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## ORIGINAL STUDIES

# Management of neuropsychiatric symptoms in people with neurocognitive disorder - using add-on antidepressants or NMDA antagonists in relieving agitation

Bogdan Mircea Petrescu<sup>1</sup>, Sorin Riga<sup>2</sup>

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### Abstract

**Background.** Alzheimer’s disease (AD) is by far the most common type of dementia and it is commonly considered as a memory disorder although behavioral and psychological (including psychiatric) symptoms (BPSD) are largely represented in these patients. Psychosis could explain the worsening of the functional prognosis in these patients, therefore antipsychotic drugs are commonly prescribed. The risks associated with antipsychotics use limit their recommendation and antidepressants or NMDA (N-methyl-d-aspartate) antagonists could represent an alternative.

**Aims.** The aim of this study was to evaluate changes in the clinical status of the psychomotor agitated patients with neurocognitive disorder on stable antidementia therapy after the addition of antidepressants or NMDA antagonists.

**Methods.** The primary variables of this study are related to the severity of agitation under the action of pharmacological factors. Agitation as part of the BPSD was evaluated by CMAI (Cohen-Mansfield Agitation Inventory)-short version. A total of 37 subjects (24 female, 14 male) participated in this observational study. They received as add-on antidepressants between weeks 1-8 or NMDA antagonists between weeks 8-16. Inclusion criteria were DSM IV-TR criteria for diagnosing dementia, AD and vascular dementia (VD) and also NINDS-ADRDA clinical criteria. Data analysis was achieved through SPSS software, version 20, using ANOVA- paired t-tests and independent t tests.

**Results.** The efficacy of memantine over general agitation was significantly superior to antidepressants. Regarding the modulation of the CMAI scores evolution by the type of neurocognitive disorder, treatment and duration, it was observed that the statistical difference between groups became significant after 8-16 weeks of memantine treatment. At the endpoint visit the decrease in agitation was superior in the AD versus VD group ( $p = 0.012$ ).

**Conclusions.** The overall trend was toward a decrease of the agitation severity after each treatment trial for both types of dementia, including cumulative drugs effects. In the literature, the data are controversial in terms of prescribing antidepressants in the neurocognitive disorders even when BPSD is important, the keystone being the general consensus of limiting the use of antipsychotics and polypharmacy.

**Keywords:** aging, psychosis, Alzheimer dementia, vascular dementia, beta amyloid, agitation

## Introduction

Alzheimer’s disease (AD) is a neurodegenerative disease of the brain, of unknown etiology, usually characterized by obvious memory deficits (\*\*\*, 2004), which has a specific anatomopathological substrate, consisting of senile plaques and neurofibrillary tangles. Over time, AD causes neurochemical dysfunction and prominent brain atrophy. AD is by far the most common form of dementia, being the cause of about 75% of cases of dementia either *per se* or in combination with other conditions.

More than 45 million people worldwide are currently living with dementia (Livingston et al., 2017). While AD is commonly considered a memory disorder, behavioral and psychological symptoms of dementia (BPSD) are nearly universal and include psychotic symptoms (Livingston et al., 2017; Ballard & Corbett, 2009). Also, more than 50% of patients with AD will present with psychosis during their illness (Murray & Kumar, 2014; Ropacki & Jeste, 2003). These phenomena could explain these patients’ overall worse prognosis, including accelerated cognitive

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decline, earlier admission to institutional care (El Haj et al., 2017), more hospital admissions (Beydoun et al., 2015), and increased mortality (Peters et al., 2015). Currently, no treatments have been approved for AD psychosis (Cummings et al., 2019).

### **Pathology and neurochemistry**

Microscopically, Alzheimer's pathology consists of two main features: senile plaques and neurofibrillary tangles. Currently, the exact relationship between beta amyloid, plaque, clots, cognitive impairment and disease progression is an active area of research. The senile plaques contain a specific amyloid, called beta amyloid - " $\beta$ A". This  $\beta$ -amyloid is a peptide of either 40 or 42 amino acids, and it is a fragment of the parent molecule known as APP, amyloid precursor protein, a transmembrane glycoprotein. The function of  $\beta$ -amyloid is currently unclear, the senile plaques are located extracellularly and they contain dystrophic neural processes in addition to  $\beta$ -amyloid. Therefore, the axonal disconnection from the dendrites results in poor inter-neuronal communication. And because the microglial cells support the removal of  $\beta$ -amyloid and axonal-dendritic debris, the inflammatory reaction will increase and trigger even more cellular toxicity.

The main neurotransmitter involved in the pathogenesis of AD is acetylcholine. From the early onset of the disease, there is a loss of acetylcholinesterase with a decrease in the reuptake of choline in the synaptic cleft, as well as a decrease in acetylcholine synthesis. Subsequent studies have shown a directly proportional correlation of acetyltransferase loss with cognitive impairment (López et al., 2013). Therefore, the cholinergic hypothesis of AD and the initiation of anti-dementia treatment with acetylcholinesterase inhibitors emerged. In the last decade, research has shown that, in addition to acetylcholine, a plethora of neurotransmitters are involved such as norepinephrine, glutamate, or dopamine, but also, in the foreground, serotonin.

Also, it seems that maintenance of the proteome and organelle population is an important key to the augmentation of lifespan and/or attenuation of many pathologies associated with the aging process. Knowing that regular exercise promotes healthy aging and mitigates age-related pathologies, it is possible that a common pathway in health and longevity may exist (Petrescu et al., 2021).

### **Neuropsychiatric symptoms in people with dementia**

It is known that age is the greatest risk factor for major or minor neurocognitive disorder (\*\*\*, 2013). Dementia affects 5% of adults over the age of 65 and up to 30% of people over the age of 85. Between 80 and 90% of people with dementia have psychosis, agitation or discomfort, collectively referred to as neuropsychiatric symptoms (BPSD) (Ballard et al., 2009). In addition, 20% of people diagnosed with Alzheimer's disease living in the community and 40-60% living in long-term care (LTC) units have varying degrees of psychomotor agitation.

Moreover, up to 15% of people living in the Alzheimer's community experience delusional ideas, visual hallucinations or auditory hallucinations and 20% of them have moderate to severe clinical depression (Ballard & Corbett, 2010). Neuropsychiatric symptoms often lead to decreased quality of life or increased risk behaviors that

can be life-threatening for patients, leading to difficulties in managing healthcare. People with these symptoms may need long-term institutional care and can be a considerable treatment challenge for all medical and support staff (Seitz et al., 2011; Kalapatapu & Neugroschl, 2009).

Patients with psychosis or agitation are frequently treated with antipsychotic drugs (Ballard et al., 2009; Wang et al., 2005). In 18 randomized controlled trials with short-term monitoring, atypical antipsychotic drugs used to treat neuropsychiatric symptoms have been associated with three times the risk of stroke and almost twice the risk of death compared with placebo (Ballard & Corbett, 2010). Haloperidol treatment was associated with a higher risk of mortality than treatment with atypical antipsychotics (Wang et al., 2005), and typical and atypical antipsychotics have been associated with an increased rate of cognitive decline compared with placebo (Ballard et al., 2009). Antipsychotics are used off-label for BPSD, especially when agitation, aggression and psychotic symptoms are present. However, these agents may pose an increased risk of mortality when used for dementia-associated psychosis (Schneider et al., 2005; Gill et al., 2005; Wang et al., 2005; Sahlberg et al., 2015). Other side effects of antipsychotics include extrapyramidal symptoms, metabolic changes, or even cognitive decline due to anticholinergic effects. Due to the risks associated with antipsychotics, many clinicians are looking for other pharmacological options for polymorphic BPSD when non-pharmacological therapies fail. Several studies show that selective serotonin reuptake inhibitors (SSRIs) are effective in treating BPSD. In clinical trials, citalopram, escitalopram and sertraline are the most studied drugs in this class (Gaber et al., 2001; Finkel et al., 2004).

Due to the risks associated with antipsychotic use and the literature supporting SSRI treatment for BPSD, clinicians may want to use SSRIs instead of antipsychotics. In general, clinical trials have shown little benefit after the use of antipsychotics commonly prescribed today with the increasing incidence of symptoms of agitation and psychosis in elderly patients. In addition, adverse effects (e.g., cognitive impairment, morbidity) often outweigh the perceived benefits of using antipsychotics. Given these factors, the guidelines recommend "assessing the psychological and behavioral symptoms of dementia, developing a comprehensive treatment plan, evaluating the benefits and antipsychotic risks and the prudent use of antipsychotics, including the specifics of dosage, duration and monitoring" (Martin, 2016).

### **Objectives**

It is estimated that up to 8 out of 10 people with major neurocognitive disorders suffer from polymorphic BPSD. These symptoms are divided into 4 clusters that include:

- hyperactivity: agitation, aggression, euphoria, disinhibition, irritability, behavioral disorders;
- psychosis: hallucinations and delusional ideas;
- mood disorders: depression and anxiety, and
- instinctual disorders: appetite disorders, hypnotic disorders or apathy.

The working hypothesis is that general serotonin deficiency in patients with neurocognitive disorder may

contribute to many of these symptoms.

Antipsychotics are used off-label for this syndrome, especially when agitation, aggression and psychotic symptoms are present, but their use in clinical practice may lead to an increase in mortality, extrapyramidal symptoms, metabolic disorders or even cognitive decline due to anticholinergic effects.

Due to the risks associated with antipsychotics and the literature that does not support antipsychotic treatment for BPSD, clinicians could use SSRIs instead of antipsychotics. The aim of this study was to evaluate changes in the clinical status of psychomotor agitation in patients with neurocognitive disorder on stable anti-dementia therapy after the addition of SSRI/NaSSA (noradrenergic and specific serotonergic antidepressant) to treatment.

*a. General-theoretical objectives:*

Determination of the pharmacological factors (SSRI/NaSSA or NMDA antagonists) and clinical variables that impact BPSD as well as cognitive and functional decline in patients diagnosed with AD, vascular dementia (VD) or mixed dementia (vascular aggravated Alzheimer's) with or without depressive symptoms. Establishing the ways in which pharmacological factors modulate agitation in the study population.

- Clinical practice-oriented objectives:

- Establishing a model of pharmacological intervention in cognitive disorders, based on the efficacy and tolerability of anti-dementia agents in combination with antidepressants (SSRIs/NaSSA) or NMDA glutamatergic agonists in combination with drugs with different but synergistic pharmacological properties, weighing the remaining options or switch, depending on the particularity of the case (e.g., severity of agitation or depression). If patients present depressive symptoms objectified by the Geriatric Depression Scale,  $GDS > 5$  at V1, and at V4 - at 8 weeks will have remission of depressive symptoms objectified by  $GDS \leq 5$ , antidepressants will be continued. If patients have  $GDS > 5$  at V1, and at V4 at V8 they do not have remission of depressive symptoms objectified by  $GDS \geq 5$ , they can be considered responders but not remitters, and they will receive memantine (switch). If patients do not have depressive symptoms with  $GDS < 5$  at V1, they will also receive memantine at V4 (switch).

- Correlation of changes in all parameters with the type of pharmacological intervention and the severity of symptoms. From the perspective of ranking the objectives, we established two categories, according to the research hypotheses stated below.

*The main objective of the study:* the observational study compared the benefits of SSRIs - sertraline, NaSSA - mirtazapine, and memantine - an NMDA receptor antagonist with a pro-cognitive role in neurocognitive disorders, as an add-on therapy to pre-existing anti-dementia medication (mainly cholinesterase inhibitors). Participants are eligible if they meet the criteria for dementia in AD, VD, or mixed dementia, without depressive symptoms, mild or moderate, determined by GDS-15 score  $\leq 10$ .

*Secondary objectives:* to evaluate the effectiveness of antidepressants / memantine on:

- Functionality
- Global clinical impression

- Safety objective - assessment of the safety and tolerability of antidepressants/memantine during treatment.

Also, establishing how certain clinical or social factors (e.g., social or family support, level of schooling, change in mild depressive symptoms) reduce patients' responsiveness to anti-dementia pharmacological agents.

Other results considered for the inclusion/exclusion criteria were laboratory results and brain CT/MRI, also to rule out stroke, trauma or concussion (Constantin et al., 2018). Lab results were considered for the monitoring of the treatment safety profile.

Data analysis was done through SPSS software, version 20 (\*\*\*, 2011) using ANOVA-paired t-tests and independent t tests.

The criteria for inclusion in the study were the existence of the diagnosis of AD or VD at the time of admission, as well as the recording of possible comorbidities according to the DSM IV-TR and ICD-10 criteria. For all patients who met the criteria for inclusion in the study and for whom the consent to participate was obtained, somatic, psychiatric and psychological evaluation was performed for diagnosis confirmation. The patients included did not present severe comorbidities and had no contraindications to the drugs used.

## Hypotheses

For this study we stated the following hypotheses:

1. The evolution of the parameters in patients diagnosed with neurocognitive disorders differs depending on the type of pharmacological agents used and the duration of the treatment.

2. The therapeutic response is influenced differently by pharmacological agents modulated by the variable 'agitation'.

3. Depending on the type of neurocognitive disorder (Alzheimer's or vascular), patients will respond differently to treatment.

## Materials and methods

All patients participated based on the free consent expressed prior to the first investigations. They completed and submitted their written consent to the proper authorities, more specifically to the Psychiatry Department of 'Carol Davila' University Emergency Central Military Hospital (Bucharest, Romania).

Data confidentiality was ensured throughout the study. Drug therapy was administered according to national and international treatment guidelines for BPSD (1); (\*\*\*, 2019) and in accordance with the indications in the summary of product characteristics for the respective antidepressants and glutamatergic agonists. No invasive methods were used and no special blood samples were taken for the study. There was no conflict of interest.

### Research protocol

*a) Period and place of the research*

Patients were consulted in the Psychiatry Department of the University Emergency Central Military Hospital in Bucharest, or in its integrated outpatient clinic during March 2018 - November 2019.

*b) Subjects and groups*

The inclusion and exclusion criteria in this research

described below were assessed at the initial visit and underlay the formation of the study group.

The inclusion criteria were DSM IV-TR criteria for diagnosing dementia, AD and VD, and also the clinical criteria according to NINDS and ADRDA (National Institute of Neurological Disorders and Stroke/Alzheimer's Disease and Related Disorders Association) (McKhann et al., 2011) were met. The initial MMSE examination at screening was 12-26. CT / MRI imaging corroborated with the Haciniski score (Moroney et al., 1995) is considered to highlight:

- for AD: medial temporal atrophy plus Haciniski score of ischemia  $\leq 4$
- for RV: Haciniski score  $\geq 7$
- for mixed dementias Haciniski score = 5 or 6.

Patients with vascular dementia had a history of stroke.

The minimum age limit for inclusion was 55 years, with no maximum age limit. GDS score (Greenberg, 2006) at inclusion had a maximal value of 10, corresponding to a depression of mild or moderate intensity. The CGI-S score (Guy, 1976) was at least 3 (mild severity of global symptoms). Patients did not take more than one acetylcholinesterase inhibitor, treatment was used continuously for at least 2 months prior to the screening visit, and they did not receive prior treatment with memantine.

A total of 37 subjects participated in the research, which presented the following demographic characteristics: 13 subjects (35.1%) were male and 24 (representing 64.9%) were female. The gender distribution was in favor of females, with a female / male ratio of about 2: 1. A slightly supra-unitary ratio of the "sex" variable (women / men) is allowed in the general population in the case of the prevalence of neurocognitive disorders, with women having a longer life expectancy.

According to the "age" variable, the following structure of the study group is registered: out of the total number of patients included in the study, most were included in the age range 71-75 years (n = 12), followed by those aged between 76 and 80 years (n = 6), those over 80 years (n = 5) and patients aged 60 years (n = 4). Also, the distribution according to the type of neurocognitive disorder was very balanced - Fig. 1.

The age distribution was normal, with an average of 72.22 years, a median of 71.00, Std. Deviation (SD) 7.269, with a minimum age of 58 and a maximum age of 90 years. The percentiles show the following stratification: 25-67.00, 50-71.00, 75-77.00.

According to the environment in which the patient's current domicile was located: the urban / rural average ratio was almost unitary, the patients in the urban environment being slightly more numerous (51.4% -19 patients).

- According to the type of neurocognitive disorder, the AD/VD ratio is almost unitary, the patients being in almost equal numbers (51.4% -19 patients with AD).

- Interestingly, patients presented the same basic characteristics, so the distribution was uniform at visit 1 (week 0).

- Secondly, the distribution of the average ages can be observed in Fig. 2.

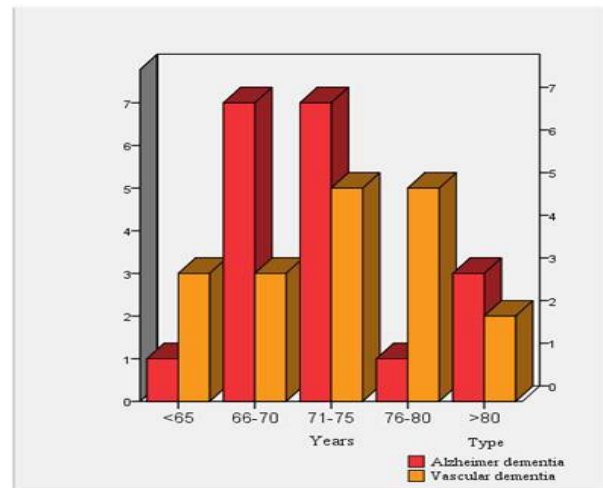


Fig. 1 – Age categories by dementia type.

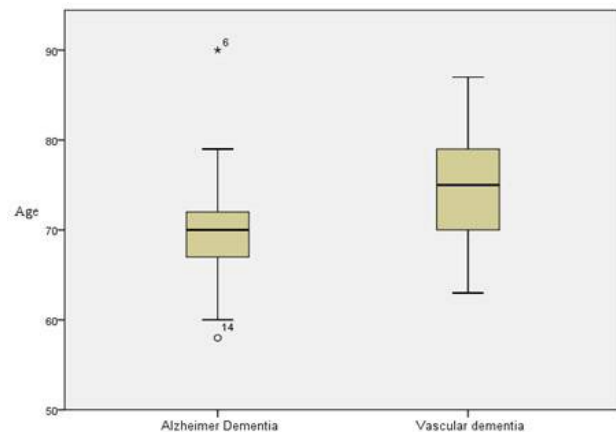


Fig. 2 – Distribution of mean age.

According to the level of education, the following structure of the group stands out: the average number of classes is 10.43, the average 8.00 and SD 4.688. The minimum value is 4 and the maximum value is 17. The percentiles are: 25-8.00, 50-8.00, 75-16.00. Regarding the level of education, it was found that most patients belonged to the category of those with a lower level (primary school or middle school), followed by those with an intermediate level (high school or vocational school), and 29.7% (11 patients) representing almost a third of the participants had college / college or postgraduate studies.

From the point of view of the clinical variables detected at the first visit, the following can be observed:

- patients were on treatment for at least 4 weeks on stable doses of donepezil, rivastigmine and galantamine, in doses according to their summary of product characteristics;

- patients had up to 2 previous treatments and only a minority of subjects (7 patients - 18.9%) were diagnosed with neurocognitive disorder for the first time;

- the average scores of MMSE/CDR correspond to moderate-mild severity (Folstein et al., 1975; Morris et al., 1995; Morris et al., 1997), but the extreme values show the inclusion in the study of patients with all forms of dementia, except the severe one;

- with the coexistence of depressive disorders in 29/37 of the evaluated patients, 8 patients representing 21.6% did not show depressive symptoms;

- CGI-S scores at V1 correspond to neurocognitive disorder severity scores, with an average value of 4.30, minimum 3, maximum 6, SD 1.077;

- safety indicators, respectively physiological parameters, have average values within normal limits, even if extreme values are recorded, congruent with comorbid diagnoses.

The distribution of the study group according to demographic parameters and initial clinical variables is found in Table I.

**Table I**  
Distribution of the study group according to demographic parameters and variables at the initial clinical visit.

Indicator	Min	Max	Mean	Std. Dev
Age	58	90	72.22	7.269
Education level (yrs)	4	17	10.43	4.688
MMSE score week 0	12	25	20.68	3.859
CDR score week 0	3.0	11.0	5.716	2.6603
CGI-S week 0	3	6	4.30	1.077
GDR week 0	1	10	6.59	2.608
CMAI week 0	19	42	31.11	5.130

The pharmacological classes used in this clinical study were: antidepressant between weeks 1-8: SSRI - sertraline or NaSSA - mirtazapine, and weeks 8-16: NMDA glutamatergic antagonist - memantine. Absolute values indicate the following stratification: 26 of the 37 patients received sertraline, and 11 received mirtazapine treatment. Regarding the maximum doses received by patients, these were: sertraline 100 mg/day, mirtazapine 30 mg/day and memantine 20 mg/day. At the end of week 7, antidepressants will be discontinued in a maximum of 3 days. Then, after complete discontinuation, memantine 5 mg will be initiated at the beginning of week 8, which will be gradually increased according to protocol in the following weeks until the end of the study.

#### c) Applied tests

##### Definition of dependent and independent variables.

The primary variables analyzed in this study are related to the severity of agitation symptoms under the action of pharmacological factors. A part of BPSD defined by side A - "AGITATION" was evaluated by the CMAI (Cohen-Mansfield Agitation Inventory) scale-short version, which has 3 subscales (score between 14 and 70) (Cohen-Mansfield, 1986). The elements related to monitoring the tolerability of pharmacological therapy were body weight and BMI - body mass index, waist circumference, QTc interval, systolic and diastolic blood pressure values. The dependent variables are therefore the scores for assessing the severity of agitation and depression, cognitive performance and overall functionality, executive performance, fluency and language, duration of treatment.

The independent variables consist mainly of the classes of pharmacological agents administered, and also the type of neurocognitive disorder, the presence or absence of the diagnosis of severe depressive disorder as well as comorbidity in secondary analyzes.

#### d) Statistical processing

The primary efficacy analysis is based on the change in CMAI scores at visit 4 from the initial visit, and then the change in CMAI scores at visit 6 compared to visit 4 and the initial visit. A secondary analysis of efficacy is based on CGI-S scores.

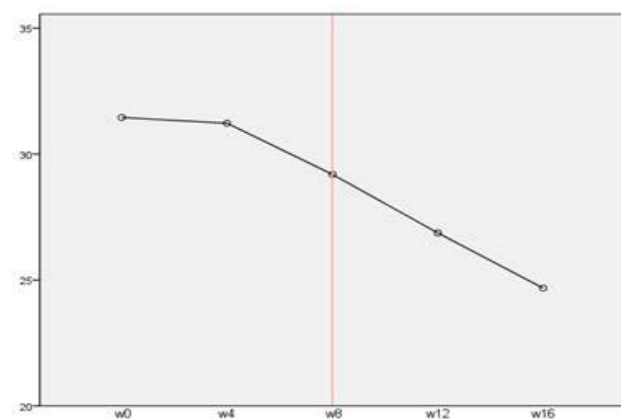
The method of data processing regarding the analysis of changes in dependent variables according to the action of pharmacological agents was the t test for dependent samples,  $df = 30$  (36), the result being related to a threshold of significance  $\alpha = 0.05$  bilateral.

The impact of add-on pharmacological agents (sertraline or mirtazapine, then memantine) during treatment on the variable was evaluated using unifactorial ANOVA,  $df = 30$ ,  $p < 0.05$  bilateral.

The Pearson association test was applied to verify the links between agitation (on a continuous scale) and: cognition and functionality, depression severity, age/dementia type, etc.

## Results

*Evolution of CMAI agitation scores under treatment.* The t test was used for dependent samples, at an alpha value = 0.05 bilaterally,  $df = 30$ . The data obtained show a decrease in general agitation less under the action of antidepressants at visit 4-week 8 compared to the initial visit V1-week 0 than under the action of memantine, the averages  $\Delta CMAI1$  and  $\Delta CMAI 2$  being -2.2581 and -4.5161, respectively (SD = 3.56808, se = 0.64085 and SD = 5.12426, se = 0.92034, respectively). The reduction was statistically significant, with an average difference of 2.25806, SD = 5.17022, se = 0.92860,  $p = 0.021$ , and  $t = 2.432$ . The effect size (d Cohen) calculated  $d = t / \sqrt{n}$ ,  $n = 31$  was 0.43, which is a modest value; therefore the effect size is small. What is interesting is the linear decrease in time of the general agitation score and the better response in the second part of the treatment according to Fig. 3.



**Fig. 3** – Means of CMAI scores in weeks 0, 4, 8, 12 and 16.

The analysis of differences between agitation modification groups (CMAI) depending on the type of neurocognitive disorder, treatment and duration (including the total effect between V0-V16 after the 2 treatments) included 3 defined groups: 1 - antidepressants lasting 8 weeks - 'ADT' group, 2 - memantine with a duration of 8 weeks - 'MEM' group, and 3 - treatment 1 then 2 with a duration of 16 weeks - 'ADT + MEM' group.

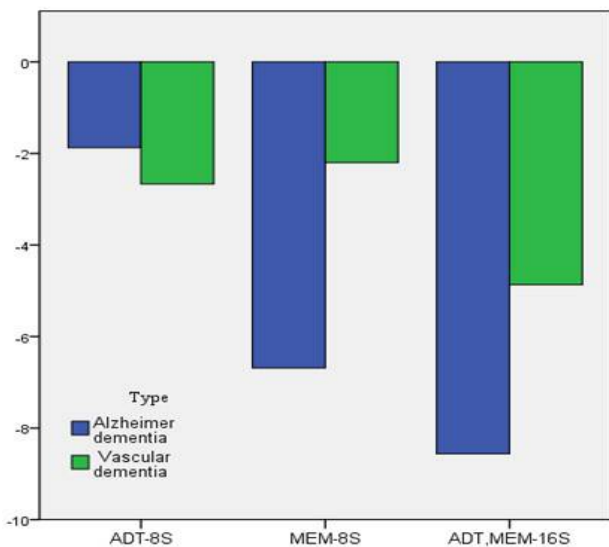
**Table II**  
Description of parameters - Decreased agitation score (CMAI) of Alzheimer's and vascular dementia treatment function and duration ANOVA.

Indicator		Sum of squares	df	Mean square	F	Sig.
dCMAI1	between groups	4.852	1	4.852	.373	.546
	in groups	377.083	29	13.003		
	Total	381.935	30			
dCMAI2	between groups	155.904	1	155.904	7.156	.012
	in groups	631.838	29	21.788		
	Total	787.742	30			
dCMAIf	between groups	105.749	1	105.749	2.142	.154
	in groups	1431.671	29	49.368		
	Total	1537.419	30			

Indicator	N	Mean	SD	SE	95%CI for mean		Min	Max	
					min	max			
dCMAI1	Alzheimer dementia	16	-1.8750	3.66742	.91686	-3.8292	.0792	-12.00	3.00
	Vascular dementia	15	-2.6667	3.53890	.91374	-4.6264	-.7069	-11.00	3.00
	Total	31	-2.2581	3.56808	.64085	-3.5668	-.9493	-12.00	3.00
dCMAI2	Alzheimer dementia	16	-6.6875	5.53436	1.38359	-9.6366	-3.7384	-13.00	2.00
	Vascular dementia	15	-2.2000	3.50917	.90606	-4.1433	-.2567	-9.00	2.00
	Total	31	-4.5161	5.12426	.92034	-6.3957	-2.6365	-13.00	2.00
dCMAIf	Alzheimer dementia	16	-8.56	8.214	2.053	-12.94	-4.19	-25	3
	Vascular dementia	15	-4.87	5.475	1.414	-7.90	-1.83	-14	2
	Total	31	-6.77	7.159	1.286	-9.40	-4.15	-25	1

The one way ANOVA test was used for the 3 groups, with the threshold of statistical significance  $\alpha = 0.05$  bilateral. It can be observed that there are differences between the actions of pharmacological agents on certain symptomatic dimensions (factors) which, even if they do not reach the level of significance, indicate a favorable trend for one treatment in relation to another. All analyzes aimed to detect significant differences between pharmacological agents regardless of the dependent variable pursued. The aim was to define the F value, as well as the  $\eta^2$  value in order to identify the proportion of the influence of the independent variable in the fluctuation of the dependent variable.



**Fig. 4** – (Decreased) CMAI score of Alzheimer's and vascular dementia depending on treatment and duration.

According to the graph, the decrease of the CMAI score in Alzheimer's and vascular dementia can be observed depending on the treatment and duration in the 3 compared groups 1, 2 and 3, respectively (Fig. 4).

The statistical difference was obvious in weeks 8-16 after memantine treatment, at the end of which the decrease in agitation in Alzheimer's dementia was superior to vascular dementia, statistically significant according to Table II,  $F = 7.15$ ,  $p = 0.012$ .

### Discussion

A limitation of this study is the small number of patients, statistical power increasing with large groups. In the literature, data are controversial in terms of prescribing antidepressants in the neurocognitive disorder even when BPSD is important, the keystone being the unilateral consensus in limiting the use of antipsychotics and polypharmacy, in general. This paper shows a partial and stratified improvement of a limited number of patients, and that the creation of a clinical profile of the typical patient could lead us to practice a personalized medicine, adapted to the geriatric population.

Currently, only short-term symptomatic treatment is available. Although there is ongoing research in the field in this area, there is a need for exponential research dynamics. At the same time, there needs to be more collaboration and a multidisciplinary approach in the field of research for neurocognitive disorders. The review of grants should be supported by governmental and non-governmental institutions through the facilitation of cooperation between neurobiologists, clinicians and psycho-pharmacologists. Innovation and continuous work are needed to encourage the diversity of therapeutic options for the ongoing fight against dementia.

## Conclusions

1. The efficacy of memantine in decreasing the severity of the general agitation is significantly superior to that of antidepressants, and this is probably due to the multiple therapeutic factors involved.

2. Regarding the differences between the agitation modification groups (CMAI) depending on the type of neurocognitive disorder, treatment and duration, it was observed that the statistical difference was obvious in weeks 8-16 after memantine treatment, at the end of this treatment the decrease in agitation in Alzheimer's dementia being superior to vascular dementia ( $p = 0.012$ ); the general trend was to decrease agitation after each treatment, including cumulative, for each type of dementia.

3. The primary endpoint, i.e. the benefits of treatment with SSRI/NaSSA/NMDA glutamatergic antagonists as adjunctive therapy to cholinesterase inhibitors are correlated with reduced severity of agitation symptoms and increased overall functionality in patients aged  $\geq 55$  years diagnosed with neurocognitive disorders (Alzheimer and vascular dementia).

4. This paper proposes a pharmacological strategy in the treatment of neurocognitive disorder, not only for decreasing agitation, but for a better global functionality for patients, and also helping carriers with better care.

## Conflicts of interests

None declared.

## Acknowledgments

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## Aorta modifications in oral gold nanoparticles administration in rats

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### Abstract

**Background.** Nanotechnology developed multiple systems that may be involved in drug delivery to the target tissue, among them, gold nanoparticles (AuNPs) being considered potent and safe.

**Aims.** The study aims to investigate oxidative stress and the modifications of the aorta wall after administration of gold nanoparticles, as the single component or functionalized with *Cornus mas* L. extract.

**Methods.** Adult female rats received solutions by gavage, as follows: *group C (control)*, saline solution; *group I (citrate)*, trisodium citrate dehydrate; *group II (AuNPs)*, gold nanoparticles solution; and *group III (AuNPsCM)* solution of gold nanoparticles functionalized with *Cornus mas* L. extract. Oxidative stress parameters were investigated in the serum and aorta, biochemical parameters from blood, diameters and blood flow velocity were measured and transmission electron microscopy (TEM) was performed on ascending aorta ring sections.

**Results.** LDL was significantly reduced; MDA decreased significantly in serum; in the aorta, endothelin 1 and TNF- $\alpha$  were significantly increased in AuNPs and AuNPsCM groups, iNOS increased and MDA decreased in all treated groups, compared to the control group. The aorta diameters significantly decreased, consequently the blood flow increased significantly in the treated groups, in comparison with the control group. TEM investigation showed intima and media alterations in groups that received citrate and AuNPs, and only intima modifications in the AuNPsCM group.

**Conclusions.** The aorta wall presented oxidative stress and histological modifications in all treated rats.

**Keywords:** gold nanoparticles, aorta, *Cornus mas*, trisodium citrate dihydrate, oxidative stress

### Introduction

Nanotechnology developed nanoparticles that may be used for drug delivery, cancer imaging and other medical applications (Moore & Chow, 2021), their size, composition, shape, surface functionalization influencing their action (Yetisgin et al., 2020). Gold nanoparticles (AuNPs) are considered potent and safe delivery systems for synthetic drugs or for natural compounds to the target

tissue cells (Zugravu Pop et al., 2020) and several studies presented their efficacy in researches performed on experimental models, *in vitro* (Domsa et al., 2020) or *in vivo* (Chen et al., 2018). Gold nanoparticles are efficient transducers of light energy that can be used in photothermal therapy (Shi et al., 2021). AuNPs functionalized with different extracts or chemical solutions were used in experimental models to study their bio-distribution that

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was discovered to depend on their physicochemical properties (Tiwari et al., 2011). Researches conducted with AuNPs on different cancer types showed that these nanoparticles may destroy the vessel wall in neoplasia and can diffuse from the administration area (Volkov et al., 2019). Several studies indicated that gold nanoparticles may initiate oxidative stress (Jawaid et al., 2020), are cytotoxic and can affect cell viability, according to their morphology (Bhamidipati & Fabris, 2017).

Trisodium citrate dehydrate is used for blood preservation and may be also utilized to suspend nanoparticles in solutions that may be administered for experimental purposes. The blood vessel wall is exposed to numerous endogenous or exogenous factors that can induce lesions in the endothelial cell layer and even deeper, which must be continuously investigated through numerous experimental models.

*Cornus mas* L., part of Cornaceae family, is a plant found in Europe and Asia, rich in flavonoids, phenolic acids, anthocyanins, carotenoids, tannins, vitamins and fatty acids, natural compounds with many effects (antidiabetic, hepatoprotective, cardioprotective, anti-inflammatory, cytotoxic, etc.) (Dinda et al., 2016). Considering its favourable effects in different pathological situations, *Cornus mas* L. extract was used to functionalize the gold nanoparticles investigated in the present study.

## Hypothesis

The experiment started from the hypothesis that AuNPs, as a single component or functionalized with *Cornus mas* L. extract, may improve aorta functionality.

## Material and methods

### Research protocol

#### a) Period, place, materials used in the research

The experiment was performed in the Physiology Department of Iuliu Hațieganu University of Medicine and Pharmacy, Cluj-Napoca, under the approval of the University Ethics Committee (no. 158/11.03.2019), respecting the Directive 86/609/EEC. It consisted of administering treatment (AuNPs and AuNPs<sub>CM</sub>) for 30 days to rats with a standard diet. On the 31<sup>st</sup> day of the experiment, the animals, under mild anaesthesia, were weighed and blood samples were collected for biochemical and oxidative stress parameter determination. The animals were then euthanized using deep anaesthesia. The entire visceral adipose tissue was collected, weighed, and aorta was taken for microscopic and oxidative stress examination.

#### b) Subjects and groups

The study used 28 Sprague Dawley adult female rats, age 5-6 months, weight  $300 \pm 10$  g, purchased from the Cantacuzino National Medico-Military Institute for Research and Development, Bucharest, Romania. The rats were randomly allocated to 4 groups and hosted in cages at a standard temperature of  $21 \pm 2^\circ\text{C}$  and a relative humidity of  $55 \pm 5\%$  and were fed with standard food. The animals received for 30 days, between 7 a.m. and 8 a.m., by gastric tube gavage, 0.5 mL/day solution, in the following manner: *group C (control)* - 0.9% saline solution, *group I (citrate)* - 1% trisodium citrate

dihydrate, *group II (AuNPs)* - gold nanoparticles solution, and *group III (AuNPs<sub>CM</sub>)* - solution of gold nanoparticles functionalized with *Cornus mas* L. extract.

*Gold nanoparticles (AuNPs)* were synthesized through Au<sup>3+</sup> ion reduction from tetrachloroauric acid through a green method. The mixture was stirred without heating for 30 minutes and the colloidal gold synthesis was observed through colour changing from pale yellow into violet-cherry red. The obtained gold nanoparticles were suspended in citrate solution.

*Gold nanoparticles functionalized with Cornus mas L. extract (AuNPs<sub>CM</sub>)* were obtained through Au<sup>3+</sup> ion reduction from tetrachloroauric acid through a green method, using as a reducing and stability agent this natural extract. For this purpose, 25 mL of *Cornus mas* L. extract, 25 times diluted and brought to pH=7.5 with NaOH 0.1M solution, were added by dropping over 100 mL boiling HAuCl<sub>4</sub> solution. The obtained mixture was stirred (without heating), for 30 minutes, period of time during which the colloidal gold formation was observed through the solution colour modification, from pale-yellow to mauve-cherry red. The gold colloidal solution was centrifuged, for 30 minutes at 12000 rpm, the supernatant was decanted and the residue was washed two times with bidistilled water.

The obtained gold nanoparticles were characterised by UV-Vis spectrophotometry (using a Perkin Elmer Lambda 25 spectrophotometer) and by transmission electron microscopy (using a Hitachi Automatic H-7650 microscope). TEM image shows the obtained gold nanoparticles, spherical in shape, non-agglomerated, with a mean diameter of 19 nm.

### c) Applied tests

#### Serum biochemical parameters

Several biochemical parameters were investigated using the BioSystems A15 analyzer with specific reagents for every blood element.

#### Oxidative stress investigation

Oxidative stress parameters were investigated using the following methods: malondialdehyde (MDA) by Conti's method (Conti et al., 1991), reduced glutathione (GSH) using Hu's method (Hu, 1994) and oxidised glutathione by Vats' method (Vats et al., 2008). The GSH/GSSG ratio was calculated as an important indicator of oxidative stress.

#### Endothelin 1, inducible Nitric Oxide Synthase (iNOS) and Tumour Necrosis Factor-alpha (TNF-α)

The inflammatory factors from the aorta wall were determined using spectrometer-based ELISA readers, absorbance 450 nm, at 37 °C, and with Magellan data analysis software.

#### Ultrasound (US) examination

Sonography was performed using an 8–40 MHz linear array transducer on a Sonotouch Tablet System (Ultrasonix Medical Corporation, Richmond, Canada), using a 20MHz frequency for all the scans. The aorta diameter was measured on transverse scans, using two-dimensional US, near the level of the aortic valve. The highest anterior-posterior diameter obtained on the image was measured.

The presence of the flow in the aorta was detected using colour or power Doppler US. At the pulsed Doppler examinations, the highest velocity obtained on the specific scale was measured (cm/sec).

*Transmission Electron Microscopy (TEM)*

Ascending aorta ring sections of 60–80 nm were examined on a JEOL JEM 1011 transmission electron microscope (JEOL, Tokyo, Japan) and the images were captured using a GGG camera (Olympus, Soft Imaging System, Münster, Germany).

*d) Statistical processing*

The parameter values were analysed statistically using GraphPad Prism version 5.03 for Windows, GraphPad Software (San Diego California USA), one-way ANOVA followed by post-test Tukey. The body weight was observed over the experiment days and the results were statistically analysed by two-way ANOVA followed by Bonferroni post-tests. The threshold significance level was set at  $p < 0.05$ .

**Results**

In serum, several biochemical parameters were determined: C-reactive protein (CRP), triglycerides, cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), glucose, glycohaemoglobin (HbA1c) and gamma-glutamyl transferase (gamma-GT). From all the investigated biochemical parameters, only LDL presented significant decreases ( $p < 0.05$ ) in group III (AuNPsCM), compared to the control group (Table I).

In serum, oxidative stress was investigated and the results showed a significant decrease of MDA ( $p < 0.05$ ) in group II that received AuNPs for 30 days. The antioxidant protection examined through the GSH/GSSG ratio did not present any significant modifications (Figure 1).

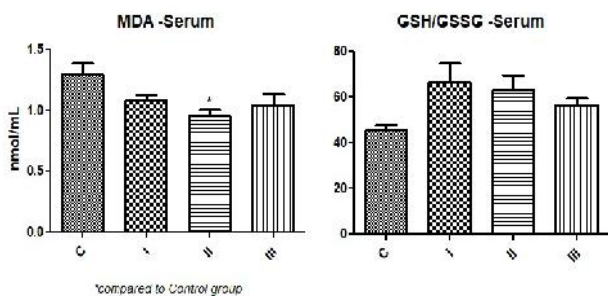


Fig. 1 – Oxidative stress parameters in the serum of rats.

In the aorta, oxidative stress was investigated to determine the effects of treatment administration. The aorta lipid peroxidation was determined by malondialdehyde (MDA) levels that were decreased significantly in all treated groups, I ( $p < 0.01$ ), II and III ( $p < 0.001$ ), compared to the control group. Nitric oxide synthase (iNOS) increased significantly in the test groups ( $p < 0.001$ ) compared to the control group. AuNPs (group II) and AuNPsCM (group III) administration induced a significant increase of iNOS ( $p < 0.001$ ), compared to citrate solution (group I) ingestion. Endothelin 1 (ET1) levels increased in group II ( $p < 0.001$ ) compared to the control group and group I, significant increases being also recorded in group III compared to group I ( $p < 0.01$ ) and group II ( $p < 0.001$ ). Tumour Necrosis Factor alpha (TNF- $\alpha$ ) presented significant increases in group II ( $p < 0.001$ ) compared to the control group and group I, while in group III, this parameter showed significant increases compared to the control and citrate (I) groups ( $p < 0.05$ ), and also compared to group II ( $p < 0.001$ ) (Figure 2).

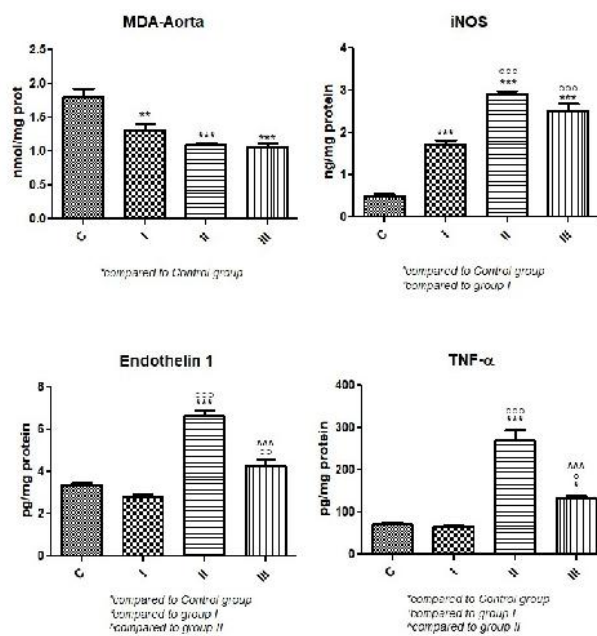


Fig. 2 – The aorta levels of MDA, iNOS, endothelin 1 and TNF-alpha.

Table I  
Mean and standard deviations of the investigated serum biochemical parameters (\*compared to the control group,  $p < 0.05$ ).

Serum Parameter	C	I	II	III
CRP	1.65±0.23	3.06±0.30	2.77±0.33	2.73±0.30
Triglycerides	135.98±9.30	170.80±17.64	167.4±7.16	160.60±4.61
Cholesterol	61.78±3.95	76.80±5.58	74.40±4.66	72.40±2.96
HDL	45.38±3.59	51.16±3.33	46.73±3.38	47.92±1.64
LDL	7.45±0.53	8.94±1.09	7.91±0.34	6.97±1.51*
Glucose	83.30±6.00	83.40±9.07	78.80±5.97	79.00±3.34
HbA1c/HbTotal	2.28±0.20	2.18±0.19	2.07±0.20	2.12±0.11
Gamma-GT	1.27±0.39	1.60±0.54	1.20±0.44	1.80±0.44

The rats were weighed to determine the effects of treatment on the total body and visceral fat amount. The results showed that, compared to the control group, the visceral fat mass decreased significantly ( $p < 0.001$ ) in all rats of the tested groups, but the body weight did not present any significant modifications (Figure 3).

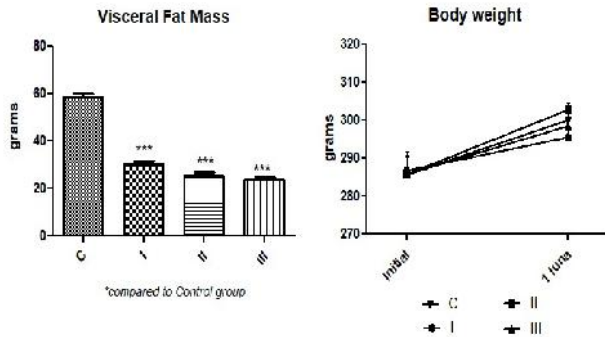


Fig. 3 – Visceral fat mass and body weight in the rat groups.

Ultrasound examination of the aorta showed a significantly reduced diameter in the treated groups (I, II, III) compared to the control group ( $p < 0.001$ ). Significant decreases in the aorta diameter were also observed in group III compared to group I ( $p < 0.05$ ) and group II ( $p < 0.01$ ) (Figure 4).

The blood flow was measured in the ascending aorta and the results showed significant increases in all treated groups ( $p < 0.001$ ) compared to the control group (Figure 5).

Transmission Electron Microscopy was used to investigate the ultrastructural aspects of the aortic wall.

In the *control group*, TEM investigation revealed normal ultrastructures. The intima presented endothelial cells (Ec) that delimited the vascular lumen in which few red blood cells (Rbc) were visualized. The first elastic lamina (el) separated the intima from the media. The subendothelial connective layer (scl) was visible and contained collagen fibres. The aorta media was composed of many muscular-elastic layers (with smooth muscle cells – smc), separated by concentric elastic laminae (not shown) (Figure 6).

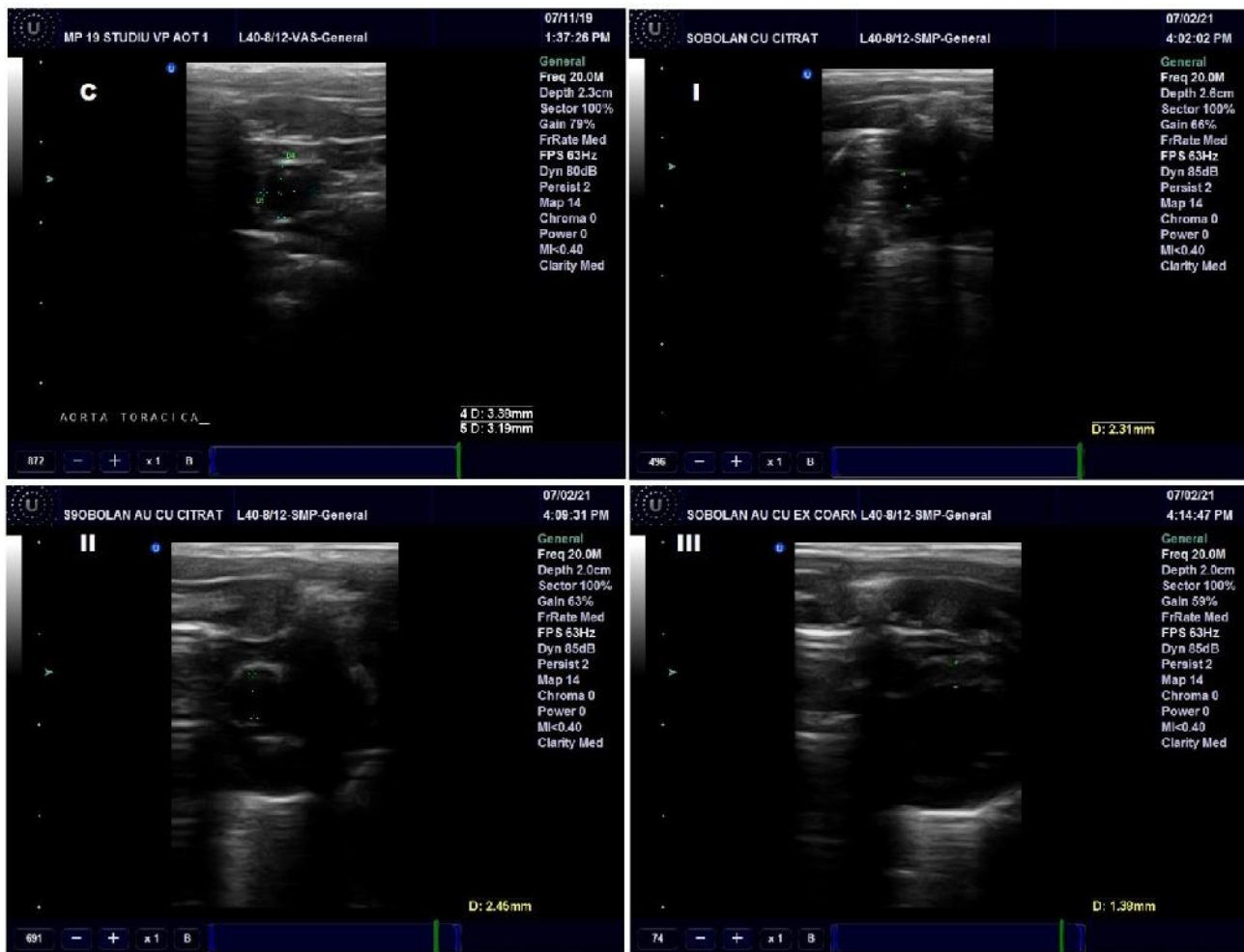


Fig. 4 – Ascending aorta diameter variations.

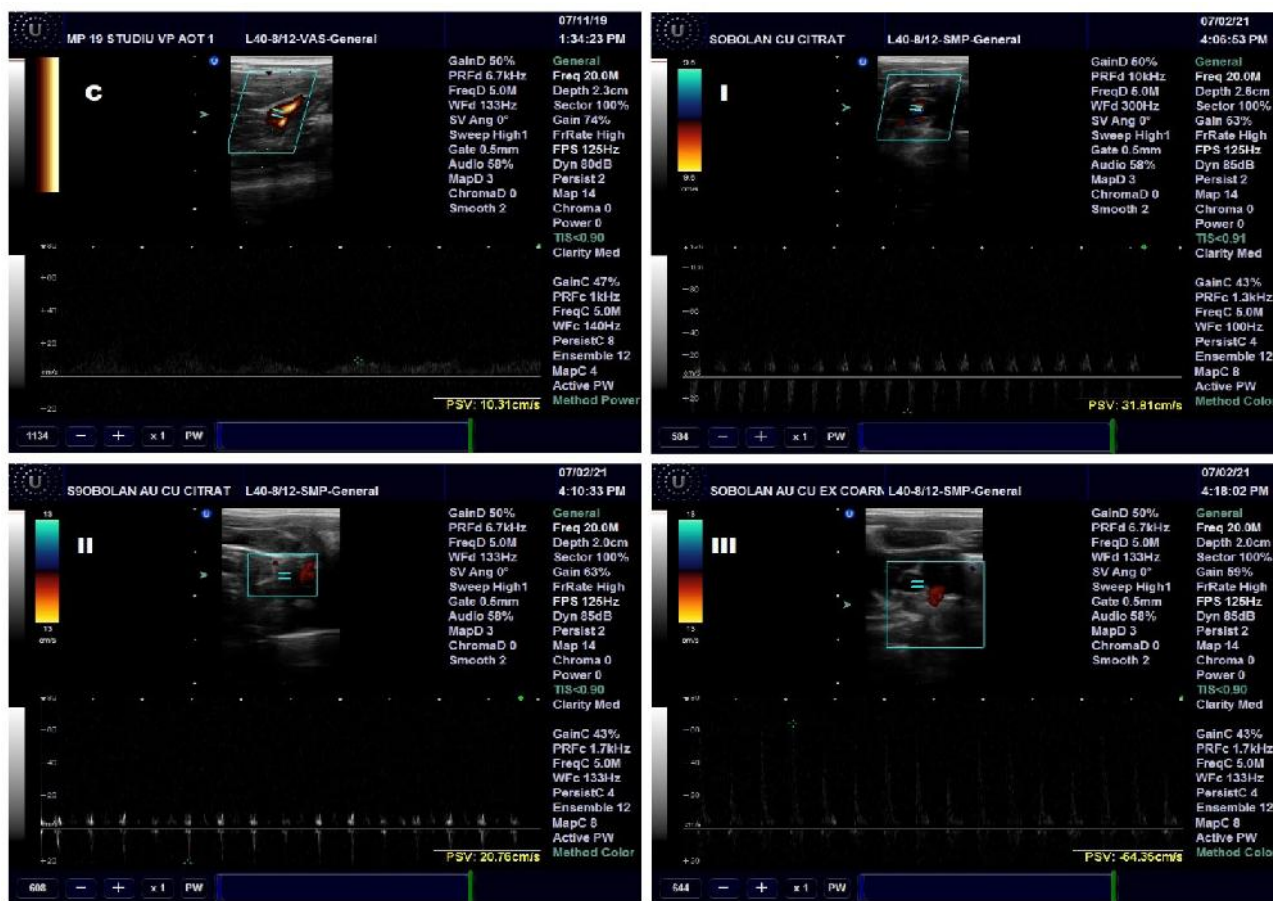


Fig. 5 – Ascending aorta blood flow velocity.

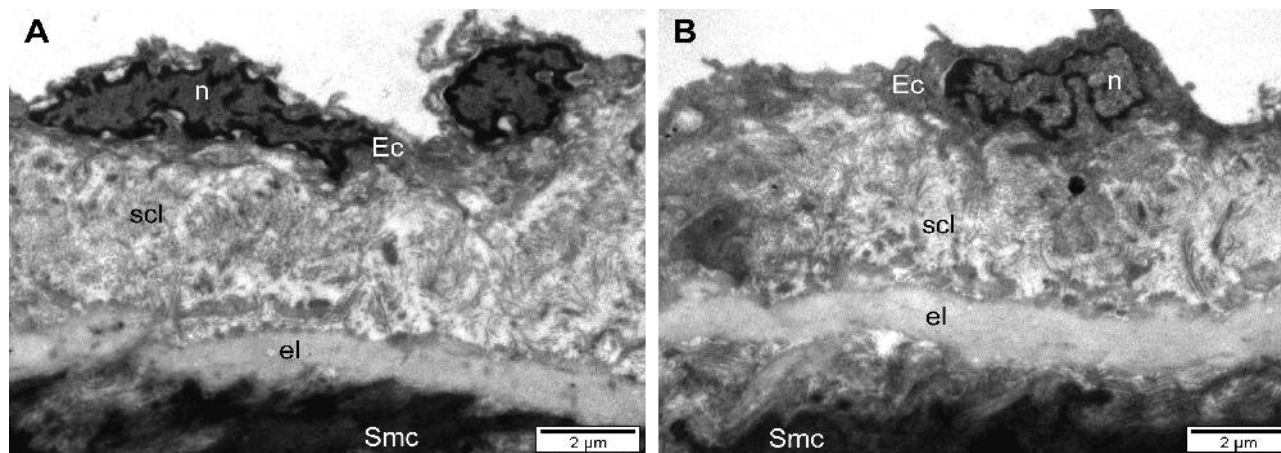
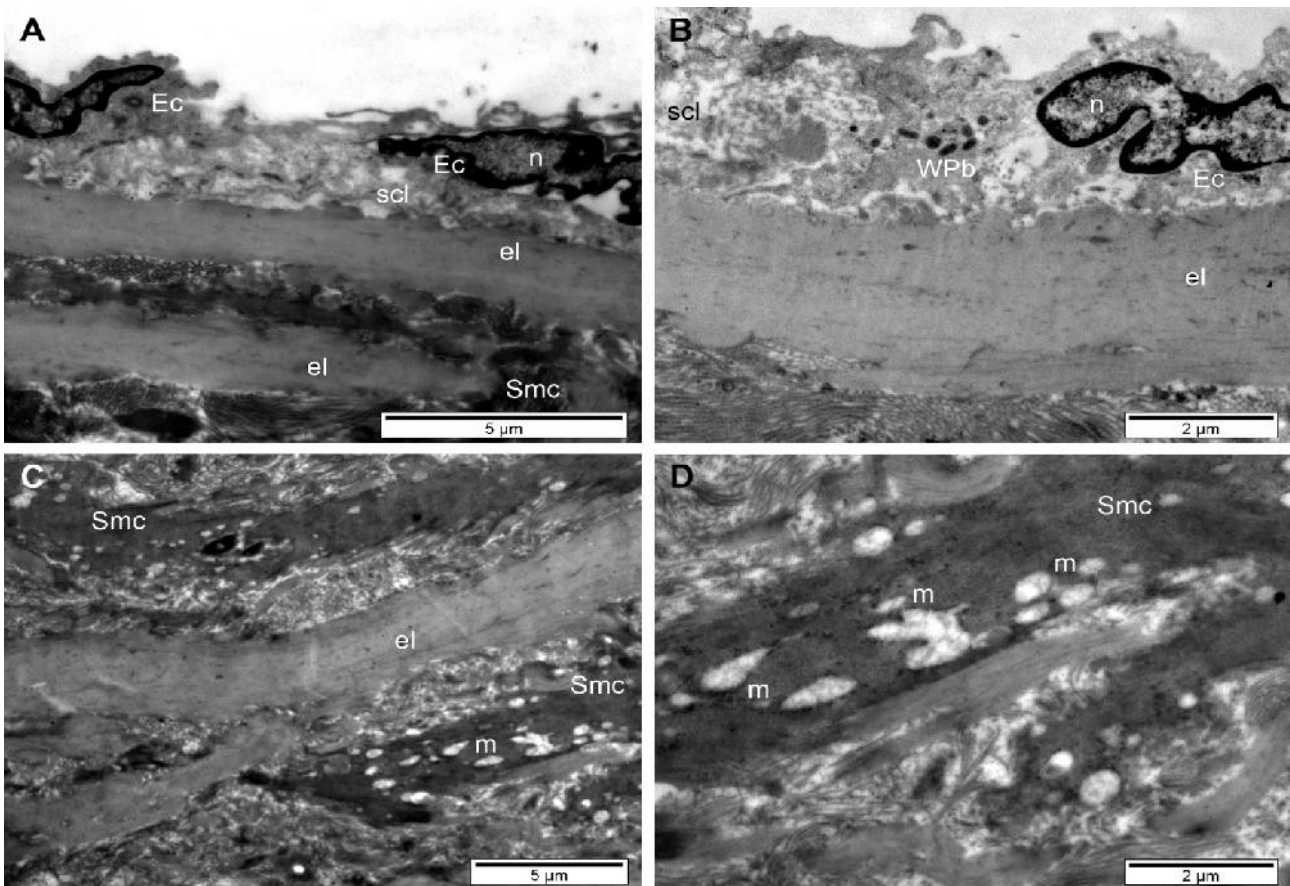


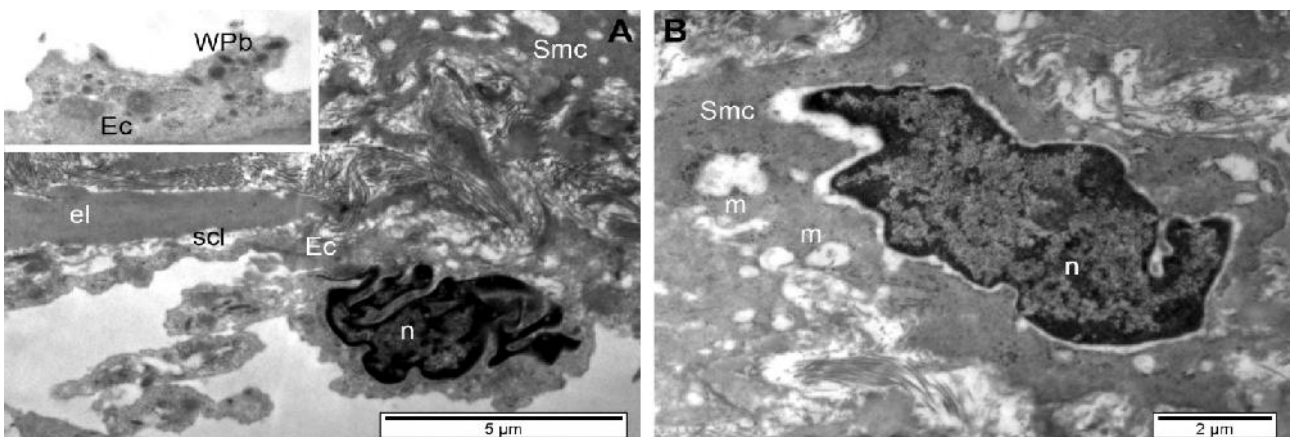
Figure 6. Ultrastructural aspects of the aorta in the control group (Ec, endothelial cell; el, elastic lamina; scl, subendothelial connective layer; smc, smooth muscle cell; n, nucleus).

In the *citrate group (I)*, ultrastructural changes were recorded both in the intima and the media (Figure 7). The tunica intima showed a thin (Figure 7 A, B) and discontinued (not shown) endothelium. The cytoplasm of endothelial cells contained many Weibel-Palade bodies (Figure 7 B). A low number of transcytosis vesicles were also noted. Some endothelial cells were more prominent into the lumen (not shown). The subendothelial connective layer was extremely thin and discontinued, in some regions difficult to be

identified. The internal elastic lamina presented a normal aspect (Fig. 7 A, B). In the tunica media, the smooth muscle cells contained ballooned mitochondria with no cristae and electron-transparent matrix, and the perinuclear space was enlarged (not shown). The elastic laminae had a normal aspect, and the elastin-collagen fibres were in general uniformly distributed (Figure 7 C, D), but in some sections, this network in the first muscular-elastic layer was very rarefied (not shown).



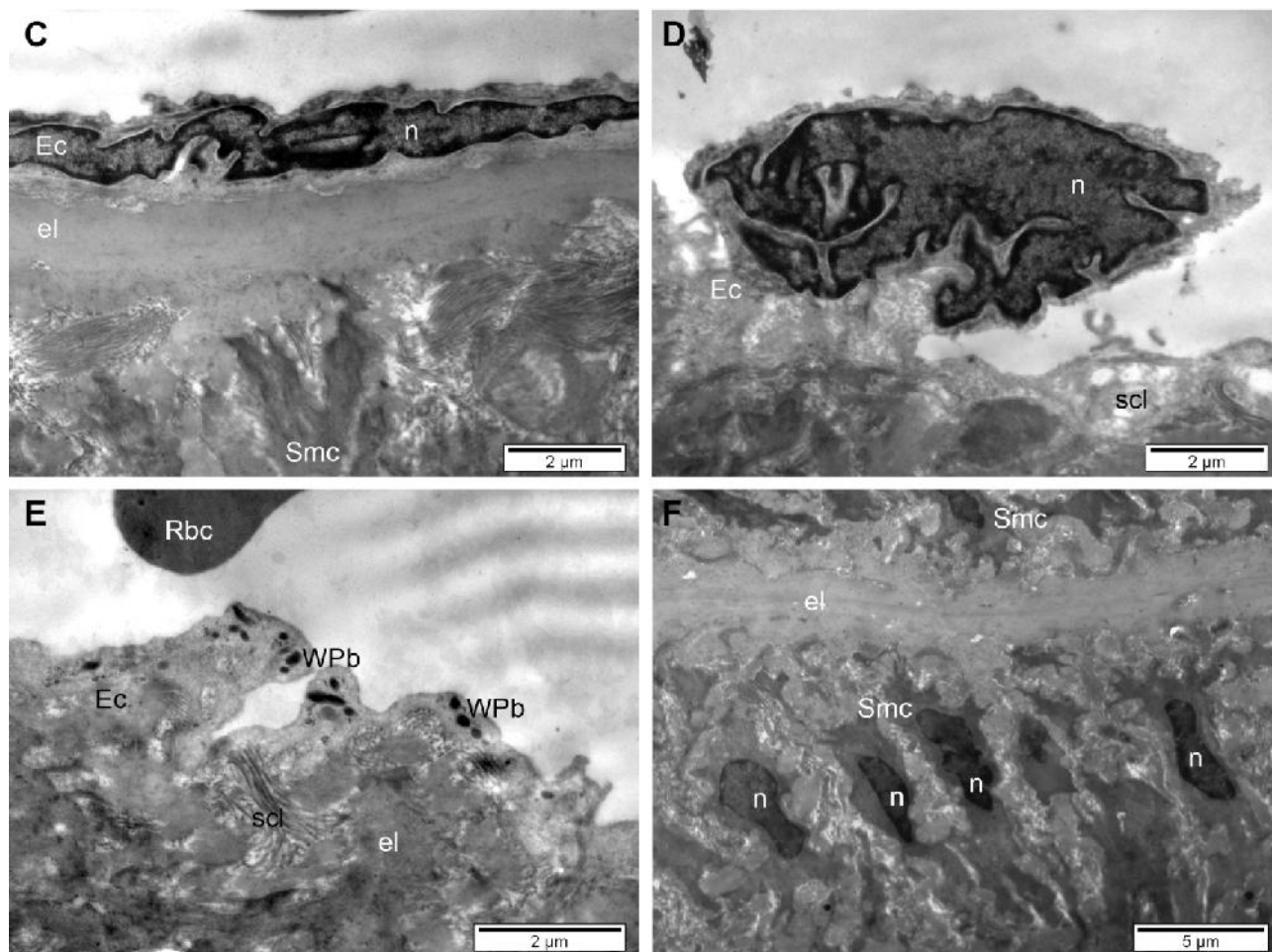
**Fig. 7** – Ultrastructural aspects of the aorta in the citrate (I) group. The intima (A, B) was thin due to thinned endothelial cells (Ec) and to a reduced subendothelial connective layer (scl). The endothelial cells contained many Weibel-Palade bodies (WPb). In the media (C, D) the smooth muscle cells (Smc) had swollen mitochondria (m) and normal elastic laminae (el) and elastin-collagen fibres (n, nucleus).



**Fig. 8** – Ultrastructural aspects of the aorta in group II (A, B) and group III (C-F). In group II, the intima displayed prominent endothelial cells (Ec), with many Weibel-Palade bodies (WPb) (inset), as well as a thin and disorganized subendothelial connective layer (scl) (Figure 8 A). The media contained smooth muscle cells (smc) with swollen mitochondria (m) (Figure 8 B) (el – elastic lamina; n – nucleus; Rbc – red blood cell).

In *group II*, the ultrastructural alterations of the aorta were more severe. The internal elastic lamina, with uneven thickness, was devoid of intima components on large areas (not shown). In most of the sections, the intima was present, but the endothelial cells were either extremely prominent into the lumen or almost entirely detached into the lumen (not shown). They contained many vacuoles and Weibel-Palade bodies, and almost no transcytosis vesicles. In the

regions with continuous endothelium, its thickness was reduced. The subendothelial connective layer was very thin and disorganized (Figure 8 A). In the media, the smooth muscle cells showed ballooned mitochondria, and enlarged perinuclear space (Figure 8 B). The elastic laminae were unaffected, and the elastin-collagen fibres had a normal density, with some exceptions in the first muscular-elastic layer, where its density was reduced (not shown).



**Fig. 8** – Ultrastructural aspects of the aorta in group II (A, B) and group III (C-F). In group III, the intima was thin and continuous (Figure 8 C-E). Endothelial cells (Ec), flat (Figure C) or prominent into the lumen (Figure D, E), with many Weibel-Palade bodies (WPb) (Figure E), were attached to a thin subendothelial connective layer (scl). The media had a normal ultrastructural aspect (Figure F) (el – elastic lamina; n – nucleus; Rbc – red blood cell).

In *group III*, the intima was thin, but the endothelium was continuous (Figure 8 C, D), despite the fact that some endothelial cells were more or less prominent into the lumen (Figure 8 D, E). In the cytoplasm of the endothelial cells, many Weibel-Palade bodies were found, while the transcytosis vesicles were present in a low number (Figure 8 E). The reduced thickness of the intima was mainly due to the presence of a very thin subendothelial connective layer with normal density (Figure 8 C), or with rarefied regions (Figure 8 D, E). The internal elastic lamina was normal from the ultrastructural point of view (Figure 8 C). The tunica media consisted of unaffected smooth muscle cells, separated by elastin-collagen networks with normal density. The elastic laminae separating the muscular-elastic layers had normal density and shapes (Figure 8 F).

## Discussions

Administration of gold nanoparticles by gavage showed several important modifications, especially in the aorta wall.

The administration of AuNPs increased cholesterol, HDL and LDL insignificantly, results that are in accordance with those presented by Ibrahim et al. in their

study performed in rats that received gold nanoparticles intraperitoneally (Ibrahim et al., 2018). Functionalization of AuNPs with *Cornus mas* L. extract significantly decreased the levels of LDL, showing a protective effect against the atherosclerotic processes. To the best of our knowledge, this is the first study that investigated the oxidative stress in serum, in a rat experimental model with AuNPs administration and showed a significant decrease of lipid peroxidation.

In the aorta, all three administered solutions produced oxidative stress.

*Citrate solution* induced a significant decrease of lipid peroxidation and a significant increase of iNOS, an inflammatory parameter that may increase nitric oxide (NO) synthesis up to high levels that can produce cellular injuries. Our results are in accordance with those presented by Zotta et al. in their review in which citrate is presented as a key factor in immunity (Zotta et al., 2020). Bienholtz et al. showed the favourable effects of citrate in rats with acute kidney ischemia, the inhibition of damages after reperfusion (Bienholtz et al., 2017), effects that in our experiment were indirectly seen by measuring the blood flow velocity, the higher speed ensuring tissue nutrition.

In the study performed by Tang et al. (Tang et al., 2013), citric acid, the metabolic product of trisodium citrate, decreased TNF- $\alpha$  production, an effect that was also seen in the present study, even if we did not record a significant decrease. Previous research showed the protective role of citric acid on endothelial cells (Chang et al., 2001), but in our study with citrate solution, TEM investigation showed intima and media modifications with altered endothelial and altered smooth muscle cells respectively.

*AuNPs* solution had the same effects on aorta oxidative stress parameters as citrate solution and furthermore, significant increases of endothelin 1 and TNF- $\alpha$  were recorded, additional factors for oxidative stress, a mechanism that was also mentioned by Gao et al. in their review related to cancer treatment (Gao et al., 2021). AuNPs treatment affected the aorta, significantly decreasing the diameter and therefore increasing the blood flow velocity. Our results that show the acceleration of blood flow are concordant with those presented by Zhao et al. in their study performed in mice with experimental colorectal cancer that revealed the thinning effect of AuNPs on collagen fibres (Zhao et al., 2018). The ultrastructural aspects of the intima and media were much more severe than in the group that received citrate solution, intima thickness being reduced because of the thin subendothelial connective layer. As Abdelhalim reported in his research conducted in rats, the size of AuNPs is important in lesion production; the smaller they are, the higher is their penetration and oxidative stress production (Abdelhalim, 2011). In our research, AuNPs size was 19 nm, small enough to produce aorta wall alterations and oxidative stress.

*AuNPsCM* solution administration produced the same modifications of oxidative stress parameters as AuNPs solution, but less intense. The diameter of the aorta was the smallest and consequently, the blood flow velocity was the highest. AuNPsCM induced some intima alterations but protected the media, probably because of the chlorogenic acid that is found in *Cornus mas*, a chemical compound with antioxidant, anti-inflammatory (Mitrea et al., 2020a; Mitrea et al., 2020b) and vasorelaxant effects (Bujor et al., 2019).

All the treated groups presented a high number of Weibel-Palade bodies in the cytoplasm of endothelial cells. Oxidative stress represents one of the factors that may stimulate the accumulation of Weibel-Palade bodies, also triggering the release of endothelin 1, inflammatory factors (IL-8, P-selectin, etc.), von Willebrand factor, and other components of these subcellular organelles (Rondaj et al., 2006) (Streetley et al., 2019). The citrate and AuNPs solutions produced oxidative stress that was demonstrated in previous studies to be linked to mitochondria dysfunctionality and swelling (Plotnikov et al., 2019), a mechanism that may explain the mitochondria alteration seen in our TEM investigation. AuNPsCM presented a relative protective effect on the aorta wall.

## Conclusions

1. All administered treatments produced oxidative stress, altered the aorta wall, significantly decreased the ascending aorta diameter and increased the blood flow velocity.

2. Functionalization of gold nanoparticles with *Cornus mas* L. extract produced lower oxidative stress and less severe aorta wall alteration.

## Conflict of interests

None declared

## Acknowledgments

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# Kinetoprophyllaxis of work position-induced lesions by alternating the support surface

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## Abstract

**Background.** The use of the Global Postural System GPS 600 device to identify postural deficit induced by working posture, combined with a physical therapy program for the spine proved to be beneficial. Based on the data obtained from a complete posturography, customized kinetotherapy and medical recovery programs were developed.

**Aims.** The aim of this study was to prove the importance and benefits of a physical therapy program for prevention and treatment of the degenerative diseases of the spine. The study focused on adults involved in work activities that required maintaining a sitting position at the office. This study included 13 subjects with the age between 25 to 47 years old; the mean age was 32 years.

**Methods.** To remedy the musculoskeletal disorders that appear during the work in the office, our research team proposed a unique method of treatment by the technique of alternating support surfaces. The methods used for evaluation were joint and muscle balance as well as the visual analogue scale of pain, and the evaluation data provided by the GPS 600 system.

**Results.** At the end of the 14 days of treatment and physical therapy program, all subjects had a relief of symptoms and the alignment of the spine was significantly corrected.

**Conclusions.** The treatment using the Global Postural System GPS 600 combined with physical therapy is important to prevent degenerative diseases of the cervical spine both for the effect on the joints and for the general effect of postural balance.

**Keywords:** physical therapy, work posture, prevention

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## Introduction

### The influence of the working posture at the desk for a long time on the musculoskeletal system

While maintaining the same prolonged static position, the muscles which support the body's posture suffer a prolonged state of contraction, which leads to a decreased efficiency in the transport of sugars and oxygen to the dynamically contracted muscles and this leads to an accumulation of waste products in the muscles, such as carbon dioxide and lactic acid. Those changes can lead to muscle spasms and muscle fatigue. Sitting in the same position for a prolonged period also contributes to countless health problems such as lumbar and cervical pain, circulatory and renal diseases (Mani, 2018).

A study conducted in 2009 and published in “The Australian Journal of Physiotherapy” indicates that people who present pain at the cervical level have higher muscular activity and less rest for the cervical muscles (Szeto et al., 2009).

In addition to higher muscle activity, another study shows anterior positioning of the head, shoulder

protraction, and stiffness of the upper trapezius muscle when the patient is working at the desk space (Kocur et al., 2019).

The musculoskeletal changes caused by maintaining an incorrect desk posture were researched by us and published in a study in 2019 (Chelaru & Bulduș, 2019).

The study included a screening phase attended by 150 subjects aged between 18-42 years, which aimed to identify the signs of physical deconditioning in the persons holding the position for 6-8 hours/day.

The result analysis reflected that 96% of the subjects presented anteriorization of the head: 32% in a range between 3 to 7 cm and 64% over 7 cm.

The projection of the gravity center was anteriorized by 1 to 7 cm in 62% of the subjects.

The subjects had a difference in loading the body weight on both feet: 46% overloaded the left foot and 38% overloaded the right foot. In total, 84% of subjects had a predominant balance on the left or right foot, which means an imbalance of the weight bearing.

In 84% of the subjects, the angle values represented a

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rotation that in time can produce spine lesions.

Based on the data obtained from a complete posturography, customized kinetotherapy and medical recovery programs were developed.

Reports in the scientific literature have suggested that computer users are at increased risk for upper extremity musculoskeletal disorders (MSD). Early studies often found high rates of MSD outcomes among keyboard users compared to non-users. Attention soon focused on specific aspects of the keyboard that could be responsible for the increase in the observed rate. Postural misalignments are an independent risk factor of modest magnitude for MSD among computer users. It appears that decreasing the height of the keyboard at or below elbow height and supporting the arms on the surface of the desk or armrests is associated with a reduced risk of MSD for the neck and shoulder. In general, the literature shows that daily or weekly computer use hours are more consistently associated with hand and arm MSD than neck and shoulder MSD (Gerr et al., 2004).

To date, the influence of specific sitting posture on head / neck posture and cervicothoracic muscle activity has been insufficiently investigated. In 2020, Chelaru et al. studied the influence of biofeedback in the treatment of ailments of head/neck and cervicothoracic posture deficiencies. Caneiro et al. (2009) in a study investigated whether three different thoracolumbar positions affect the posture of the head / neck and cervicothoracic muscle activity. There were significant differences in the lumbar and thoracic curves in the 3 different positions. This study shows that different sitting positions affect the posture of the head / neck and cervicothoracic muscle activity. The potential importance of postural adjustment of the thoracolumbar spine when training the head / neck posture is highlighted.

More neutral sitting positions reduce the demand on the cervical extensor muscles and modify the relative contribution of the cervical and thoracic extensors to the control of head and neck posture. Postures that promote these patterns of muscle activity can reduce cervical spine load and the development of posture-related neck pain (Edmondston et al, 2010).

In a study of the biomechanics and muscle function of the cervical spine, skilled workers simulated standardized electromechanical assembly work in eight positions of the spine in the sitting position. In the position with the trunk slightly tilted back, the arm suspension reduced the trapezoid overload. These findings indicate that arm support or arm suspension can be used to reduce the muscular load on the neck. A marked reduction in the level of activity was obtained when a posture with a slightly backward thoracolumbar spine was used (Schüldt, 1988).

This study contributes to the knowledge of the influence of body posture and stool configuration on the activity of postural muscles. Reducing biomechanical loads on postural muscles should be aimed at improving user comfort and safety (Bertolaccini et al., 2016).

The pelvis tilted to the maximum in a stable sitting position can induce low back pain due to unbalanced muscle activities (Watanabe et al., 2014).

Nowadays, a lot of office workers must stay at the office for many hours while doing their job. While

sitting, the pelvis rotates back, and the lumbar lordosis is flattened. At the same time, it increases the load on the intervertebral discs and on the spine. Sitting in an inclined position is known to increase disc pressure even further and to aggravate chronic low back pain (Watanabe et al., 2007).

Tilt forward and lower tilt of the chair can increase lordosis, but subjects give a high degree of comfort to adjustable seats, which allow changes in position (Harrison et al., 1999).

Static sitting is thought to be related to low back pain. Among the various regular seating positions, the reclining sitting was suggested to cause viscoelastic creep. This, in turn, can compromise torso muscle activity and proprioception and increase the risk of low back pain (Wong et al., 2019).

In ergonomic clinical interventions that alter the curves of the spine and sagittal balance in sitting, the muscle activity used in those positions may differ between people with and without a history of back pain (Claus et al., 2018).

#### **The optimal posture for desk work**

The study published by Mani et al. in 2018 regarding ergonomics education for office computer workers researched the ideal posture for desk work and concluded that the ideal posture at the desk is with the back straight or slightly inclined at about 90-100°, the shoulders abducted less than 20°, the elbows bent at about 90-100°, the forearms pronated, and the wrist in a neutral position.

In the case of the thigh, the angle that proved to be optimal is 20-30° and this indicates a flexion of the thighs at an angle between 120-135°.

The knee joint should be flexed at about 80-90° so that the leg is perpendicular to the ground and the support is made along the entire surface of the soles (Mani, 2018).

To correct the deficient posture of the head and neck, lumbar support and an inclination of the seat backrest at an angle of 110° can be used (Horton et al., 2010).

#### **Kinetotherapy and kinetoprophylaxis of musculoskeletal injuries caused by the working posture**

To remedy musculoskeletal disorders that occur during desk work, our research team proposes a unique method of treatment by the technique of alternating support surfaces (TASS). This technique is based on the alternation of anatomical topographic regions of support on the chair during desk work hours and requires the use of a chair specially designed to support the body on other support surfaces than normal.

#### **Objectives**

The objectives of this study are to determine the improvement of postural alignment using postural biofeedback and by implementing a method of prophylaxis of musculoskeletal injuries.

#### **Hypothesis**

The aim of this study is to prove the importance and benefits of a physical therapy program for prevention and treatment of the degenerative diseases of the spine using the technique of alternating support surfaces (TASS) and postural biofeedback.

## Material and methods

For this study we had the approval of the Ethics Commission for conducting the research. The informed consent of the subjects participating in the research was obtained.

### Research protocol

#### a) Period and place of the research

The period of the research was 14 days, between 31.01.-15.02.2021, at the HC Kinetic office, and treatment was performed with the *reverse Chair* at the workplace of each subject.

#### Subjects and groups

The study focused on adults involved in work activities that require maintaining a sitting position at the office. This study included 13 subjects aged between 25 and 47 years old; the mean age was 32 years.

#### b) Applied tests

The tests used in the study were:

- pain scale;
- head anteriority, center of gravity anteriorization obtained from the posturography;
- ground index test

Postural analysis was performed with The Posturograph or Global Postural System (GPS) which is an advanced postural analysis system that uses non-invasive diagnostic and evaluation techniques and methods in the field of medical recovery.

The posturograph includes 2 diagnostic units and one software:

- Podoscope - is used in the analysis of static foot disorders and the position of the center of gravity; with its help the captured images are processed, the exact length of each leg, the existence of static plantar disorders (flat foot, hollow, etc.), as well as possible deviations at the ankle level being determined.

- The unit of postural analysis - is used to determine the deficiencies in the spine, through a system of video cameras that allow the acquisition of high-resolution images that are then processed through the software, in order to analyze all segmental or global deviations of the body.

Postural analysis is performed from the front, back and profile and can diagnose the deficiencies of the spine in the sagittal or frontal plane (scoliosis, kyphosis, hyperlordosis).

The software allows the storage of the patient's medical data, both those resulting from the posturographic tests and those related to the medical history or the medical treatments that the patient follows. It is useful for monitoring the evolution of subjects and the effectiveness of the recommended therapies. The posturograph offers information in real time that can be used to perform postural biofeedback.

The alternate Chair or *Reverse Chair (RC)* is designed to support the body in anatomical regions other than those on which the support is made when a normal chair is used and to provide the possibility of alternating these surfaces. At the same time, the chair is configured and adjusted according to the instructions showed in Fig. 1.

The intervention protocol was:

- the biofeedback method - performed with GPS 600, included 2 sessions per week, each session consisted of maintaining the correct posture as indicated by the devices 10 times for 20 seconds.

- the method of alternating support surfaces by using the reverse seat. The use of the reverse chair was recommended for at least 2 hours from the work schedule.

#### c) Statistical processing

The applied computer statistical program was Microsoft Office/16/EXCEL EXE 2016.

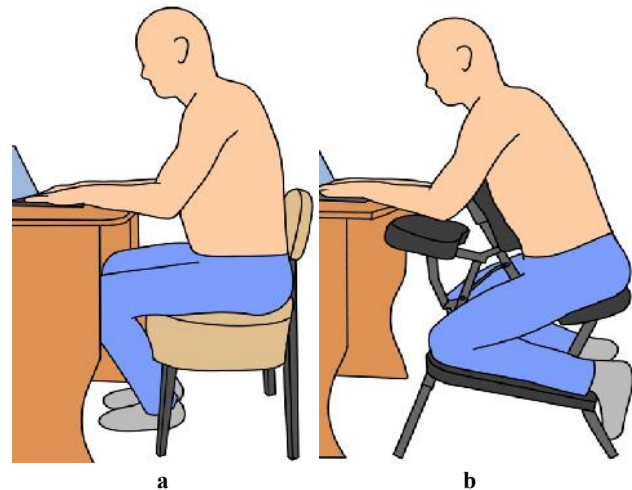


Fig. 1 – Work posture at the desk using normal (a) and reverse chair (b).

## Results

The initial and final values of the pain scale are presented in Fig. 2.

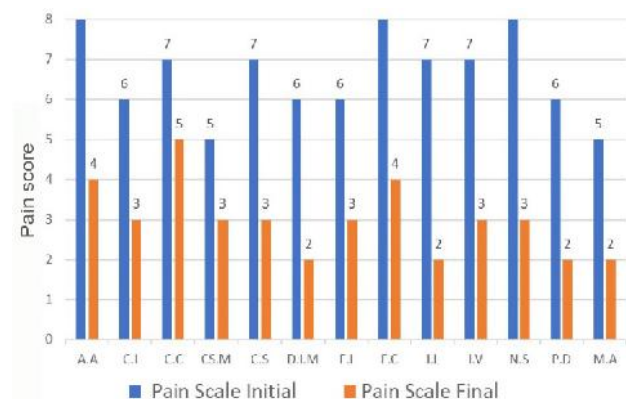


Fig. 2 – Initial and final results of the pain scale.

The pain decreased significantly in all 13 subjects, as follows:

- in 15% subjects it decreased by 5 units;
- in 46% subjects it decreased by 4 units;
- in 23% subjects it decreased by 3 units;
- in 15% subjects it decreased by 2 units.

The initial and final results of the head anteriority are presented in Fig. 3.

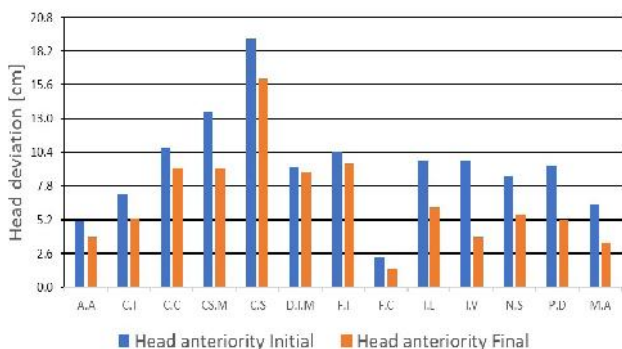


Fig. 3 – Initial and final results of head anteriority.

The head anteriority was changed as follows:

- in 46% subjects the anteriority of the head was reduced between 0.0-2.0 cm;
- in 30% subjects the anteriority of the head was reduced between 2.1-4.0 cm;
- in 15% subjects the anteriority of the head was reduced between 4.1-5.0 cm;
- in 7% subjects the anteriority of the head was reduced between 5.1-6.0 cm.

The initial and final results of center of gravity anteriorization are presented in Fig. 4.

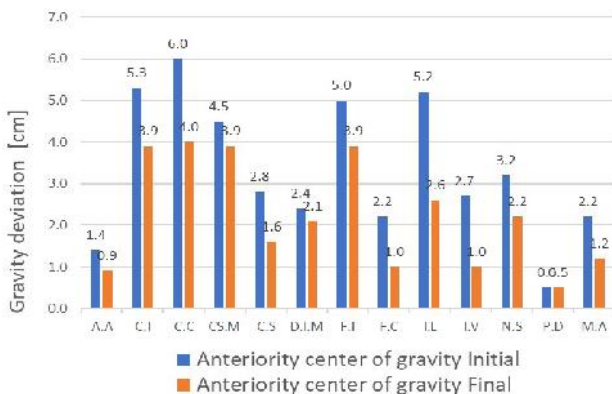


Fig. 4 – Initial and final results of center of gravity anteriority.

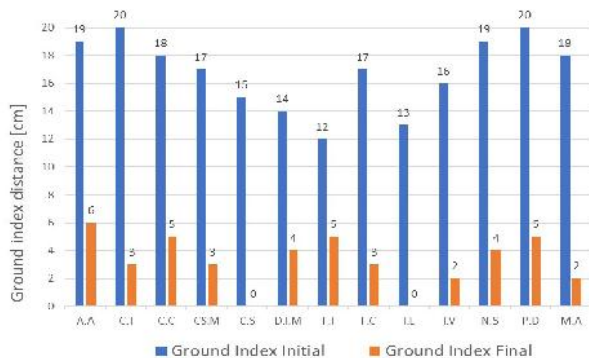


Fig. 5 – Initial and final results of ground index.

The center of gravity projection in anteriority was reduced by the following values:

- in 38% subjects between 0-1 cm;
- in 46% subjects between 1.1-2 cm;
- in 7% subjects between 2.1-3 cm;
- in 7% subjects it showed no changes.

The initial and final results of the ground level index distance are shown in Fig. 5.

The ground level-index distance difference changed as follows:

- in 7% subjects it changed by 7 cm;
- for 30% subjects it changed between 7-13 cm;
- in 61% subjects it changed between 14-17 cm.

Table I  
Statistical significance of the studied indicators.

Indicators	IR	FR	p
Pain scale	6.51	3.00	0.0001
Head anteriority	9.37	6.74	0.0001
Center of gravity	634	644	0.0020
Ground index	16.76	3.2	0.0001

IR=initial results; FR=final results.

### Discussions

The method of treatment and prophylaxis proposed by us in this study had positive effects.

The most important results are that the pain decreased in all the test subjects, by alternating the support points during the sitting position on the chair. In 8 of 13 subjects, the pain decreased by 50%.

The anteriority of the head changed in all the subjects, which means that the sitting position on the chair alternating the support points is also beneficial for the muscles of the cervical spine and the entire cervical muscle belt. In 10 subjects out of 13, the anteriority of the head was reduced by up to 4 cm.

The anteriority of the center of gravity projection decreased, which means that the standing stability improved. Alternating the support points in the sitting position on the chair leads to an improved condition with the anterior muscle chain working in balance with the posterior muscle chain.

The values in the ground level-index test for 12 subjects out of 13 improved between 10-17 cm, which indicates an increase in the mobility of the lumbar spine and an increased flexibility of the tissues in the lumbar area in 90% of the test subjects.

The use of the method proposed by us, which includes the alternation of the supporting surfaces, can be a method of prophylaxis of the muscular-skeletal injuries induced by the office position.

The center of gravity deviations and ground index are statistically significantly reduced (Table I).

### Conclusions

1. The anteriority of the center of gravity projection deviation decreased statistically significantly after the intervention.
2. Head anteriority decreased statistically significantly after the intervention.
3. The pain scale index decreased statistically significantly after the intervention.

4. The ground level-index test improved after the intervention, which indicates an increase in the mobility of the lumbar spine and an increased flexibility of the tissues in the lumbar area.

### Conflict of interests

No conflicts

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# Can recreational physical activity improve trunk and hamstring flexibility in older adults in the Covid-19 pandemic?

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## Abstract

**Background.** It is well-known that flexibility is related to the range of motion of the muscles and joints. Trunk and hamstring flexibility was found to be related to low back pain and falls, health and well-being.

**Aims.** This study aimed to investigate the impact of two recreational physical activity (RPA) programs, Harmonic Gymnastics and Fitness exercise, on the flexibility of the trunk and hamstring muscles in adults aged 50+. A secondary aim was to analyze the relationships between flexibility, BMI and gender.

**Methods.** Flexibility was measured in 32 subjects, mean age 61.40, from Tel Aviv, Israel, by the Back Saver Sit and Reach test. They were divided into two groups (16 subjects in each group).

**Results.** The paired samples t-test revealed significant differences after the program only in the Harmonic Gymnastics group ( $p = 0.00$ ;  $d = 1.34$ ). The correlation analysis indicated that after the program, flexibility scores were negatively related to higher BMI in women ( $r = -0.508$ ,  $p = 0.031$ ), and women had higher flexibility scores than men before and after the intervention program.

**Conclusions.** This research shows that the Harmonic Gymnastics recreational physical activity program had a significant influence on the flexibility of older adults, even in pandemic conditions of Covid-19. Regarding the relationships between flexibility, BMI and gender of the subjects, women revealed higher flexibility scores than men, and higher BMI was related to lower flexibility scores in women.

**Keywords:** flexibility, hamstring muscles, harmonic gymnastics, fitness, older adults

## Introduction

Recreational physical activity (RPA) is related to various physical activities, practiced at different levels of metabolic equivalent of task (METs) energy expenditure and in different types of exercise activities practiced during leisure time such as: walking, jogging, cycling, aerobic, Yoga exercises, Pilates, dancing, etc. (Ainsworth et al., 2011). Studies have shown great benefits of RPA in healthy adults, older adults and also people with higher genetic risk of illnesses and people with chronic diseases (Kehm et al., 2020; García-Esquinas et al., 2021; Wang et al., 2017). On the other edge, sedentary behavior was found to be one of the main factors associated with everyday basic activities functioning declines in older age. Flexibility of the lower limbs was found to be one of the indirect mediating factors of the association between sedentary behavior and functioning abilities (García Meneguci et al., 2021). It appears that this association also occurs in young adults, as was found by Fatima et al. (2017), in 200 university students. Long hours without physical activity significantly

resulted in tightened hamstring muscles.

Flexibility refers to the range of motion of a joint or series of joints, and to the length of the muscles that cross the joints to induce movement. It has been found to be related to a more efficient movement, and to the ability to move the joints smoothly and without pain (Alter, 2004). Iyengar (1979) defined flexibility as the ability to direct and focus awareness and attention, and to control oneself. Additionally, flexibility decreases unnecessary and uncoordinated movements, preventing injuries and musculoskeletal pain. Flexibility was found to be beneficial to the quality of life, by reducing pain, stress, and tension and by improving body and mind relaxation, posture and body symmetry, self-regulation, quality of sleep and sex life (Alter, 2004; Álvarez-Yates & García-García, 2020; da Silva et al., 2017). In addition, flexibility was found to contribute to muscle activation and growth, especially in older adults and people with physical disabilities (Wang et al., 2021).

Clinical studies indicated that flexibility decreases

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steadily during lifespan as the child grows up, and as adults and older adults age (McKay et al., 2017), especially in older ages (Kulkarni & Fernande, 2017). The decrease in flexibility in older ages is also related to the general decline in the physical body systems and specifically to the structural and biomechanical changes expressed in the tenocytes and collagen molecules in the joints, tendons and ligaments (Ueda et al., 2019). Age related decline in flexibility was also found to increase the risk of falls (Turusheva et al., 2020), and the risk of cardiovascular diseases and death following the decrease in elasticity of connective tissues and the artery stiffness process (Chen et al., 2020; Yamamoto, 2017). Furthermore, Komatsu et al. (2017) showed that older adults who had high trunk flexibility scores had lower systolic blood pressure and central pulse pressure.

There are two main types of flexibility training: *static* flexibility practice and *dynamic* flexibility. The static way of practicing flexibility is performed through passive stretching exercises that are intended to reach up to the point which is uncomfortable but can be held for 15-20 seconds. In contrast, dynamic flexibility is related to functional movements and is performed while moving. Dynamic flexibility is used mainly in track and field warm-up and other dynamic sports. It is characterized by exercising transitions from one position to another such as: "The lunge walk", "The walking leg swing to opposite hand", etc. (Hedrick, 2000). In most fitness exercise programs, subjects exercise *static flexibility*, but there are also other types of physical activities, in which flexibility is practiced in the dynamic way such as: Pilates, Feldenkrais method, Tai-Chi, etc.

Hamstring muscles include three main posterior thigh muscles: biceps femoris, semitendinosus and semimembranosus. All three of them are attached to the ischial tuberosity in their origin and clutch at the fibula and tibia edges. These are biarticular tendon-muscles, who cross two joints: the hip and the knee. Crossing these two joints may double the need of flexibility of these muscles in order to provide flexion ability of the trunk and extension in the lower limbs (Napolitano & Gupta, 2021). This may be the reason why hamstring muscles have a great impact on lower back pain, and therefore on quality of life. A meta-analysis by Sadler et al. (2017) of 5,459 subjects revealed that low back pain increased when the range of motion of the hamstring and trunk muscles was restricted. Moreover, Radwan et al. (2015) found that the tighter the hamstring muscles, the greater the severity of low back pain.

## Objectives

The main purpose of this research was to investigate the impact of Harmonic Gymnastics (HG) and Fitness (F) RPA programs on the flexibility of hamstring and trunk muscles of older adults. Another goal was to investigate whether there is any relationship between flexibility and the BMI of the subjects, and whether there are any gender differences.

## Hypotheses

In this research we started from the following hypotheses:

- The participation of older people (aged 50+) in recreational physical activities can have the effect of improving flexibility.

- The degree of flexibility will be dependent on the type of physical activity exercise, BMI and gender of the subjects.

## Material and methods

### Research protocol

#### a) Period and place of the research

The research study was approved by the Babes-Bolyai University (U.B.B.) Ethics Commission, Cluj-Napoca, as part of a research in the Physical Education and Sports Doctoral Studies Faculty of the U.B.B. The actual research study was conducted in Tel Aviv, Israel, in February 2020, three weeks before the Covid-19 pandemic imposed social restrictions. The program continued for three months under the new conditions of Covid-19, outdoors and by digital channels.

#### b) Subjects and groups

A total of 47 subjects agreed to participate in the study voluntarily and signed a consent form. They were divided into two groups, depending on the type of recreational physical activity program in which they wanted to participate: the Fitness (F) RPA or Harmonic Gymnastics (HG) recreational PA. The subjects began the program in the studio and the fitness club, but, after three weeks, had to deviate from the original program and participate through web application (Zoom) and in outdoor facilities, following Covid-19 pandemic restrictions. During participation in the intervention programs, one subject was excluded because of illness and 14 subjects did not come for the final measurements because of the fear from gathering together in Covid-19 pandemic conditions. Some of the subjects did not adjust to the changes in the program and did not agree to participate through web applications or practice by themselves. Therefore, only 32 subjects (16 in each group) remained in the program and came for the measurements after three months. The subjects' total mean age was 61.40 (9.48). The mean age of the F group was 63.44 (8.25), while in the HG group it was 59.37 (10.71) years old. Each group consisted of 9 women and 7 men. Most of the subjects of both groups had academic education (68.7% in the F group and 81.2% in HG). Most of the subjects of both groups were married (68.7% in both).

The participants in the F group practiced muscle strengthening, endurance and aerobics. When they trained together at the gym club, before the Covid-19 restrictions, they started with a warm-up that included static stretching exercises, aerobic running or walking on a treadmill, cycle ergometer or stepper, and after the cyclic training of muscle strengthening on the machines, they practiced static flexibility exercises to complete the session. Following Covid-19 restrictions, some of the participants trained through web applications at home and some trained in outdoor RPA facilities, walking, jogging, outdoor cycling, etc., 2 times a week, for 50 minutes in each practice for three months. They performed simple static flexibility stretching exercises as practiced in the gym club.

The Harmonic Gymnastics type of practice is a low intensive RPA, which is focused on strengthening

and flexing the muscles and joints in the most efficient qualitative way. In HG, flexibility is practiced in a dynamic way, while moving. Each exercise combined a series of several movements that are performed in a sequence. The trainees exercised transitions from one position to another and expanded their movement possibilities, range of motion and muscle power, at a slow pace through attention and body awareness. In addition, the trainees also practiced coordination, proprioceptive and vestibular ability (Mullan, 2016; Stebbins, 1892). They exercised 2 times a week, for 50 minutes in each practice for three months. At the beginning, the practices were performed on mats at the studio, but in Covid-19 conditions the practices were conducted through the Zoom application from home.

*c) Applied tests*

In this research, the flexibility of the hamstring muscles was measured by the Back Saver Sit and Reach test (BSSR). This is a very well-known and practical tool for hamstring and low back flexibility measurement. It was found to be more suitable for the spine than the classical Sit and Reach test, because in BSSR one leg is bent and this way imposes less load on the spine vertebrae (Hui & Yuen, 2000). In fact, BSSR had the strongest correlation with hamstring flexibility (Dhayal et al., 2019; Hajdarević, 2019).

Following the BSSR Protocol, the subject sat on the mattress, with the tested leg straight forward while the other leg was bent with the foot at the level of the tested leg's knee. The subject held the sliding bar of the box's ruler and moved it forward as far as he/she could in this position in a flowing and continuous motion, as shown in Figure 1.



**Fig. 1** – Back Saver Sit and Reach (Retrieved from [topendsports.com](http://topendsports.com)).

*d) Statistical processing*

The statistical plan included a report of

sociodemographic data such as: age, gender, marital status, education and BMI. The comparisons of the BSSR scores before and after the three month program of all participants and the mean scores by the groups were conducted following distribution analysis by the Kolmogorov-Smirnov and Shapiro-Wilk tests of normality. The paired t-tests were conducted for the comparisons of the data before and after the program in the normal distributions and the Wilcoxon tests for the non-normal distributions. Descriptive analysis and comparisons of the mean scores of males and females and BMI scores in each group were conducted by the independent sample tests and paired t-tests before and after the program, in addition to Pearson correlation for the relationship between flexibility and gender, flexibility and BMI.

**Results**

According to the Shapiro Wilk test, data for the variables BMI and BSSR were normally distributed in the HG and in the F group ( $p > 0.05$ ). The independent sample t-test presented in Table I shows that there were no differences between the groups before the program in the BMI and the BSSR measurements of both groups.

The comparison of the means of the variables analyzed in all subjects, as a result of the scores recorded at the beginning and at the end of the intervention program, using the t-test for paired samples (Table II), shows that there were no significant differences in BMI scores, but significant differences in BSSR scores after the program ( $t = -3.44$ ,  $df = 31$ ,  $p = 0.002$ ,  $d = 0.6$ ).

Table III indicates the comparisons of the BMI and the BSSR scores between before and after the program in each group, according to the type of PA program. Data show that there were no differences within the Fitness group between before and after the program in the BMI ( $t = -1.25$ ,  $df = 15$ ,  $p = 0.232$ ), or in the BSSR scores ( $t = 0.34$ ,  $df = 15$ ,  $p = 0.737$ ). In the HG group, the difference between the mean BMI scores was not significant ( $t=1.77$ ,  $df=15$ ,  $p=.097$ ), while in the BSSR variable, the difference between the means recorded at the beginning and at the end of the intervention program was significant ( $t=7.62$ ,  $df=15$ ,  $p=.000$ ,  $d=-1.34$ ).

In the comparisons of the means of the subjects ( $N = 32$ ) by gender, the t-test for independent samples (sig 2 tailed), shown in Table IV, revealed no differences in

**Table I**  
Comparisons of mean BMI and BSSR scores in the HG and the Fitness group before (1) and after (2) the program ( $N = 32$ ).

Variable	RPA group	Descriptive statistics				Independent Samples Test			
		N	Mean	Std. Dev.	Std. Error Mean	t	df	Sig. (2-tailed)	Size effect
BMI 1 kg/m <sup>2</sup>	F	16	27.63	4.443	1.110	0.157	30	0.877	0.027
	HG	16	27.42	2.918	0.729				
BMI 2 kg/m <sup>2</sup>	F	16	27.79	4.500	1.125	0.438	30	0.665	0.077
	HG	16	27.18	3.218	0.804				
BSSR 1 (cm)	F	16	20.58	7.755	1.938	-0.034	30	0.973	0.006
	HG	16	20.67	6.266	1.566				
BSSR 2 (cm)	F	16	20.35	8.303	2.075	-1.742	30	0.092	0.307
	HG	16	24.96	6.567	1.641				

**Table II**

Comparisons of mean BMI and BSSR scores before and after the program (N = 32)

Paired Samples Statistics				Paired Samples Test					
Pair	Variable	Mean	N	Std. deviation	Std. error mean	t	df	Sig. (2-tailed)	Size effect
Pair 1	BMI 1 kg/m <sup>2</sup>	27.5322	32	3.69953	.65399	0.406	31	.687	.071
	BMI 2 kg/m <sup>2</sup>	27.4924	32	3.86082	.68250				
Pair 2	BSSR 1 (cm)	20.6297	32	6.93623	1.22616	-3.440	31	.002	-.601
	BSSR 2 (cm)	22.6641	32	7.72736	1.36602				

**Table III**

Comparisons of the mean BMI and BSSR according to the group, before (1) and after (2) the program.

Group	Pair	Mean	Std. deviation	Std. error mean	t	df	Sig (2-tailed)	Size effect
F (N=16)	BMI 1 kg/m <sup>2</sup>	27.6363	4.44347	1.11087	-1.25	15	0.232	-.311
	BMI 2 kg/m <sup>2</sup>	27.7950	4.50048	1.12512				
	BSSR 1 (cm)	20.5875	7.75587	1.93897	0.34	15	0.737	.085
	BSSR 2 (cm)	20.3594	8.30310	2.07577				
HG (N=16)	BMI 1 kg/m <sup>2</sup>	27.4281	2.91853	.72963	1.77	15	0.097	.441
	BMI 2 kg/m <sup>2</sup>	27.1898	3.21807	.80452				
	BSSR 1 (cm)	20.6719	6.26679	1.56670	-7.62	15	0.000	-1.34
	BSSR 2 (cm)	24.9688	6.56752	1.64188				

**Table IV**

Paired Samples t-test for the BSSR scores of male and female subjects in the Fitness and HG group.

Paired Samples Statistics			Paired Samples Test			
Program (N)	BSSR-1 Mean (STD)	BSSR-2 Mean (STD)	t	df	Sig (2-tailed)	Size effect
Fitness Female (9)	24.26 (7.84)	24.08 (8.53)	0.186	8	0.857	0.043
Fitness Male (7)	15.86 (4.68)	15.57 (5.25)	0.298	6	0.776	0.079
HG Female (9)	21.13 (6.70)	26.25 (7.13)	-6.38	8	0.000	-1.504
HG Male (7)	20.07 (6.11)	23.32 (5.85)	-5.166	6	0.002	1.93

**Table V**

Pearson correlation analysis of BMI and BSSR scores in men and women before and after the program (N = 32).

Gender	Variable	BMI 1 (kg/m <sup>2</sup> )	BMI 2 (kg/m <sup>2</sup> )	BSSR 1 (cm)	BSSR 2 (cm)
Male (14)	BMI 1 (kg/m <sup>2</sup> )	Pearson Correlation	1	0.990**	0.163
		Sig. (2-tailed)		0.000	0.579
	BMI 2 (kg/m <sup>2</sup> )	Pearson Correlation	0.990**	1	0.156
		Sig. (2-tailed)	0.000		0.595
Female (18)	BMI 1 (kg/m <sup>2</sup> )	Pearson Correlation	1	0.991**	-0.426
		Sig. (2-tailed)		0.000	0.078
	BMI 2 (kg/m <sup>2</sup> )	Pearson Correlation	0.991**	1	-0.402
		Sig. (2-tailed)	0.000		0.098

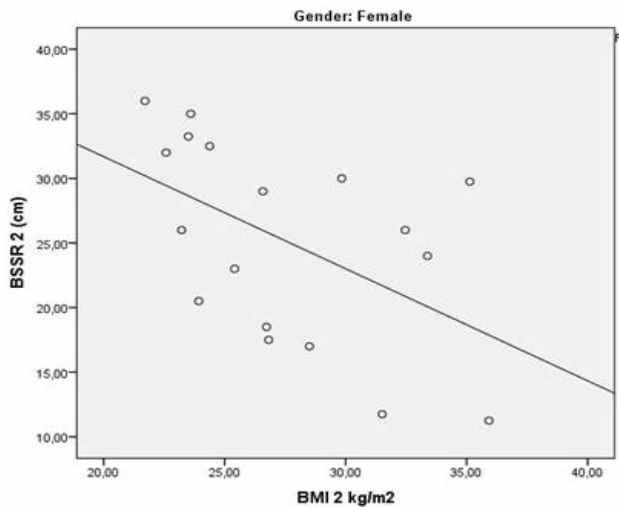
\*\* Correlation is significant at the 0.01 level (2-tailed); \* Correlation is significant at the 0.05 level (2-tailed).

BMI between men and women before ( $t = 0.066$ ,  $df = 30$ ,  $p = 0.948$ ) and after the program ( $t = -.030$ ,  $df = 30$ ,  $p = 0.976$ ), but significant differences in the BSSR scores before ( $t = -2.00$ ,  $df = 30$ ,  $p = 0.05$ ,  $d = -0.353$ ) and after the program ( $t = -2.20$ ,  $df = 30$ ,  $p = 0.035$ ,  $d = 0.388$ ). Women had higher flexibility scores than men before [22.70 (7.26) cm. vs 19.44 (6.68) cm.] and after the program [25.16 (7.71) vs 19.44 (6.68)]. The paired samples t-tests in Table IV indicated there were no significant differences after the program in men ( $p = 0.776$ ) and women ( $p = 0.857$ ) in the Fitness group, while in the HG group, men and women

had significantly increased BSSR scores after the program, from 20.07 (6.11) to 23.32 (5.85),  $p = 0.002$ ,  $d = 1.93$  in men and from 21.13 (6.70) to 26.25 (7.13)  $p = 0.000$ ,  $d = -1.50$  in women.

The Pearson correlation presented in Table V indicates there were no significant correlations between the mean BMI and BSSR scores in men before or after the program, while in women there were significant correlations between the BMI and BSSR scores after the program, indicating that a higher BMI was correlated with lower flexibility scores in women after the program ( $r = -0.508$ ,  $p = 0.031$ ).

By examining the scatter plot of the relationship between BMI and BSSR, Figure 2 shows that there is no evidence of a curvilinear relationship or the negative influence of outliers.



**Fig. 2** – Dispersion diagram illustrating the relationship between BMI and BSSR in female subjects.

## Discussions

Studies show that RPA is considered beneficial for many parameters, especially in older adults (Bruce et al., 2002; García-Esquinas et al., 2021); however, it was not clear whether the Fitness or the HG type of exercise would gain any changes in flexibility measures. In this research study, statistical analysis did not reveal significant changes in the Fitness group, in contrast to the HG group, which significantly improved the trunk and hamstring flexibility after the program in men and in women. Although the Fitness group practiced mainly muscle strength and aerobic ability, part of the practice included static flexibility exercises in the warm-up before the practice and at the end of the practice. These results follow many studies showing that regular PA intervention programs which included flexibility did not always gain differences in flexibility (Stathokostas et al., 2012). Takeshima et al. (2007) investigated the impact of different training programs such as: aerobic, resistance training, balance practice, Tai-Chi and flexibility training on functional fitness. They found improvements in cardiovascular ability, upper and lower body strength, balance and agility, but flexibility was not improved by these practices. Furthermore, flexibility workout in some cases was found to reduce muscle ability, power and performance (Lima et al., 2019). Nikolaidis et al. (2018) found that in women who practice recreational marathon running, the group who scored highest in flexibility measured by the sit and reach revealed the slowest running time. Finally, Nuzzo (2020) suggested to delete this component from the physical fitness major capabilities, because of its small impact on performance, as was seen by the fitness programs.

Flexibility of hamstring muscles significantly improved in our study only in the HG group ( $p = 0.00$ ), which exercised flexibility thoroughly and in a dynamic way. This may be related to the dynamic way of practice which is

included in the HG program, in contrast to the static type of training practiced in the Fitness program. In HG practice, every exercise comprises a sequence of several movements so that the muscles and joints are flexed and strengthened simultaneously. Many studies have shown that the dynamic flexibility way of practice produces better results than other modes of training, and improved the range of motion along with muscle power, agility and balance (Chatzopoulos et al., 2014; Opplert & Babault, 2018). Moreover, Herzog (2014), explained the mechanism of dynamic stretching, based on experimental observations on active stretching. He found that in contrast to the concentric and isometric contractions in passive stretching, the active flexibility practice is more likely to be related to the ability of titin stiffness activation. These proteins are engaged in muscle contractions and contribute to the elasticity of the muscle fibers, but also to their stiffness ability and the reduction of the free spring length. In active stretching, titins are able to bind to calcium and to actin, a process which enables them to gain resistance ability. This way, the muscles are lengthened without losing force, and are also protected from injuries at times when the isometric and concentric mechanisms are unstable.

Harmonic Gymnastics also involves the practice of coordination, proprioceptive and vestibular ability in addition to attention and body awareness. These components were also proven to be important in improving flexibility. Flexibility improvements along with functional basic physical performances were seen in various PA programs which involved dynamic flexibility and the practice of coordination, proprioceptive and vestibular abilities such as: Feldenkrais, Pilates and Tai-Chi, which in many ways resemble Harmonic Gymnastics (Bueno de Souza et al., 2018; Ghram et al., 2020; Zou et al., 2019). For example, in HG, as is usually performed in these PA programs, exercises that are related to the pelvic movement ability such as: anterior-posterior and medial-lateral pelvic tilt are practiced. These exercises were found important in improving trunk endurance and hamstring muscle flexibility along with better gait movement, knee and hip flexion and extension (Mendiguchia et al., 2020).

The fact that part of the time, some of the Fitness group participants continued practicing outdoors by themselves following Covid-19 restrictions in preventing the practice in gyms, sports clubs and any gatherings of any kind probably influenced this research outcomes (Grabowski & Maddox, 2020). Regardless of the Covid-19 pandemic, researchers have found that in general, social conditions contributed to the PA level of people more than other components such as physical environment or other facilitations (Chaudhury et al., 2016; Kleppang et al., 2018). In fact, Atad & Yanuv (2020) indicated that practicing in a group and practicing with a trainer revealed higher health and well-being scores in older adults. The HG group, although isolated in their homes, met by the Zoom application and sort of practiced together. Researchers have shown that digital behavior promoted PA levels and health among older adults in the Covid-19 period of time (Stockwell et al., 2019; Swechya et al., 2020). Nevertheless, the HG group may have had an advantage over the Fitness group because the participants still practiced together through a shared application.

Interestingly, McKay et al. (2017), have found that waist circumference was a significant predictor of flexibility changes in adolescents, adults and older adults. A greater waist circumference was related to lower flexibility. In this study, a significant negative correlation was also found between flexibility and BMI scores after the program in women ( $r = -0.508$ ,  $p = 0.031$ ), indicating that a higher BMI was related to lower flexibility scores in women of this research sample. These results also follow the study of Jeong et al. (2018), where significant decreases in joint flexibility was found in 22 movements, among people who were defined as obese or pre-obese compared to people with a normal BMI. The same trend was found in overweight boys and girls compared to normal weight peers. It appears that obesity has a negative impact on the joints' ability to move efficiently, and fatty particles in the joint area create a blockage of the range of motion (Martínez-López et al., 2019).

In this research study, although in a small sample, women revealed higher flexibility scores than men, before and after a three months program. These results are in contrast to the findings of McKay et al. (2017) after screening 1000 children, adults and older adults, which showed no differences in flexibility scores by gender. On the other hand, Lopes et al. (2021) showed in 545 men and women that men achieved higher scores in power and strength measures, but women scored better in flexibility. The same trend was found in 10,036 adolescents (Martínez-López et al., 2019).

## Conclusions

1. This research highlights the possibility of flexibility improvements following recreational physical activity in adults aged 50 years and older, even in pandemic Covid-19 conditions.

2. Flexibility was improved following the dynamic type of flexibility training as was practiced by the Harmonic Gymnastics PA program.

3. Women revealed higher flexibility scores than men, and a higher BMI was related to lower flexibility scores in women.

## Limitations

The research program was conducted in Covid-19 pandemic conditions, which restricted practice in studios and gym clubs, therefore the program changed during the research practice time. Also, limitations of this study are caused by the small number of subjects participating in the study.

## Conflicts of interests

The authors declare no conflict of interests.

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## REVIEWS

# Myositis ossificans: a short review

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### Abstract

Myositis ossificans (MO, heterotopic ossification) consists of lamellar bone formation in soft tissues, without ossification properties under physiological circumstances. MO can be primary (isolated or associated with various congenital disorders) or secondary in the site of a pre-existing lesion, such as inflammation, a neoplasm or a benign tumor. Primary forms are rare, present systemic symptoms and usually have a worse prognosis. MO is relatively frequent after sports lesions, hip arthroplasty or central nervous system injuries. Posttraumatic MO complicates about 20% of large hematomas after muscle contusions and strains. Diagnosis can be made through imaging or histopathological methods. Although characteristic features can be distinguished on simple radiographic images, magnetic resonance imaging, computed tomography and ultrasonography provide diagnosis in the earlier stages. Despite MO not having a universal prophylaxis or treatment, nonsteroidal anti-inflammatory drugs proved to be efficient in certain forms, while surgical excision and extracorporeal shock wave therapy might be useful therapeutic options.

**Keywords:** heterotopic ossification, physical activity, posttraumatic myositis, bone formation

### Introduction

Myositis ossificans (MO), otherwise known as heterotopic ossification, consists of non-neoplastic formation of lamellar bone in the muscle or other soft tissues which do not have ossification properties under physiological circumstances, without any direct connection to underlying bone tissue or the periosteum. MO is always extra-articular, although sometimes attachment to the joint capsule can be observed, without its disruption. MO can appear in the skin, subcutaneous tissue and skeletal muscles, causing inflammation and restricted, painful motion, severely influencing the quality of life of the patient and interfering with the career of professional athletes (Maheswarappa et al., 2004; Orava et al., 2017).

### Epidemiology

MO complicates about 20% of the large hematomas after muscle contusions and strains in contact sports; nevertheless, a similar percentage of MO occurs after total hip arthroplasties (Torrance et al., 2011). MO is responsible for significant morbidity, with pain, tenderness and stiffness

lasting over 1 year (Torrance et al., 2011). It was estimated that in athletes 9-20% of quadriceps injuries or contusions resulted in MO (Devilbiss et al., 2018).

### Pathogenesis

The pathogenesis of MO is not fully known, but several underlying biological pathways were identified, such as bone morphogenetic protein (BMP) receptor signaling, ALK1 pathway, insulin pathway, PDGFR-beta signaling pathway, EGF receptor (ErbB1) signaling pathway, growth differentiation factor 15 (GDF15), etc. (Ruschke et al., 2012; Strelau et al., 2003; Schindowski et al., 2011).

In MO, a differentiation of primitive mesenchymal cells from soft tissues such as muscle, fascia, periosteum and bone marrow into osteoprogenitor cells is triggered which will produce osteoblastic tissue. In non-hereditary forms, histologically we can distinguish six different stages: perivascular infiltration of lymphocytes, migration of lymphocytes into the soft tissues, fibroproliferation, neovascularization, cartilage formation and ossification (Ohlmeier et al., 2019; Foley et al., 2018; Cholok et al., 2018).

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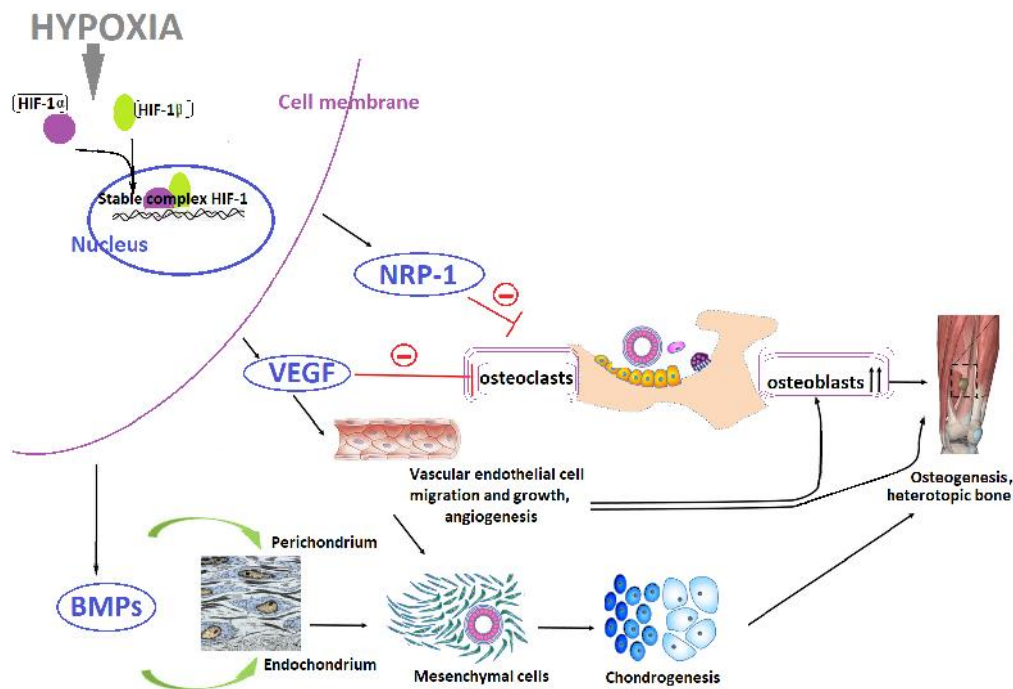
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**Table I**  
Types of heterotopic ossification (Huang et al., 2020; Bastepe, 2018).

Types	Etiology	Mechanism	Process of new bone formation
Inherited	Mutations in FOP gene (fibrodysplasia ossificans progressiva)	Gain of function of ACVR1 (activin receptor A type1) gene	Endochondral ossification
	Mutations in PHO gene (progressive osseous heteroplasia)	Loss of function of the GNAS gene [encoding the alpha-subunit of the stimulatory heterotrimeric G protein (G $\alpha$ )]	Intramembranous ossification
Acquired	Injuries	Injury to the nervous system	Distal to injury endochondral and intramembranous ossification
		Injury to the musculoskeletal system	Near the injury



**Fig 1** – The molecular mechanisms involved in the formation of heterotopic bone (adapted after Huang et al., 2020, Cholok et al., 2018).

Hypoxic microenvironment enhances the stability of HIF - hypoxia-inducible factors (HIF-1 $\alpha$  and HIF-1 $\beta$ ) which up-regulate a complex network including bone morphogenetic proteins (BMPs), vascular endothelial growth factor (VEGF) and neuropilin-1 (NRP-1). These promote angiogenesis, the proliferation and differentiation of cartilage and osteoblasts and inhibit the proliferation and differentiation of osteoclasts, thus being implicated in ossification (Fig. 1).

Two useful mnemonics were created by Bell et al. to help the memorizing of the causes of soft tissue calcification: My GHOSTS: Myositis ossificans, Gout, Hyperparathyroidism, Ochronosis, Scleroderma and other connective tissue diseases, Tumoral calcinosis, Sarcoma, and TIC MTV: Tumor, Inflammation/infection (dermatomyositis, scleroderma, parasitic infestation, leprosy, pancreatitis, calcific myonecrosis, bursitis/tendinitis), Congenital (Ehlers-Danlos syndrome, myositis ossificans progressiva), Metabolic (primary/secondary hyperparathyroidism, metastatic calcification, calcium pyrophosphate deposition disease, calcium hydroxyapatite deposition), Trauma (myositis ossificans, burn injury, hematoma) and Vascular

calcification (Bell & Niknejad, 2021).

Regarding the types of heterotopic ossification (Table I), MO can be primary (isolated or associated with various congenital disorders, such as Albright’s hereditary osteodystrophy (given by inactivating mutations in G $\alpha$ -coding GNAS exons), progressive osseous heteroplasia and fibrodysplasia ossificans progressiva) or secondary in the site of a pre-existing muscular or connective tissue lesion, such as inflammation, a neoplasm or a benign tumor (Hoda et al., 2014).

Secondary MO usually occurs after trauma (e.g. injuries suffered during sport activities), surgical intervention (e.g.: total hip or knee arthroplasty or hip arthroscopy) or neurological injury (Iorio et al., 2002; Lespasio et al., 2020). In sports medicine, MO is known to be a troublesome sequela of muscle lesions including voluminous haematomas, contusions, strains or repeated injuries causing an important setback in the athletes’ career, in certain cases even permanent joint impairment. Brachialis, quadriceps and adductor muscle groups are most commonly affected in MO (Orava et al., 2017; Simon et al., 2016; Devilbiss et al., 2018).

Posttraumatic MO can also frequently develop after significant injuries such as gunshot wounds, blast injury, burns, acetabular fractures and elbow injuries. Military injuries were first described in the literature in connection with the American civil war. Most cases of posttraumatic HO were reported during the Iraq and Afghanistan conflicts, which can be explained by the increased number of blast injuries due to frequent use of explosives (Eisenstein et al., 2017).

Para- or tetraplegic patients usually develop myositis ossificans circumscripta which only affects the motor level of the spinal cord lesion, explaining why this type of MO is more common in posttraumatic para- and tetraplegics with a more extensive spinal cord injury compared to spinal disc herniation or tumoral cases (Knudsen et al., 1982). Central nervous system complications of acquired immune deficiency syndrome (AIDS) can also be associated with MO (Drane et al., 1987).

Furthermore, MO can appear in autoimmune diseases as anti-NMDA receptor encephalitis, Guillain-Barre syndrome, dermatomyositis or inflammatory arthritis (Eckardt et al., 1981; Wang et al., 2016; Zeilig et al., 2016).

### Symptoms

Patients with MO usually present pain aggravated by physical activity, persistent local edema, decreased range of motion and muscle strength, often accompanied by palpable firm protrusion within the muscle. Symptoms are increased after 2-3 weeks (Orava et al., 2017).

### Diagnosis

Radiographically, MO has a phasic and dynamic image: in the early stages, ossification cannot be detected on radiographs. The typical appearance is a demarcated radiodense mass with a calcified outer shell, otherwise known as “eggshell calcification” (Kransdorf et al., 1993; O’Brien et al., 2012; Kaplan et al., 2000). Hereditary forms usually have a characteristic radiographic appearance: in FOP HO appears as a well-circumscribed area corresponding to a certain skeletal muscle, while in POH it is represented as a “cocoon-like web” connecting the connective tissues and the skeletal muscles (Kaplan & Shore, 2000).

Ultrasonography has been reported to be useful in the early diagnosis of MO, the signs occurring between the 3<sup>rd</sup> and the 5<sup>th</sup> week (Simon et al., 2015). Before the appearance of the classic radiological aspects, a unique “zone phenomenon” can be identified by ultrasonography, serving as an early, cost-efficient diagnostic method (Thomas et al., 1991). Power Doppler in muscles provides clues regarding neovascularization and thus healing, and its absence may suggest the possibility for the athlete to resume the sport (Simon et al., 2015).

Computed tomography (CT) can appreciate with precision the maturation of the lesion, although in the early stages only a hypoechogenic mass can be identified; therefore, if MO is suspected, follow-up CT scans are recommended. Cross sectional CT imaging is also important in preoperative planning (McCarthy & Sundaram, 2005).

By MRI, MO appears as a well-demarcated mass with heterogeneous signal, surrounded by perilesional edema

(Kransdorf et al., 1991). MO signs appear 2 weeks earlier than ultrasonographic signs (Simon et al., 2015).

The histopathological aspect of early MO lesion is hypercellular, with little bone matrix, and it can be difficult to differentiate it from a soft tissue sarcoma. In later phases, prominent bone formation of a characteristic peripheral ossification can be observed (Hoda et al., 2014).

### Differential diagnosis

Secondary MO must be differentiated from congenital forms of heterotopic ossification. Albright hereditary osteodystrophy is a genetic disorder associated with short stature, obesity and shortened fourth and fifth metacarpal and metatarsal bones. Progressive osseous heteroplasia presents with the progressive ossification of soft tissues, frequently resulting in deformity. Patients with fibrodysplasia ossificans progressiva (also known as myositis ossificans progressiva) exhibit bilateral hallux malformation at birth, progressively presenting disabling ectopic skeletogenesis with poor prognosis (Eichenfield et al., 2008).

Most importantly, MO must be distinguished from more aggressive tumoral processes, such as parosteal osteosarcoma, synovial sarcoma or malignant fibrous histiocytoma. In parosteal osteosarcoma, central calcification extends towards the periphery. The typical radiological appearance is the string sign - a thin, radiolucent line separating the tumor from the cortex that can also be seen in MO. A transition between woven bone and mature lamellar bone is found, which enables the distinction of MO from extraskeletal osteosarcoma (Hoda et al., 2014). Synovial sarcoma is a rare and aggressive periarticular soft tissue tumor with sharply demarcated and cystic or multi-lobulated MRI image. Malignant fibrous histiocytoma appears as a soft tissue mass on radiographs, near the diaphysis of a long bone with punctate calcification (Luczynska et al., 2014).

### Treatment

MO may have a self-limiting course, when spontaneous resolution occurs, thus the “wait and see” approach is applied initially. Prophylaxis using the “RICE” (rest, ice, compression, elevation) method is important after every sports injury. There are several therapeutic approaches (Table II); conservative treatment including nonsteroidal anti-inflammatory drugs and physical therapy may be sufficient for recovery (Al-Qattan et al., 2017; Torrance & deGraauw, 2011; Simon et al., 2015).

For symptomatic patients with non-hereditary MO, surgical intervention is often the sole viable management option to mitigate the painful or restricted motion or discomfort caused by prominent bone structure. Optimally, the procedure is performed after the completion of maturation (approximately 6 months after initiation), using complete excision. Athletes can resume light physical activity by 1-3 months, full activity by 6 months, and reaching their preinjury level in 1 year postoperatively (Orava et al., 2017; Simon et al., 2016; Devilbiss et al., 2018). In certain cases incomplete excision remains the only option, as the intervention may result in the lesion of major neurovascular structures, causing neurovascular injuries (Winkler et al., 2015).

**Table II**  
Classification, types of therapeutic approaches.

Pathogenesis	Types of therapy	Mechanisms	References
<b>Addressing tissue hypoxia</b>	Shock wave therapy	Microdisruption of avascular tissues, neovascular angiogenesis; mechanotransduction to myocytes, fibroblasts and ECM	Torrance & deGraauw, 2011; Hara et al., 2020
	Radiotherapy	Angiogenesis inhibition	Delos et al., 2013
	Moderate activity	Vasodilation; ECM remodeling	Vanden et al., 2005
	Vasoactive agent (phentolamine, safflower injection)	Promote vasodilatation, blood flow to the injury site	Huang et al., 2020; Wang et al., 2018; Joyner et al., 2014
	HIF-1 $\alpha$ inhibitors (PX-478, Rapamycin)	Inhibition of <i>HIF-1<math>\alpha</math></i> gene expression	Liu et al., 2015; Wu et al., 2019; Koh et al., 2008; Qureshi et al., 2017; Kaplan et al., 2018
	Selective HIF-1 $\alpha$ knockout (in animal studies)	Decrease target gene expression	Huang et al., 2020
<b>Addressing inflammation</b>	NSAID (Nonsteroidal anti-inflammatory drugs)	Inhibition of COX, reduce inflammatory response	Huang et al., 2020; Ma et al., 2018; Xue et al., 2011
	Colchicine	Inhibits heterotopic ossification	Dudkievics et al., 2005
<b>Addressing ossification</b>	Bisphosphonates	Decrease mineralization of bone matrix; useful in post-trauma prophylaxis rather than therapy	Mavrogenis & Soucacos, 2011; Barra de Moraes et al., 2012; Hara et al., 2020
	Ascorbic acid	Modulation of procollagen III synthesis	Barra de Moraes et al., 2012
<b>Surgical removal</b>	Excision of ossified myositis	Surgical timing is critical (a year-long after injury to ensure full maturation and minimize recurrence)	Vanden Bossche & Vanderstraeten, 2009; Delos et al., 2013

NSAID: non-steroidal anti-inflammatory drugs; ECM: extracellular matrix; HIF-1 $\alpha$ : hypoxia-inducible factor-1 $\alpha$ ; COX: cyclooxygenase

In elite and sub-elite athletes the use of extracorporeal shock wave therapy proved to be an efficient treatment alternative (Torrance & deGraauw, 2011). Colchicine has been found to reduce MO after total hip arthroplasty through its tissue mineralization and cell proliferation inhibitor properties (Salai et al., 2018). The absence of power Doppler hypervascularisation may be a useful method to monitor the response to therapy and return to sport, in athletes (Simon et al., 2015).

## Conclusions

1. MO is a rare but serious, often misdiagnosed disorder.

2. While hereditary forms generally have poor prognosis, secondary MO may also present potentially disabling consequences.

3. Although there are no universal therapeutic or prophylactic measures, there are some possible options to prevent or mitigate the symptoms of this disease.

## Conflict of interests

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report.

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## Should Creatine Kinase be tested at baseline in athletes?

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### Abstract

Creatine kinase (CK) level depends on muscle mass, age, race, physical activity and various pathologies involving the muscles or the heart. Resistance training elicits the greatest release of CK, and is the best way to attain muscle hypertrophy. The highest post-exercise serum enzyme level is found after prolonged exercise such as ultradistance marathon running or weight-bearing exercises and downhill running, which produce eccentric muscular contractions. Persistently elevated CK levels in apparently healthy subjects may indicate a late-onset underlying condition. The decrease in the serum enzyme level depends on the period of rest after exercise, as short-term physical inactivity may reduce the lymphatic transport of CK and the release of the enzyme from the muscle fibres. We discuss the source and level of CK in various situations, the different CK isoenzymes and also when to test for an underlying myopathy or other pathologies which may impact the long-term athletic performance. It is likely safe for athletes with suspected myopathy to continue physical activity at a lower intensity to prevent muscle damage, and allow appropriate rest to favour recovery. Thyroid dysfunctions and drug-induced myopathies should be ruled out. History and clinical examination could help clarify whether other muscle-directed investigations are required.

**Keywords:** creatine kinase, athlete, physical training, rhabdomyolysis, myopathy, statins

### Creatine kinase - biological functions

Creatine kinase (CK) is a crucial enzyme in the metabolism of creatine, catalyzing the formation of creatine phosphate and ADP from creatine and ATP (Fig. 1).

Creatine (Cr), or N-aminoiminomethyl-N-methylglycine, is mainly but not exclusively synthesized in the pancreas and in the kidney, which have high AGAT (L-arginine:glycine amidinotransferase) activity, as well as in the cells of the liver, where high concentrations of

GAMT (S-adenosyl-L-methionine: N-guanidinoacetate methyltransferase) can be found. From the organs of synthesis, creatine is transported via the bloodstream to the tissues which use creatine (mainly the brain and muscles), where both the endogenously synthesized creatine and the creatine derived from dietary sources is taken up by a creatine transporter (CRTR, or SLC6A8), a sodium dependent system enhanced by insulin (Stockler-Ipsiroglu et al., 2016; Lange et al., 2020).

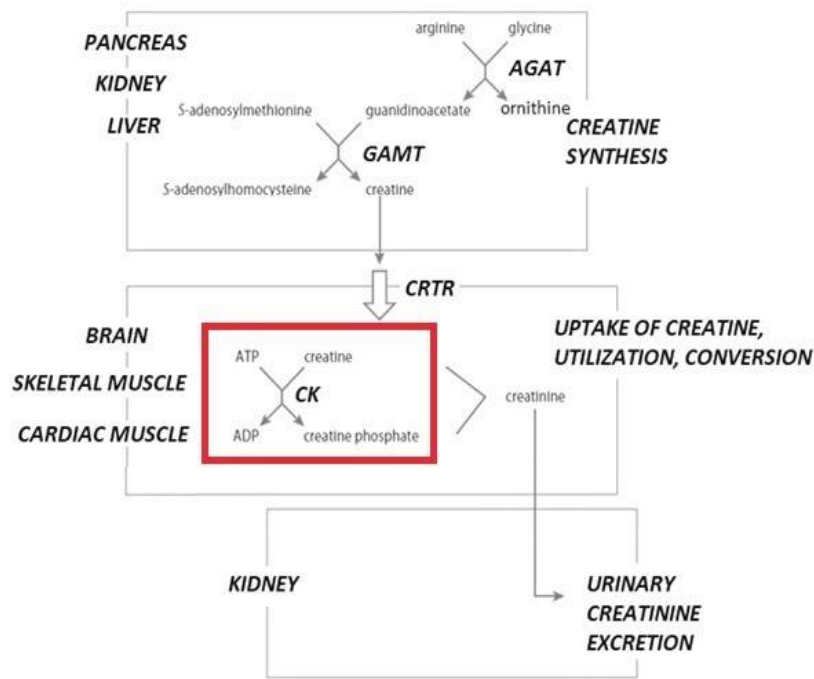
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**Fig. 1** – Metabolic pathway of creatine/creatine phosphate involving CK (image adapted after Stockler-Ipsiroglu et al., 2016). Legend: AGAT, L-arginine: glycine amidinotransferase; GAMT, N-guanidinoacetate methyltransferase; CRTR, creatine transporter; ATP, adenosine triphosphate; ADP, adenosine diphosphate; CK, creatine kinase

CK is a compact enzyme found both in the cytosol and in the mitochondria of tissues, where energy demands are high. In the cytosol, CK is composed of two polypeptide subunits, which can be of two types: M (muscle type) and B (brain type). These subunits allow the formation of three tissue-specific isoenzymes: CK-MB (cardiac muscle), CK-MM (skeletal muscle) and CK-BB (brain) (Schlattner et al., 2006).

CK is also found in macroenzymes. Macro-CK type 1 is a complex of CK (most often CK-BB) and immunoglobulin (most often IgG) and is typically greater than 200 kDa in size. Macro-CK type 2 is a polymer of Mt-CK (mitochondrial creatine kinase – an isoenzyme found in the mitochondria between the inner and outer membranes, with a molecular mass greater than 300 kDa). These forms of CK are expressed during disease and/or a dysfunction. For example, macro-CK 1 is associated with cardiovascular and autoimmune disease and macro-CK 2 with cancer (Liu et al., 2010).

In normal serum, total CK is represented almost entirely by CK-MM of muscular origin. Total CK levels depend on age, gender, race, muscle mass, physical activity, climatic condition and various pathologies involving the muscles or the heart (Stomme et al., 2004). CK values vary greatly among individuals. At rest, CK values are much lower in females than in males. The sex-linked differences are also present after exercise; estrogen is likely involved in maintaining post-exercise membrane stability, thus limiting CK leakage from the damaged muscle cells (Stomme et al., 2004; Enns & Tiidus, 2010).

During prolonged intense training, the damage of muscle tissue leads to an increase in the level of serum

CK. This may be a consequence of both metabolic and mechanical factors (Amelink et al 1988; Fu et al 2002). The impact of physical training may vary on CK values between athletes. The type of exercise also influences CK values. The highest values are seen after prolonged exercise such as ultramarathon, weight-bearing exercise and downhill running (Brancaccio et al., 2007). An explanation could reside in the decrease of the membrane resistance of a metabolically exhausted fiber after an increase in  $Ca^{2+}$  ions leading to K channel activation (Brancaccio et al., 2007; Fink & Luttgau, 1976).

Persistently elevated CK levels in apparently healthy subjects may indicate an underlying condition with late onset. In some athletes with asymptotically high CK values, the type of training, muscle size and the predominantly involved muscle fiber type should be assessed (Brancaccio et al., 2007; Munjal et al., 1983).

### Creatine kinase and muscle activity

Creatine kinase (CK) level depends on the muscle mass, age (Table I), race, physical activity, and various pathologies involving the muscles or the heart. CK values vary greatly among individuals.

Serum CK activity and the profile of the isoenzyme are important indicators of the occurrence of muscle cell necrosis and tissue damage due to disease or trauma.

While the level of CK is important, there is no consensus regarding the upper limit of the reference range. Regular preventative exercise with relatively constant muscle stress is often not associated with CK increases (Kindermann, 2016). Nevertheless, CK should be assessed after one week free of exercise, which is difficult to impose to elite

athletes (Kindermann, 2016). CK should be assessed along with the liver enzymes, and a parallel increase of the TGO transaminase (of muscle origin) could be orientating as well, mostly when the CK level exceeds 3-4 times the upper limit of the reference range (Kindermann, 2016).

**Table I**  
Reference values for CK at different ages (Department of Clinical Biology and Anatomopathology, Academic Hospital - Vrije University Brussel, 2001).

Age	Male (IU/L, 37°C)	Female (IU/L, 37°C)
0-3 days	up to 3-4 times the adult values	
< 1 year	up to 2 times the adult values	
1-3 years	60-305	
4-6 years	75-230	
7-9 years	60-365	
10-11 years	55-215	80-230
12-13 years	60-330	50-295
14-15 years	60-335	50-240
16-19 years	55-370	45-230
> 19 years	< 145	< 130

Moderate-intensity exercise, mainly of long duration, may increase CK levels to meet the criteria for rhabdomyolysis; eccentric muscle contractions, such as weight lifting or downhill running, could also lead to rhabdomyolysis (Latham et al., 2008). The potential complications are disquieting for the treating physician. Nevertheless, the clinical significance is unclear, as neither renal complications of rhabdomyolysis, nor correlations between the CK level and renal dysfunction have been observed (Latham et al., 2008). The patient should be instructed to report symptoms such as myalgia, weakness or dark urine, and CK should be further monitored.

Resistance training elicits the greatest release of CK, but it is also the best way to attain muscle hypertrophy. Thus, the enzyme is normally confined to the muscle cell - so the question arises: is the reason for the elevated CK levels after exercise the muscle damage and loss of muscle cell integrity, or is there some other molecular explanation reflecting a temporal disturbance of muscle processes? (Brancaccio et al., 2007).

Some individuals might have high levels of serum CK compared to other similar individuals when following the same exercise protocol (including moderate exercise), even when main comparability factors such as gender, age, and training status are accounted for in data analysis. In certain cases, this variability may indicate underlying myositis, but in many others the cause is unknown. There appears to be no established link between habitual exercise or acute high-intensity eccentric exercise and the high incidence of kidney dysfunction or muscle disorder in normal healthy individuals, even in the presence of CK levels >20000 IU/L. The contribution of additional factors such as genetic disposition, environmental conditions, or disease may increase the risk of exertional rhabdomyolysis, resulting in acute renal failure. Individuals who regularly participate in high-volume, intense exercise tend to have significantly raised baseline levels of CK compared to sedentary and moderately active individuals. Raised levels of serum CK

were also found in regularly exercising pre-menopausal women compared to similar sedentary individuals; this suggests that CK flux into the serum is a natural and normal reaction to regular exercise (Clarkson et al., 2006).

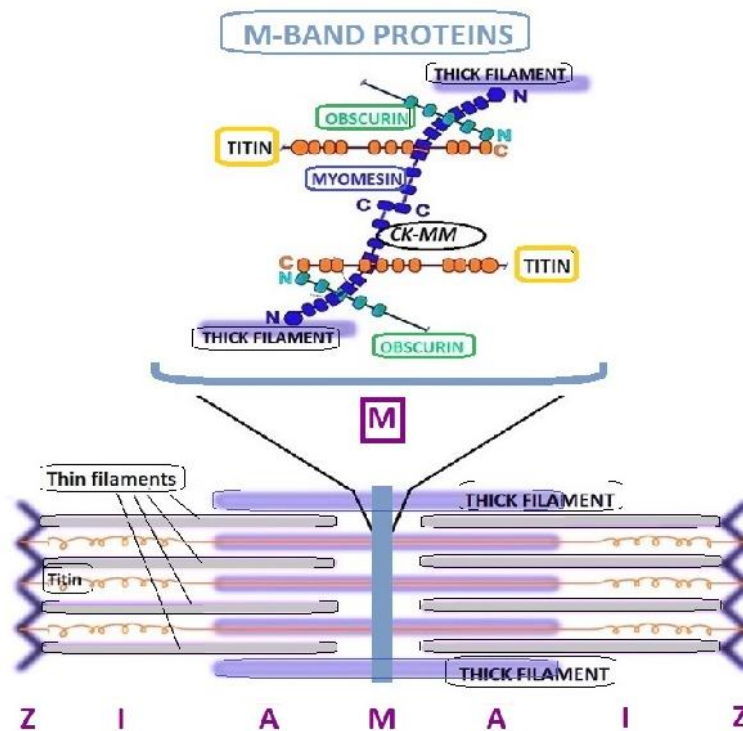
Myofibrillar CK-MM is bound to the M-line of the sarcoplasmic reticulum of myofibrils and is also found in the I-band sarcomeres providing support for muscle energy requirements. Animal studies on mice lacking the isoenzyme CK-MM have shown that the mice are viable, but have impaired muscle function upon challenge, proving that CK-MM at the M-band is required for optimal contractile response and physiological performance (Lange et al., 2020).

Apart from the myomesin family members, which are the major structural linkers in the M-band, several other proteins (titin, obscurin and others) were found in this region of the sarcomere (Fig. 2). CK-MM (the muscle isoform of creatine kinase) was shown to bind to the central domains of both myomesin and M-proteins and is very likely the cause for the electron dense signal that is picked up in electron micrographs as M-lines (González-Morales et al., 2017; Lange et al., 2020).

Factors such as extreme temperatures, alcohol abuse, or sporadic strenuous exercise (such as ultramarathons) can result in more severe disturbance and may require medical intervention to prevent permanent renal damage, primarily due to the nephrotoxic effects of myoglobin (Khan, 2009). The highest post-exercise serum enzyme activity is found after prolonged exercise such as ultradistance marathon running or weight-bearing exercises and downhill running, which produce eccentric muscular contractions. There is a breakpoint at 300-500 IU/L of CK serum release after exercise, and the level of the enzyme is associated with distinctive individual muscular properties. Daily training may result in persistent serum elevation of CK, and resting CK levels are higher in athletes, but the significant post-exercise increases of CK are usually lower in trained subjects when compared with untrained subjects. In fact, if athletes and sedentary subjects undertake the same physical exercise test, the CK levels of athletes are lower than those recorded in matched healthy control subjects (Karamizrak et al., 1994).

Total serum CK activity is markedly elevated for 24 h after a prolonged exercise bout, and remains markedly elevated for 48 h when subjects train in the first week post-exercise. The release of CK following eccentric exercise peaks 96 h after the exercise bout, and an additional exercise session produces only small increases of serum CK, probably from accelerated enzymatic clearance. More intense activity, such as two football training sessions a day, leads to a significant increase of CK during the fourth day of training. CK levels decrease between days 4 and 10, which could be an adaptation to training. A bout of exercise performed 48 h after an initial bout does not change the time course of the CK leakage (Smith et al., 1994).

The decrease in the serum enzyme level depends on the period of rest after exercise, as short-term physical inactivity may reduce both the lymphatic transport of CK and the release of the enzyme from the muscle fibres. Manual lymph drainage after treadmill exercise is associated with a faster decrease in the serum levels of



**Fig. 2** – The sarcomere - the basic unit of a myofibril - with the M-band at the centre (image adapted after Lange et al., 2020). Legend: Z, Z-discs; I, I-band linking systems; A, A-bands; M, M-bands.

muscle enzymes. Another factor that may reduce muscle damage and serum concentrations of CK following prolonged exercise is supplementation with branched-chain amino acids, often used in sports (Schillinger et al., 2006; Coombes & McNaughton, 2000).

Persistently increased serum CK levels are occasionally encountered in healthy individuals. CK values are also markedly increased in the pre-clinical stages of muscle diseases. In some studies on subjects with high levels of CK at rest, muscle weakness developed after several years, suggesting that early myopathy may be asymptomatic. Nevertheless, other studies on patients with elevated resting serum CK values demonstrated that in most cases, hyperCKemia probably does not imply disease. Frequently, the diagnosis is not formulated following routine examination with the patients at rest, as symptoms become manifest only after exercise (Smith et al., 1994).

In athletes, the study of CK at rest and after exercise could be an important tool for coaches and clinicians. Athletes have higher resting CK values when compared with untrained subjects, probably because of the greater muscle mass and the daily training performed. However, after exercise, CK serum activity depends on the level of training: although athletes experience greater muscle soreness when compared with untrained subjects, their peak serum activity is lower. Furthermore, the most marked increase in CK occurs in the less trained subjects.

High serum CK levels in athletes following absolute rest and without any further predisposing factors should prompt a full diagnostic workup with special regards to signs of muscle weakness or other simple signs that, in both athletes and sedentary subjects, are not always promptly

evident. These include cranial asymmetry and asymmetric position of the inferior angle of the scapulae and the iliac spines. Mutation in sarcomeric proteins is the prime cause of a major class of genetic diseases that affect cardiac function, such as familial hypertrophic cardiomyopathy, or lead to a variety of other myopathies including limb-girdle muscular dystrophy type 2G (telethonin), limb-girdle muscular dystrophy type 1A (myotilin), nemaline myopathy (actin, tropomyosin and nebulin), desmin-related myopathy (desmin), and other myopathies (plectin). In these subjects, repeated intense prolonged exercise does not induce the physiological muscle adaptations to physical training, given the continuous loss of muscle proteins (Laing 1999; Morimoto 2008). Muscle mass growth occurs by hypertrophy via growth hormone and testosterone. While hypertrophy is readily reversible, loss of muscle cells as a result of damage would be progressively more serious (Brown et al., 1999).

Statins are impact factors that may be associated with increased CK levels in amateur athletes who may take these cholesterol lowering drugs as part of a healthier lifestyle (Laufs et al., 2015). About 5% of statin users have muscle symptoms of different severity, from muscle pain and isolated increased CK to rhabdomyolysis (Laufs et al., 2015; Mancini et al., 2016). There are several types of grading the statin-induced muscle symptoms and a simple CK elevation should be weighed against the long-term benefit on survival, i.e. prevention of cardiovascular events (Rosenson, 2014). The patients with a four-time CK increase should discontinue the administered statins (Stroes et al., 2015). In patients with mild, incidentally found CK increments, both thyroid function and the

exercise level should be checked, and a long-term follow-up is required (Stroes et al., 2015). Amongst the common medications, several can be associated with myopathy (for instance oral antifungals for athlete's foot such as itraconazole, miconazole; beta-blockers and others). In healthy individuals, other factors which may increase CK - such as the use of recreational drugs (cocaine, etc.), chronic alcohol consumption or binge drinking - should also be taken into account.

## Discussions

The molecular mechanisms that result in CK release from muscle after mild exercise are unclear. More clarification could provide important information for athletes concerned about muscle hypertrophy, performance, and the importance of periods of rest between exercise sessions. Future studies should include an exploration of ethnic variations in CK levels in response to exercise. In the absence of any mechanical muscle damage, a question remains - whether raised CK after exercise does represent a degree of actual muscle damage or some form of disruption in energy control processes, or some other molecular reaction mechanism should be subject to further studies.

## Conclusions

1. It is likely safe to advise athletes with suspected myopathy to continue to undertake physical activity at a lower intensity, so as to prevent muscle damage from high intensity exercise and allow appropriate rest to favour adequate recovery.

2. The patient's history and the clinical examination should help to clarify whether more invasive investigations, including muscle biopsies, should be performed.

## Conflict of interests

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report.

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# The importance of motor behavior and balance training in the acquisition of physical activity/sports-related motor skills among children – review

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## **Abstract**

Proper motor skill aptitude execution in childhood is critical since it empowers the advancement of other formative spaces. Besides, motor execution may too be necessary for successful life skills, such as having a physically dynamic way of life and scholastic accomplishment. Be that as it may, despite its significance, children's levels of motor skills execution have diminished essentially over the past decades.

In the present review, the first aim was to highlight the importance of motor behavior throughout childhood and beyond. Secondly, to emphasize the effect of balance-specific training in everything related to acquiring motor skills in close connection with general motor behavior. Finally, the desire to highlight the process of acquiring physical activity / sports-related motor skills among children and its importance throughout the ontogenetic period.

**Keywords:** motor behavior, balance training, motor skills

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## **Introduction**

Infancy is the particularly crucial time of a person's life and the fastest period for complete and healthy movement throughout human existence, as well as cognitive development (\*\*\*, 2017); expanded physical action may give sports and cognitive benefits throughout childhood and adolescence (Riethmuller et al., 2009; Fisher et al., 2011). Therefore, understanding the potential of physical activity in improving underage youngsters' motor skills and knowledge is crucial, and it can provide pediatricians and additional well-being professionals with information on its effectivity as an involvement method. There is some pressing need for comprehensive RCT studies to determine the impact of sports and physical activity regarding the level of motor skills and cognition and determine the dose-response relationship in the community of preschool youngsters (Zeng et al., 2017).

The early stage of childhood is seen as a critical time for adopting healthy behaviors (such as physical activity) (Ward et al., 2010). The physical activity plan provides an environment for developing motor skills for young children, and motor skills are the basis for physical activities in the early and subsequent years (Jones et al., 2011). Today's young children show insufficient motor skills (Hardy et al., 2010). Young children's environments play a significant involvement in encouraging physical activity/sports

participation and motor ability improvement because these environments usually have the resources to implement physical behavior and motor ability programs (Ward et al., 2010; Khan & Hillman, 2014; Zeng et al., 2017).

Exercise and language are essential for early development from one to three years of age. Language is the best indicator of cognitive function. Fine motor skills are related to self-help ability. The most typical development in early life is to form one's own identity. Through the period of three years, the youngster may be self-reliant. In this stage of early childhood, children acquire independent life skills such as eating behavior, toilet training, and self-dressing. Early childhood development promotes the development of questioning skills (Balasundaram & Avulakunta, 2021) (Fig.1).

Middle and late youth is the period when youngsters progress from subordinate preschoolers to youthful grown-ups who influence their family and local area organizations. Their reasoning develops more distinctively, their feelings and practices become more controlled, and their choices become more unrestricted. The middle and late childhood periods, which interest us in this article, are when neurons are answerable for astuteness, language, and social/sports capacities/skills (Szabo et al., 2020a; Szabo et al., 2020b; Szabo et al., 2020c; Tulbure et al., 2020) are framed (Mah & Ford-Jones, 2012) (Fig. 1).

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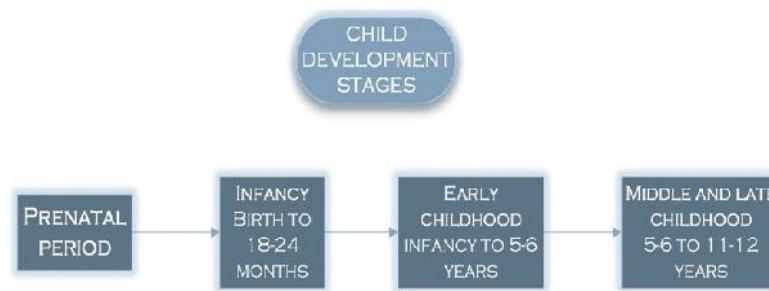


Fig. 1 – Child development stages.

Throughout the life cycle, the advantages of physical behavior are not limited to physical health, but also extend to cognitive function, which refers to the mental abilities involved in the basic process of perception and action. A recent systematic review and consensus statement positively correlated children's physical activity, health, cognition, and academic performance (Donnelly et al., 2016). In addition, cross-sectional research has demonstrated that adolescents and children with higher physical fitness or who regularly participate in physical exercises have better cognitive functions than adolescents and children with poor physical fitness or sedentary activity (Ballester et al., 2018; Ballester et al., 2015; Chueh et al., 2017; Pontifex et al., 2012; Formenti et al., 2021).

Throughout the premature phases of childhood, children may decide to participate in open or closed skill sports. Therefore, because of the differences in open and closed ability sports requirements, this option may be preferable and help affect their motor skill acquisition and cognitive development. Physical skills represent a multi-dimensional concept, including health-related (cardiovascular health, BMI, strength and muscle endurance, flexibility) and skill-related components. The latter, also known as sports health, consists of the capacity to learn and perform motor skills (reaction time, speed, agility, strength, and in our case, balance), which may also be related to cognitive performance in the areas of perceptual speed and executive function (\*\*\*, 2018; McMorris, 2015; Formenti et al., 2021).

Therefore, the objective of this review article is to methodically examine the existing evidence to examine the impact of balance and motor control on the acquisition of sports-related skills and cognitive improvement in healthy children. Specifically, this review aims to identify, synthesize, and interpret the best available evidence for the minimum and optimal physical activity required to acquire children's cognitive development and motor skills development. In addition, this review seeks to assist academics and health professionals in understanding the advantages of regular physical exercise and developing evidence-based physical activity guidelines for children.

### The Development of Motor Behavior

Motor development research was previously considered *the icing on the cake* of developmental science: the core of children's experience, but it has received little attention (Rosenbaum, 2005; Adolph et al., 2010). The historically

mature methods of motor skills were dominant in the early 20th century. It was mainly believed that motor development was carried out through predetermined biological changes, and there was almost no intervention from the environment or the cognitive domain (Gonzalez et al., 2019).

Motor development is often broadly divided into gross motor and fine motor skills. Gross motor abilities involve significant muscular movements, such as sitting independently, crawling, walking, or sprinting. Fine motor skills entail using smaller muscles, such as grabbing, manipulating objects, or sketching (Gonzalez et al., 2019).

Previous research has established a close connection between sports experience and developments in other fields. As part of this research topic (Michel et al., 2016) regarding the evolution of infant hand preferences, it was found that infants with consistent hand preferences in the early stages of development also showed advanced cognitive development. This indicates that infants who show stable hand preference in the early stage may follow a different developmental path, rather than those who develop hand preference later and provide evidence for the influence of exercise experience on cognitive development (Libertus & Hauf, 2017).

Motor behavior includes various movements from unconscious twitches to goal-oriented actions, different components of the physique from head to toe, and various physical and social environments from playing alone to group interaction. Motor behavior improvement happens through the life cycle, beginning with the leading embryonic motion and ending with the final breath (Adolph et al., 2017). Participation in movement education, where children discover body awareness, space, relationship, and effort, has historically resulted in learning fundamental motor skills and their progression to various, complex movement forms (Castelli, 2019).

According to the formative system, sports behaviors cannot be comprehended in isolation, and they cannot be separated from the physical, environmental, and social/cultural backgrounds in which they occur (Adolph & Robinson, 2015). Movement is inevitably nested in the body-environment system. The body and the environment develop simultaneously. New or strengthened motor skills enable new parts of the environment to function, thereby providing new or enhanced opportunities for learning and doing things. The nursing practice promotes and limits the

development of sports. Therefore, differences in the way caregivers construct the environment and interact with children affect the form of new skills, the age at which they first appear, and the shape of their developmental trajectory (Adolph et al., 2017).

### **Balance Ability and Balance Training**

Balance, especially the balance of the human body, refers to the body being in a balanced state under stress not to fall (Pollock et al., 2000). The different balance domains may be under static conditions, where the center of gravity (CoG) remains the same, or under dynamic conditions, where the balance must be maintained when moving under the foundation support (Patton et al., 1999). Balance ability can determine the performance of extremely concerted sports (i.e., gymnastics, alpine skiing, figure skating), but it can also predict the risk of injury, especially in the lower limbs (Hrysomallis et al., 2011). Physical activity is universally acknowledged as requiring balance skills (Sopa & Pomohaci, 2021), and stability workouts are extremely incorporated into almost all sports training programs. Although sports static balance and stability are typically demonstrated to be better than in non-sports practitioners, little is known about the differences in balance control between them, especially in different foot positions (Harmon et al., 2020).

Several original studies have shown the efficacy of balance training in increasing several components of children's and adolescents' balance performance (Heleno et al., 2016; Pau et al., 2012; Schedler et al., 2020a), and these discoveries have been summarized in reviews and systematic reviews (Gebel et al., 2018; Gebel et al., 2020). On the contrary, the advice on designing balance training for different load dimensions (for example, training volume, training intensity) so that it is most effective for skills acquisition in children and adolescents is rather unspecific and only comes from review articles (Gebel et al., 2018; Granacher et al., 2011). For example, reducing the basis of support/sensory input and tasks involving unstable surface/cognitive and motor interference has been proposed as an effective means to increase the task difficulty, thereby improving young people/children (Granacher et al., 2011). However, although these recommendations seem reasonable based on the existing literature, there is still a lack of empirical evidence. In a systematic review (Gebel et al., 2018), a meta-analysis was conducted to analyze the impact of balance training on youth balance performance and the dose-response relationship. However, this method should be used to compare dose-response relationships indirectly rather than directly. In other words, for example, comparing the results of a study with a short intervention period to the results of a study with a more extended intervention period but not comparing the effects of different intervention periods in a single study. In addition, the dose-response relationship of children's balance training can only be quantified for specific training methods (i.e., training time, training frequency). In summary, the following studies are needed: directly comparing different training methods in a single study and investigating load dimensions that have not yet been analyzed (Schedler et al., 2020b).

A published meta-analysis quantified the balance training dose-response relationship in healthy young individuals (Lesinski et al., 2015a). These authors quantified the training frequency, period, and training volume; however, the intensity was not quantified because there is no psychometrically reliable measurement method to describe balanced exercise intensity for children (Farlie et al., 2013). The meta-analysis results show that the training method is mainly in the shape of an inverted U, indicating the best training stimuli below and above the threshold. We hypothesized that the balance training dose-response connection in the elderly might show a model-specific inverted U-shaped transition compared to healthy young people and children. The difference in training status/physical level may require an age-specific balance training protocol to achieve the best training effect. The perfect training doctrine of enlightened overload means that the training method (for example, training frequency, training volume) should be compared to the current preparing state of a specific person to avoid overloading of their respective biological systems (Ackland et al., 2009). In addition to the training status, advanced age, and related neuromuscular degeneration processes (e.g., the decrease in the amount and dimension of type II muscle fibers, as well as the loss of sensory and motor neurons), the time pattern of the adaptation process after training appears to have an impact (Pew & Van Hemel, 2004). Based on some suppositions, there are sufficient reasons to ascertain the phase-particular dose-response relationship after balance training (Lesinski et al., 2015b).

### **Acquisition of Physical Activity/Sports-Related Motor Skills**

The discovery about neuroplasticity, that is, the brain's ability to reorganize itself by forming new neural connections in white matter and gray matter, does confirm that people can learn new things in later life; however, for the development of fundamental motor skills and physical awareness, the best time is in early childhood (Dayan & Cohen, 2011). People would think that children living in industrialized and economically developed countries have access to technological innovation, a high standard of living, and advanced medical screening and treatment. Compared to children living in substandard human conditions, they are more effective in mechanical and muscular conditions. There is an advantage in bones, but this is not the case at present; genetic and psychological elements have a more significant influence than physical aspects—cultural and background factors (Baker & Horton, 2004; Castelli, 2019).

Excellent motor skills are supposed to stand crucial for children's physical, social, and psychological development (Gallahue & Ozmun, 2002), and they may even be the basis for an active lifestyle since numerous studies have established a link between good motor skills and more significant proportions of physical behavior (Lubans et al., 2010; Williams et al., 2008). As a result, there is evidence that improving motor abilities has several health advantages. For example, it has been shown that excellent motor skills have a beneficial impact on cardiorespiratory fitness (Lubans et al., 2010; Okely et al., 2001), body weight (Lubans et al., 2010; Krombholz, 2013), and sports

participation (Lubans et al., 2010; Krombholz, 2006); all of this suggests that the early ability of motor skills may have significant health implications and is essential for general well-being (Viholainen et al., 2014). However, most available motor performance studies are cross-sectional and do not give evidence of a probable causal link or only involve short-term follow-up (Hestbaek et al., 2017).

MSC (motor skill competence) is described as the development of common core motor skills, especially object control (e.g., throwing, kicking) and locomotor abilities (e.g., running, jumping, hopping) (Stodden & Goodway, 2008). Because learning to move is a fundamental skill underlying future physical activity, the improvement of motor skill proficiency has been postulated as a causal predictor supporting physical fitness, physical activity behaviors, and health outcomes in infancy (Stodden & Goodway, 2008; Stodden & Goodway, 2007). Studies have demonstrated that motor skill growth in adolescence and childhood is related to improved cardiovascular fitness, muscular endurance, muscular strength, physical activity, and perceived competence (Barnett et al., 2009; Hands et al., 2009). Longitudinal studies in youngsters show that higher motor skill competence is connected to long-term physical activity levels and health-related physical fitness (Barnett et al., 2008; Gao & Wang, 2019).

Motor learning is a person's capacity to acquire motor abilities with a reasonably permanent change in performance due to practice or experience (Schmidt, 2005). The resulting behavioral outcome is now the most often utilized approach to measure motor learning (Schmidt, 2005). In order to enhance motor learning processes, instructions and additional feedback are key influencing variables. Athletes, and in our case, children, are provided with instructions on the proper movement pattern or technique in nearly any training setting where motor skills are taught (Wulf, 2013). Instructional language impacts both movement performance and motor learning outcomes (Fraizer & Mitra, 2008). A skill must be practiced consistently in order to develop proficiency and induce a motor learning adaptation. When determining how practice should be structured, several elements include the type of practice and the timetable. Successful procedure planning should enhance immediate performance impacts and encourage long-term learning by improving skill retention and transfer. Furthermore, task-specific or task-oriented practices relevant to the child should be employed (Gokeler et al., 2019).

Regarding the methodology of physical education and sports, first, Göhner (Göhner, 2013) emphasized the usefulness of functional sports analysis in segmenting sports to facilitate the learning of complex motor skills. In this sense, it is possible to deduce that if and only if the results are partly meaningful from a functional point of view, if and only if they reflect certain functions, and these functions are associated with specific functions, the movement should be split into sub-goals. In addition, when pursuing the parts method, a question arises, that is, whether the initial functional state of a particular moving part can be sufficiently guaranteed. If this is not the case, the instructor or coach should be consulted and ensure that the lost previous function is appropriately supplied

due to the isolation. Finally, while separating movement portions, the learner may be presented with the learning of units referring to auxiliary sub-actions, suggesting that the learner would presumably attempt to achieve a sub-goal that may subjectively not match the overall movement objective (Hossner et al., 2015).

## Conclusions

1. The current review encourages the use of organized sports to improve motor performance, by means specific to balance training and not only in normally growing youngsters, and offers a foundation for determining whether involvement in organized sports could be beneficial for children by forming acquisitions of physical activity / sports-related motor skills.

2. It will be essential to investigate the long-term impact and sustainability of novel physical activity programs on various aspects of child development, which will lead to a better grasp of how different approaches can be used in communities and schools to promote physically active lifestyles.

3. Longitudinal studies will be required to ascertain if the link between balance training and the acquisition of physical activity/sports-related motor abilities in youngsters changes over time.

4. More research is needed, mainly longitudinal studies in early life/childhood.

## Conflicts of interest

Nothing to declare.

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## EVENTS



### The annual meeting of veteran athletes of the „U” Cluj Club (25)

From the very beginning, we mention that the last meeting, the 24th, took place on 1 September 2018. This discontinuation was due to objective reasons: on 28 September 2019, the *Centenary Gala* of the University Cluj Club was held, an event reported by us in the new title journal *Health, Sports & Rehabilitation Medicine*; and September 2020 was already marked by the interdictions due to the COVID-19 pandemic.

In this year's meeting, 14 veterans participated. The main objective of the discussions was related to the restoration of the monument, until the meeting of 3 September 2022, when inauguration is scheduled. The project, the company that will execute the work and, most importantly, the provision of the necessary budget were discussed.

**Traian Bocu**  
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The group of younger veterans (left), led by Dr. Mariana Nedelcu-Simplăceanu and Draga Comșa-Crișan.

The group of older veterans (right), represented by Vasile Sărucan, Vasile Bogdan, Eva and Carol Zörgö-Raduly, Ladislau Tuka.



The meeting point.



A friendly talk.



A working group.

## FOR THE ATTENTION OF CONTRIBUTORS

### The subject of the journal

The journal has a multidisciplinary nature oriented toward biomedical, health, exercise, social sciences fields, applicable in activities of physical training and sport, so that the dealt subjects and the authors belong to several disciplines in these fields. The main rubrics are: “Original studies” and “Reviews”.

The Journal is aimed at adapting the profile of the journal to scientific contemporaneity in the field of medical and pharmaceutical sciences and interdisciplinary integration with health, physical activity and biopsychosocial rehabilitation.

The journal will have the same contents: editorials, original articles, review articles, case reports, recent publications, events. The journal is open for publication to all members of the national and international scientific community and offers the possibility to promote young people involved in research, along with top researchers in the above mentioned fields.

Regarding “Reviews” the main subjects that are presented are: oxidative stress in physical effort; mental training; psycho-neuroendocrinology of sport effort; physical culture in the practice of the family doctor; extreme sports and risks; emotional determinatives of performance; the recovery of patients with spinal column disorders; stress syndromes and psychosomatics; olympic education, legal aspects of sport; physical fitness/exercise in the elderly; psychomotricity disorders; high altitude sportive training; fitness; biomechanics of movements; EUROFIT tests and other evaluation methods of physical fitness; adverse reactions of physical fitness; sport endocrinology; depression in sportsmen/women; classical and genetic drug usage; Olympic Games etc.

Among articles devoted to original studies and researches we are particularly interested in the following: the methodology in physical education and sport; influence of some ions on effort capacity; psychological profiles of students regarding physical education; methodology in sport gymnastics; the selection of performance sportsmen.

Other articles approach particular subjects regarding different sports: swimming, rhythmic and artistic gymnastics, hand-ball, volleyball, basketball, athletics, ski, football, field and table tennis, wrestling, sumo.

The authors of the two rubrics are doctors, professors and educators, from universities and preuniversity education, trainers, scientific researchers etc.

Other rubrics of the journal are: the editorial, editorial news, reviews of the latest books in the field and others that are presented rarely (inventions and innovations, universitaria, preuniversitaria, forum, memories, competition calendar, portraits, scientific events).

We highlight the rubric “The memory of the photographic eye”, where photos, some very rare, of sportsmen in the past and present are presented.

Articles signed by authors from the Republic of Moldova regarding the organization of sport education, variability of the cardiac rhythm, the stages of effort adaptability and articles by some authors from France, Portugal, Canada must also be mentioned.

The main objective of the journal is highlighting the results of research activities as well as the permanent and actual dissemination of information for specialists in the field. The journal assumes an important role regarding the achievement of necessary scores of the teaching staff in the university and pre university education as well as of doctors in the medical network (by recognizing the journal by the Romanian College of Physicians), regarding didactic and professional promotion.

Another merit of the journal is the obligatory publication of the table of contents and an English summary for all articles. Frequently articles are published in extenso in a language with international circulation (English, French).

All the content of the journal is available immediately upon publication and is Open Access.

The Editorial Board of the Health, Sports & Rehabilitation Medicine journal informs its collaborators and readers that access to the journal is open and free. The journal does not have article processing or submission charges.

The journal is published quarterly and the works are accepted for publication in English language. The paper is sent by e-mail at the address of the editorial staff. The works of contributors that are resident abroad and of Romanian authors must be mailed to the Editorial staff at the following address:

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### **Objectives**

Our intention is that the journal continues to be a route to highlight the research results of its contributors, especially by stimulating their participation in project competitions. Articles that are published in this journal are considered as part of the process of promotion in one’s university career (accreditation that is obtained after consultation with the National Council for Attestation of University Titles and Diplomas).

We also intend to encourage the publication of studies and research, that include original relevant elements especially from young people. All articles must bring a minimum of personal contribution (theoretical or practical), that will be highlighted in the article.

In the future we propose to accomplish criteria that would allow the promotion of the journal to superior levels according international recognition.

### **THE STRUCTURE AND SUBMISSION OF ARTICLES**

The manuscript must be prepared according to the stipulations of the International Committee of Medical Journal Editors (<http://www.icmjee.org>).

The number of words for the electronic format:

- 4000 words for original articles;
- 2000 words for case studies;
- 5000-6000 words for review articles.

**Format of the page:** edited in WORD format, A4. Printed pages of the article will be numbered successively from 1 to the final page.

**Font:** Times New Roman, size 11 pt.; it should be edited on a full page, with diacritical marks, double spaced, respecting equal margins of 2 cm.

**Illustrations:**

**The images** (graphics, photos etc.) should be numbered consecutively in the text, with arabic numbers. They should be edited with SPSS or EXCEL programs, and sent as distinct files: „figure 1.tif”, „figure 2. jpg”, and at the editors demanding in original also. Every graphic should have a legend, written **under** the image.

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## PREPARATION OF THE ARTICLES

**1. Title page:** includes the title of article (maximum 45 characters), the name of authors followed by surname, work place, mail address of the institute and mail address and e-mail address of the first author. It will follow the name of article in the English language.

**2. Abstract:** For original articles a summary structured like this is necessary: (Background, Aims, Methods, Results, Conclusions), of maximum 250 words, followed by 3-8 key words (if is possible from the list of established terms). All articles will have a summary in the English language. Within the summary (abstract) abbreviations, footnotes or bibliographic references should not be used.

*Background, Aims.* Description of the importance of the study and explanation of premises and research objectives.

*Methods.* Include the following aspects of the study: Description of the basic category of the study: of orientation and applicative. Localization and the period of study. Description and size of groups, sex (gender), age and other socio-demographic variables should be given. Methods and instruments of investigation that are used.

*Results.* The descriptive and inferential statistical data (with specification of the used statistical tests): the differences between the initial and the final measurement, for the investigated parameters, the significance of correlation coefficients are necessary. The specification of the level of significance (the value p or the dimension of effect d) and the type of the used statistical test etc are obligatory.

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### 3. Text

Original articles should include the following chapters which will not be identical with the summary titles: *Introduction* (General considerations), *Hypothesis*, *Materials and methods* (including ethical and statistical informations), *Results*, *Discussions* results, *Conclusions* and suggestions. The conclusions should be formulated briefly, without comments extracted from the research, and numbered. Other type of articles, as orientation articles, case studies, Editorials, do not have an obligatory format. Excessive abbreviations are not recommended. The first abbreviation in the text is represented first in extenso, having its abbreviation in parenthesis, and thereafter the short form should be used.

Authors must undertake the responsibility for the correctness of published materials.

### 4. References

The references should include the following data:

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*Articles:* Pop M, Albu VR, Vişan D et al. Probleme de pedagogie în sport. *Educație Fizică și Sport* 2000; 25(4):2-8.

*Books:* Drăgan I (coord.). *Medicina sportivă*, Editura Medicală, 2002, Bucureşti, 2002, 272-275.

*Chapters from books:* Hăulică I, Bălţatu O. Fiziologia senescenţei. In: Hăulică I. (sub red.) *Fiziologia umană*, Ed. Medicală, Bucureşti, 1996, 931-947.

Starting with issue 4/2010, every article should include a minimum of 15 bibliographic references and a maximum of 100, mostly journals articles published in the last 10 years. Only a limited number of references (1-3) older than 10 years will be allowed. At least 20% of the cited resources should be from recent international literature (not older than 10 years).

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- the informed consent of adult subjects, patients and athletes, for their participation;
- malpractice insurance certificate for doctors, for studies in human subjects;
- certificate from the Bioethical Committees, for human study protocols;
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The data will be mentioned in the paper, in the section Materials and Methods. The documents will be obtained before the beginning of the study. Will be mentioned also the registration number of the certificate from the Bioethical Committees.

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