny a badanymi zmiennymi.

**Wyniki:** W porównaniu z osobami z grupy kontrolnej w AD stwierdzono podwyższone wartości adiponektyny całkowitej i frakcji MMW. W grupie AD wykazano korelacje między profilem adiponektyny a parametrami antropometrycznymi i biochemicznymi. Po wyłączeniu BMI jako czynnika zakłócającego obserwowano wyższe stężenia adiponektyny całkowitej oraz frakcji HMW i MMW. Stwierdzono ujemną korelację między frakcją LMW a wynikiem MMSE.

**Wnioski:** Uzyskane wyniki wskazują na możliwość obecności związku między zmianami stężeń frakcji adiponektyny a chorobą Alzheimera. Autorzy niniejszej pracy przypuszczają, że zmiany w profilu adiponektyny obserwowane w AD wynikają z mechanizmów kompensacyjnych przeciwstawiających się procesom neuropatologicznym, jak również z zaburzeń w zakresie homeostazy adiponektyny. **(Endokrynol Pol 2018; 69 (5): 550–559)**

**Słowa kluczowe:** *adiponektyna, frakcje adiponektyny, choroba Alzheimera*

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## Introduction

Dementia is a global health and social problem. Nowadays, there are a growing number of demented individuals around the world. It is predicted that by the year 2025 there will be 1.2 billion people worldwide in the age group 60 years and over [1]. According to the WHO, the total number of people with dementia is projected to reach 82 million by 2030. It is widely accepted that Alzheimer's disease (AD) is the main cause of memory impairment in the elderly. Typical clinical features of AD include gradual memory loss, social dysfunction, and physical impairment. Pathological alterations in the brain in the course of Alzheimer's disease consist of extracellular accumulation of beta-amyloid, deposits of pathological tau protein, inflammation, and activation of microglia and astrocytes [2]. Although the pathological findings in the central nervous system are well known, all aetiological factors leading to this neurodegenerative disease have not been established yet.

In recent years, researchers have formulated several hypotheses about the role of metabolic disturbances in the development of neurodegeneration found in AD. The wide spectrum of metabolic abnormalities that could be involved in pathological changes of the central nervous system (CNS) include obesity and all processes that are connected with excess fat accumulation [1]. Moreover, imbalanced carbohydrate and insulin homeostasis may also be correlated with pathological processes seen in AD brains [3]. Interestingly, it has been established that mid-life obesity could be a risk factor of AD [4]. On the other hand, fat deposits are responsible for unfavourable metabolic profile [5]. Indeed, obesity is related to diabetes, hyperlipidaemia and cardiovascular disease [6]. Undeniably, adipocytes are able to produce biologically active molecules named adipokines that possess multi-functional activity. Adiponectin, one of the adipocyte-derived substances, acts as an anti-inflammatory and metabolism regulating factor [7]. An inverse correlation between adiponectin concentration and the amount of adipose tissue has been established. Additionally, adiponectin levels are reduced in obesity, insulin resistance, and diabetes mellitus type 2 [8]. Moreover, decreased levels of adiponectin have been associated with the presence of different kind of cancers [9]. Aside from fat tissue, it has been suggested that adiponectin could be secreted in much smaller amounts by other tissues [10]. In the peripheral blood adiponectin circulates in three main forms, which differ in the number of molecules and molecular weight. There are three forms of adiponectin: trimers LMW (low molecular weight); hexamers MMW (medium molecular weight); and multimers HMW (high molecular weight). In addition, these adiponectin complexes exert different biological activity because HMW adiponectin is the most active form in the peripheral blood [11]. Moreover, HMW adiponectin plays a role in improving insulin sensitivity and protecting against diabetes [11]. This statement was confirmed in the study of Yamauchi and Kadowaki, who reported that a decrease in HMW adiponectin concentration plays a crucial and causal role in obesity-linked insulin resistance and metabolic syndrome [12].

Until now, three kinds of adiponectin receptors have been found: AdipoR1, AdipoR2, and T-cadherin [13]. Several mechanisms are reported to be involved in AdipoRs signalling pathways. The most important kinase associated with adiponectin activity is AMP-activated protein kinase (AMPK). It possesses the ability to regulate intracellular signalling molecules, influencing metabolic processes including insulin sensitivity, mitochondrial biogenesis, and oxidative metabolism. Furthermore, adiponectin by binding to the AdipoRs may also activate p38-MAPK (p38 mitogen-activated protein kinase) and inhibit GSK-3β (glycogen synthase kinase 3 beta) activity [14].

Adiponectin receptors are found in the CNS, and adiponectin is detectable in the cerebrospinal fluid (CSF) with concentrations much lower than in the peripheral blood [15]. AdipoR1 and AdipoR2 expression, with a predominance of AdipoR1, was found in different brain regions, including the hypothalamus, cortex, hippocampus, pituitary, and area postrema [16]. The presence of T-cadherin in the hippocampus was also confirmed, suggesting an important role of adiponectin in the cognitive processes [17].

It has also been established that the pattern of adiponectin isomers in the cerebrospinal fluid is different from the distribution observed in peripheral blood. Most CSF adiponectin are trimeric forms (approximately 80%), and the remaining are hexamers [16].

Adiponectin may regulate energy expenditure, food intake, inflammation, cell death, and protection in the central nervous system [18]. Considering that adiponectin possesses diversified activity, it could be hypothesised that this peptide might modulate the course of Alzheimer's disease. Recently, it has been speculated that the reduction of adiponectin concentration or impairment of adiponectin signalling could affect AD pathogenesis resulting in cognitive dysfunction [16]. A study performed on the animal model revealed that aged mice with chronic adiponectin deficiency had spatial memory and fear-conditioned memory impairments as well as anxiety. Moreover, AD-like abnormalities, including an enhancement of beta-amyloid oligomers synthesis and hyperphosphorylated tau protein depositions, were found in adiponectin knockout mice. Finally, neuroinflammation in the form of

microglial reactivation with elevated proinflammatory cytokines was also reported in this animal model [19]. In addition, the group of Kim reported that AdipoR1 knockdown mice exhibited memory impairment and neuronal apoptosis, and these features were similar to those observed in the AD model. The authors concluded that AdipoR1 is an essential receptor for protecting against neuronal cell death and spatial and learning memory impairment [20]. Another group of researchers reported that in the APP/PS1 (amyloid precursor protein/presenilin 1) transgenic mice model of AD an altered expression of AdipoR1 and AdipoR2 in the hippocampus and the prefrontal cortex could be found [21]. Thus, the above results confirm a downregulated signalisation of adiponectin in the course of AD.

Also, there are metabolic alterations found in the central nervous system of AD subjects [22]. It has been reported that insulin resistance in the periphery and impaired carbohydrate homeostasis might be considered as a risk or even causative factor of Alzheimer's disease [23]. On the other hand, there is a connection between peripheral levels of adiponectin and insulin homeostasis [24]. AD is characterised by impaired brain glucose uptake, reduced insulin signalling, and decreased insulin receptor activity in the central nervous system, resulting in central functional hypoglycaemia and hypometabolism. Insulin resistance occurring in the central nervous system of AD patients was named type 3 diabetes (T3D) [25].

It is very important to understand how peripheral metabolic impairments influence the course of AD. Thus, in the current study, we aimed to examine whether adiponectin fractions in combination with metabolic parameters, especially insulin and insulin resistance, correlate with the stage of AD.

To the best of our knowledge, this is the first time that all adiponectin isoforms have been investigated in AD.

## Material and methods

### *Subjects*

The study group comprised 58 women with sporadic Alzheimer's disease (AD) and 40 women with normal cognition as the controls, matched for age and body mass index (BMI).

Although it is widely reported that subjects suffering from Alzheimer's disease lose weight in the course of the disease, we decided to include in our research only these AD individuals whose BMI did not differ from the BMI of the controls.

AD patients were recruited from a single medical centre: the Alzheimer's Disease Department of the Central Clinical Hospital of the Ministry of Interior in Warsaw, Poland in collaboration with the Department of Neurodegenerative Disorders, Mossakowski Medical Research Centre, Polish Academy of Science in Warsaw, Poland. The diagnosis of AD was based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria [26] and was in concordance with novel recommendations [27]. Neurological examination, neuropsychological assessment, and MRI (magnetic resonance imaging) or CT (computed tomography) scan was performed in AD group. To assess the severity of memory impairment the Mini Mental State Examination (MMSE) was carried out. Consequently, the AD group was divided into two subgroups according to the results of MMSE: moderate to severe stage of AD with MMSE score $\leq 15$ (27 women; mean age 73.07 ± 4.12 years; MMSE 10.44 ± 4.32) and early stage of AD with MMSE score $> 15$ (31 women; mean age 74.13 ± 4.98 years; MMSE 21.32 ± 3.26).

The group of controls consisted of forty females (mean age 72.68 ± 7.74 years), who were healthy volunteers. To exclude cognitive deficits amongst the controls, medical examination and MMSE were performed. On this basis, these individuals were found to be non-demented.

All participants were Caucasian, non-related females living in the Mazovian District in central Poland. The group under study comprised women only to avoid any sex-dependent differences in examined parameters, especially adiponectin. Exclusion criteria included chronic renal, liver, heart, and pulmonary dysfunction, and history of neoplasm. The previous history of diabetes also excluded individuals from the study. None of the examined subjects had signs of acute infections in the medical examination. A history of excessive alcohol consumption eliminated individuals from the study.

The study protocol was approved by the Ethical Commission of the Centre of Postgraduate Medical Education, Warsaw, Poland. Informed consent was obtained from all subjects or the patients' caregivers.

### *Medical examination and anthropometric measurements*

All participants attended the medical examination to assess their health status and to collect clinical and anthropometric data. Height was measured with the use of a wall-mounted ruler. Weight was assessed using a digital scale. Then, BMI was calculated according to the formula: weight (kg) divided by height$^2$ (m$^2$).

Clinical data are presented in Table I.

### *Analytical methods*

Blood samples were taken after at least six hours of fasting. Blood was collected in tubes containing EDTA and aprotinin as protease inhibitors. Immediately after

**Table I.** *Anthropometric and biochemical measurements*

**Tabela I.** *Wyniki pomiarów antropometrycznych i badań biochemicznych*

| | Alzheimer's disease (n = 58) | Controls (n = 40) | p-value |
|---|---|---|---|
| Age (yrs) | 73.64 ± 4.59 | 72.68 ± 7.74 | ns |
| BMI [kg/m$^2$] | 24.00 ± 3.82 | 25.02 ± 3.06 | ns |
| Waist [cm] | 86.22 ± 10.72 | 81.90 ± 9.36 | < 0.05 |
| Hip [cm] | 102.11 ± 9.75 | 98.82 ± 6.69 | < 0.05 |
| Systolic blood pressure [mmHg] | 137.63 ± 19.48 | 131.50 ± 14.69 | ns |
| Diastolic blood pressure [mmHg] | 79.54 ± 8.11 | 80.63 ± 11.56 | ns |
| MMSE | 16.26 ± 6.64 | > 27 | |
| Total adiponectin [$\mu$g/ml] | 9.14 ± 3.55 | 7.64 ± 3.56 | < 0.05 |
| HMW adiponectin [$\mu$g/ml] | 4.57 ± 2.19 | 3.87 ± 2.29 | ns |
| MMW adiponectin [$\mu$g/ml) | 2.58 ± 1.23 | 2.00 ± 1.63 | < 0.01 |
| LMW adiponectin [$\mu$g/ml] | 1.99 ± 1.67 | 1.77 ± 1.31 | ns |
| Total cholesterol [mg/dl] | 209.12 ± 43.14 | 217.25 ± 49.05 | ns |
| HDL cholesterol [mg/dl] | 64.40 ± 16.99 | 58.80 ± 14.70 | ns |
| LDL cholesterol [mg/dl] | 117.79 ± 35.60 | 128.10 ± 40.52 | ns |
| Triglycerides [mg/dl] | 109.60 ± 43.23 | 145.76 ± 80.76 | < 0.01 |
| Insulin [$\mu$IU/ml] | 11.17 ± 6.24 | 9.01 ± 8.95 | < 0.05 |
| Glucose [mg/dl] | 91.07 ± 15.05 | 98.15 ± 22.74 | < 0.05 |
| HOMA-IR | 2.57 ± 1.68 | 2.29 ± 2.54 | ns |

collection, the samples were centrifuged at 4°C and isolated plasma was frozen at –70°C for further analysis.

Plasma total adiponectin and HMW, MMW, and LMW adiponectin concentration were measured using a commercial ELISA Kit (ALPCO Diagnostics, Windham, NH, USA). The sensitivity of the assay was 0.019 ng/ml. The intra-assay and inter-assay coefficients of variation for total adiponectin, HMW, MMW, and LMW were 5.4%, 5%, 10.2%, and 7.3%, respectively.

Plasma insulin concentrations were determined using immunoradiometric assay (DIA Source Immunoassay SA, Nivelles, Belgium). The detection limit was 1 $\mu$IU/ml. Intra- and inter-assay coefficients of variation were 2.1% and 6.5%, respectively.

Fasting plasma glucose levels and lipid profiles were estimated using routine laboratory tests. Insulin resistance was calculated from the results of fasting plasma insulin and glucose using the homeostasis model assessment of insulin resistance (HOMA-IR) formula: fasting plasma glucose (mmol/l) x fasting plasma insulin concentration ($\mu$IU/ml)/22.5. Insulin resistance was defined as HOMA-IR > 2.5.

### *Statistical analyses*

All statistical analyses were performed using STATISTICA 10 software (StatSoft Inc., USA).

The normality of distribution was evaluated using the Shapiro-Wilk test. Evaluation of the differences between groups was performed using the Kruskal-Wallis rank test followed by the Mann-Whitney U-test. To calculate the correlation coefficient between adipokines and anthropometric parameters as well as biochemical data, the Spearman test was applied. Adiponectin and its fractions were adjusted for BMI.

Statistical significance was accepted at $p < 0.05$.

## Results

Basic demographic, clinical, and laboratory data of all subjects were calculated and are shown in Table I. Subjects with Alzheimer's disease presented significantly increased waist and hip measurements when compared to the controls (86.22 ± 10.72 cm vs. 81.90 ± 9.36 cm, $p < 0.05$ and 102.11 ± 9.75 cm vs. 98.82 ± 6.69 cm, $p < 0.05$, respectively). However, there was no difference in BMI between these two groups. The results of blood pressure measurement did not differ when AD subjects were compared to their non-demented counterparts.

The results of the biochemical analysis showed that only triglycerides (109.60 ± 43.23 mg/dl vs. 145.7 ± 80.76 mg/dl; $p < 0.01$) and glucose (91.07 ± 15.05 vs. 98.15 ± 22.74 mg/dl; $p < 0.05$) levels were significantly lower and insulin values were higher in AD subjects than in the controls (11.17 ± 6.24 $\mu$IU/ml vs. 9.01 ± 8.95 $\mu$IU/ml; $p < 0.05$). No differences were found when analysing HOMA-IR.

Total adiponectin and MMW adiponectin levels were markedly higher in individuals with AD in comparison to the results of the controls (9.14 ± 3.55 $\mu$g/ml vs. 7.64 ± 3.56 $\mu$g/ml; $p < 0.05$ for total adiponectin and 2.58 ± 1.23 $\mu$g/ml vs. 2.00 ± 1.63 $\mu$g/ml; $p < 0.01$ for MMW adiponectin, respectively). The results of HMW and LMW adiponectin were comparable between the two examined groups.

When the results of the group of Alzheimer patients were divided according to the stage of the disease, as shown in Table II, it was revealed that AD early stage individuals had markedly lower BMI in comparison to the controls (23.55 ± 3.32 kg/m$^2$ vs. 25.02 ± 3.06 kg/m$^2$; $p < 0.05$). When results of the waist and hip measurements were compared, we found that these two parameters were significantly higher in women with moderate/severe AD than in the control group (88.63 ± 10.95 cm

**Table II.** *Anthropometric and biochemical measurements after division of AD individuals into subpopulations according to the disease stage*

**Table II.** *Wyniki pomiarów antropometrycznych i badań biochemicznych po podziale grupy z chorobą Alzheimera w zależności od stadium zaawansowania choroby*

| | Moderate to severe stage of AD (n = 27) | Early stage of AD (n = 31) | Controls (n = 40) | p-value |
|---|---|---|---|---|
| Age (yrs) | 73.07 ± 4.12 | 74.13 ± 4.98 | 72.68 ± 7.74 | ns |
| BMI [kg/m$^2$] | 24.53 ± 4.33 | 23.55 ± 3.32 | 25.02 ± 3.06 | < 0.05[c] |
| Waist [cm] | 88.63 ± 10.95 | 84.13 ± 10.23 | 81.90 ± 9.36 | < 0.01[b] |
| Hip [cm] | 104.19 ± 10.23 | 100.29 ± 9.09 | 98.82 ± 6.69 | < 0.01[b] |
| Systolic blood pressure [mmHg] | 135.81 ± 16.81 | 139.16 ± 21.63 | 131.50 ± 14.69 | ns |
| Diastolic blood pressure [mmHg] | 80.04 ± 6.37 | 79.13 ± 9.42 | 80.63 ± 11.56 | ns |
| MMSE | 10.44 ± 4.32 | 21.32 ± 3.26 | > 27 | < 0.001[a] |
| Total adiponectin [$\mu$g/ml] | 9.19 ± 3.61 | 9.09 ± 3.56 | 7.64 ± 3.56 | = 0.07[b]<br>= 0.06[c] |
| HMW adiponectin [$\mu$g/ml] | 4.18 ± 2.01 | 4.90 ± 2.30 | 3.87 ± 2.29 | < 0.05[c] |
| MMW adiponectin [$\mu$g/ml] | 2.67 ± 1.38 | 2.50 ± 1.31 | 2.00 ± 1.63 | < 0.05[b,c] |
| LMW adiponectin [$\mu$g/ml] | 2.34 ± 1.66 | 1.68 ± 1.64 | 1.77 ± 1.31 | ns |
| Total cholesterol [mg/dl] | 204.81 ± 37.89 | 212.87 ± 47.54 | 217.25 ± 49.05 | ns |
| HDL cholesterol [mg/dl] | 62.22 ± 16.32 | 66.29 ± 17.60 | 58.80 ± 14.70 | ns |
| LDL cholesterol [mg/dl] | 112.67 ± 27.75 | 122.26 ± 41.18 | 128.10 ± 40.52 | ns |
| Triglycerides [mg/dl] | 115.81 ± 44.82 | 104.13 ± 41.76 | 145.76 ± 80.76 | < 0.05[b]<br>< 0.01[c] |
| Insulin [$\mu$IU/ml] | 12.07 ± 7.34 | 10.39 ± 5.10 | 9.01 ± 8.95 | = 0.07[a]<br>< 0.05[b] |
| Glucose [mg/dl] | 89.30 ± 9.93 | 92.61 ± 18.42 | 98.15 ± 22.74 | < 0.05[b] |
| HOMA-IR | 2.68 ± 1.70 | 2.47 ± 1.69 | 2.29 ± 2.54 | ns |

[a]moderate and severe AD vs. early stage, [b]moderate and severe AD vs. control group, [c]early stage vs. control group

vs. 81.90 ± 9.36 cm, $p < 0.01$ for waist and 104.19 ± 10.23 cm vs. 98.82 ± 6.69 cm, $p < 0.01$ for hip measurements, respectively).

No differences between the groups in cholesterol profile were observed. However, triglyceride concentrations significantly varied between some of the examined pools; results of both AD groups were markedly higher than those of the controls (115.81 ± 44.82 mg/dl vs. 145.76 ± 80.76; $p < 0.05$ for moderate/severe AD vs. controls and for 104.13 ± 41.76 mg/dl vs. 145.76 ± 80.76 mg/dl; $p < 0.01$ for early stage vs. control group, respectively).

There was a tendency for enhanced insulin levels in AD patients with a significant difference observed between individuals with advanced AD and the control group (12.07 ± 7.34 $\mu$IU/ml vs. 9.01 ± 8.95 $\mu$IU/ml; $p < 0.05$). However, glucose concentration decreased with deterioration of the disease. The markedly lower values of glucose were found in individuals with moderate/severe AD when compared to those of healthy individuals (89.30 ± 9.93 mg/dl vs. 98.15 ± 22.74 mg/dl; $p < 0.05$). There was a trend towards higher HOMA-IR in AD patients; however, the differences were non-significant.

After dividing the AD group into subgroups, we found that the previously observed significantly higher concentration of total adiponectin diminished as the differences became non-significant. However, the trends remained unchanged. Moreover, there was a trend towards increased MMW adiponectin concentration with the progression of AD. Markedly higher MMW adiponectin concentration was observed in both subpopulations of AD patients in comparison to the control group (2.67 ± 1.38 $\mu$g/ml vs. 2.00 ± 1.63 $\mu$g/ml, $p < 0.05$ for moderate/ severe AD vs. controls, and 2.50 ± 1.31 $\mu$g/ml vs. 2.00 ± 1.63 $\mu$g/ml, $p < 0.05$ for early stage vs. control group, respectively).

On the other hand, the HMW adiponectin value was markedly higher in AD individuals with an early stage of the disease when compared to the results of the controls (4.90 ± 2.30 $\mu$g/ml vs. 3.87 ± 2.29 $\mu$g/ml; $p < 0.05$).

To avoid the role of BMI as a confounding factor in adiponectin assessment we adjusted the adiponectin profile to BMI (Table III). When the results of AD patients as the whole group were analysed, a significant increase in total adiponectin, and HMW and MMW

**Table III.** *Adiponectin profile after adjustment to BMI*

**Table III.** *Profil adiponektyny po wyłączeniu BMI jako czynnika zakłócającego*

| | Alzheimer's disease (n = 58) | Controls (n = 40) | p-value adjusted to BMI |
|---|---|---|---|
| Total adiponectin [μg/ml] | 9.14 ± 3.55 | 7.64 ± 3.56 | < 0.05 |
| HMW adiponectin [μg/ml] | 4.57 ± 2.19 | 3.87 ± 2.29 | < 0.05 |
| MMW adiponectin [μg/ml] | 2.58 ± 1.23 | 2.00 ± 1.63 | < 0.01 |
| LMW adiponectin [μg/ml] | 1.99 ± 1.67 | 1.77 ± 1.31 | ns |

fractions in AD was found when compared with the controls (9.14 ± 3.55 μg/ml vs. 7.64 ± 3.56 μg/ml, $p < 0.05$; 4.57 ± 2.19 μg/ml vs. 3.87 ± 2.29 μg/ml, $p < 0.05$; 2.58 ± 1.23 μg/ml vs. 2.00 ± 1.63 μg/ml, $p < 0.01$; respectively). Differences in LMW adiponectin concentrations were non-significant.

When the subgroups of AD were singled up and the adiponectin array was adjusted to BMI, as presented in Table IV, markedly higher results of total adiponectin were found in advanced AD when compared to the results of healthy counterparts (9.19 ± 3.61 vs. 7.64 ± 3.56 μg/ml, $p < 0.05$). HMW adiponectin concentration was significantly higher in individuals in early stages of the disease than in the controls (4.90 ± 2.30 μg/ml vs. 3.87 ± 2.29 μg/ml, $p < 0.05$). Finally, the MMW fraction level was highest in subjects with advanced AD and lowest in the controls. We revealed significant differences of MMW concentration between all groups in this study (2.67 ± 1.38 μg/ml vs. 2.50 ± 1.31 μg/ml, $p < 0.01$ for moderate/severe AD vs. early stage AD; 2.67 ± 1.38 μg/ml vs. 2.00 ± 1.63 μg/ml, $p < 0.01$ for moderate/severe AD vs. controls; and 2.50 ± 1.31 μg/ml vs. 2.00 ± 1.63 μg/ml, $p < 0.01$ for early stage AD vs. controls; respectively).

Correlations of adiponectin array found in the AD group are presented in Table V. We observed a positive correlation between total adiponectin and HDL-cholesterol ($R = 0.29$, $p < 0.05$) and a negative correlation between total adiponectin and HOMA-IR ($R = –0.26$, $p < 0.05$). MMW adiponectin correlated negatively with BMI ($R = –0.25$, $p < 0.05$), waist and hip measurements (for both parameters $R = –0.27$, $p < 0.05$), triglycerides ($R = –0.34$, $p < 0.01$), insulin ($R = –0.27$, $p < 0.05$), and HOMA-IR ($R = –0.31$, $p < 0.05$). A positive correlation was found between MMW adiponectin and HDL-cholesterol ($R = 0.36$, $p < 0.01$). Only one parameter correlated with MMSE; we found a negative correlation between LMW adiponectin and MMSE ($R = –0.35$, $p < 0.01$).

**Table IV.** *Adiponectin profile after adjustment to BMI in AD subpopulations divided according to the disease stage*

**Table IV.** *Profil adiponektyny po wyłączeniu BMI jako czynnika zakłócającego po podziale grupy z chorobą Alzheimera w zależności od stadium zaawansowania choroby*

| | Moderate to severe stage of AD (n = 27) | Early stage of AD (n = 31) | Controls (n = 40) | p-value adjusted to BMI |
|---|---|---|---|---|
| Total adiponectin [μg/ml] | 9.19 ± 3.61 | 9.09 ± 3.56 | 7.64 ± 3.56 | < 0.05[b] |
| HMW adiponectin [μg/ml] | 4.18 ± 2.01 | 4.90 ± 2.30 | 3.87 ± 2.29 | < 0.05[c] |
| MMW adiponectin [μg/ml] | 2.67 ± 1.38 | 2.50 ± 1.31 | 2.00 ± 1.63 | < 0.01[a, b, c] |
| LMW adiponectin [μg/ml] | 2.34 ± 1.66 | 1.68 ± 1.64 | 1.77 ± 1.31 | ns |

[a]moderate and severe AD vs. early stage, [b]moderate and severe AD vs. control group, [c]early stage vs. control group

**Table V.** *Correlations in AD group*

**Table V.** *Korelacje w grupie z chorobą Alzheimera*

| Parameter A | Parameter B | R | p-value |
|---|---|---|---|
| Total adiponectin | HDL-cholesterol | 0.29 | < 0.05 |
| Total adiponectin | Insulin | –0.21 | = 0.09 |
| Total adiponectin | HOMA-IR | –0.26 | < 0.05 |
| HMW adiponectin | HDL-cholesterol | 0.24 | = 0.06 |
| HMW adiponectin | Waist | –0.23 | = 0.07 |
| MMW adiponectin | BMI | –0.25 | < 0.05 |
| MMW adiponectin | Waist | –0.27 | < 0.05 |
| MMW adiponectin | Hip | –0.27 | < 0.05 |
| MMW adiponectin | HDL-cholesterol | 0.36 | < 0.01 |
| MMW adiponectin | Triglycerides | –0.34 | < 0.01 |
| MMW adiponectin | Insulin | –0.27 | < 0.05 |
| MMW adiponectin | HOMA-IR | –0.31 | < 0.05 |
| LMW adiponectin | MMSE | –0.35 | < 0.01 |

Correlation of adiponectin and its fractions concentration with the control group is presented in Table VI. In detail, in this model, as could be predicted, total adiponectin correlated negatively with BMI ($R = –0.46$, $p < 0.01$), waist ($R = –0.47$, $p < 0.01$), and hip ($R = –0.48$, $p < 0.01$), and positively with HDL-cholesterol ($R = 0.41$, $p < 0.01$). HMW adiponectin correlated similarly with the same parameters (BMI: $R = –0.38$, $p < 0.05$; waist: $R = –0.35$, $p < 0.05$; hip: $R = –0.49$, $p < 0.01$). There was a negative correlation between MMW fraction and waist measurement ($R = –0.43$, $p < 0.01$). LMW fraction

**Table VI.** *Correlations in control group*
**Table VI.** *Korelacje w grupie kontrolnej*

| Parameter A | Parameter B | R | p-value |
|---|---|---|---|
| Total adiponectin | BMI | –0.46 | < 0.01 |
| Total adiponectin | Waist | –0.47 | < 0.01 |
| Total adiponectin | Hip | –0.48 | < 0.01 |
| Total adiponectin | HDL-cholesterol | 0.41 | < 0.01 |
| HMW adiponectin | BMI | –0.38 | < 0.05 |
| HMW adiponectin | Waist | –0.35 | < 0.05 |
| HMW adiponectin | Hip | –0.49 | < 0.01 |
| HMW adiponectin | HDL-cholesterol | 0.42 | < 0.01 |
| MMW adiponectin | Waist | –0.43 | < 0.01 |
| LMW adiponectin | BMI | –0.42 | < 0.01 |
| LMW adiponectin | Hip | –0.34 | < 0.01 |



correlated negatively with BMI ($R = –0.42$, $p < 0.01$) and hip measurement ($R = –0.34$, $p < 0.01$).

## Discussion

The study focused on adiponectin levels in different stages of Alzheimer's disease in correlation with the metabolic status of the patients. To the best of our knowledge, this is the first report in which the whole array of adiponectin forms in Alzheimer's disease were evaluated.

The effect of adiponectin on pathological processes in AD may have a multifactorial basis. Adiponectin enhances AMPK activity via AdipoR1, and, in turn, AMPK activation represses amyloidogenesis, decreases mTOR signalling, and enhances autophagy and lysosomal degradation of beta-amyloid [28]. GSK-3β is recognised as another signalling molecule in adiponectin receptor signalling pathway [14]. It should be highlighted that GSK-β is involved in tau and beta-amyloid production [29], and it is regarded as a critical molecular link between two histopathological hallmarks of AD: senile plaques and neurofibrillary tangles [30]. Because negative regulation of AMPK by GSK-3β has been reported [14], a possible interaction between the AMPK and GSK-3β signalling pathways may play a role in AD. The group of Kadowaki revealed that adiponectin secretion is upregulated by PPAR-gamma (peroxisome proliferator-activated receptor gamma) [31]. On the other hand, PPAR-gamma activation was found to play a role in amyloid clearance [32].

Anti-inflammatory properties of adiponectin may also have an impact on the pathological processes observed in AD. This peptide decreases expression of pro-inflammatory cytokines and increases expression of anti-inflammatory molecules. Furthermore, adiponectin is able to modulate T-cell activation and additionally influences the activity of natural killer cells [33]. It has been suggested that by decreasing IL-6 and TNF-α synthesis, adiponectin may indirectly affect inflammatory signalling across the BBB (blood–brain barrier) and within the brain. Therefore, proinflammatory cytokine influx across the BBB might be reduced due to high levels of circulating adiponectin [34].

The results from the study of Ng et al. on aged mice confirmed a connection between chronic adiponectin deficiency and Alzheimer's disease-like cognitive impairments and pathologies. The main mechanisms involve AMPK inactivation and cerebral insulin resistance [19]. Not only deficiency of adiponectin but also impairment of adiponectin signalling, e.g. desensitisation of adiponectin receptors, might affect AD pathogenesis. Recently, two experimental studies supported this hypothesis. Altered expression of AdipoR1 and AdipoR2 in the hippocampus and the prefrontal cortex was demonstrated in transgene murine model of AD. Interestingly, a weak response of these receptors to chronic stress was observed as well [21]. The group of Kim reported that suppression of AdipoR1 promoted memory dysfunction and Alzheimer's disease-like pathologies. In detail, AdipoR1 knockdown mice exhibited metabolic abnormalities and failed to perform behavioural tests correctly. Moreover, AdipoR1 knockdown animals were found to have AD-like pathologies including insulin signalling dysfunction, abnormal protein aggregation, and neuroinflammatory responses similar to the brain pathologies observed in adiponectin-knockout mice [20].

Another point that should be discussed is the BBB permeability and adiponectin influx to the brain. The peripheral adipose tissues are likely to be a major source of adiponectin in the CNS [35]. It has been reported that the trimeric and hexameric forms of adiponectin may enter the brain by passing through the blood–brain barrier [18]. Moreover, the BBB breakdown was found in Alzheimer's disease. Notably, BBB impairment leads to an increase of the influx of different kinds of substances and causes enhancement of neuronal injury, synaptic dysfunction, loss of neuronal connectivity, and neurodegeneration [36]. Thus, we presume that plasma adiponectin array reflects the pathological process occurring in the CNS in the course of AD.

We observed a marked increase in total adiponectin and MMW fractions in AD in comparison to the controls. However, when analysing the results of AD subpopulations according to the stage of disease, we found a significantly higher MMW adiponectin presence in early and advanced stages of disease patient subpopulations. Additionally, a marked increase of HMW adiponectin in the early stage of AD was observed in comparison to

the control group. Furthermore, after adjustment of the obtained data to BMI, we revealed an enhancement of total adiponectin, and HMW and MMW fractions in AD patients with respect to the controls. It is important to notice that in the studied group of Alzheimer's disease patients, there were no correlations observed between adiponectin array and markers of adiposity: BMI, and waist and hip measurements. Therefore, it could be speculated that the production of adiponectin and its isoforms in AD is at least partially independent of body mass. However, this hypothesis needs confirmation in further studies.

To date, there is no expanded database concerning adiponectin fractions in neurodegenerative diseases including AD. The Kitagawa research group examined HMW-adiponectin as a possible factor in the development of dementia. Results from their prospective research indicate that the risks of dementia in patients with increased and decreased HMW adiponectin levels were similar. The authors concluded that the level of HMW adiponectin in serum has no association with future dementia including AD [37]. In concordance with those results, we also did not observe a marked correlation between HMW adiponectin and MMSE. Interestingly, in individuals with Alzheimer's disease, we revealed only one correlation (negative) between LMW adiponectin and MMSE.

Furthermore, little is known about adiponectin levels in the central compartment, the brain itself, and cerebrospinal fluid. Interestingly, the majority of adiponectin circulating in the CNS in healthy humans represents the trimer form of adiponectin [38]. This is in opposition to the pattern of adiponectin forms in the periphery [31], where the major biological activity is expressed by HMW. The total concentration of adiponectin in the central compartment of CSF is low and it is about 0.01% of the peripheral concentration, and it decreases in the course of AD [14, 38]. Waragai et al. revealed that in AD patients, CSF adiponectin concentration correlated positively with the MMSE scale. Moreover, in AD brains adiponectin was stained in neurofibrillary tangles, and immunoblot analysis showed that LMW trimer was significantly lower than in brains of non-demented individuals [39]. On the other hand, Une et al. did not show a significant difference in total adiponectin levels in CSF between AD and normal cognitive subjects, but the group of AD individuals was small (27 subjects) [40]. These results indicate that adiponectin homeostasis is probably disturbed in the brains and CSF of individuals suffering from AD.

There are significantly more reports concerning the peripheral concentrations of total adiponectin in AD patients. Our findings of higher total adiponectin concentration in the peripheral blood of AD individuals are in agreement with published data. The study of Khemka et al. confirmed that adiponectin concentration is elevated in individuals suffering from AD [41]. Also, Une et al. revealed that the level of plasma adiponectin was enhanced in AD when compared with the controls [40]. Similarly, the group of Waragai reported that serum levels of adiponectin were significantly increased in AD patients in comparison with healthy controls [39]. Moreover, total adiponectin in sera in this study, similarly to our findings, did not correlate with clinical assessment of cognitive decline with use of MMSE [39]. Furthermore, a meta-analysis concerning adiponectin in AD confirmed higher peripheral levels of this peptide in AD individuals with respect to the controls [42]. Waragai et al. hypothesised that an enhanced concentration of adiponectin in the course of AD may reflect a compensatory response to the abnormally reduced activity of insulin/IGF-1 receptor signalling pathways in AD or might instead be due to decreased activity of adiponectin receptor signalling [14]. Interestingly, results from the Framingham Heart Study indicate that women in whom increased total adiponectin levels were found had a higher risk of AD and all-cause dementia in comparison to those with adiponectin values less than the median [43].

Conversely, the results of Warren et al. did not reveal any significant differences in total adiponectin levels between AD individuals and cognitively normal controls. However, their studied group contained participants of both sexes (males and females). Moreover, BMI significantly varied between the analysed populations [44]. Bigalke et al. also failed to find any significant differences in total adiponectin levels between AD subjects and age- and weight-matched healthy controls [45]. Interestingly, the group of Dukic reported that adiponectin concentration was not markedly different between AD, vascular dementia, and controls with and without mild cognitive impairment (MCI) [46].

In contrast, the group of Teixeira found that circulating adiponectin levels were lower in individuals with mild cognitive impairment, regarded as a prodromal stage of AD, and Alzheimer's disease than in the non-demented controls. Furthermore, the results of total adiponectin measurements did not predict a cognitive decline, from normal cognition to MCI or from MCI to AD in the follow-up [47]. Also, adiponectin results were reported to be independent of confounding factors including BMI and gender. Regrettably, the authors included individuals with diabetes mellitus and dyslipidaemia. Nevertheless, these medical conditions may negatively influence total adiponectin measurements.

Previous studies have reported the impairment of central and peripheral glucose and insulin homeostasis

in AD [25, 48, 49]. It was also established that the risk of AD is increased by 50–60% in individuals with type 2 diabetes [49]. Under physiological conditions, insulin binds to insulin receptors that subsequently activate insulin receptor substrate 1 (IRS1), extracellular signal-related kinase/mitogen-activated protein kinase, and PI3 kinase/Akt pathways. Moreover, insulin also inhibits glycogen synthase kinase-3 [50]. Improper insulin activity affects beta-amyloid accumulation and the phosphorylation of tau [29]. The results of the study by Ng et al. provided evidence of the relationship between insulin and adiponectin. The authors found in the animal model of adiponectin-knockout mice that cerebral insulin resistance developed in aged adiponectin-KO mice with attenuated AMPK activation and impaired insulin signalling. Furthermore, these authors, in the in vitro part of the experiment, revealed that adiponectin improved neuronal insulin activity because insulin sensitivity was enhanced. Finally, AdipoR1-mediated adiponectin activation resulted in a decrease of beta-amyloid production, presumably through GSK3β inhibition [19].

Our research revealed enhanced insulin values in AD patients in comparison to the controls. However, we failed to find any significant differences when analysing HOMA-IR between the groups, but we found in the AD group several correlations between insulin and HOMA-IR, and other examined parameters. We reported a negative correlation between total adiponectin and HOMA-IR. Subsequently, MMW adiponectin concentration correlated negatively with insulin level and HOMA-IR. It should be noticed that participants of our study did not suffer from diabetes mellitus type 2.

Data of other authors are contradictory. A longitudinal study from Luchsinger et al. resulted in the conclusion that fasting hyperinsulinaemia is a risk factor of developing AD [51] . Contrary, Van Himbergen et al. indicated that in the cohort of subjects from the Framingham Heart Study, the levels of plasma insulin, glucose, and glycated albumin were not associated with Alzheimer's disease or all-cause dementia. On the other hand, Ma et al. in their meta-analysis confirmed an increased peripheral insulin level in subjects suffering from AD [42]. Waragai et al. observed also that in individuals with AD, plasma insulin and triglycerides were decreased and HDL and LDL cholesterol levels were higher than in the controls [39]. Moreover, et al. confirmed that insulin levels were enhanced in subjects diagnosed with AD [41].

Summarising, the discussed data above suggest that metabolically important factors, adiponectin, adiponectin fractions and insulin, are disturbed in the course of Alzheimer's disease. Our results indicate a possible link between adiponectin variations and AD. Also, other issues concerning the role of adiponectin in AD are still under discussion and further extensive investigation is needed.

We are aware of some limitations of our study, which include the size of the study group, especially after dividing into subgroups, or not including an analysis of the potential role of acetylcholinesterase inhibitors as hypothetical disruptors of adiponectin secretion. Nevertheless, the reported study is the first analysis of the full spectrum of adiponectin forms in the course of Alzheimer's disease. We hypothesise that the changes in adiponectin profile observed in our AD group result from a compensatory mechanism against neuropathological processes and central adiponectin homeostasis impairment. Up-regulation of peripheral adiponectin production may result from AdipoRs dysfunction.

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### *Declaration of interest*

All authors declare no conflict of interests.

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