

A leaky gut contributes to postural dysfunction in patients with Alzheimer's disease

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ABSTRACT

Background: Postural dysfunction is a common problem in patients with Alzheimer's disease (AD) and may lead to functional dependency and increasing morbidity and mortality. However, the pathophysiology of postural dysfunction in AD patients remains poorly understood.

Objectives: Elevated intestinal permeability is an underlying contributor to multiple diseases, including AD. We aimed to investigate the association of elevated intestinal permeability with postural dysfunction in AD patients.

Design Setting, Participants, Measurements: We conducted a cross-sectional, observational study on older adults, including controls and AD patients. We investigated the associations of postural balance with plasma zonulin, a marker of elevated intestinal permeability in geriatric controls (n = 74) and patients with mild (n = 71) and moderate (n = 66) AD. We used a standardized physical performance battery to measure balance in supine, tandem, and semi-tandem positions. We also measured handgrip strength (HGS), and gait speed as markers of physical capacity.

Results: AD patients exhibited lower balance scores, HGS, and gait speed and higher plasma zonulin than in controls (all $p < 0.05$). Plasma zonulin levels demonstrated significant areas under the curves in diagnosing poor balance in AD patients (all $p < 0.05$). Moderate AD was associated with lower balance and physical capacity, and higher zonulin than mild AD (ALL $P < 0.05$). Poor scores on balance scale were associated with higher expressions of markers of inflammation, oxidative stress, and muscle damage providing a mechanistic link between increased intestinal permeability and postural dysfunction in AD patients.

Conclusion: The results of our study show that plasma zonulin measurement may be used to diagnose postural dysfunction in AD patients. The study is relevant to non-ambulant and/or comatose AD patients with postural dysfunction. Our findings also highlight the therapeutic potential of repairing the intestinal leak to improve postural control and reduce the risk of falls in AD patients.

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1. Introduction

Postural dysfunction, defined as an inability to achieve, maintain, or restore balance during any posture or physical activity, is a critical problem in the geriatric population [1]. Defects in cognitive, sensory, and/or musculoskeletal systems are prime drivers of postural dysfunction [1,2]. These defects are partly due to an advanced age. The increasing life expectancy is also associated with an increase in the occurrence of age-related diseases [3,4]. Among them, the age-related muscle loss, termed sarcopenia may be relevant here since sarcopenic patients exhibit difficulty in maintaining posture and balance [1]. The patients also have difficulty performing the activities of daily living and are more susceptible to fall and fall-related injuries than age-matched controls [5].

Sarcopenia is characterized by muscle weakness, atrophy, and reduced gait speed in older adults [6]. Sarcopenic patients also demonstrate low endurance and physical capacity. Several age-related degenerative conditions induce and/or exacerbate sarcopenia in the geriatric population [7–9]. Among them, Alzheimer's disease (AD) may be of primary relevance because of its harmful effects on multiple body systems [10]. The neuropathy underlying AD has a prominent motor component. We have previously reported an advanced form of sarcopenia in patients with AD [11]. Specifically, these patients exhibit higher muscle loss, weakness, and physical compromise than the control population [11,12]. There is also evidence for a reduced ability to maintain balance in patients with AD. For example, a direct association is suggested between postural dysfunction and cortical volume in AD patients [2]. Impaired balance is a critical contributor to an increase in falls, fractures, and reduced quality of life [5]. However, the pathophysiology of balance impairment in patients with AD remains poorly understood.

In healthy individuals, the intestinal mucosal barrier prevents the entry of several harmful molecules into the systemic circulation [13]. A pathological increase in intestinal mucosal permeability is the underlying contributor to several systemic disorders, including autoimmune, degenerative, metabolic, and infective diseases [13]. Patients with increased intestinal permeability are also more likely to develop physical dependence and sarcopenia [14]. Our recent studies indicate a direct association of increased intestinal permeability with loss of muscle mass and strength in geriatric patients with age-related diseases [11,14,15]. Specifically, plasma zonulin, a marker of increased intestinal permeability, exhibited inverse correlations with handgrip strength and gait speed in AD patients [11]. Similarly, plasma levels of lipopolysaccharides-binding protein, a marker of plasma bacterial load, are elevated in patients with cancer cachexia [16]. These bacteria and their products induce myotoxicity, which causes muscle weakness and atrophy. A causal association has also been established by showing that the repair of intestinal leak partly mitigates muscle weakness and atrophy in older adults [17,18]. In addition, an increase in physical capacity and endurance is also reported following the mitigation of intestinal leak. These findings validate and extend the establishment of the gut-muscle axis. Interestingly, we also found an inverse association of plasma zonulin with cognitive decline in AD patients [11]. Together, these findings indicate the potential contributions of increased intestinal permeability to muscle and neuronal decline in AD patients. Considering the critical contribution of skeletal muscle and the nervous system to postural control, it is imperative to hypothesize an association between intestinal leak and postural dysfunction in older adults with neurodegenerative diseases. However, to our knowledge, no such study has been conducted on geriatric adults. Moreover, similar investigations in the settings of AD remain elusive.

In the current study, we investigated the associations of plasma zonulin levels with postural control in a selected group of geriatric population, including controls and patients with AD. We also investigated handgrip strength (HGS) and gait speed as markers of muscle strength and physical capacity in the context of postural control. Lastly, we measured plasma markers of inflammation and oxidative stress to dissect the potential mechanistic link between intestinal leak and postural dysfunction in the study population. We hypothesized that increased intestinal permeability contributes to postural dysfunction in patients with AD, which is at least partly due to the decline of skeletal muscle and physical capacity.

2. Materials and methods

2.1. Study design & participant

We recruited controls ($n = 74$) and patients with AD ($n = 137$) at the Department of Neurology and Stroke Medicine, Rehman Medical Institute, Peshawar, Pakistan, after obtaining written informed consent. The diagnosis of AD was based on the mini-mental state examination (MMSE) scores, and the patients were divided into mild (MMSE score = 21–25, $n = 71$) and moderate (MMSE score = 10–20, $p = 66$) AD, as described by us previously [11]. The recruitment criteria of participants are previously described by us in detail [11,19]. Briefly, patients with recent hospitalization, joint diseases, major organ failure, and recent surgeries were excluded. The study includes Caucasian men, and ethics approval was obtained from the hospital ethics committee before data collection. This study was conducted under the declaration of Helsinki [20].

2.2. HGS and body composition

HGS was measured using a digital handgrip dynamometer (CAMRY, South El Monte, CA, USA), as described elsewhere by us [21]. We used a bioelectrical impedance analysis scale (RENPHO, Dubai, UAE) to measure body composition, including fat mass, skeletal muscle mass (SMM), skeletal muscle mass index (SMI), and phase angle, as described elsewhere by us [22].

2.3. Measurement of physical capacity

We measured standing balance using a physical performance tool. Briefly, the participants were asked to stand unassisted without

the help of a stick or walker. The balance for side-by-side, semi-tandem, and fully tandem standing was measured with a timer for 10 s or unless the participants moved. We used timed quartiles to assign the scores ranging from zero (worst performance) to four (maximal performance), as described elsewhere in detail [23]. We used a smartwatch pedometer to measure the daily step count, and the mean values from the daily counts of the past four weeks were reported, as described previously by us [17].

2.4. Measurement of circulating biomarkers

The blood samples were collected in morning hours following an overnight fast, centrifuged at 3000 rpm for 20 min, and plasma was stored at -80°C for further analysis, as described previously [24]. We used an ELISA kit to measure plasma zonulin (Cat #K5601, Immundiagnostik AG, Bensheim, Germany), according to the manufacturer's instructions [15]. We used ELISA kits to measure plasma c-reactive proteins (CRP) (R&D Systems, Minneapolis, MN, USA), 8-isoprostanes (Cayman Chemical, Ann Arbor, MI, USA), and creatine kinase, as described previously [17,18].

2.5. Statistical analysis

A one-way analysis of variance with Tukey's post-hoc test was used to compare the differences among the groups. We used simple linear regression to investigate the correlations of plasma zonulin with CRP, 8-isoprostanes, and creatine kinase. The diagnostic potentials of plasma zonulin in reduced balance was assessed by calculating the areas under the curve (AUC) using receiver operating characteristics (ROC) analysis. Data are presented as mean and standard deviation, and the p -value < 0.05 was taken as statistically significant. Data were analyzed using GraphPad Prism 8 (Graphstats technologies private limited, Bangalore 560,035, India).

3. Results

3.1. Characteristics of the study participants

The age and BMI were similar among the three groups of participants (Table 1). However, the patients with mild and moderate AD had lower SMI, phase angle, and daily step count than controls (all $p < 0.05$). Patients with AD also had lower MMSE scores than controls ($p < 0.05$). The occurrence of hypertension and diabetes mellitus was higher in AD patients than in control (both $p < 0.05$). Among routine clinical investigations, we found higher plasma urea levels in AD patients than in controls ($p < 0.05$) (Table 1). However, the plasma HbA1c, creatinine, LDL- and HDL-cholesterol, and Hb levels were similar among the three groups of participants. Lastly, the prevalence of sarcopenia was higher among all AD patients than in controls (both $p < 0.005$) (Table 1).

Table 1

Baseline characteristics of the study population. Values are expressed as mean $\pm$ SD, one-way analysis of variance. * $p < 0.05$ vs. controls; # $p < 0.05$ vs. AD. (Alzheimer's disease; AD, BMI; body mass index, ASM; appendicular skeletal mass, ASMI; appendicular skeletal mass index, MMSE; mini-mental state examination, HbA1c%; glycated hemoglobin, LDL-cholesterol; low density lipoproteins-cholesterol, HDL-cholesterol; high density lipoproteins-cholesterol, Hb; hemoglobin).

	Controls (n = 74)	Mild AD (n = 71)	Moderate AD (n = 66)
Age (years)	74.9 $\pm$ 5.3	77.3 $\pm$ 4.7	73.1 $\pm$ 5.4
BMI (kg/m^2)	24.2 $\pm$ 2.3	23.6 $\pm$ 3.3	25.2 $\pm$ 2.2
SMM (kg)	25.4 $\pm$ 3.2	23.1 $\pm$ 2.7	22.5 $\pm$ 2.8*
SMI (kg/m^2)	7.85 $\pm$ 0.6	7.35 $\pm$ 0.9*	7.19 $\pm$ 0.71*#
Percent fat	28.2 $\pm$ 3.5	27.1 $\pm$ 3.8	25.5 $\pm$ 3.3
Phase angle	5.92 $\pm$ 0.7	5.74 $\pm$ 0.6*	5.68 $\pm$ 0.6*
Daily steps count	6983 $\pm$ 1218	4671 $\pm$ 1006*	3681 $\pm$ 1191*
Balance scores	3.15 $\pm$ 0.7	2.68 $\pm$ 0.7*	2.62 $\pm$ 0.7*
MMSE scores	27.5 $\pm$ 2.8	16.3 $\pm$ 3.6*	22.2 $\pm$ 2.1#
Comorbidities			
Hypertension, n (%)	14 (18.92)	38 (53.52) *	15 (22.73)
Diabetes Mellitus, n (%)	7 (9.46)	15 (21.13) *	9 (13.64)
Others, n (%)	5 (6.76)	8 (11.27)	6 (9.09)
Clinical investigations			
HbA1c %	5.4	5.8	5.9
Systolic blood pressure (mm Hg)	140	150	145
Diastolic blood pressure (mm Hg)	80	85	85
Plasma urea (mg/dl)	19	25*	22
Plasma creatinine (mg/dl)	1.29	1.26	1.35
LDL-cholesterol (mg/dl)	147	165	156
HDL-cholesterol (mg/dl)	42	38	40
Hb (g/dl)	12.7	10.8	11.3
Sarcopenia cases, n (%)	9 (12.16)	15 (21.13) *	16 (24.24) *

3.2. AD patients exhibited poor balance and physical capacity and higher plasma zonulin

We next investigated the balance control in the study population. We observed a higher proportion of participants with balance scores of ≤ 2 among AD patients than in controls (both $p < 0.05$) (Fig. 1A). Among the three study groups, participants with balance scores of ≤ 2 exhibited higher plasma zonulin levels than participants with balance scores of 3 (all $p < 0.05$) (Fig. 1B). These participants also exhibited lower HGS than participants with balance scores of 3 or 4 among controls and patients with AD (all $p < 0.05$) (Fig. 1C). Lastly, balance scores of ≤ 2 were also associated with lower gait speed irrespective of disease status (all $p < 0.05$) (Fig. 1D).

3.3. AD patients exhibited higher plasma CRP, 8-isoprostanes, and creatine kinase levels

We next asked if plasma zonulin can cause systemic inflammation, oxidative stress, and muscle damage in controls and patients with AD. We investigated the levels and associations of plasma CRP, 8-isoprostanes, and creatine kinase levels with plasma zonulin in the study population (Fig. 2). Levels of plasma CRP, a marker of systemic inflammation, were similar among participants with different balance scores in controls and patients with mild AD (Fig. 2A). Conversely, patients with moderate AD having balance scores of ≤ 2 exhibited higher CRP levels than patients with balance scores of 3 ($p < 0.05$) (Fig. 2A). Similarly, plasma 8-isoprostanes, a marker of systemic oxidative stress, was higher in all AD patients with balance scores of ≤ 2 than in patients with higher balance scores (both $p < 0.05$) (Fig. 2B). Lastly, participants with balance scores of ≤ 2 also exhibited higher plasma creatine kinase, a marker of muscle damage, in all three groups of study participants (all $p < 0.05$) (Fig. 2C).

We next investigated the correlations of plasma CRP, 8-isoprostanes, and creatine kinase with zonulin levels. Plasma CRP exhibited weak, albeit statistically significant correlations with zonulin in controls ($r^2 = 0.081$, $p = 0.014$), and patients with mild ($r^2 = 0.073$, $p = 0.021$) and moderate AD ($r^2 = 0.087$, $p = 0.015$) (Fig. 2D). Conversely, plasma 8-isoprostanes exhibited relatively robust correlations with plasma zonulin in controls ($r^2 = 0.106$, $p = 0.002$), and patients with mild ($r^2 = 0.133$, $p = 0.001$) and moderate AD ($r^2 = 0.115$, $p < 0.005$) (Fig. 2E). Lastly, plasma creatine kinase showed statistically significant associations with zonulin only in patients with mild AD ($r^2 = 0.085$, $p = 0.013$) (Fig. 2F).

3.4. Plasma zonulin demonstrated high efficacy in diagnosing poor balance control

We next asked if plasma zonulin can be useful in diagnosing poor balance control in the study population. We defined poor balance control as balance scores of ≤ 2 and generated ROC curves for plasma zonulin to differentiate participants with poor balance from those with balance scores of 3 or 4. We found a modest, albeit statistically significant efficacy of plasma zonulin in diagnosing poor balance in control group (AUC = 0.739, 95% CI = 0.571–0.908, $p = 0.015$) (Fig. 3A). Conversely, plasma zonulin exhibited a higher efficacy in diagnosing poor balance in patients with mild (AUC = 0.778, 95% CI = 0.657–0.898, $p < 0.001$) (Fig. 3B) and moderate AD (AUC = 0.846, 95% CI = 0.749–0.942, $p < 0.001$) (Fig. 3C).

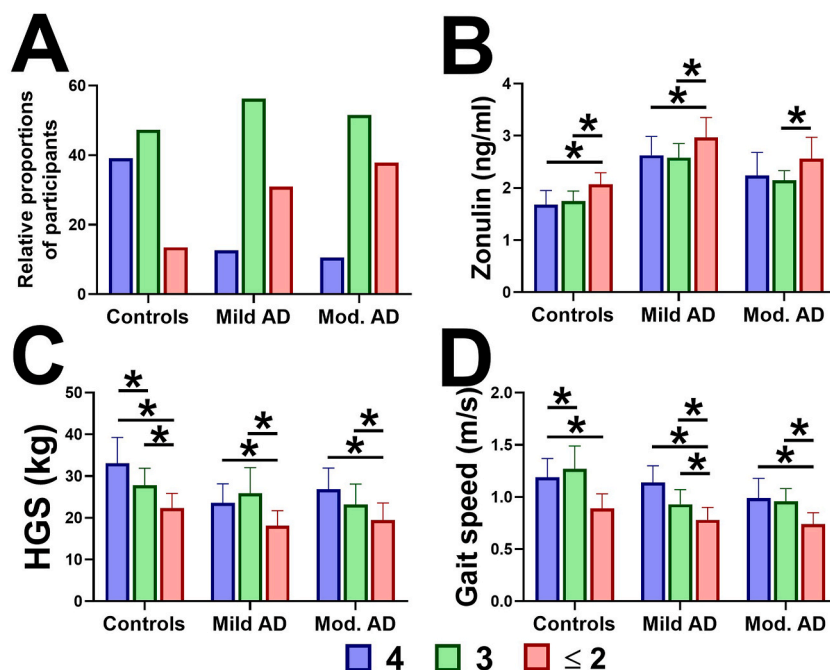


Fig. 1. The relative proportions of participants (A), plasma zonulin levels (B), HGS (C), and gait speed (D) in controls ($n = 74$), and patients with mild ($n = 71$) and moderate ($n = 66$) AD according to balance scores, * $p < 0.05$. (Alzheimer's disease; AD; HGS; handgrip strength).

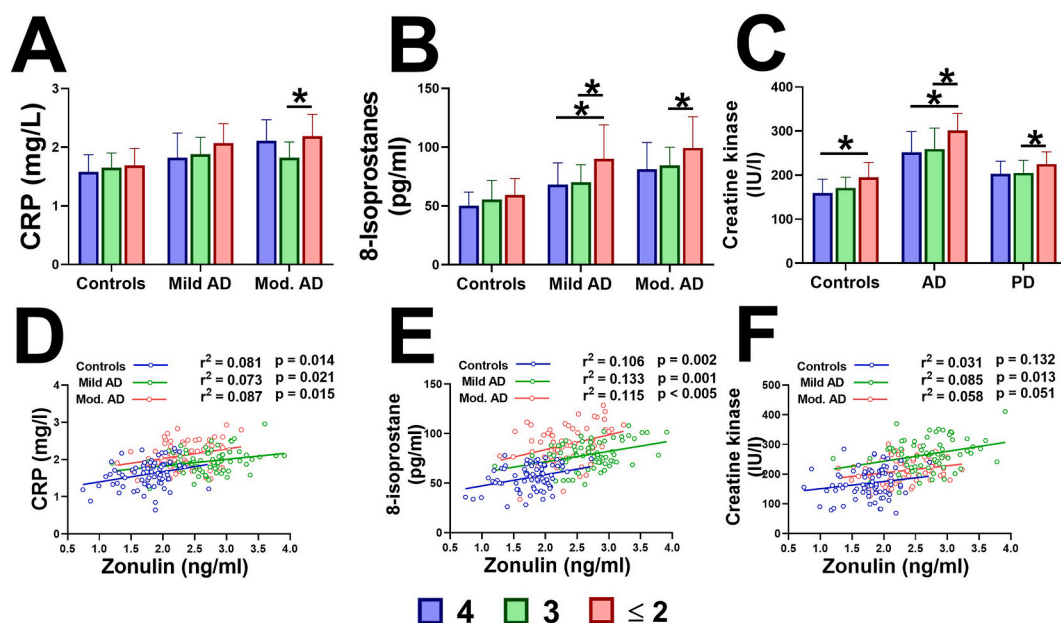


Fig. 2. Plasma CRP (A), 8-isoprostanes (B), and creatine kinase (C) levels according to balance scores and the correlations of plasma CRP (D), 8-isoprostanes (E), and creatine kinase (F) with plasma zonulin in controls ($n = 74$), and patients with mild ($n = 71$) and moderate ($n = 66$) AD, according to balance scores, * $p < 0.05$. (Alzheimer's disease; AD, PD; CRP; c-reactive protein).

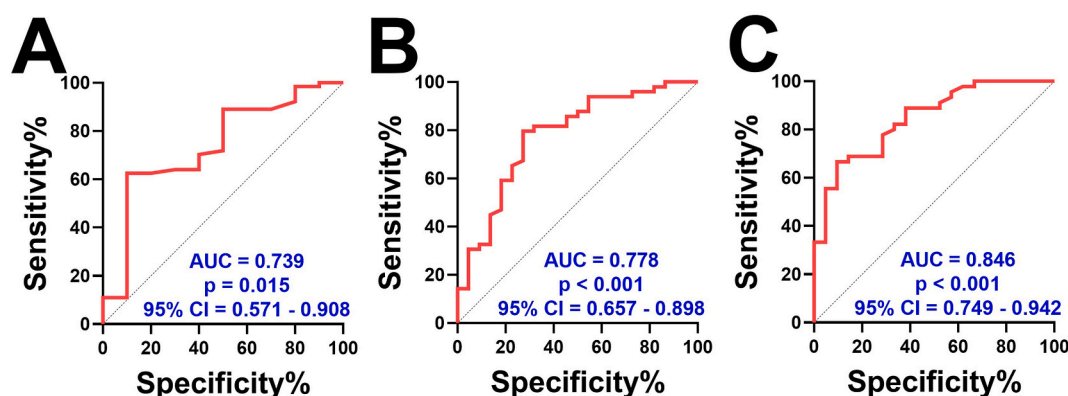


Fig. 3. ROC curves based on plasma zonulin levels for the diagnosis of poor balance (defined as balance score ≤ 2) in controls ($n = 74$) (A), and patients with mild ($n = 71$) (B), and moderate AD ($n = 66$) (C). (ROC; receiver operating characteristics, Alzheimer's disease; AD, PD).

Plasma zonulin exhibited negative association with physical capacity and positive associations with plasma markers of inflammation and oxidative stress. Lastly, we asked if plasma zonulin can predict HGS, ASMI, gait speed, CRP, 8-isoprostanes, and CK levels (Table 2). Plasma zonulin levels were correlated with HGS in all patients with mild AD, irrespective of the balance scores. Conversely, there were no correlations between zonulin and ASMI irrespective of the disease status and balance scores. Zonulin exhibited varying degrees of correlations with gait speed, which were most robust in controls with balance scores of 3 or 4. The correlation between zonulin and CRP was significant only in participants with balance scores of 3, irrespective of disease severity. The most robust correlation of zonulin with 8-isoprostanes was in controls with balance scores of 4. Lastly, the correlation between zonulin and creatine kinase was significant only in AD patients with a balance score of 3 (Table 2).

4. Discussion

To our knowledge, this is the first study investigating the contribution of increased intestinal permeability to postural dysfunction in AD patients. We found reduced balance scores and higher plasma zonulin in AD patients than in controls. Plasma zonulin levels exhibited a significant predictive potential in diagnosing poor balance in AD patients. In addition, these patients demonstrated higher plasma CRP, 8-isoprostanes, and creatine kinase levels, which provide a potential mechanistic explanation between increased

Table 2

Correlation coefficients of plasma zonulin with HGS, ASMI, gait speed, CRP, 8-isoprostanes, and CK in controls, and patients with mild and moderate AD according to the balance scores, * $p < 0.05$. (Alzheimer's disease; AD, PD; ASMI; appendicular skeletal mass index, CRP; c-reactive proteins).

	HGS	ASMI	Gait speed	CRP	8-isoprostanes	Creatine kinase
Controls (n = 74)						
4	0.083	0.046	0.181*	0.028	0.188*	0.045
3	0.195*	0.016	0.158*	0.137*	0.057	0.051
≤2	0.057	0.032	0.103	0.088	0.137*	0.028
Mild AD (n = 71)						
4	0.103*	0.062	0.106	0.029	0.075	0.107
3	0.168*	0.019	0.096	0.141*	0.152*	0.128*
≤2	0.193*	0.028	0.138*	0.066	0.139*	0.031
Moderate AD (n = 66)						
4	0.116*	0.083	0.095	0.095	0.128	0.063
3	0.088	0.062	0.122*	0.136*	0.144*	0.051
≤2	0.104*	0.028	0.101*	0.108	0.095	0.047

intestinal permeability and impaired balance in AD patients.

Consistent with a previous report, we found a higher occurrence of postural imbalance in AD patients than in controls [2]. Additionally, moderate AD was associated with a higher postural imbalance than mild AD, indicating the potential effects of advanced neurodegeneration to impaired balance [2]. This finding is consistent with a higher reduction in HGS in moderate than mild AD with relevance to the neuromuscular coupling [11]. Maintenance of balance control requires a composite interaction of several body systems in addition to neural control and skeletal muscle [1,5]. Thus, a biomarker of generalized health may be more relevant to balance control. We found higher plasma zonulin in patients with mild AD, which was further increased in moderate AD. These patients also exhibited poor balance control, revealing the potential association of increased intestinal permeability to the two prime drivers of balance, namely neurons and skeletal muscle. Previous studies have reported the contributions of intestinal leak to neurodegeneration in the geriatric population [25,26]. Specifically, these patients exhibit cognitive decline and reduced sensorineural function. Our previous studies also highlight the contributions of intestinal leak to muscle weakness and compromised physical capacity in geriatric patients with AD [11]. Together, these findings support the occurrence of higher plasma zonulin in patients with lower balance scores in our study cohort of AD patients. The ROC analysis also revealed the discriminative power of plasma zonulin in poor balance control. Interestingly, we found higher AUCs for zonulin in AD patients than in controls. Moreover, moderate AD was associated with higher AUC than mild AD. These findings indicate that the contribution of increased intestinal permeability to postural dysfunction increases with advancing neuronal and muscle decline. The intestinal leak may also be the primary driver of neurodegeneration in age-related neurodegenerative conditions [26]. The neurodegeneration and muscle detriment are not two separate phenomena, as previous studies report an interface between neuronal and muscle decline [27,28], which is strengthened in patients with advanced AD [11]. Further, advanced neurodegeneration is also associated with a progressive increase in intestinal dysbiosis and/or permeability [29]. These reports are consistent with our previous report of higher plasma zonulin and lower HGS and MMSE scores in patients with advanced AD [11]. While the relevant data in the literature is scarce, our finding is supported by a direct association of intestinal dysbiosis with postural instability in patients with Parkinson's disease [26]. AD share several pathophysiological features with Parkinson's disease, including intestinal dysbiosis and neurodegeneration. Intestinal dysbiosis is a common driver of a pathological increase in intestinal permeability in these diseases, indirectly supporting our finding of elevated zonulin in patients with postural dysfunction.

The elevated levels of plasma CRP and 8-isoprostanes provide a mechanistic connection between increased intestinal permeability and postural dysfunction in AD patients. It is recognized that the patients with leaky gut exhibit higher levels of systemic inflammatory cytokines and oxidative stress [30,31]. This is attributed to the leakage of harmful bacterial endotoxins from the intestinal lumen into the blood [32]. These endotoxins negatively affect motor neurons and skeletal muscle, possibly contributing to postural dysfunction [33]. Similarly, elevated oxidative stress may cause postural imbalance by exacerbating neuropathy and myopathy in AD patients [34]. The higher levels of plasma creatine kinase also support this finding and indicate muscle damage in conditions of increased intestinal permeability. Moreover, intestinal leak can also modulate nervous system through several other means, such as sending the bacterial metabolites through vagus nerve, releasing neurotransmitters and hormones, and controlling the secretion of gut peptides from enteroendocrine cells [26]. These effects, collectively, cause damage to the nervous system, which may further contribute to postural dysfunction in AD patients.

This study has several strengths. It is a monocentric study, which ensures consistency in evaluation techniques and laboratory investigations. All participants belonged to a similar ethnic and cultural profile, which reduces potential variations of intestinal microbiota and permeability due to diet and lifestyle variations [35]. The ELISA technique required to measure plasma zonulin can be performed in most clinical laboratories and can be a useful assessment tool in non-ambulant patients. We performed an objective assessment of balance control using a well-recognized and standardized tool as a part of short physical performance battery assessment. The adequate sample size strengthens the biological significance of our data.

5. Limitations of the study

The major limitation of this study is the recruitment of only the male population. However, this may be a strength as well since it

prevents gender-bias. We did not include patients with advanced AD. There may be a selection bias due to recruitment of patients with ambulance and selective survival.

6. Conclusion

Altogether, we report the potential contribution of elevated intestinal permeability to postural dysfunction in AD patients. Moreover, plasma zonulin may be a useful biomarker of balance control in AD patients. We propose heightened systemic inflammation and oxidative stress as a potential mechanistic interface between elevated intestinal permeability and postural dysfunction in AD. Our study unravels the intestinal leak as a therapeutic target to improve physical capacity and balance control in AD patients. Several potential interventions are available to repair the intestinal leak in geriatric patients [13,35]. Future studies should investigate the therapeutic potential of repairing the intestinal leak to improve postural control and reduce the risk of falls in AD patients.

Ethics statement

The study was conducted after obtaining an ethics approval (reference number: HREC-19-02-03-01) from the Human Research Ethics Committee of Rehman Medical Institute, Peshawar.

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Author contribution statement

Rizwan Qaisar, Asima Karim: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper. M. Shahid Iqbal: Performed the experiments; Contributed reagents, materials, analysis tools or data. Firdos Ahmad: Conceived and designed the experiments; Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper. Ahmad Shaikh: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data. Hossam Kamli: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper. Nizar A. Khamjan: Contributed reagents, materials, analysis tools or data; Wrote the paper.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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