ORIGINAL ARTICLE

EFFECTS OF OXIDATIVE STRESS AND PHARMACOLOGYCAL TREATMENT ON GERIATRIC SYNDROMES IN THE HOSPITALIZED ELDERLY PATIENTS

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Abstract

Oxidative stress is an important risk factor in ageing process and influences the evolution of most diseases and geriatric syndromes in the elderly. This evolution is also affected by the pharmacokinetics and pharmacodynamics age-induced particularities of the elderly, which lead to an increased risk for negative side effects and drug-induced toxicity than in the adult patient. We performed a cohort, prospective study on 139 patients aged over 65 years. The aim of the study was to determine the effects of oxidative stress and cardiovascular pharmacological treatment on geriatric syndromes in the elderly patients. Oxidative stress was quantified by measuring the advanced glycated end products (AGE) with a skin auto-fluorescence method. Geriatric syndromes were determined with comprehensive geriatric assessment. Cardiovascular drugs studied were: beta blocker, angiotensin converting enzyme inhibitors (ACE-I) and anticoagulants. The mean age in the study cohort was 75.35 ± 6.46 and the mean level of AGEs was 2.87 (3.27 - 2.56) AU. The levels of AGE were significantly correlated with the presence of heart failure ($p = 0.014$, $r = 0.280$) and with the cognitive status ($p < 0.05$, $r = 0.206$). ACE-I treatment had a positive correlation with a low depression score ($p < 0.05$, $r = 0.235$) and beta blocker treatment correlated with a low score on abilities to live independently ($p < 0.05$, $r = 0.233$). The anticoagulant therapy was associated with the cognitive impairment ($p < 0.05$, $r = -0.214$), patients with anticoagulant treatment had a higher score in the mini mental state examination (MMSE) than patients without anticoagulant treatment ($p < 0.05$). Oxidative stress and pharmacological treatment had correlations with geriatric syndromes.

Rezumat

Stresul oxidativ este o verigă importantă în procesul de îmbătrânire şi în evoluţia atât a comorbităţilor cât şi a sindroamelor geriatrice la vârstnic. De asemenea, vârstnicul are particularităţi de farmacocinetică şi farmacodinamie ce duc la reacţii adverse, toxicitate sau alte efecte mai puţin întâlnite la pacientul adult. Am efectuat un studiu prospectiv, de cohortă pe un numar de 139 pacienţi cu vârsta peste 65 ani, pentru a stabili efectele stresului oxidativ şi ale tratamentului farmacologic asupra sindroamelor geriatrice. Stresul oxidativ a fost cuantificat prin determinarea produşilor de glicare avansată (AGE) cu ajutorul autofluorescenţei cutanate. Sindroamele geriatrice au fost determinate cu ajutorul evaluării geriatrice comprehensive. A fost studiată următoarea medicaţie cardiovasculară: beta-blocantele, inhibitorii enzimei de conversie ai angiotensinei (ACE-I) şi anticoagulantele. Vârsta medie a fost de 75,64 ani, iar nivelul mediu al AGE 2,87 (3,27 - 2,56) AU. Nivelul AGE s-au corelat semnificativ statistic cu prezenţa insuficienţei cardiace ($p = 0,014$, $r = 0,280$) şi cu statusul cognitiv $p < 0,05$, $r = 0,206$). Tratamentul cu ACE-I s-a corelat pozitiv cu un scor scăzut al depresiei ($p < 0,05$, $r = 0,235$), iar tratamentul beta-blocant cu un grad de independenţă scăzut ($p < 0.05$, $r = 0,233$). Tratmentul anticoagulant s-a corelat cu tulburările cognitive ($p < 0,05$, $r = -0,214$), pacienţii cu tratament anticoagulant având o examinare minimă a stării mentale (MMSE) mai crescut decât pacienţii fără tratament ($p < 0,05$). Patologiile asociate pacientului geriatric sunt corelate atât cu stresul oxidativ cât şi cu tratamentul farmacologic.

Keywords: elderly patients, cardiovascular treatment, advanced glycated end products (AGE), oxidative stress

Introduction

One of the ageing theories is the theory of the oxidative stress, involving advanced glycated end products (AGEs). AGEs are a heterogeneous group of macromolecules which are formed through non-enzymatic glycation of proteins, lipids and nucleic acids. AGEs from endogenous and exogenous sources accumulate in the organism. The effects of their high concentration are found in every tissue and organs. They are cited to be involved in ageing and in pathogenesis of sarcopenia, arterial stiffness, heart failure, atrial fibrillation, chronic kidney disease, Alzheimer disease, progression of diabetes. Some studies correlate AGEs levels with cardiovascular mortality or with any cause mortality [10, 13, 14].

Geriatric syndromes are frequent in elderly and their presence lead to a high morbidity and mortality. For a geriatric syndrome, multiple risk factors and multiple organ systems are often involved.

Cognitive impairment, immobility, instability, depression, insomnia, malnutrition and newer heart failure, all are geriatric syndromes. The global assessment instrument of the geriatric patient is the comprehensive geriatric evaluation (CGE). CGE comprise many components: medical, psychological, cognitive, social behavioural, and benefits of geriatric evaluation scales. The geriatric evaluation scales, as part of CGE, are useful tools in detecting geriatric syndromes. Because an elderly with even one geriatric syndrome is exposed to a higher risk for mortality, morbidity and fragility, and many elderly patients are exposed to polypharmacy, it is important to know the relations between drugs and geriatric syndromes [4, 11, 15].

The elderly show an increased risk for adverse drug reactions, different from the adult. They are prone to drugs' toxicity due to the age – associated changes in pharmacokinetics and pharmacodynamics, but also due to their poly-pathologies that cogenerate drug interactions. Diuretics, antihypertensive, antiarrhythmics, anticoagulants, hypoglycaemic are between the most cited classes of drugs concern. The risk of an adverse drug reaction increases exponentially with the number of drugs used and with the presence of comorbidities and geriatric syndromes [5].

Materials and Methods

This clinical study is a prospective cohort study and included 139 elderly patients. The study subjects were selected from the patients admitted in the "Dr. C. I. Parhon" Geriatric Clinic Hospital, Iasi, Romania, from July 2013 to June 2014. The study was approved by the Hospital's Ethics Committee. The protocol has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). Before initiating any of the study procedures, all subjects gave their volunteered and signed informed consent to participate in the study. The exclusion criteria were: lacks of informed consent, terminal stage neoplasia, alterations of the skin, such as scars, tattoos, arm depigmentation, where the AGE measurements were performed, acute systemic infections and medication with florescent properties because they interfere with the AGE levels.

All patients underwent a comprehensive geriatric evaluation in order to identify the presence of geriatric syndromes such as: Mini Mental State Evaluation (MMSE) used for detection of cognitive impairments, 16 items Geriatric Depression Scale (GDS-16) used for detection of the risk for depression, Mini Nutritional Assessment (MNA) used for detection of malnutrition, Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) used for the detection of the degree of dependence. Also demographic data and data regarding the comorbidities and the concomitant treatment were collected.

Levels of tissue advanced glycation end products (AGE) were measured for the oxidative stress. Skin auto-fluorescence (SAF), a measure of skin AGE deposition was assessed using an AGE Reader™ device. Three measurements were made on the left arm avoiding areas of skin with tattoos, depigmentation, and blood vessels near to the skin surface. The values are expressed in arbitrary units (AU). The most accurate method for determining the AGE concentration is the skin biopsy. Merwaldt *et al.* validated the use of skin auto-fluorescence as a new, non-invasive method. They measured the AGE concentrations with skin auto-fluorescence and they performed biopsy on the exact location used as previous measure. They found a strong correlation between skin auto-fluorescence and the contents of AGE (both fluorescent and non-fluorescent) from biopsied skin. The intra-individual Altman error percentage was of 5.03% with SAF measurement determined over one day. The SAF technique has some limitations: not all AGEs exhibit fluorescent properties, but in the validation study, SAF correlated also with non-fluorescent AGE from the biopsied skin; the value of SAF as a marker of AGE increase is valid only on non-pigmented skin [16].

The SPSS statistical software was used to analyse data. All variables were expressed as frequencies and percentages for categorical data, as means ± SD for normally distributed data and as medians and interquartile ranges for skewed data. Comparisons between groups were made by Student t test, Mann-Whitney U test or the χ^2 test as appropriate. A 2-tailed p value < 0.05 was considered statistically significant.

Results and Discussion

The mean age in the study cohort was 75.35 ± 6.46 with a preponderance of female than male (53.1% *vs.* 43.9%) (Figure 1).

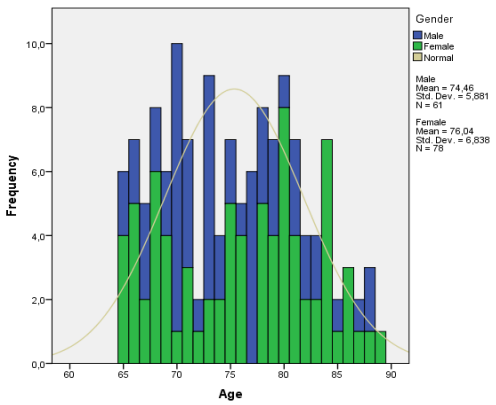

Figure 1.
The histogram representing the patients distribution based on age and gender

The mean level of AGEs was 2.87 (3.27 - 2.56) AU (Figure 2). The general characteristics of the study subjects are shown in Table I.

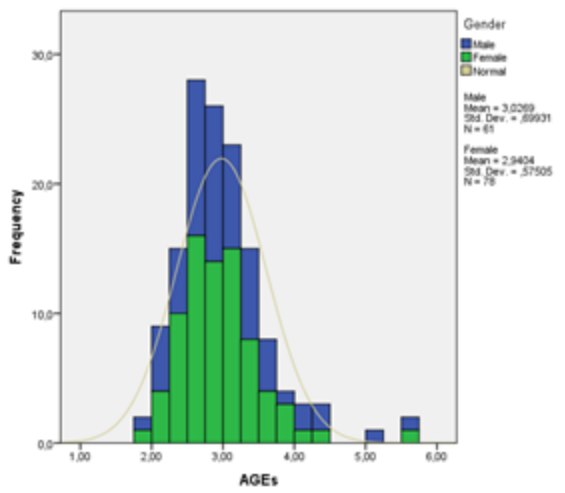

Figure 2.
The histogram representing the patients' distribution based on AGEs levels and gender

Table I
The geriatric evaluation scores of geriatric syndromes, clinical and treatment data of clinical subjects

Geriatric evaluation scales	MMSE	24 (27 - 20)
	MNA	21.5 (24 - 19)
	ADL	6 (6 - 5)
	IADL	7 (8 - 6)
	GDS	6 (9 - 4)
Comorbidities	heart Failure	108 (77.39%)
	hypertension	84 (60.4%)
	ischemic heart disease	103 (74.1%)
	atrial fibrillation/flutter	91 (65.5%)
	stroke	30 (21.6%)
	peripheral arterial disease	10 (7.2%)
	diabetes	27 (19.4%)
Concomitant treatment	beta-blockers	48 (34.5%)
	calcium blockers	37 (26.6%)
	ACE inhibitors	23 (16.5%)
	AT_2R I	9 (6.5%)
	diuretics	73 (52.5%)
	nitrates	85 (61.2%)
	antiplatelet	54 (38.8%)
	anticoagulant	57 (41%)
	amiodarone	15 (10.81%)

MMSE = Mini Mental State Evaluation; MNA = Mini Nutritional Assessment; ADL = Activities of Daily Living; IADL = Instrumental Activities of Daily Living; GDS = Geriatric Depression Scale; ACE = angiotensin converting enzyme; AT_2R-I angiotensin2 receptor inhibitors

The levels of AGEs were significant correlated with the presence of heart failure ($p = 0.014$, $r = 0.280$) (Figure 3) and the MMSE score ($p < 0.05$, $r = 0.206$); there were no others significant correlations between AGEs and any other comorbidities. Also there were no statistically significant correlations between levels of AGEs deposition and any associated treatment.

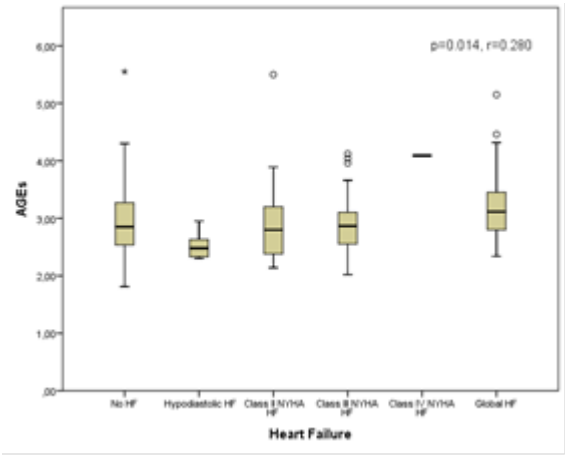

Figure 3.
The correlations of AGEs with the presence and the severity of heart failure

The AGEs role in pathogenesis and prognostic of heart failure was intensely studied in the past few years. The plasmatic levels of AGEs correlated with the severity and the prognostic of heart failure in a study with 102 patients [7]. Another two interventional studies, DIAMOND and PEDESTAL confirmed the effect of increased levels of AGEs on the prognosis of heart failure. In these studies patients with heart failure received a treatment with AGE antagonist. The results were an improvement of diastolic function and a reduction of left ventricle mass [9, 17]. The mechanism cited to be involved in the pathogenesis of heart failure are complex and numerous. AGE depositions determine excessive cross-linkage which leads to an increased vascular stiffness and secondary diastolic dysfunction. The linkage AGE to RAGE (receptor of AGE) leads to myocardial fibrosis and a decreased calcium uptake determining an increased repolarization in the muscular fibre contraction expressed in a diastolic dysfunction [18].

Regarding the associations between AGE and the presence of studied geriatric syndromes, there was a positive statistically significant association between levels of AGEs deposition and MMSE score ($p < 0.05$, $r = 0.206$). This finding is in contrast with the literature data [19]. In patients with Alzheimer disease, higher concentration of AGE were detected, AGE finding confirmed also in diabetic patients with Alzheimer disease and in elderly patient with cardiovascular disease and cognitive impairment. One mechanism involved is increased oxidative stress due to higher concentration and deposition of AGE and the consecutive effect of the lipid profile [19]. The contrast data is probably secondary to one limitation in our study where we

perform the MMSE only once. In the hospitalized geriatric patient may appear variations in the MMSE due to hospitalization stress and in these cases the test must be repeated also in the ambulatory conditions. Another aspect is the fact that, in none of the studies which showed an association between AGE and cognitive status, dementia or brain atrophy, MMSE was used as a tool for cognitive status evaluation. Yaffe *et al.* used Modified Mini-Mental State Examination (3MS) and Digit Symbol Substitution Test (DSST) [20], Wilson *et al.* used Clinical Dementia Rating (CDR) and Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [21], Moran *et al.* used other cognitive tests, other than MMSE [22], and in the Maastricht study MMSE was not an option used [23]. It is possible that MMSE is not a single – reliable test for assessing cognitive function in elderly and a more complex evaluation of the cognitive status should be used, in order to reveal other facts.

The ACE-I treatment was positively associated with a low depression score ($p < 0.05$, $r = 0.235$), the beta-blocker treatment was associated with an impairment in daily living activities ($p < 0.05$, $r = 0.233$) and the anticoagulant therapy was associated with both cognitive impairment ($p < 0.05$, $r = -0.214$) and malnutrition ($p < 0.05$, $r = 0.185$).

The characteristics of patients' geriatric syndromes depending on the presence or absence of studied concomitant cardiovascular medication: β-blocker, ACE-I, anticoagulants, are shown in Table II. All other cardiovascular medication described in Table I had no significant correlations with the geriatric syndromes.

Table II

The geriatric syndromes depending on medication

	β-blocker treatment			ACE-I treatment			Anticoagulant treatment		
	Yes (n = 48)	No (n = 91)	p	Yes (n = 23)	No (n = 116)	p	Yes (n = 57)	No (n = 82)	p
GDS (median)	6	6	NS	4	6	p < 0.05	6	7	p < 0.05
ADL (median)	5	6	p < 0.05	6	6	NS	6	6	NS
IADL (median)	6	7	NS	7	7	NS	7	7	NS
MNA (median)	22	21.5	NS	22	21.5	NS	22	21.5	NS
MMSE (median)	24	24	NS	24	24	NS	26	23	p < 0.05

GDS = Geriatric Depression Scale; ADL = Activities of Daily Living; IADL = Instrumental Activities of Daily Living; MNA = Mini Nutritional Assessment; MMSE = Mini Mental State Evaluation

The patients with ACE-I treatment had a statistically significantly lower GDS score than the patients without ACE-I treatment ($p < 0.05$). These finding may suggest a protective role of ACE-I treatment for depression in elderly patients. A few case series and an open label study found that certain ACE-I are effective in the treatment of depression, but in an adult population [8, 12]. On the other hand the Hallas study find a significant correlation between ACE-I use and concomitant antidepressant use [6]. Further studies are needed to confirm the correlation between GDS and ACE-I, studies on large populations and with match controls.

Beta-blocker treatment was associated with an impairment in daily living activities ($p < 0.05$, $r = 0.233$), a finding also confirmed from the data presented in Table II. In the patient group with beta-blocker therapy is a lower score of ADL, statistically significant, and IADL, not statistically significant compared with patients with no beta-blocker therapy. The correlation between beta-blocker therapy and impaired autonomy in the elderly patient may be due to the lower tolerability of beta-blocker therapy in the elderly and due to the higher rate of side effects [2].

In the present study, the presence of anticoagulant treatment in the elderly is negatively associated with cognitive impairment; patient with anticoagulant treatment had a higher score in MMSE than patients without anticoagulant treatment (26 *vs.* 23, $p < 0.05$). Is there a protective role of anticoagulant therapy for cognitive deterioration? Stott *et al.* found that older patient with increased markers of thrombin generation are with an increased risk for cognitive decline and disability, probably secondary to greater risk cerebral ischemic damage due to pro-thrombotic state [15]. Also there are a few reported cases of improvement of cognitive impairment after anticoagulant therapy in the elderly patient [3].

Conclusions

Oxidative stress has an important role, both in ageing process and in pathogenesis and progression of heart failure. Skin auto-fluorescence, an easy and non-invasive technique, could be a useful tool for the monitoring of the elderly patient regarding the heart failure evolution or the pathological ageing.

In elderly patient anticoagulant treatment may have a protective role for the cognitive impairment, one of the most frequent geriatric syndromes. This fact may be in contrast with the fact that the anti-coagulant treatment is underused and under-

prescribed in the elderly mostly due to their side effects or the compliance to treatment [1]. New classes of anticoagulants may provide a solution for this problem, resolving the compliance issue due to the lack of the coagulation parameters monitoring.

ACE-I have, beside their cardio- and nephron-protective effect, a potential protective role in the risk for depression in elderly patients. Further studies should be done and investigate the benefits of ACE-I treatment in elderly with depression or at risk for depression, a common geriatric syndrome. Also, further studies are needed to investigate the levels of AGE after administration of different cardiovascular drugs and to determine the exact correlation between treatment, oxidative stress and associated cardiovascular pathology.

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