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# Association of adipose tissue inflammation and physical fitness in older adults

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## Abstract

An active lifestyle is of key importance for reduction of obesity and inflammation, as well as circulating levels of adipokines. Therefore, the aim of our study was to assess the relationship of physical fitness with chronic inflammatory status, and to evaluate biomarkers useful in the analysis of adipose tissue dysfunction. Sixty-three older adults (69.6 ± 5.1 years) were allocated to a high $n = 31$ (women $n = 23$ and men $n = 8$ male) or low physical fitness $n = 32$ (women $n = 29$ and men $n = 3$) group based on gait speed values (1.4–1.8 m/s or ≤ 1.3 m/s). The gait speed correlated with hand grip strength ($r_s = 0.493$, $p = 0.0001$) and with leptin level ($R = -0.372$, $p = 0.003$), which shows the benefits of physical activity on muscle strength and circulating adipokines. In low physical fitness group, 58.1% individuals had adiponectin to leptin ratio (Adpn/Lep) < 0.5 revealing dysfunction of adipose tissue and high cardiometabolic risk; 20% of the group were obese with BMI ≥ 30 kg/m$^2$. In high physical fitness group, 25.8% of individuals had Adpn/Lep ≥ 1.0 i.e., within the reference range. Markers of systemic inflammation were significantly related to physical fitness: CRP/gait speed ($r_s = -0.377$) and HMGB-1/gait speed ($r_s = -0.264$). The results of the ROC analysis for Adpn (AUC = 0.526), Lep (AUC = 0.745) and HMGB-1 (AUC = 0.689) indicated their diagnostic potential for clinical prognosis in older patients. The optimal threshold values corresponded to 1.2 µg/mL for Adpn (sensitivity 74.2%, specificity 41.9%, OR = 1.4, 95%CI 0.488–3.902), 6.7 ng/mL for Lep (sensitivity 56.2%, specificity 93.5%, OR = 14.8, 95%CI 3.574–112.229), 2.63 mg/L for CRP (sensitivity 51.6%, specificity 84.3%, OR = 4.4, 95% CI 1.401- 16.063) and 34.2 ng/mL for HMGB-1 (sensitivity 62.0%, specificity 86.6%, OR = 12.0, 95%CI 3.254—61.614). The highest sensitivity and specificity were observed for Leptin and HMGB-1. The study revealed changes in inflammatory status in older adults at various levels of physical fitness and demonstrated diagnostic usefulness of adipokines in the assessment of adipose tissue inflammation.

**Keywords** Physical fitness, Older adults, Proinflammatory cytokine, Adipose tissue, Adipokine

## Introduction

The global obesity pandemic is affecting all age groups. Assessing obesity is important for developing effective strategies for both treatment and prevention of obesity. There are various methods for measuring obesity, each with its strengths and weaknesses [1]. The most popular method for assessing obesity is the body mass index (BMI). According to the World Health Organization (WHO), a body mass index (BMI) of 30 kg/m$^2$ or more is considered obesity. Increased BMI has been shown to be pathogenically associated with an increased risk of

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insulin resistance (IR), type 2 diabetes (T2D) and metabolic syndrome (MetS), the presence of which increases the risk of cardiovascular events [2]. Other methods also recognized by the WHO include the waist-to-hip ratio (WHR), where abdominal obesity is defined as a WHR > 0.90 for men and 0.85 for women [1]. Obesity superimposed on aging is an additional risk factor for older age groups, where the incidence of chronic diseases and complications increases [3]. According to Khanna et al. [4] increasing visceral fat in older adults is involved in systemic inflammation development due to its direct access to and secretion of free fatty acids and inflammatory cytokines into the portal circulation.

White adipose tissue (WAT), the most abundant type of fat in humans, is not only an energy store in the body, but also an important regulator of both metabolic pathways and inflammation [4]. Adipocyte hypertrophy and reorganization of the tissue environment accompany reduced expansion of restricted adipocytes, which causes them to be distant from blood vessels, resulting in hypoxic areas, immune cell infiltration, and inflammatory signaling. WAT expansion is dependent on tight regulation of transcription factors, gene expression, and multiple inflammatory signaling mediators such as cytokines, which play a role in lipogenesis and lipolysis, and thus energy regulation, as well as in remodeling the surrounding microenvironment [5]. Since individuals with obesity show a greater tendency towards older biological age, the term "adipaging" has been used to define the inflammatory state associated with chronic obesity [6]. Adipose tissue aging is accelerated by obesity, and increased oxidative stress and thus greater production of reactive oxygen species may result in decreased immune function [7]. Overabundance of classical proinflammatory cytokines interleukin-1β (IL-1β), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNF-α) in obese individuals may outbalance the effects of the anti-inflammatory adipokines and contribute to the redistribution of lipids in favor of central adiposity [8]. The accumulation of triglycerides in different tissues is an essential and important risk factor for diabetes and cardiovascular disease and an essential indicator of adipose tissue dysfunction [9]. Leptin, produced mainly by white adipose tissue, plays various roles in the immune and hormonal systems. The interactions between leptin and inflammation are bidirectional: proinflammatory cytokines increase leptin synthesis and release, which in turn may perpetuate a loop of chronic inflammation [10]. Vega and Grundy [11] and Frühbeck et al. [12] proposed the adiponectin/leptin (Adpn/Lep) ratio as a new marker of adipose tissue dysfunction. As this emerging biomarker is significantly reduced in patients with the metabolic syndrome, it is found to correlate better with insulin resistance than adiponectin or leptin alone [12] and is also negatively correlated with markers of low-grade chronic inflammation, such as C-reactive protein (CRP) [13]. The high mobility group protein B1 (HMGB-1) seems to be a promising indicator for the early diagnosis of obesity and antagonizing HMGB-1 inflammatory pathway could bring on new therapeutic targets to counteract obesity-associated pathologies [14].

Inflammation contributes to malnutrition through reduced food intake, as well as altered metabolism with increased resting energy expenditure and increased muscle catabolism. The Global Leadership Initiative on Malnutrition criteria for the diagnosis of malnutrition listed hand grip strength as a possible criterion to define malnutrition [15, 16].Other alternative possibilities of controlling malnutrition in the elderly may be nutritional indices: Prognostic Nutritional Index (PNI) which takes into account albumin level and lymphocyte value in its formula and The Geriatric Nutritional Risk Index (GNRI) which also takes into account albumin and body weight [17]. Taking care about proper eating habits, calorie restriction and regular physical activity in particular, enhance the reduction of inflammation in obesity and related metabolic dysfunctions [4]. According to De la Rosa et al. [18] and Bouassida et al. [19] regular physical activity contributes to reduction of inflammatory markers such as CRP, IL-6 and TNF-α, reduces the level of body fat, plays an important role in energy expenditure and has a positive effect on the concentration of hormones (insulin, cortisol) or metabolites (free fatty acids, triglycerides). In old age, mobility problems resulting in decreased walking speed are considered important but also early warning signs of functional disability [20]. In fact, walking is a component of activities of daily living (ADL), and it is important for the main determinants of quality of life in older age such as maintaining independence in ADL, enjoying an adequate level of social interaction, and retaining good emotional vitality. In older adults, gait speed has been described as the 'sixth vital sign' because it is a core indicator of health and function in aging and disease. In fact, gait speed is an objective measure of physical functioning, with slower performances associated with mobility disability and other adverse health-related outcomes in older age. Gait speed lower than 0.8 m/sec may be a reliable cut-off to identify subjects at increased risk for disability, hospitalization, institutionalization, and increased mortality while improvement of usual gait speed may ensure a longer survival in older adults. Gait speed measured over long distances (400 m) is a good indicator of cardio-respiratory fitness, and it may be a better early indicator of the overall physical health compared to gait speed over short distances [21]. Previous studies have highlighted

the important role of gait speed scores, where an increase of 0.1 m/s in gait speed is associated with an increase in predictable survival with a variability of 19 to 87% for men and 35% to 91% for women [22]. High levels of physical activity and high performance of gait speed are essential for safely performing instrumental activities of daily living. Gait speed of 1 m/s and higher is considered the ideal minimum threshold for an older adult to have a more stable gait patter, and also is a strong indicator of health and quality of life [20]. According to Middleton et al. [23] and Studenski [24] emphasize that the value of gait speed > 1.3 m/s defines elderly people as extremely fit, which is related to the high level of physical activity that has been developed throughout life. There are still few studies that have assessed the association between physical activity and BMI in older people [25]. For example, a study by Woo et al. [26] on a group of four thousand men and women showed an increased impairment in activities of daily living in people aged ≥ 65 years with obesity compared to those with low or normal body weight. Contrastingly, another study involving 6,279 community dwelling adults aged ≥ 60 years demonstrated a lower probability of impairment in physical and functional fitness in older obese people who engaged in moderate or vigorous intensity exercise at least once a week [27]. Findings from studies between gait speed and IL-6 indicate that higher levels of IL-6 may be associated with poorer outcomes in older adults and an increased risk of severe mobility disability [21]. In turn research conducted by Gomez-Merino et al. [28] also showed significant benefits of a three-week activity programme on lowering leptin levels, which was linked to the decrease in catecholamines and hypoinsulinemia induced by the analyzed exercise. Results from the meta-analysis conducted by Guo et al. [29] indicated that both aerobic and resistance exercises could significantly reduce CRP levels in the obese and overweight population, with the former showing a more pronounced regulatory effect on CRP. The recent literature has also highlighted an association between slow gait speed, overweight, and obesity in a nationwide population-based sample of older adults [30]. Research conducted by Orchard et al. [31] showed that even such easy-to-perform and widely available tests/measurements as hand grip strength and gait speed can predict the development of cognitive decline or dementia. Nevertheless, there are not many studies that assess the relationship between the physical fitness of older people (measured by the gait speed value) and the impact on reducing inflammation. Our research hypothesis is that daily physical activity assessed by gait speed measurement in older adults has a beneficial effect on body weight, which translates into a reduction in chronic inflammation. In turn, understanding the importance of regular physical activity in older adults can prevent falls, and malnutrition, and also favorably affect the incidence of lifestyle diseases. Therefore, the aim of our study was to assess the relation of current physical fitness with adipose inflammatory status and, secondly, to assess biomarkers useful in the analysis of adipose tissue dysfunction.

## Materials and methods

### Participants

One hundred and four older adults from Poland aged 69.6 ± 5.1 were recruited for the study. The Polish group recruited for the study were students at the University of the Third Age (U3A). It is an organization that aims to activate seniors socially and intellectually and to prevent social exclusion of older people. The seniors recruited for the study were active participants of U3A and their activity was related to participation in various forms of activity, e.g. learning languages, crocheting, choir. All of the recruited older adults have the same access to medical health care which means that health care standards and facilities were accessible to the patients regardless of their financial resources or place of residence. The participants' current health status was assessed using a standardized health questionnaire described by Durstine and Moore [32]. Furthermore, the current health status of the participants was assessed on the basis of medical records at a routine follow-up visit to a primary care physician. The inclusion criteria included the age ≥ 60 years, the ability to participate in the study independently, and no hospitalization in the last 6 months. The exclusion criteria involved: neurological disorders, acute infectious and oncologic diseases, or an implanted cardiac pacemaker. Eventually, 63 participants (women $n = 52$ and men $n = 11$) were qualified for the study as 41 individuals were excluded owing to hospitalization ($n = 12$), active infections ($n = 10$), lack of motivation or availability to attend the study ($n = 19$). The medications taken by the participants only included antihypertensive and hypolipidemic drugs as well as anticoagulants including anti-platelet agents. All the patients were classified into two groups according to Middleton et al. [23] recommendations: high physical fitness $n = 31$ *(*$n = 23$ female and $n = 8$ male), and low physical fitness $n = 32$ ($n = 29$ female and $n = 3$ male) if their gait speed was 1.4–1.8 m/s and ≤ 1.3 m/s respectively.

### Consent of the bioethics committee

The Bioethics Commission at Regional Medical Chamber Zielona Gora, Poland approved the study (No21/103/2018) in accordance with the Helsinki Declaration. Signing an informed consent for participation in the study by each participant was also a prerequisite for their inclusion.

### Biomedical data

Assessment of obesity in older patients can be performed using impedance analysis. It involves electrical resistance measurement, which consists of resistance and reactance of soft tissues through which a low-intensity electric current is passed. It is a noninvasive method of measuring body composition widely used in clinical practice. Body mass (BM), fat-free mass (FFM) and fat mass (FM) were estimated by a bioelectrical impedance method using Tanita Body Composition Analyzer MC-980 (Japan) calibrated prior to each test session in accordance with the manufacturer's guidelines. Duplicate measures were taken with the participants in a standing position; the average value was used for the final analysis. The recurrence of measurement was 98%. The measurements were performed in the morning between 7:00 and 9:00 a.m., before blood sampling after an overnight rest with an empty bladder. Patients were advised to avoid alcohol consumption 24 h before the examination. Moreover, the study participants were also advised to refrain from caffeine consumption and physical exertion about 12 h before the test. Contraindication included implanted metal materials, such as: pacemaker, defibrillator, stent and metal suture in the heart or blood vessel. According to WHO recommendations [33], normal weight was determined where body mass index (BMI) ranged from 18.5 to 24.9 kg/m$^2$, overweight meant that the values ranged from 25 to 29.9 kg/m$^2$, and obesity was indicated by the values $\geq$ 30 kg/m$^2$. Waist circumference (WC) [cm] was measured using a non-elastic tape at the midpoint between the last rib and the upper edge of the iliac crest at the end of the expiratory movement. A WC greater than or equal to 94 cm for men and greater than or equal to 80 cm for women is often used as a criterion to identify central or abdominal obesity [34]. WHR used in this analysis considers body fat distribution. WHR is obtained by dividing the WC by the hip circumference using the same units of measurement for both. The World Health Organization defines abdominal obesity as a WHR value above 0.90 for the male population and above 0.85 for the female population [2]. According to Kamińska et al. [35] each of the anthropometric variables, including BMI or WHR, provides information about comorbidities of old age, including metabolic syndrome, which are related to inflammation. Moreover, the results of Malshe and Udipi [36] also indicate that WHR assessment is an effective and simple anthropometric variable that has the potential to detect central obesity and its associated inflammation even in women with a BMI that falls within the reference range. The isometric hand grip strength was measured using a hand dynamometer KERN type MAP130 (Germany). Hand grip strength was measured twice in a sitting position with arms raised at the sides. Participants were instructed to squeeze the dynamometer as hard as they could. The results were averaged and reported in kg. According to the meta-analysis of normative data, hand grip strength values of 16 kg for women and 27 kg for men could be accepted as cut-offs point for undernutrition risk across Europe, Canada, United States, Australia, and Japan [37].

### Functional fitness

The 6-min walk test (6MWT) was accomplished according to technical standards of European Respiratory Society and American Thoracic Society [38]. A marked walkway was laid out in a 50-m rectangular area (dimensions: 20 × 5 m), with cones placed at regular intervals to indicate the distance covered. The aim of the test was to walk as fast and as far as possible within the allotted time (6 min). Before starting the test, the patient rested for about 10 min in a sitting position as recommended. The study was performed in patients on an empty stomach or after a light meal. Study participants were informed that flat sports shoes were required to take part in the test. Participants' blood pressure was measured both before and after the test. The exclusion criteria included a heart attack one month before the planned examination and blood pressure $\leq$ 180/100 mmHg. Every 60 s each patient was encouraged by the following phrases: "Keep up the good work"; „You have 5 min to go" or „You are doing well"; „You have only 3 min to go". For safety reasons, there was a doctor and a paramedic in the room where the test took place, and the study participants were informed that they could stop/end the test at any stage. The total distance walked in the test was recorded and the 6MWT gait speed was then calculated by the following equation: 6MWT gait speed (m/s) = total distance(m)/360 s. After a period of rest of about 15–20 min, blood pressure (BP) was measured by automatic manometry using a GE HealthCare (Germany) with an appropriate cuff size based on our previous research by Tylutka et al. [39]. The gait speed ranging from 1.4 to 1.8 m/s classified the participants as physically active older adults and the gait speed $\leq$ 1.3 m/s classified them as inactive older adults according to Middleton et al. [23].

### Peripheral blood samples

Blood samples from the patients were taken in the morning from the median cubital vein using S-Monovette-EDTA $K_2$ tubes (Sarstedt, Austria) for morphology and S-Monovette—serum tubes were used for other biochemical markers. The patients were fasting 12 h before the examination. Serum samples were left to clot for 45 min before centrifugation and then centrifuged at 3000 g for 10 min. A DM0412 clinical centrifuge was used to centrifuge the biological material. Aliquots of serum were stored at -80 °C until testing according to our previous research by Tylutka et al. [39–41].

### Hematological variables

The hematological parameters: white blood count (WBC) granulocytes (%GRA), lymphocytes (%LYM), red blood cells (RBC), hemoglobin (HB), hematocrit (HCT), mean corpuscular volume (MCV), mean cells hemoglobin (MCH), mean corpuscular/hemoglobin concentration (MCHC), platelets (PLT) were determined by using 3 diff BM HEM3 Biomaxima (Poland) based to our previous research by Tylutka et al. [39–41].

### Biochemical and nutritional variables

Triglycerides (TG), high density lipoprotein (HDL), low density lipoprotein (LDL), and total cholesterol (TC), were determined by using BM200 Biomaxima (Poland). Before starting the analysis, each study was calibrated using the low and high controls dedicated to the BM200 analyzer. Non-high-density lipoprotein (non-HDL) cholesterol was calculated by subtracting HDL from the total cholesterol concentration. Oxidized low-density lipoprotein (oxLDL) was determined using ELISA kits from SunRed Biotechnology Company (Shanghai, China). The serum glucose was evaluated by using commercially available reagents and a mobile spectrophotometer DP 310 Vario II (Germany). Insulin was measured using a high sensitivity assay in duplicate by means of commercial fir for DRG International (USA) of 0.001 mg/L. Homeostatic Model Assessment Insulin Resistance (HOMA-IR) was calculated according to Sitar-Tăut et al. [42], HOMA-IR = insulin (μU/mL) × glycaemia (mg/dL)/405. Nutritional assessments were performed using a Prognostic Nutritional Index (PNI). Albumin needed to calculate the PNI was converted from g/l units to g/dl units. PNI was calculated using the formula PNI = (10 × albumin g/dL) + (0.005 × total lymphocyte counts/$mm^3$) according to Zhang et al. [43]. Albumin in the formula that represents the nutritional status of the organism, and lymphocytes are an important immune indicator. An imbalance between albumin and lymphocytes is closely correlated with a poorer prognosis for the patient in old age [44]. Another nutritional parameter i.e. Geriatric Nutritional Risk Index (GNRI), was calculated using the formula by Bouillanne et al. [45]. The GNRI index is used to identify nutritional complications in the elderly and can assess the nutritional status of patients with different age-related diseases. It has been shown to correlate with mortality in the elderly [46].

$$GNRI = [1.489 \times albumin\ (g/L)] + [41.7 \times (weight/WLo)]$$

where: WLo is the ideal weight, which was calculated by the following formula:

$$For\ men:\ H - 100 - [(H - 150)/4]$$

$$For\ women:\ H - 100 - [(H - 150)/2.5]$$

where: $H$ is the height.

Based on the values of GNRI, four grades of nutrition-related risk were defined: major risk (GNRI: < 82), moderate risk (GNRI: 82–92), low risk (GNRI: 92–98), and no risk (GNRI: > 98).

### Immunological variables

Adiponectin, leptin and ghrelin were determined by using ELISA kit from R&D system (USA), DRG International (USA) and SunRed Biotechnology Company (Shanghai, China). The adiponectin/leptin (Adpn/Lep) ratio was calculated according to Frühbeck et al. [12]. In turn, leptin/adiponectin (Lep/Adpn) ratio was calculated according to Chen et al. [47]. A proinflammatory HMGB-1 was determined by using ELISA kits from SunRed Biotechnology Company (Shanghai, China) with detection limits of 0.526 ng/mL. HMGB-1 plays a key role in both the innate and adaptive response to promote immune response to infectious stimuli. Targeting the release and activity of HMGB-1 provides a strategy for the treatment of various diseases, especially infection/inflammation or tissue damage. CRP was measured using a high-sensitivity assay in duplicate by means of a commercial kit from DRG International (USA) with a detection limit of 0.001 mg/L. The albumin level was also determined by using BM200 Biomaxima (Poland).

### Statistical analysis

All statistical analyses were performed using R system 4.2.1 [48] (accessed Jun 2, 2023). The data were described as measures of central tendency (mean and medians) and measures of dispersion [standard deviation (SD) or interquartile range (IQR)] for numerical variables. To check data normality, the Shapiro–Wilk test was applied. A variable was considered as having a normal distribution if $p < 0.05$ and as asymmetrical distribution if $p > 0.05$. When the normal distribution was assumed, Student's $t$-test was used, and when the assumptions of the normal distribution were not met, the Wilcoxon—test was used. Spearman rank correlation coefficient ($r_s$) or Pearson correlation coefficient (R) was used to assess the agreement between lifestyle exercise and the continuous independent variables. The optimal threshold value for clinical stratification (cut-off value) was obtained by calculating the Youden index. Statistical significance was set at $p < 0.05$ and 95% confidence interval.

## Results

### Biomedical data and basic characteristics of the group

Body mass index values ranged from 20.7 to 36.2 kg/$m^2$ in the low physical fitness group, and from 18.0 to 33.9 kg/$m^2$ in the group of high physical fitness (Table 1). In the low physical fitness group, 50% of the

**Table 1** Basic characteristics of the study group

| Variables | References value | Low physical fitness<br>*n* = 32<br>*n* = 29 female and *n* = 3 male | | High physical fitness<br>*n* = 31<br>*n* = 23 female and *n* = 8 male | | *p*-value |
|---|---|---|---|---|---|---|
| | | mean ± SD | med (iqr 25%-75%) | mean ± SD | med (iqr 25%-75%) | |
| Age [years] | - | 70.6 ± 6.0 | 70 (67.0–74.7) | 67.0 ± 3.5 | 66.0 (65.0–70.0) | 0.013 |
| Weight [kg] | - | 69.5 ± 11.4 | 68.8 (62.2–75.6) | 69.0 ± 14.2 | 64.4 (58.0–78.0) | 0.881 |
| Height [cm] | - | 159.9 ± 7.0 | 157.7 (156.0–162.3) | 164.6 ± 8.2 | 163.7 (160.3–171.0) | 0.018 |
| BMI [kg/m$^2$] | 18.5–24.9 | 27.1 ± 3.8 | 27.1 (24.8–29.6) | 25.0 ± 3.4 | 23.8 (22.7–27.1) | 0.021 |
| FFM [kg] | - | 45.4 ± 7.6 | 43.2 (40.9–46.8) | 48.9 ± 10.2 | 44.6 (41.7–54.1) | 0.277 |
| FM [kg] | - | 24.2 ± 6.7 | 22.9 (20.3–28.4) | 20.1 ± 7.4 | 18.0 (14.5–23.6) | 0.028 |
| FM% | M: 12–25<br>F: 24–36 | 34.4 ± 5.9 | 34.0 (31.1–38.5) | 28.7 ± 9.7 | 29.0 (25.0–33.4) | 0.001 |
| MM [kg] | - | 42.8 ± 7.2 | 40.8 (38.6–44.2) | 46.4 ± 9.7 | 43.2 (39.6–51.4) | 0.208 |
| WC [cm] | M: ≤ 94<br>F: ≤ 80 | 87.8 ± 10.7 | 88.0 (80.7–94.5) | 84.6 ± 11.6 | 81.0 (74.7–94.0) | 0.205 |
| HC [cm] | - | 104.4 ± 7.2 | 103.0 (99.7–110.0) | 100.9 ± 5.6 | 101.0 (96.0–106.0) | 0.049 |
| WHR | M: < 90<br>F: < 85 | 0.8 ± 0.1 | 0.8 (0.8–0.9) | 0.8 ± 0.1 | 0.8 (0.8–0.9) | 0.417 |
| Hand grip strength | M: > 27<br>F: > 16 | 21.8 ± 6.0 | 20.7 (19.0–24.7) | 26.9 ± 11.1 | 24.2 (20.5–32.9) | 0.030 |
| 6MWT [m] | | 416.3 ± 52.0 | 435.0 (373.8–462.2) | 530.3 ± 32.8 | 530.0 (500.0–552.5) | < 0.001 |
| Gait speed [m/s] | > 0.8 | 1.2 ± 0.1 | 1.2 (1.0–1.3) | 1.5 ± 0.1 | 1.5 (1.4–1.6) | < 0.001 |
| SBP [mmHg] | < 140 | 137.5 ± 16.1 | 138.0 (124.0–143.0) | 137.2 ± 18.9 | 134.0 (125.5–146.0) | 0.935 |
| DBP [mmHg] | < 90 | 82.5 ± 11.0 | 82.5 (76.7–85.2) | 82.4 ± 9.6 | 82.0 (76.0–89.5) | 0.966 |
| Heart rate [bpm] | 60–70 | 75.8 ± 10.5 | 73.0 (67.7–87.0) | 71.7 ± 7.4 | 71.0 (66.0–76.5) | 0.074 |

*BMI* Body mass index, *FFM* Fat-free mass, *FM* Fat mass, *MM* Muscle mass, *WC* Waist circumference *HC* Hip circumference, *WHR* Waist-hip-ratio, *6MWT* 6-min walk test, *SBP* Systolic blood pressure, *DBP* Diastolic blood pressure, *SD* Standard deviation, *Me* Median, *IGR* Interquartile

individuals were classified as overweight (BMI 25.0—29.9 kg/m$^2$) and 28% of them had normal body weight (BMI 18.5–24.9 kg/m$^2$), whereas, in the high physical fitness group 10% were classified as obese (BMI ≥ 30 kg/m$^2$), 33% of individuals had overweight and the majority of these respondents (57%) had normal body weight. There were statistically significant differences between the groups in standard anthropometric indices like: FM ($p = 0.028$) and FM% ($p = 0.001$). The BMI value was strongly correlated with FM ($R = 0.880$, $p < 0.001$), FM% ($R = 0.635$, $p < 0.001$) and FFM ($R = 0.421$, $p = 0.0006$). Women accounted for 91% of the respondents in the low physical fitness group and 74% of the respondents in the high physical fitness group. Regardless of the disproportions in the groups, we showed significant differences between women and men in BMI, FM%, muscle mass (MM) or FFM ($p < 0.01$) which confirms anthropometric gender differences and the physiological effect of hormones on adipose tissue. In the low physical activity group, $n = 12$ respondents (37.5%) showed WHR higher than 90 in men or 85 in women, while in the high physical fitness group, $n = 6$ (19.4%) participants showed WHR above the reference value. Hand grip strength, a simple measurement used to assess the general health of the elderly, showed statistically significantly higher values in physically active older adults (26.9 ± 11.1) compared to the group with low physical fitness (21.8 ± 6.0). Hand grip strength in the low physical fitness group indicating malnutrition was shown by 15.6% of the subjects. In the high physical fitness group, only one patient (3%) achieved a value below the indicated reference values. The result of 6MWT was higher by 40% in the high than the low physical fitness group. Above 94% of the participants achieved a normal gait speed ≥ 1 m/s according to the reference values by Middleton et al. [23]. The gait speed values were negatively correlated with the level of leptin ($R = -0.372$, $p = 0.003$) and correlated positively with hand grip strength ($r_s = 0.493$, $p = 0.0001$) which is related to the benefits of a physical fitness on adipokine levels and hand grip strength.

#### Hematological variables

In both groups, white blood cells count was recorded within the reference values. In the red blood cell system, only RBC was significantly lower in the high physical fitness group than low physical fitness individuals ($p = 0.029$). Mean hemoglobin levels were within the reference range and amounted to 14.1 ± 1.0 g/dL for the

**Table 2** Hematological variables

| Variables | Reference values | Low physical fitness<br>*n* = 32<br>*n* = 29 female and *n* = 3 male | | Hight physical fitness<br>*n* = 31<br>*n* = 23 female and *n* = 8 male | | *p*-value |
|---|---|---|---|---|---|---|
| | | mean ± SD | med (iqr 25%-75%) | mean ± SD | med (iqr 25%-75%) | |
| Leukocytes [$10^3$/μL] | 5.0—11.6 | 6.0 ± 1.6 | 5.6 (4.9–6.8) | 5.4 ± 1.3 | 5.6 (4.9–6.0) | 0.309 |
| Lymphocytes [$10^3$/μL] | 1.3—4.0 | 2.0 ± 0.7 | 1.8 (1.5–2.6) | 1.9 ± 0.6 | 1.9 (1.3–1.8) | 0.267 |
| Granulocytes [$10^3$/μL] | 2.4—7.6 | 3.7 ± 1.3 | 3.4 (2.7–4.4) | 3.3 ± 0.8 | 3.3 (2.7–3.6) | 0.349 |
| LYM% | 19.1—48.5 | 34.4 ± 8.7 | 36.1 (27.5–41.6) | 33.8 ± 5.9 | 33.9 (29.6–37.2) | 0.719 |
| GRA% | 43.6—73.4 | 60.2 ± 8.9 | 58.3 (53.8–66.9) | 60.7 ± 5.7 | 61.4 (56.3–65.0) | 0.788 |
| RBC [$10^3$/μL] | F 4.0—5.5<br>M 4.5—6.6 | 4.6 ± 0.3 | 4.5 (4.4–4.8) | 4.4 ± 0.3 | 4.5 (4.3–4.6) | 0.029 |
| HB [g/dL] | F 12.5—16.0<br>M 13.5—18.0 | 14.1 ± 1.0 | 14.2 (13.4–14.6) | 13.7 ± 1.0 | 13.8 (13.4–14.2) | 0.184 |
| HCT [%] | F 37—47<br>M 40.0—51.0 | 37.9 ± 2.8 | 38.4 (35.8–39.9) | 36.8 ± 2.7 | 36.7 (35.6–38.2) | 0.208 |
| MCV [fL] | F 80—95<br>M 80—97 | 82.6 ± 3.5 | 82.0 (80.0–85.0) | 83.3 ± 3.5 | 84.0 (81.0–86.0) | 0.441 |
| MCH [pg] | F 27.0—32.0<br>M 26.0—32.0 | 30.7 ± 1.3 | 30.4 (29.9–31.2) | 31.0 ± 4.0 | 31.2 (29.9–31.8) | 0.407 |
| MCHC [g/dL] | F 32.0—36.0<br>M 31.0—36.0 | 37.1 ± 0.6 | 37.2 (36.6–37.6) | 37.2 ± 0.7 | 37.0 (36.6–37.8) | 0.889 |
| PLT [$10^3$/μL] | 150—400 | 231.8 ± 68.7 | 237.5 (210.5–263.0) | 249.5 ± 57.1 | 237.0 (224.0–288.0) | 0.274 |

*LYM* Lymphocytes, *GRA* Granulocytes, *RBC* Red blood cells, *HB* Hemoglobin, *HCT* Hematocrit, *MCV* Mean corpuscular volume, *MCH* Mean cells hemoglobin, *MCHC* Mean corpuscular/hemoglobin concentration, *PLT* Platelets, F Female, M Male, SD Standard deviation, Me Median, IGR Interquartile

low physical fitness group and 13.7 ± 1.0 g/dL for the high physical fitness group. Other parameters of the red blood system, such as MCV, MCH and MCHC, reached higher values in the group of high physical fitness older adults, but did not reach statistical significance. There were no statistically significant differences in the platelets count between the groups (Table 2).

#### Biochemical and nutritional variables

The mean values for triglycerides in both groups were similar and equaled 1.9 ± 0.6 mmol/L in the low physical fitness group and 1.9 ± 0.4 mmol/L in the high physical fitness group (Table 3). Statistically significant differences between the groups were noted in the level TC ($p = 0.039$). Approximately 70% of all the individuals exceeded the reference values for TG > 1.69 mmol/L and 68% of them exceeded the reference values for TC > 5 mmol/L. No significant differences were detected in other parameters of the lipid profile i.e., LDL, HDL and non-HDL. An elevated glucose level was observed in about 15% of the adults in the low physical fitness group and in about 9% of the high physical fitness group. There were statistically significant differences between the groups in the insulin level ($p = 0.046$). However, HOMA-IR value > 2.5 indicating insulin resistance dominated in the group of the low physical fitness (~ 38%). Statistically significant differences were observed between the groups in the two analyzed nutritional indices: PNI ($p = 0.007$) and GNRI ($p = 0.006$). Interestingly, the values of GNRI > 98, indicating no nutrition-related risk, were recorded in 98% of both study groups.

#### Adipokine and immunological variables

The high physical fitness adults showed a statistically significantly lower leptin concentration compared to groups with low physical fitness ($p = 0.0008$). It has already been shown that the reduced ratio of Adpn/Lep concentrations, resulting from excessive synthesis of leptin and reduced secretion of adiponectin, is a better criterion for the assessment of adipose tissue dysfunction than a separate analysis of leptin and adiponectin levels (Table 4). Therefore, Frühbeck et al. [12] suggested that the Adpn/Lep ratio should be considered as a marker of adipose tissue dysfunction with its value ≥ 1.0 regarded as normal, the ratio ≥ 0.5 or < 1.0 as a moderate-medium increased risk, and the ratio < 0.5 indicating a severe increase in cardiometabolic risk. The majority of the individuals in low physical fitness group (58.1%) had Adpn/Lep < 0.5, and in 12.9% of them Adpn/Lep ratio was recorded at ≥ 0.5 or < 1.0, while in the group of high physical fitness older adults Adpn/Lep ≥ 1.0 was observed in 25.8% of them and the ratio ≥ 0.5 or < 1.0 was recorded in 16.2% of the group. Chronic low-grade inflammation plays a key role in the early stage of pre-obesity and obesity. Regulatory

**Table 3** Biochemical variables

| Variables | Reference values | Low physical fitness<br>*n* = 32<br>*n* = 29 female and *n* = 3 male | | High physical fitness<br>*n* = 31<br>*n* = 23 female and *n* = 8 male | | *p*-value |
|---|---|---|---|---|---|---|
| | | mean ± SD | med (iqr 25%-75%) | mean ± SD | med (iqr 25%-75%) | |
| TC [mmol/L] | < 5 | 5.9 ± 1.6 | 5.9 (5.3–6.6) | 5.2 ± 1.4 | 5.4 (4.8–5.9) | 0.039 |
| TG [mmo/L] | < 1.69 | 1.9 ± 0.6 | 1.9 (1.7–2.0) | 1.9 ± 0.4 | 1.8 (1.6–2.0) | 0.483 |
| LDL [mmol/L] | < 2.6 | 3.7 ± 0.7 | 3.5 (3.2–3.9) | 3.4 ± 0.7 | 3.4 (3.1–3.6) | 0.274 |
| HDL [mmol/L] | F < 1.3<br>M < 1.0 | 1.9 ± 0.4 | 1.9 (1.6–2.2) | 1.7 ± 0.5 | 1.8 (1.5–2.0) | 0.118 |
| non-HDL [mmol/L] | < 3.37 | 3.1 ± 0.7 | 3.0 (2.8–3.4) | 3.1 ± 0.7 | 3.1 (2.9–3.4) | 0.714 |
| oxLDL [ng/mL] | - | 3168 ± 2549 | 1878 (1435–3168) | 3299 ± 2300.4 | 2610 (1490–3802) | 0.423 |
| Glucose [mg/dL] | 60—115 | 87.0 ± 28.9 | 87.0 (75.0–99.4) | 91.2 ± 22.6 | 84.4 (79.8–95.1) | 0.956 |
| Insulin [µlU/mL] | - | 11.7 ± 4.7 | 10.4 (9.2–12.7) | 9.7 ± 2.0 | 9.2 (8.7–10.0) | 0.046 |
| HOMA-IR | < 2.5 | 2.7 ± 1.6 | 2.3 (1.7–2.9) | 2.2 ± 0.9 | 1.9 (1.7–2.5) | 0.254 |
| PNI | - | 44.6 ± 2.2 | 44.6 (44.2–45.7) | 43.2 ± 1.7 | 43.2 (42.1–44.1) | 0.007 |
| GNRI | > 98 | 118.0 ± 8.3 | 118.9 (113.8–122.8) | 112.3 ± 7.0 | 111.7 (108.3–114.8) | 0.006 |

*TG* Triglycerides, *TC* Total cholesterol, *LDL* Low density lipoprotein, *HDL* High density lipoprotein, *oxLDL* Oxidized low density lipoprotein, *HOMA-IR* Homeostatic Model Assessment of Insulin Resistance, *PNI* Prognostic nutritional index, *GNRI* Geriatric Nutritional Risk Index, *SD* Standard deviation, Me Median, *IGR* Interquartile

mechanisms within lipid-laden adipocytes act to control local cytokine production and to inhibit lipid storage in hypertrophied adipocytes. This relationship may be disrupted in persistent obesity because of the chronic systemic inflammatory response [4]. Statistically significant differences between the analyzed groups were found in the level of proinflammatory cytokine HMGB-1 ($p = 0.005$) and acute phase protein—CRP ($p = 0.01$). There were also observed a negative correlation between CRP and gait speed ($r_s = -0.377$, $p = 0.002$) and also between gait speed and HMGB-1 ($r_s = -0.264$, $p = 0.041$) which strengthens the argument that gait speed is related to the severity of inflammation in older adults.

### Assessment of specific variables in the analysis of the relation between physical fitness and adipose tissue inflammation

The analysis of ROC curves showed the highest AUC values for PNI index, HMGB-1 and leptin, which were 0.777, 0.689 and 0.745, respectively (Fig. 1A and B). The cut-off values for nutritional indices were 43.9 (sensitivity 83.9%, specificity 70.9%) and 114.0 (sens. 74.2%, spec. 71.0%) for PNI and GNRI, respectively. Cut-off values oscillated at 1.2 [µg/mL] for adiponectin (AUC = 0.526; sens. 74.2%, spec. 41.9%) and at 6.7 [ng/mL] for leptin (sens. 56.2%, spec. 93.5%). In the pro-inflammatory markers, 34.2 ng/mL and 2.63 mg/L were the cut-off values for the HMGB-1 protein (sens. 62.0%, spec. 86.6%) and for CRP (sens. 51.6%, spec. 84.3%) respectively. The highest sensitivity (83.9%) and specificity (70.9%) were showed for PNI index, which in turn indicates a low level of false positive results during the diagnostic procedure. The highest average odds ratio was observed for leptin (OR = 14.8, 95%Cl 3.574—112.229), and HMGB-1 protein (OR = 12.0, 95%Cl 3.254—61.614), which highlights that these parameters are good markers of the influences of lifestyle exercise on the level of adipokine and pro-inflammatory variables (Table 5). Contrastingly, adiponectin (OR = 1.4, 95%Cl 0.488—3.902) as well as Adpn/Lep ratio (OR 1.7, 95% Cl 0.606—4.670) were demonstrated as the parameters of low diagnostic usefulness (Table 5).

## Discussion

Physical exercise interventions are associated with improvements in the physical function of older adults and should, therefore, be routinely promoted in long-term care facilities [49]. Maintaining an active lifestyle in middle age and old age does not only produce a positive effect on cognitive functions [50] but it is also associated with longevity [51]. In our study, statistically significantly lower values of FM [kg] ($p = 0.028$) and FM [%] ($p = 0.001$) were observed in the high physical fitness adults (gait speed > 1.3 m/s) (Table 1). Studies conducted by Khaleghi et al. [52] showed that the FM value and especially the FM/FFM ratio in various body regions were significantly associated with dysmobility syndrome. Moreover, we also showed statistically significant differences between the study groups and the BMI values ($p = 0.021$). Only 28% of the low physical fitness group had a normal body mass, while in the high physical fitness group, normal body mass was recorded in 57% of the participants. Regular physical activity can thus have a beneficial effect on weight loss.

The available data on the relationship between gait speed, strength and muscle mass is still scarce [53]. Our study seniors with a high physical fitness showed a statistically significant higher value in hand grip strength ($p=0.030$). Gait speed is a good proxy for mobility, and it is recommended as a simple screen of functional status in seniors [54]. In addition, slow walking predicts serious adverse effects such as falls or dementia [55, 56] In our research we also observed a positive correlation between their gait speed and the strength of hand grip ($r_s=0.493$, $p=0.0001$), which supports the argument that an active and daily lifestyle positively affects functional fitness of older adults. Moreover, the benefits of functional fitness in the elderly also translate into a reduced risk of malnutrition—in the high functional fitness group one patient ($n=1$) (3%) showed hand grip strength values below the values indicating malnutrition (F-16, M-27), while in the low physical fitness group there were five such patients ($n=5$) (15.6%). Our observations are consistent with the research by Ahn et al. [53], which showed a significant relationship between the gait speed and grip strength, which is a test factor for upper limb muscle strength. In turn, Gába et al. [57] reported that after a 10-week walking intervention the lean body mass of the lower limbs (kg) increased significantly, while the weight of the upper limbs (kg) showed no significant difference in the active (intervention) group ($n=58$) compared to the control group ($n=46$). Physical activity has a beneficial effect on physical function and mobility-related variables such as muscle strength, cardiovascular endurance, and gait speed. Studies by Nascimento et al. [20] and a cross-sectional study conducted by Spartano et al. [58] ($n=1,352$; $68.6\pm7.5$ years) showed an association between physical activity level and gait for people aged $\geq 75$ years. There is no doubt that it is not only regular physical activity (involving all muscle groups) that is needed to maintain the health and well-being of the elderly but it also involves a balanced diet with an adequate supply of protein [59]. The geriatric nutritional index and prognostic nutritional index are relatively new, simple and objective tools for the assessment of the nutritional status of elderly patients [60, 61]. The prognostic role of the GNRI is superior to a single assessment of BMI or albumin. Studies conducted by Komatsu et al. [62] highlighted the diagnostic usefulness of this indicator in health assessment in elderly patients with chronic diseases, as well as in assessing harmful effects of malnutrition in patients with malignant tumors [63]. Assessment of nutritional indicators including GNRI is particularly important in older people. Low nutritional status and low level of GNRI are associated with poorer immunity, which leads to an increased risk of lifestyle diseases. The study by Huo et al. [64] suggested that GNRI could also be a fine predictor of prognosis in elderly patients with hypertension. Our study is the first to assess the diagnostic usefulness of GNRI in older people whose level of functional fitness measured by walking speed was assessed. We showed statistically significantly lower values of these indicators in the group with high physical fitness when compared to the low physical fitness group ($p=0.007$, Table 3). The cut-off value for GNRI in our study group was 114.0 which is higher than the GNRI score assessed by Ruan et al. [60] in elderly patients with cancer cachexia (91.959). One of the reasons for the observed disproportion may be an insufficient supply of protein in elderly people who lead an active lifestyle. Another aspect to consider is that both formulas include albumin levels. Albumin is a protein synthesized in the liver (negative acute phase protein) dependent on glomerular filtration. Nevertheless, 98% of the GNRI values in our both study groups were > 98, which is not theoretically associated with inflammation, malnutrition or in-hospital mortality [65]. This requires further research and analysis of seniors' eating habits as well as an assessment of liver and kidney function.

Most studies, including Sereflican et al. [66], showed that obesity in both humans and mice caused a decrease of the level of serum adiponectin which is also negatively correlated with TNF-α or IL-6. In our study, no statistically significant differences in adiponectin levels were observed between the groups. Interestingly and surprisingly, in the low physical fitness older adults whose FM level was statistically significantly higher compared to high physical fitness group, adiponectin level reached higher values. Epidemiological studies show that older adults with relatively higher adiponectin levels tend to have more frailty components compared to older adults with lower adiponectin levels [67]. Although our study did not reveal a correlation between adiponectin levels and gait speed, the study by Ma et al. [68] demonstrated that IL-6, adiponectin, and leptin levels were negatively correlated with physical function, suggesting that inflammatory mediators and adipokines are biomarkers of frailty and reduced function in older adults. To date, several studies have reported the relationship between adiponectin and age in association with visceral fat [69], renal function [70], or disproportion in sex hormones [71]. A study conducted by Muratsu et al. [72] involving 5,673 individuals (3,467 males, 2,206 females) showed statistically significantly higher adiponectin levels in women (13.2 ug/mL) compared to men (7.9 ug/mL). In our study, women predominated in both groups, while men in the high physical fitness group accounted for 26% of the respondents, and in the low physical fitness group, only 9% of all individuals were men. This may partly contribute to the observed disproportions. Studies conducted by Wang et al. [73] showed that a 10–15% weight loss was the necessary

**Table 4** Adipokine and inflammatory variables

| Variables | References value | Low physical fitness<br>*n* = 32<br>*n* = 29 female and *n* = 3 male | | High physical fitness<br>*n* = 31<br>*n* = 23 female and *n* = 8 male | | *p*-value |
|---|---|---|---|---|---|---|
| | | mean ± SD | med (iqr 25%-75%) | mean ± SD | med (iqr 25%-75%) | |
| HMGB-1 [ng/mL] | 2–200 | 68.2 ± 56.6 | 68.2 (12.4–128.4) | 20.5 ± 19.2 | 19.8 (7.6–88.2) | 0.005 |
| Adiponectin [µg/mL] | - | 3.4 ± 3.1 | 1.9 (1.1–4.7) | 3.1 ± 3.3 | 1.6 (0.7–5.3) | 0.587 |
| Leptin [ng/mL] | F 7.36 ± 3.73<br>M 3.84 ± 1.79 | 6.8 ± 2.5 | 6.8 (5.0–7.7) | 4.9 ± 1.2 | 4.9 (4.2–5.5) | 0.0008 |
| Adpn/Lep | ≥ 1.0 | 0.7 ± 0.6 | 0.4 (0.2–1.0) | 0.6 ± 0.8 | 0.2 (0.2–0.9) | 0.306 |
| Lep/Adpn | - | 9.2 ± 17.5 | 3.2 (1.0–7.2) | 4.8 ± 6.0 | 3.8 (1.0–5.8) | 0.768 |
| Ghrelin [pg/mL] | 30 -9000 | 1688 ± 1967 | 775 (293–1688) | 1621 ± 1976 | 868 (219–1741) | 0.799 |
| CRP [mg/L] | 0.068—8.2 | 3.0 ± 2.5 | 2.4 (1.5–4.0) | 1.9 ± 1.5 | 1.3 (1.0–2.2) | 0.01 |
| Albumin [g/L] | F 37—53<br>M 42—55 | 43.1 ± 2.2 | 44.6 (44.2 -45.7) | 43.2 ± 1.7 | 43.2 (42.0–44.1) | 0.008 |

*HMGB-1* High mobility group box-1, *Adpn/Lep* Adiponectin to leptin ratio, *Lep/Adpn* Leptin to adiponectin ratio, *CRP* C-reactive protein, *SD* Standard deviation, *Me* Median, *IGR* Interquartile, *F* Female, *M* Male

condition for a change of the level of adiponectin, both circulating and genetically expressed in adipose tissue [73]. Although the BMI differed statistically significantly between our study groups, lower adiponectin levels were detected in the high physical fitness group. In turn, the study conducted by Zaidi et al. [74] did not show a significant change in the body mass before and after the intervention, which may be a partial explanation for the absence of significant changes in adipokines. The observed relationships between adiponectin and physical activity certainly require further studies independent for both sexes, also taking into account the form and type of activity adapted to the capabilities of older people. We also demonstrated no differences between the groups and low diagnostic utility in the new indices: Lep/Adpn (AUC = 0.522, Fig. 1A) and Adpn/Lep (AUC = 0.575 Fig. 1A). In the low physical fitness group, the majority of the subjects (58.1%) had an Adpn/Lep ratio of < 0.5 which suggested a high cardiometabolic risk. 12.9% of the patients in this group had an Adpn/Lep ratio of ≥ 0.5 or < 1.0 and thus a value of ≥ 1.0 Adpn/Lep was observed in 29% of the study participants. In the high physical fitness group, an Adpn/Lep value of < 0.5 was shown in 58% of the subjects, in 16.2% of the individuals the value of the ratio was in the range of ≥ 0.5 or < 1.0 while Adpn/Lep ≥ 1.0 was observed in 25.8% which is regarded as a normal value, which highlights the beneficial impact of regular physical activity on a reduction of the risk of cardiovascular diseases in older age. It is worth emphasizing the role of this Adpn/Lep ratio, because multimorbidity is quite a big problem in older people, and the largest and currently most serious type of multimorbidity in older people is cardiometabolic multimorbidity (CMM). Obesity is one of the important and widely recognized as critical risk factors that can be modified to prevent and treat cardiometabolic diseases. For example, a significant amount of evidence has shown that body mass index (BMI), a widely used indicator of overall obesity, can predict risk for both a single cardiometabolic disease and CMM [75]. Considering that adiponectin and leptin are involved in the regulation of lipolysis, the reduction in the ratio of adiponectin to leptin may also reflect changes in this process, which additionally contributes to obesity-related metabolic disorders. Since the ratio of adiponectin to leptin reflects the functionality of adipose tissue, this ratio may be clinically useful in identification of individuals susceptible to cardiometabolic diseases [14]. The Adpn/Lep ratio may also be a sensitive indicator of metabolic syndrome. The research conducted by Lubkowska et al. [76] in another Polish research center showed a negative correlation between the Adpn/Lep ratio and the TG/TCH ratio in women. Men with a high Adpn/Lep ratio were characterized by lower TG and TG/HDL ratios and higher HDL compared to patients with a low Adpn/Lep ratio, regardless of waist circumference. This also indicates the need to evaluate this ratio separately in both sexes due to sexual dimorphism in the distribution of adipose tissue. Since women outnumbered men in both our study groups, the research will be continued. Although our knowledge about the benefits of regular physical activity is quite extensive and well-researched, about the dynamics of changes in blood leptin concentration depending on the body mass, physical activity and age are still not fully understood [77]. The meta-analysis conducted by Fedewa et al. [78], which included seventy-two randomized controlled trials, showed that engaging in chronic exercise training (≥ 2 weeks) was associated with a decrease in leptin levels for individuals regardless of age and sex. Moreover, a greater decrease in leptin occurred with a decreased percentage of body fat. Weltman et al. [79] showed that

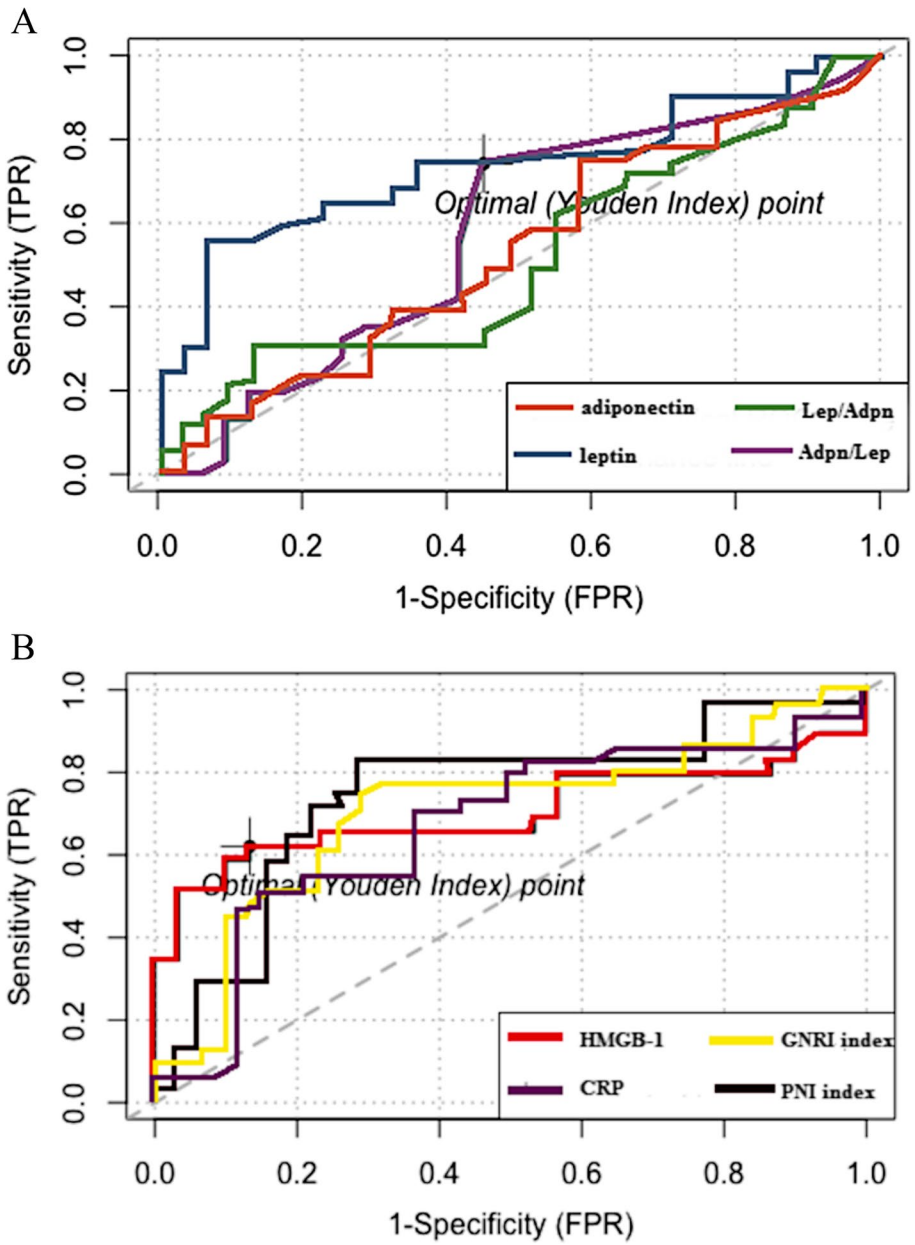


**Fig. 1** Receiver operating characteristic curves for: (**A**) adipokine variables and (**B**) for nutritional and inflammatory variables (*n*=63)

physical activity of various levels of intensity and caloric expenditure (from 150 ± 11 to 529 ± 45 kcal) in 7 healthy young men did not affect the leptin concentration during exercise but also during convalescence (3.5 h). Our research showed statistically significantly lower leptin levels in older people qualified to the high physical fitness group (4.9 ± 1.2 ng/mL) compared to in the low physical fitness group (6.8 ± 2.5 ng/mL, Table 4). In the high physical fitness group, patients also had a lower BMI of 25.0 ± 3.4 kg/m$^2$ compared to the low physical fitness group—27.1 ± 3.8 kg/m$^2$. Research conducted by a Polish group of researchers evaluated the effects of regular physical training and single exercise session on leptin levels in obese, overweight, and normal-weight women. It was shown that leptin concentrations immediately after exercise were reduced in each of the groups and in each analysis. The greatest reduction in leptin concentration was observed in obese women, which may indicate that leptin secretion is significantly inhibited under exercise stimuli, especially in obese individuals [77]. In the available literature, considerably more attention is

**Table 5** Odds ratio analysis of important variables for patients in high and low physical fitness groups ($n=63$)

| Variables | OR | 95% CI | *p*—value |
|---|---|---|---|
| PNI | 11.8 | 3.657–45.681 | < 0.001 |
| GNRI | 5.7 | 1.959—18.269 | 0.001 |
| HMGB-1 [ng/mL] | 12.0 | 3.254—61.614 | < 0.001 |
| CRP [mg/L] | 4.4 | 1.401- 16.063 | 0.010 |
| Adiponectin [µg/mL] | 1.4 | 0.488—3.902 | 0.550 |
| Leptin [ng/mL] | 14.8 | 3.574—112.229 | < 0.001 |
| Adpn/Lep | 1.7 | 0.606—4.670 | 0.325 |
| Lep/Adpn | 2.9 | 0.844—12.449 | 0.09 |

*PNI* Prognostic nutritional index, *GNRI* Geriatric Nutritional Risk Index, *CRP* C reactive protein, *HMGB-1* High mobility group box-1, *Adpn/Lep* Adiponectin to leptin ratio, *Lep/Adpn* Leptin to adiponectin ratio, *OR* Odds ratio

paid to the role of specific physical intervention on changes in leptin levels, however, some studies assessed the impact of the lifestyle of seniors on their hormone levels regulation. For example, results obtained by Kraemer et al. [80], demonstrated a decrease in leptin levels after 30 min of exercise at 80% $VO_2$max in a group of postmenopausal women. Leptin resistance is found in overweight or obese patients and was observed to exacerbate their obesity. High leptin levels are often associated with many cardiometabolic dysfunctions, such as metabolic syndromes, hypertension and type 2 diabetes. Leptin levels are closely related to the level of physical activity. Research by Shih et al. [81] on a group of 396 participants with an average age of 64.75 ± 8.75 years, which is similar to our study age group, showed that a sedentary lifestyle and lack of exercise were associated with higher leptin levels ($p<0.001$). Research by Kennedy et al. [82] showed that gender has a large impact on the relationship between serum leptin concentration and BMI, with leptin levels increasing faster as a function of BMI in women than in men. In a study, lean people with a BMI of less than 20 kg/m$^2$ or a body fat percentage of less than 25% had similar levels of leptin in men and women. In progressive obesity above these values, leptin levels in women increase 3 times faster; consequently, regardless of BMI measurement or body fat percentage, serum leptin levels are significantly higher in women than in men. Our study also showed higher leptin levels in women in both groups compared to men. Nevertheless, due to too small a group of men, reliable relationships are yet to be demonstrated and the research will be continued. However, high values of AUC = 0.745 and OR = 14.8 (95% CI 3.574—112.229, $p<0.001$, Fig. 1A) for leptin level in our study indicated high diagnostic usefulness of this indicator.

Lifestyle and behavioral interventions (e.g., increased daily physical activity and decreased caloric intake) are fundamental components of weight control [83]. Modifications to diet habits affect glucose levels, lower insulin levels and also reduce systemic inflammation [84]. The physical fitness of our study seniors proved to have a positive effect on the level of insulin (9.7 ± 2.0) compared to the group with low physical fitness (11.7 ± 4.7), and it was found to decrease the level of total cholesterol ($p=0.039$). Metabolic inflammation, commonly known as "meta-inflammation", plays a key role in the development of obesity-related metabolic complications. Meta-inflammation, in contrast to the classic, transient and acute inflammatory responses of the innate immune system, is associated with the presence of chronic, low-grade inflammation [85]. Obese and overweight people have an altered cytokine profile, and the classic inflammatory markers assessed in patients most often include the triad: IL-6, TNFα or IL-18, as well as the conventional inflammatory marker CRP [4]. In our study, we assessed the diagnostic usefulness of a new indicator HMGB-1 protein. The presence of pro-inflammatory HMGB-1 protein could promote a chronic inflammatory state in the adipose tissue, which represents a hallmark of obesity-induced metabolic complications [86]. Research by Huang et al. [87] showed that plasma HMGB-1 protein levels were an independent risk factor for the development of type 2 diabetes progression, and studies conducted by Chen et al. [88] also reported an association of HMGB-1 with subclinical cardiovascular risk among young adults. However, there are not many studies evaluating the beneficial effect of physical activity of seniors on changes in HMGB-1. Giallauria et al. [89] analyzed how inflammatory markers, including HMGB-1 concentration, were affected by structured training 3 times a week for the first 3 months and once a week for the next 9 months in women with breast cancer. The study involved 94 patients randomly divided into two groups: 61 patients (53 ± 8 years old, training group) and 33 patients (52 ± 7 years old, control group). The study results showed that moderate-intensity exercise training in breast cancer survivors was associated with

reduced HMGB-1 levels that were proportional to the level of adherence to exercise intervention, independent of other classical inflammatory molecules, thereby suggesting an exercise-induced HMGB-1-mediated anti-inflammatory effect. These observations were similar to ours, where elderly individuals with higher gait speed > 1.3 m/s had significantly lower values of the pro-inflammatory HMGB-1 protein (20.5 ± 19.2 ng/mL) compared to the older adults with low gait speed ≤ 1.3 m/s (68.2 ± 56.6 ng/mL, Table 4). Despite statistically significant differences between groups, HMGB-1 protein values within the reference range i.e., 2–200 ng/mL were observed in all our study subject. In turn, the study conducted by Brück et al. [90] on intensive care unit patients assessed the effect of physical activity and the 6-min walk test (6-MWT), the handgrip-strength test (HST), and the timed-stands test (TST) on changes in the concentration of the pro-inflammatory alarmin HMGB-1. The researchers did not demonstrate a significant relationship between plasma HMGB1 levels after 3 and 6 months and physical tests. The mean plasma HMGB1 levels in patients who completed all physical tests reached 11.5 ± 9.8 ng/ml ($n = 51$) after 3 months and 11.7 ± 6.4 ng/ml ($n = 43$) after 6 months. Nevertheless, the observed mean values in this study were significantly lower than those observed in our patients. HMGB-1 in our study reached high values of both AUC = 0.701 and OR = 12 (95% Cl 3.254—61.614, $p < 0.001$, Fig. 1B) which implies its potential application in the assessment of the impact of physical fitness on inflammation in older adults. Targeting HMBG-1 assessment may represent a credible therapeutic strategy for alleviating inflammation and inflammatory diseases [56]. Nevertheless, despite the current results of our research and the benefits of regular physical activity on the reduction of this pro-inflammatory cytokine, research still needs to be continued to complete our knowledge of the function of HMGB-1. The relationship in adipose tissue is particularly important in order to develop alternative therapeutic strategies for diseases related to obesity and inflammation. Moreover, the available data showed that even a slight increase in plasma CRP concentration was associated with an increased risk of cardiovascular diseases, sarcopenia and cognitive decline in people over 65 years of age [91]. Cut-off values for CRP > 5.0 mg/L in hospitalized geriatric patients were found to be associated with a higher risk of in-hospital mortality [92]. In our study groups reduced the level of CRP in a statistically significant manner: high physical fitness (1.9 ± 1.5 mg/L) *vs.* low physical fitness group (3.0 ± 2.5 mg/L, Table 4), which also reduces hospitalizations of elderly patients. In the low physical fitness group, CRP values exceeded the reference range (0.068—8.2 mg/L) reaching a value of > 11 mg/L in two patients. The CRP levels of all the patients in the high physical fitness group fell within the reference range. Since aging is associated with increased inflammatory activity, and walking speed is a good indicator of patient mobility, independent studies hypothesize that inflammation increases the risk of developing mobility disabilities and a loss of mobility [93]. The study by Verghesse et al. [93] showed that patients with elevated CRP levels (≥ 3 mg/L) had an 85% increased risk of developing mobility disability as well as a 0.89 cm/s per year faster decline in gait velocity compared to the remaining subjects. In our study, we showed a negative correlation between the gait speed value and the inflammatory marker CRP ($r_s = -0.377$, $p = 0.002$). The observations were similar to the research of Ravaglia et al. [94], which also showed an inverse relationship between walking speed and hsCRP value. It seems reasonable that over time, chronic inflammation might be a factor affecting denervation of muscles and changes in the neuromuscular junction [95]. As it turns out, the determination of even high-sensitivity CRP, the platelets to lymphocytes ratio or the ratio of lymphocytes to monocytes is insufficient because these indicators are mainly related to inflammation with low specificity. Taking into account the aging society and the growing tendency towards chronic diseases including obesity, our research has potential important clinical implications: it highlights the important role of physical fitness on body mass reduction and, consequently, the reduction of pro-inflammatory markers in older adults. The implementation of prevention and health programs promoting proper nutrition and regular exercise is the key to ensuring a high quality of life for older individuals. According to the recommendations of the PROT-AGE research group, in order to maintain good health of the elderly (> 65 years of age), an average protein intake of 1.0 to 1.2 g of protein per kilogram of body weight per day is recommended." In addition, endurance and resistance exercises selected and individually adjusted to the patient's capabilities are also recommended, and in the case of activities, a higher protein intake is recommended i.e., ≥ 1.2 g/kg of body weight/day [96].

Some limitations to our study should be acknowledged. Firstly, the age of our study patients is diverse, which may have an impact on the assessed biomarkers. Secondly, our sample size was not large enough for unequivocal conclusions and the recruited group was dominated by women. No detailed information about the study seniors' eating habits and incomplete information about the medications they took was obtained, which may also affect the analyzed parameters. Thirdly,

our study was performed only in the Polish population, which might not produce the outcomes generalizable to other populations. Therefore, the influence of an active lifestyle on the level of adipokines and pro-inflammatory parameters in older adults of other nationalities should be investigated.

## Conclusions

Older adults, whose walking speed exceeded 1.3 m/s, were characterized by statistically significantly lower leptin levels ($p=0.008$), which may also be related to the lower BMI ($p=0.021$) in the high physical fitness group. More than half of the low physical fitness group (58.1%) had an Adpn/Lep ratio of < 0.5, which indicated adipose tissue dysfunction and may accelerate cardiometabolic risk in this group of people. The gait speed value negatively correlated with systematic inflammation markers: CRP ($r_s=-0.377$) and HMGB-1 ($r_s=-0.264$). Although the high physical fitness group had significantly lower GNRI values ($p=0.006$), 98% of the study participants fell within the reference range, where GNRI > 98 indicates no nutrition-related risk. Our studies confirmed the diagnostic usefulness of immunological parameters such as: HMGB-1 (AUC = 701, sens. 62.0%, spec. 86.6%; OR = 12.0, 95Cl% 3.254—61.614, $p<0.001$) or CRP (sensitivity 51.6%, specificity 84.3%, OR = 4.4, 95% Cl 1.401- 16.063) in assessing the inflammation status of adipose tissue. Regular daily physical activity for seniors is crucial for maintaining good health and preventing chronic diseases.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12979-024-00468-7.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

### Authors' contributions

Conceptualization: AT. Methodology: AT, BM. Formal analysis: AT. Investigation: AZL. Writing original draft: AT, AZL. Review & editing: AT, BW, NT, JO, KŁ, PJ, AZŁ. All authors contributed to the article and approved the submitted version.

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### Availability of data and materials

The raw data supporting the conclusions of this article will be made available by the corresponding author without undue reservation.

## Declarations

### Ethics approval and consent to participate

The Bioethics Commission at Regional Medical Chamber Zielona Gora, Poland approved the study (No21/103/2018) in accordance with the Helsinki Declaration. Signing an informed consent for participation in the study by each participant was also a prerequisite for their inclusion.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

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