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ORIGINAL STUDIES

Chitosan oral administration stimulates regeneration after experimentally induced peripheral nerve injury

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Abstract

Background. Peripheral nerve injuries represent a challenging medical problem regarding rehabilitation and finding an optimal treatment method. Currently, various drugs are used for the symptomatic treatment of peripheral nerve injuries (such as pain medication, non-steroidal anti-inflammatory drugs, vitamins etc.) with inconsistent or short-term results, without providing an efficient recovery. Recently, the research has focused on different natural substances, such as chitosan, for the treatment of peripheral nerve injuries.

Aims. The present research analyzed the effects of chitosan oral administration on an experimentally induced peripheral nerve injury.

Methods. In the present applicative study, a peripheral nerve injury was induced on sixteen white male Wistar rats, divided into two equal groups. The effects of chitosan were examined during 21 days, compared to the control group, by assessing the following parameters: sciatic functional index (SFI), total body weight of the animal, pain-like behavior, serum nerve growth factor (NGF) and interleukin-6 (IL-6) levels, and also by histological studies.

Results. The obtained results were statistically evaluated using different methods (*t*-test, Bonferroni correction, GraphPad Software, ANOVA, Mann–Whitney U test), with the *p*-value significance level set at $p<0.05$. The animals treated with chitosan had a statistically significant functional improvement, compared to the control group regarding all investigated parameters and it was confirmed by the histological studies.

Conclusions. The present research suggests that chitosan administered orally can become an optimal conservative treatment method for peripheral nerve injuries, but more studies are needed to confirm these results.

Keywords: functional rehabilitation; peripheral nerve injury; chitosan.

Abbreviations: IL-6 - interleukin-6; NGF - nerve growth factor; PNI - peripheral nerve injury; SFI - sciatic functional index.

Introduction

Peripheral nerve injuries (PNI) are, in many cases, difficult to treat, especially from the rehabilitation point of view, and patients undergo long-term difficulties in their daily life activities due to different degrees of motor impairment, chronic or even cortical pain, sensitivity disorders and also psychological problems.

Nowadays, for complete nerve injuries, surgery represents the elective treatment method (Chen et al., 2007), but when it is not possible, conservative treatment is prescribed, usually involving pain medication and a physical rehabilitation program. However, rehabilitation results are inconsistent, incomplete and unpredictable in most cases that involve motor impairment (Jung et al., 2014). Therefore, finding a viable conservative treatment

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option, especially for these types of patients, represents an important research aspect.

After the onset of a peripheral nerve injury, Schwann cells (SCs) deliver neurotrophic factors and attract macrophages to the injury site (Vargas & Barres, 2007; Menorca et al., 2013), like nerve growth factor (NGF), which preserves the regenerating microenvironment for axonal elongation (Li et al., 2020). From the neurotrophin family, NGF is essential for synapse maturation and plasticity, axon targeting and neuron growth (Autry & Monteggia, 2012), stimulating axon regeneration and enhancing electrophysiological and histomorphological parameters after nerve injury (Kemp et al., 2011). In oral administration, NGF stimulates peripheral nerve regeneration (Kemp et al., 2011) by reducing the remyelination time and by enhancing the myelinated nerve fiber diameter (Li et al., 2020).

Another factor implicated in nerve regeneration is interleukin-6 (IL-6), a glycoprotein with pro-inflammatory activity, which increases the activation of T-cells and acts as a neurotrophic factor for both dopaminergic and cholinergic neurons, resulting in protection of the neurons and configuration of pain (Fregnan et al., 2012).

Over recent years, different natural compounds have been studied for the treatment of PNI, such as chitosan, obtained by deacetylation of chitin, part of the crustacean exoskeleton. Studies showed that chitosan protects the neurons, preventing Schwann cell apoptosis without any inflammatory responses (Baldrick, 2010). Recent studies demonstrated that chitosan, as part of different nerve tubes, enhances the number of axons (Chen, 2019) and provides good peripheral nerve recovery, especially regarding small nerve defects (Dietzmeyer et al., 2020). The chitosan-based nerve tube (Reaxon® Nerve Guide developed by Medovent GmbH, Mainz, Germany) was produced in 2014 and has been used with good results in the treatment of small nerve defects in experimental studies, being currently evaluated for human use (Bąk et al., 2017).

Boecker et al. noticed in their review the stimulatory effects of chitosan nerve tubes on Schwann cells and axonal regeneration, the neuroglial affinity and reduced toxicity (Boecker et al., 2019). Previous studies showed that chitosan restored axonal excitability and function, decreased the appearance of post-operative neurinoma, increased cell affinity for neurons (Boecker et al., 2019), provided a substrate for SC survival and oriented growth (Yuan et al., 2004), stimulated neuronal cell survival and differentiation (Freier et al., 2005; Simoes et al., 2011).

Moreover, animals treated with chitosan nerve tubes presented an increased number of activated SCs and axons at 21 days after the induced PNI (Haastert-Talini et al., 2013). Several studies showed that oral administration of chitosan improved functional rehabilitation (Boecker et al., 2019), without an inflammatory effect and with low toxicity (Baldrick, 2010).

Since most of the researches were performed on PNI using chitosan nerve tubes, we aimed to evaluate the effects of oral administration of this compound.

Hypothesis

The study hypothesis was to observe if oral chitosan can provide peripheral nerve regeneration, by assessing the parameters described below.

Materials and methods

Research protocol

a) Period and place of the research

The study was conducted in October-November 2020, at the Department of Physiology of "Iuliu Haţieganu" University of Medicine and Pharmacy Cluj-Napoca, Romania.

b) Subjects and groups

Sixteen white male Wistar rats, with a weight of 140-310 g, aged 16-20 weeks (provided by the Iuliu Hatieganu University of Medicine and Pharmacy's Research Base, Cluj-Napoca, Romania) were used. They were randomly divided into two equal groups: a control group - right sciatic nerve peripheral injury without treatment, and an experimental group - right sciatic nerve peripheral injury treated with chitosan.

The study complied with the ethical standards regarding animal research: the principle of the 3Rs (reduce, refine, replace), and was approved by the University Ethical Board and the Veterinary and Food Safety Direction (project authorization no. 204/10.03.2020). The animals were monitored daily and no animal had to be withdrawn from the study, as no animal exhibited any signs or symptoms of distress or disease.

c) Applied tests

Chitosan was purchased from Sigma-Aldrich (St. Louis, California, USA), with a medium molecular weight between 190,000-310,000 Daltons, the molecular weight at which chitosan is easily absorbed and incorporated. The solution administered to the animals was elaborated by dissolving chitosan in a NaCl solution 0.9%, 1 mL solution containing 0.0145g chitosan.

The experimental group received 2.5 mg/kg chitosan solution, by gavage, daily, starting the next day after the peripheral nerve injury induction until day 21. The control group received the same daily dose, by gavage, of a simple NaCl solution 0.9%. The preparation and administration method was similar to that described by the authors of a previously published study (Pop et al., 2021).

Before inducing the PNI, the animals were anesthetized with intraperitoneal ketamine 40 mg/kg and xylazine 8 mg/kg. PNI was induced using a method previously described by the authors (Pop et al., 2021): a skin incision of approximately 2.5 cm at the right femoral eminence of all animals was made, and with a non-resorbable 5.0 nylon surgical wire, a 3 mm segment of the right sciatic nerve was compressed, for 15 seconds, and strangulated at 1-1.2 cm proximal to the nerve trifurcation. The sciatic nerve was chosen for its accessibility and for the standardized evaluation of functional regeneration that is currently used (de Medinaceli et al., 1982).

The sciatic functional index (SFI) score measurement, a standardized method elaborated by Medinaceli et al. in 1982 and modified by Bain et al. in 1989, represents the mark left by the animal's posterior feet, impregnated with blue ink, when the animal moves in a controlled environment (glass tunnel). The following formula was used to calculate the SFI score for the normal foot (N) and the experimental foot (E): SFI= -38.3*PLF+109.5*TSF+13.3*ITF–8.83 (Bain et al., 1989), with the following parameters: TS (toe spread) = distance between fingers

1-5; ITS (intermediary toe spread) = distance between fingers 2-4; PL (print length) = plantar print length. Next, the following factors were calculated: PLF (print length factor) = (EPL-NPL)/NPL, TSF (toe spread factor) = (ETS-NTS)/NTS, ITF (intermediary toe factor) = (EIT-NIT)/NIT (Bain et al., 1989).

The SFI score was calculated for all animals at T0 (prior to PNI occurrence), T1 (7 days after PNI), T2 (14 days after PNI) and T3 (21 days after PNI), and the values were interpreted considering Medinaceli's criteria, in Table I (de Medinaceli et al., 1982).

Table I.
Types of functional rehabilitation regarding the sciatic functional index (SFI) (score after Medinaceli, 1982).

SFI Score	Functional Rehabilitation Degree
12 to −12	Excellent
−13 to −37	Good
−38 to −62	Medium
−63 to −87	Non-satisfactory
−88 to −137	Complete deficit

Pain-like behavior in rodents can be evaluated using the Randall-Selitto test (analgesiometry), developed in 1957, and the currently most utilized method for assessing the presence of pain in animals, by applying a mechanical stimulus and observing the animal's behavior (withdrawal of the foot or tail) (Decosterd & Woolf, 2000). The evaluation followed a previously described method by the authors (Pop et al., 2021), where a maximum mechanical force of 300 g was applied to all animals, both on the normal foot (N) and the experimental foot (E), in the same place (between the tip of the cone-shaped and the plane surface of the foot), and the animal's behavior was assessed and noted by the researcher. The analysis was performed before the nerve injury induction and at 7, 14 and 21 days after the occurrence of PNI, using a bench-top Ugo Basile (Gemonio, Italy) analgesia-meter.

Right sciatic nerve samples from both groups were harvested at day 21 of the study, after euthanasia. The samples were isolated and fixed in 10% neutral formalin solution for 48 hours. Sections were cut at 7 μm (Reichert microtome, Austria) after paraffin embedding and mounted on glass slides. Xylene was used for dewaxing and subsequently, the nerve samples were rehydrated and stained with methylene blue (Merck, Darmstadt, Germany). The sciatic nerve samples were analyzed with an incorporated camera optical microscope (Optika 383-LD2, Ponteranica, Italy).

Studies have indicated that body weight analysis can represent a general health indicator for animals, which can be associated with the presence and intensity of pain, which can influence appetite (Hogan et al., 2004; Turner et al., 2019). All animals were weighed at the beginning of the study (T0) and at 21 days after peripheral nerve injury (T3), and the values were compared statistically.

At T0 (prior to the sciatic nerve lesion), at 7 days after the lesion (T1) and at 21 days after the nerve injury (T3), blood samples were taken and analyzed for the identification of NGF and IL-6 levels (ELISA kit, Sigma Aldrich, Darmstadt, Germany), using a Sunrise microplate ELISA reader (Tecan, Grödig city, Austria) and an Asys microplate ELISA washer (Atlantis, Austria).

d) Statistical processing

The mean value, standard deviation, median, and inter-quartile range (Q1–Q3, the range between the 25th percentile and the 75th percentile) were used to describe the quantitative data. Friedman test was used for not normally distributed data. Pairwise comparisons (Wilcoxon signed-rank tests) were performed with Bonferroni correction, to compare the measurements from week 0 with each of the other weeks. To verify if there was a significant difference between the chitosan treatment and control groups for the non-normally distributed variables, Mann-Whitney U test was applied. Normally distributed data between two groups were compared using t-test for paired samples, t-test for independent samples, and Levene test for variances. A p-value equal to or lower than 0.05 was considered statistically significant. Data were analyzed using IBM SPSS software, v25 (manufactured by IBM). The obtained NGF and IL-6 values were statistically analyzed with GraphPad Prism version 5.03 for Windows, GraphPad Software (San Diego, California, USA), two-way ANOVA followed by Bonferroni post-tests, setting the threshold significance level at $p < 0.05$.

Results

Chitosan treatment efficiency by evaluating the sciatic functional index score (SFI)

A Friedman test was run to determine if there were differences in SFI scores between T0, T1, T2 and T3. SFI was statistically significantly different at the various time points for the chitosan group, $\chi2(3)=11.25$, $p=0.010<0.05$. Next, pairwise comparisons were performed with Bonferroni correction to compare the measurements from week 0 with each of the other weeks; the significance level was set at 0.0167. The median SFI score at T0 was -4.08 (within the limits of excellent functionality), at T1 the median SFI score decreased insignificantly to -4.60 after the intervention, then the median SFI score decreased at T2 and slightly increased at T3, but the differences were statistically significant only between the T0 and T3 scores (Fig. 1).

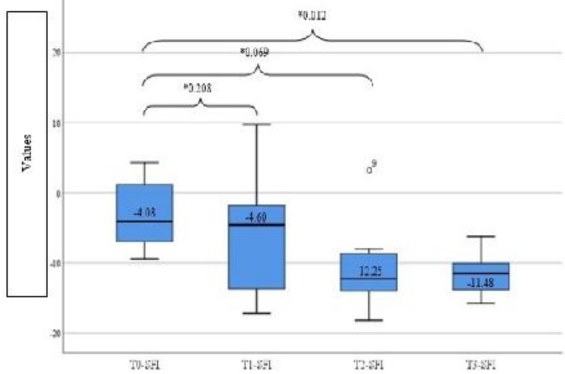

Fig. 1 – SFI score distribution (median) and evolution in time (*Wilcoxon signed-rank tests: *p*-values) for the chitosan treatment group.

A Friedman test was run to determine if there were differences in SFI scores between T0, T1, T2 and T3. SFI was statistically significantly different at the various time points for the control group, $\chi2(3)=14.55$, $p=0.002<0.05$. Pairwise comparisons were performed with Bonferroni correction to compare the measurements from week 0 with each of the other weeks; the significance level was set at 0.0167. Post hoc analysis revealed statistically significant differences in the median SFI scores at T0 (-4.59) compared to T1 (-70.07), T2 (-64.69) and T3 (-120.55), respectively (Fig. 2). The results for the control group were previously published by the authors (Pop et al., 2021).

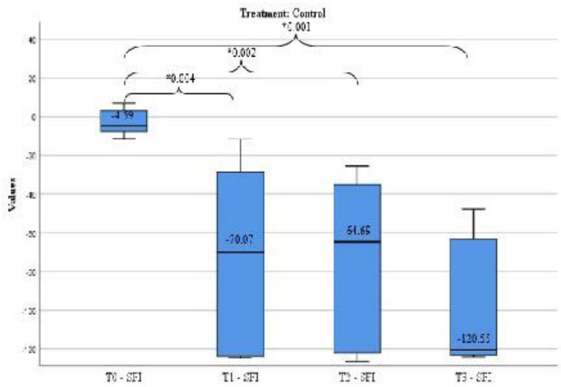

Fig. 2 – SFI score distribution (median) and evolution in time (*Wilcoxon signed-rank tests: *p*-values) for the control treatment group.

By comparing the evolution in time of the SFI score of the two groups (Fig. 3), a significant difference was observed, as the chitosan treatment group presented superior functional rehabilitation compared to the control group (according to Medinaceli's criteria presented in Table I).

Chitosan treatment efficiency by evaluating pain-like behavior

Comparing the pain scores of the control foot (healthy foot) showed no significant differences between the mean pain scores of the chitosan group and the control group for T0, T1, T2 and T3, respectively (*T*-tests for independent samples: $p>0.05$). When comparing the pain scores for T0 of the experimental foot, the chitosan treatment group mean (195.63) was not statistically significant compared to the control group mean (191.88), $t = 0.460$, $p = 0.652>0.05$. A comparison of the pain scores for T1, T2 and T3 indicated that the chitosan group had a statistically significant mean increase compared to the control group, $p < 0.001<0.05$ (Table II).

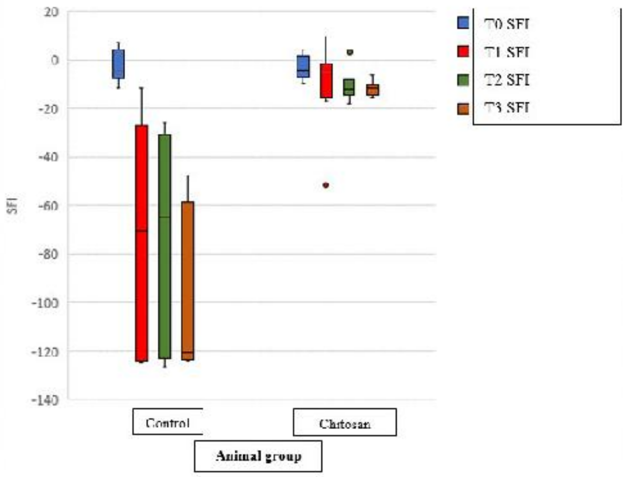

Fig. 3 – Comparative analysis of the SFI score between the control group and the chitosan treatment group (dynamic evaluation).

Figs. 4 and 5 show the comparative analysis between the two groups regarding pain-like behavior; a statistically significant difference was observed. The evolution of the chitosan group was favorable, the animals presenting better pain tolerance compared to the control group. Moreover, at 21 days after nerve injury, the chitosan group values were similar to those recorded at T0.

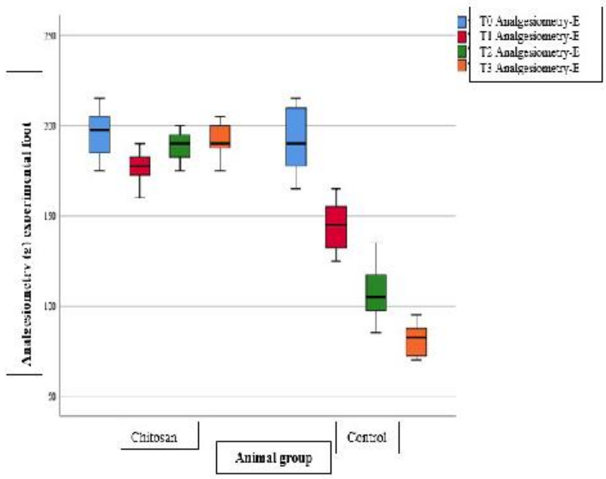

Fig. 4 – Comparative analysis of pain level between the CP group and the control group for the experimental foot.

Table II

Comparison of mean pain scores between the two treatment groups for the experimental foot.

Comparison between groups (experimental foot)	Time	Chitosan treatment		Control treatment		Independent t-test
		Mean	SD	Mean	SD	p-value
Pain scores	T0	195.63	13.63	191.88	18.50	0. 652
	T1	176.88	9.23	144.38	14.00	<0.001
	T2	188.75	8.34	107.50	15.58	<0.001
	T3	191.88	9.98	81.25	9.16	<0.001

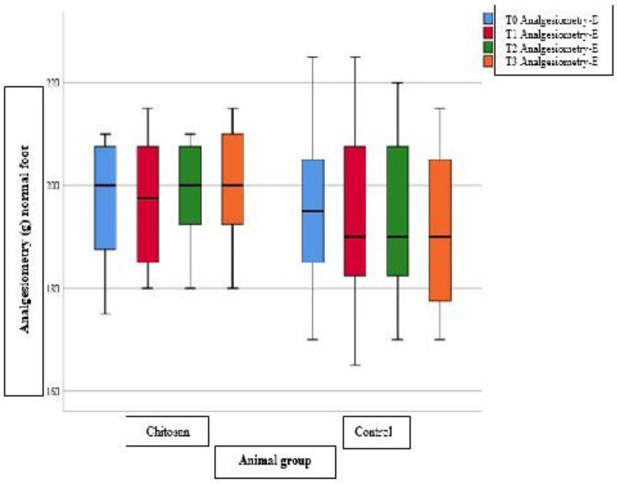

Fig. 5 – Comparative analysis of pain level between the CP group and the control group for the normal foot.

Dynamic evolution of the body weight as a possible tool to evaluate the efficiency of chitosan treatment

When comparing the weight for T0 and then for T3, the chitosan group mean was not statistically different compared to the control group mean, $p > 0.05$ (Table III). Comparing the weight scores for the chitosan treatment group revealed that the T3 mean was significantly higher than the T0 mean ($p = 0.001 < 0.05$). Comparing the weight scores for the control group revealed that the T3 mean was significantly lower than the T0 mean ($p = 0.001 < 0.05$). The comparative analysis of the two groups is shown in Fig. 6.

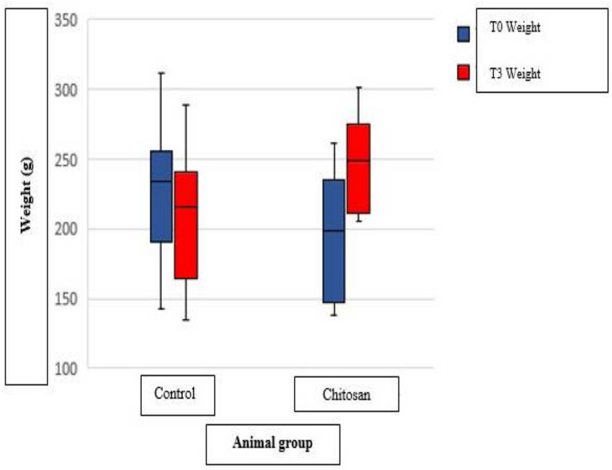

Fig. 6 – Comparative analysis of body weight evolution between the chitosan treatment group and the control group.

Chitosan treatment efficiency – histological studies

The histological analysis of right sciatic nerve samples from both groups showed that the control group presented various areas of disorganization of the myelin sheath. These areas are described as ovoid shaped vacuoles that seem to have determined the degeneration of the axon (Fig. 7). These modifications can cause changes in the myelin sheath thickness and structure, associated with a poor recovery outcome. The right sciatic nerve of the animals treated with chitosan had an almost normal or minimally altered structure (Fig. 8), in which the frequency of the ovoid formations was significantly lower compared to the control group.

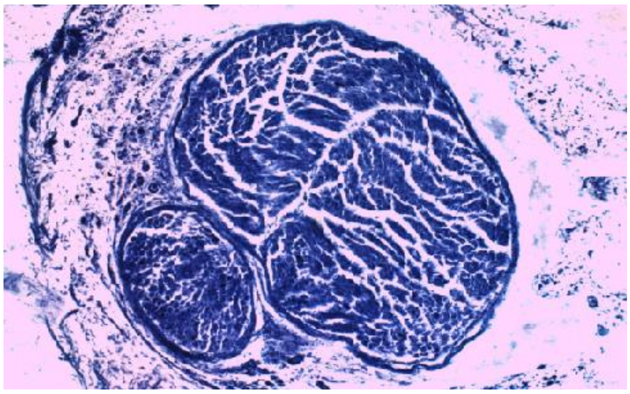

Fig. 7 – Right sciatic nerve section – control group.

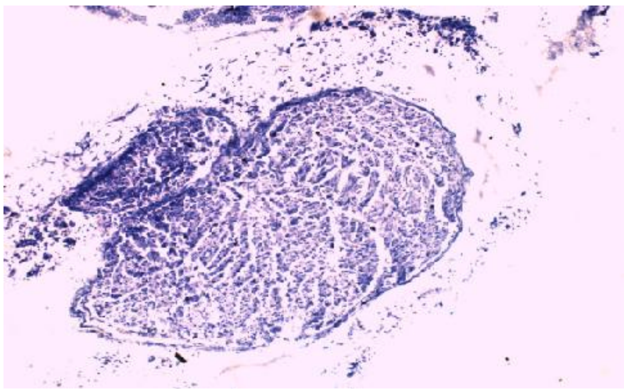

Fig. 8 – Right sciatic nerve section - chitosan treatment group.

Chitosan treatment efficiency – dynamic analysis of serum NGF and IL-6 levels

The dynamic analysis of serum NGF and IL-6 levels showed no statistically significant differences between the two groups (Figs. 9, 10). Nonetheless, the chitosan group had marginally constant higher values of serum NGF between the levels recorded at the beginning of the experiment and those registered at 21 days compared to the

Table III

Comparison of mean weight between the two treatment groups.

Comparison between groups	Time	Chitosan treatment		Control treatment		Independent t-test
		Mean	SD	Mean	SD	p-value
Weight (g)	T0	196.25	45.07	228.50	50.56	0.204
	T3	246.75	35.48	209.62	49.03	0.105

control group. The serum NGF levels of the control group were increased at seven days after the sciatic nerve injury, and subsequently, the NGF values followed a constantly decreasing tendency until day 21.

There were no significant differences between the two groups regarding serum IL-6 levels during the study. However, for both groups there was a constantly increasing tendency of IL-6 levels, as more time passed from the nerve injury onset.

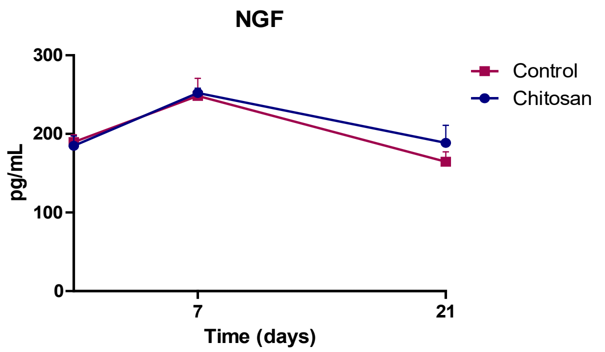

Fig. 9 – Serum NGF levels for the chitosan treatment group and the control group.

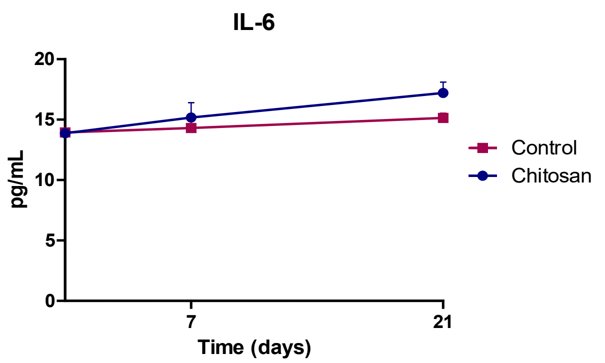

Fig. 10 – Serum IL-6 levels for the chitosan treatment group and the control group.

Discussions

The chitosan treatment group presented excellent functional rehabilitation at the end of the study, according to Medinaceli's criteria (Table I), as well as good pain tolerance and an increased body weight. Serum NGF and IL-6 levels were not statistically different compared to the control group, but the NGF levels of the chitosan treated group tended to remain slightly increased, suggesting that chitosan might be able to stimulate NGF secretion. Literature data showed significantly lower serum NGF levels for diabetic neuropathy patients compared to healthy patients, suggesting that the NGF results of the chitosan group in the present study can be associated with a positive peripheral nerve rehabilitation outcome (Giannaccini et al., 2017). In addition, Rui et al. reported in their study that NGF had neurotropism, promoted neurogenesis and its expression started within the same day after a PNI, accelerating the growth and myelination of the new cells (Li et al., 2020). These results were correlated with histological findings and therefore, the study hypothesis was confirmed: chitosan solution, administered orally, daily can represent an optimal treatment method for peripheral nerve injuries.

Like the present study, previous researches revealed the stimulating and regenerating action of chitosan on Schwann cells and axons, pointing out that chitosan had reduced cellular toxicity and did not promote any inflammatory response (Assa et al., 2017). These findings are consistent with our results, which showed that the serum IL-6 levels of the chitosan treated group were not significantly modified compared to the control group, indicating that chitosan administration does not cause notable inflammation. On the other hand, literature data suggest that the increase of IL-6 in both nerve cells and glia enhances the gene expression of regeneration-associated genes and multiple growth factors, playing an important role in nerve regeneration (Fregnan et al., 2012). Therefore, the increasing tendency of serum IL-6 levels can be interpreted as a sign of an enhanced nerve regeneration process.

The animals that received chitosan gained weight (significantly compared to the control group), results that correlate with other studies that observed a higher weight of muscles on the healthy side compared to the muscle weight of the injured site in animals treated with chitosan nerve guides (Meyer et al., 2016). In our study, we appreciated that the total body weight could represent a possible tool to assess the animal's general behavior and health. The weight loss of the control group could have been caused by the presence of motor impairment, resulting in a possible poor food reach. On the other hand, the animals of the control group could have also suffered from decreased appetite, in correlation with the intensified pain-like behavior that was observed.

Similarly to our study findings, other literature data revealed that chitosan administered orally for incomplete nerve lesions induces an excellent functional rehabilitation (Shakhbazau et al., 2012), making chitosan a potential treatment alternative for PNIs.

Although the present study results are encouraging, there were some limitations. The number of animals used, chosen in consideration of the ethical principles, can be considered low. Nonetheless, despite this low number, the results of the study were statistically significant. The number of animals could be increased in future researches, to observe if the initial results can also be obtained with a higher number of animals. Another limitation could be the subjective manner in assessing the SFI score and pain-like behavior, but, on the other hand, both methods are standardized and have been used in animal research for many years now. Therefore, chitosan administered orally could become a viable treatment option for peripheral nerve injuries, but more studies are needed in order to confirm this hypothesis.

Conclusions

1. Regarding the studied parameters, chitosan oral treatment seems to enhance peripheral nerve rehabilitation.
2. The results showed statistically significant differences between the chitosan treated group and the control group in relation to the sciatic functional index, total body weight, pain-like behavior, with a good rehabilitation outcome for the chitosan treated group, results that were confirmed by histological images.

3. No statistically significant differences were observed between the groups regarding the serum levels of NGF and IL-6, with a slightly increasing tendency of NGF and IL-6 values at the end of the study for the chitosan group, suggesting that the administration of chitosan might stimulate NGF secretion and the nerve regeneration process, with no statistically significant inflammation.

4. The results of the research confirm the hypothesis that orally administered chitosan could provide peripheral nerve regeneration and contribute to finding an efficient conservative treatment for peripheral nerve injuries.

Conflict of interests

None declared.

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Feeding practices patterns in Romanian infants 6-23 months old: findings from a national representative sample

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Abstract

Background. Besides breastfeeding, complementary feeding is necessary to meet the nutritional needs that foster healthy growth in children 6–23 months old. In 2007, WHO, UNICEF, USAID, UCDAVIS, IFPRI experts elaborated a set of indicators to evaluate infants and young feeding practices. These indicators are specific to children under 6 months and respectively 6-23 months. In this study three key indicators were used to measure complementary feeding practices: minimum acceptable diet (MAD), minimum meal frequency (MMF), and minimum dietary diversity (MDD).

Aims. The aims of the present study were to determine the prevalence of adequate and inadequate minimum acceptable diet (MAD), minimum meal frequency (MMF), and minimum dietary diversity (MDD) among children 6-23 months of age, in relation to infant or mother's risk of demographic factors.

Methods. A nationally representative sample with 1,532 children (713 girls and 819 boys) 6 to 23 months of age (M = 14.26; SD = 5.15) was included in our analyses. All eight macro-development regions within Romania were represented and participants were randomly recruited from at least two counties in each of these regions.

Results. It was found that the rates of achieved minimum acceptable diet were relatively high (72.3%), as well as the minimum acceptable dietary diversity (76.1%), and minimum meal frequency (96.1%).

Conclusions. The results of the study showed that the prevalence of children 6-23 months who have an adequate complementary diet in terms of the three indicators exceeds 72%. But there are also population groups that do not reach this prevalence.

Adequate complementary nutrition is generally achieved around the age of 1 year and less than 6-9 months, when the development needs of children already require animal foods rich in micronutrients.

Keywords: Romania, minimum acceptable diet, minimum meal frequency, minimum dietary diversity.

Introduction

The current study is the fourth of its kind to examine nutritional status and dietary practices in Romanian children under the age of two. The first was orchestrated in 1991, the second took place between 1993-2000 (Stănescu, 2002), through the analysis of the Nutrition Surveillance Data, and the third study was completed in 2004 (Nanu et al., 2006).

The results of these studies indicated that 91-92% of children aged 12 months were breastfed (BF). Complementary feeding was introduced early, around 4 months, through additional liquid or semifluid food. According to various sources (Callen & Pinelli, 2004; Agostoni et al., 2009), it is recommended that children be exclusively breastfeed up to six months of age, and this practice should be accompanied by complementary foods up to two years or beyond this age (Lanigan et al., 2001; Wasser et al., 2011; Carlett et al., 2017; Jabri et al., 2020).

With stunting and wasting becoming a growing concern in many regions, such as South Asia, it is critical to increase not only breastfeeding practices, but also other

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complementary feeding factors. According to Harding and colleagues (Harding et al., 2018), the prevalence of child wasting in South Asia is 16%, and that of stunting is 36%. Thus, children under two years of age should have access to high nutrient food supporting their growth and development (Dewey, 2016). This focus on children aged two years and younger would provide a window of opportunity to prevent growth deficits such as wasting and stunting (Lutter, 2000).

Besides breastfeeding, other complementary feeding practices are necessary to meet nutrient needs that foster healthy growth in children. As shown (Dewey, 2016), infants aged 6-8 months need nine times more iron and four times more zinc than an adult male. Micronutrient needs are high, while the caloric intake remains relatively low during these first 1000 days of life, thus presenting a challenge to parents in making sure that their child receives as many nutrients as possible. However, if adequate micronutrient intake can be attained, linear growth can take place (Onyango et al., 2014).

Hypothesis

The aim of the present study was to determine the prevalence of adequate and inadequate minimum acceptable diet (MAD), minimum meal frequency (MMF), and minimum dietary diversity (MDD) among children 6-23 months of age, in relation to infant or maternal risk of demographic factors.

Material and methods

All parents of the participants completed and submitted their written consent to the proper authorities before the study began, more specifically to the "Alessandrescu-Rusescu" National Institute for Mother and Child Health (Bucharest, Romania).

Research protocol

a) Period and place of the research

The current study drew the data from a more exhaustive cross-sectional survey run during the latter half of 2010. The larger study, entitled *Evaluating the effectiveness of interventions included in national programs on the nutrition of children under 2 years* (Nanu et al., 2011), *Part 2: Assessment of the Current Situation of Breastfeeding and Nutrition Practices for Children from Birth to Two Years Old* (Stativa & Stoicescu, 2011), utilized a national family physician database and stratified random sampling to determine a sample of Romanian children aged 0-23 months, N = 2,117. This is a nationally representative sample, for it included all eight macro-development regions of Romania, and the participants were randomly recruited from at least two counties of each of these regions (16 total). Within each county, children from two urban districts (two sectors of the capital, Bucharest, and rural communities of the Bucharest region that was not the capital) and four to five villages were arbitrarily recruited. In congruence to the area of residence, the data are also nationally representative due to the age range of each dyad, a mother and her child, who were assigned an identification code and invited to their physician's office. Health-related inquiries were implemented by two or three of 17 trained and experienced investigators. Once the interview process was completed, the investigators drew blood samples from the children and measured their weight and height.

b) Subjects and groups

The study investigators were experienced individuals who were also trained for the specific demands of the interview process. The interviewers worked in dyads or triads and verbally queried participants and recorded data in a face-to-face, in situ interview process. All questions were pretested (N = 80) before official data collection started to affirm consistency among all researchers administering them. The mothers were questioned at their family doctor's office regarding their prenatal consultation and iron prophylaxis use during the current pregnancy; initiation, knowledge, and practices of breastfeeding; child feeding practices; maternal smoking; and iron and vitamin D prophylaxis (Nanu et al., 2011). Complete data were collected over a four-month period (Stativa et al., 2014).

In the current study, sampling data were ensured to be evidence of the most modern pattern in children's nutrition research, by only selecting children aged 6-23 months for this analysis. Therefore, the sample encompassed 1,532 children (713 girls and 819 boys) 6 to 23 months of age (M = 14.26; SD = 5.15).

c) Applied tests

- *Complementary feeding indicators*

WHO's infant and young child feeding indicators were implemented for the current study (1); these indicators were measured based upon the interviewed mother's recollection of food given to her child within the last 24 hours before the survey. For this study, minimum acceptable diet (MAD) measures were estimated by taking into consideration the minimum dietary diversity (MDD) and minimum meal frequency (MMF). MDD and MMF are indicators which were based on the mother's report of food given to her child in the 24 hours before the survey.

- *Minimum acceptable diet (MAD)*

This variable reflects the proportion of breastfed children aged 6-23 months who had at least the minimum dietary diversity and the minimum meal frequency during the previous day. To calculate the indicator, information on breastfed and non-breastfed children is combined by adding the following two fractions: Breastfed children 6-23 months of age who had at least the MDD and the minimum meal frequency during the previous day / Breastfed children 6-23 months of age and Non-breastfed children 6-23 months of age who received at least 2 milk feedings and had at least the MDD not including milk feeds and the minimum meal frequency during the previous day / Non-breastfed children 6-23 months of age. MAD was expressed as a dichotomous variable with category 1 for meeting the complementary feeding indicator (adequate) and category 2 for not meeting that indicator (inadequate). As presented above, MAD was computed by considering the minimum dietary diversity (MDD) and minimum meal frequency (MMF).

- *Minimum dietary diversity (MDD)*

This variable is the proportion of children 6-23 months of age who received foods from four or more of the seven food groups during the previous day. The seven foods groups used for tabulation of this indicator were: (1) grains, roots, and tubers; (2) legumes and nuts; (3) dairy products (e.g., milk, yogurt, cheese); (4) flesh foods (e.g., meat, fish, poultry, and liver/organ meats); (5) eggs; (6) vitamin-A rich fruits and vegetables; and (7) other fruits and vegetables. MDD was expressed as a dichotomous variable with category 1 for meeting the complementary feeding indicator (yes) and category 2 for not meeting that indicator (no).

- *Minimum meal frequency (MMF)*

This variable is the proportion of breastfed and non-breastfed children aged 6-23 months who received solid, semi-solid or soft foods (but also includes milk feeds for non-breastfed children) the minimum number of times or more (minimum is defined as two times for breastfed infants 6-8 months, three times for breastfed children 9-23 months, and four times for non-breastfed children 6-23 months) on the previous day. MMF was expressed as a dichotomous variable with category 1 for meeting the complementary feeding indicator (adequate) and category 2 for not meeting that indicator (inadequate).

- *Explanatory factors*

The following demographic variables regarding mothers' characteristics were used as categorical explanatory variables (EVs): mother's age, domicile (*urban vs. rural*), ethnicity (*Romanian vs. Hungarian vs. German vs. Roma*), whether the mother was a smoker (*yes vs. no*), and education (*no school/gymnasium - completed or not vs. high/technical school vs. college*). Education-related categories were created based on the years of school attended: no school/gymnasium (0-8 years), high/technical school (9–12 years), and college (13 years or more). Additionally, mother's marital status was defined by two categories, *married mothers vs. other* (the "other" category included cohabitation, divorced/separated/widow, and unmarried). Also, included in our analyses was socioeconomic status (SES) which was coded as *low*, *medium*, or *high*. To determine SES, participants were asked whether they owned 12 items: a stove, television, refrigerator, washing machine, mobile phone, flush toilet, central heat, private car, private housing, personal computer, video recorder, and vacation home. Participants who owned up to four goods or services were classified as low SES; those who owned at least five and up to eight were classified as medium SES; and those who owned at least nine were classified as high SES.

Additionally, infants' characteristics were used as categorical explanatory variables (EVs): infant's sex (*male vs. female*), age, birth order (*first born vs. second born vs. third and up born*), whether the infant was born at term or not (*at term, 37-40 weeks vs. before term, 27-36 weeks*), and hemoglobin level. Regarding the latter, blood samples were drawn from infants presumed to be healthy. A finger-prick sample of capillary blood was collected, and hemoglobin concentration was measured using a portable battery-powered hemoglobinometer (HemoCue). Afterward, parents were informed about their child's iron status. Initially, four levels were established to categorize hemoglobin concentration (Hb), namely Hb$\geq$ 11.0 g/dL (no anemia); Hb 9-10.9 g/dL (mild anemia); Hb 7-8.9 g/dL (moderate anemia), and Hb <7.0 g/dL (severe anemia) (Stativa et al., 2014).

d) Statistical processing

All analyses, including accuracy of data coding and entry and statistical assumptions of the tests, were conducted using SPSS version 19.0, R program, and JASP (2018) (***, 2010; ***, 2018).

Logistic regression was utilized to adjust for complex sampling design and variable measurements. Models were built using stepwise backward regression to determine the variables that were significantly associated with unsuitable complementary feeding practices. The models formulated by backward elimination followed the following guidelines: (1) the variables used in the backward elimination models had a *p*-value <0.20 in univariate analysis; (2) possible confounding variables were included in the model and non-significant values (p >0.05) were removed step by step; and (3) collinearity was tested as well. Odds ratios with 95% confidence intervals were computed with the intent of assessing the adjusted risk of independent variables; those with p <0.05 remained in the final model. The relationships among all variables/indicators were analyzed regarding idiosyncratic child, parental health care and household characteristics within a multiple logistic regression model.

Results

Table I

Demographic frequencies and percentages of mothers and their children (N = 1,532).

Indicators	Descriptives n	%
Child's gender		
Male	819	53.5
Female	713	46.5
Child's age		
6-11 months	593	38.7
12-17 months	511	33.4
18-23 month	428	27.9
Mother's domicile		
Urban	789	51.5
Rural	743	48.5
Ethnicity		
Romanian	1291	84.3
Hungarian	104	6.8
German	11	0.7
Roma	126	8.2
Marital status		
Married	1247	81.4
Other	285	18.6
Education		
No school/gymnasium	541	35.3
High/technical school	652	42.6
College	339	22.1
Socioeconomic status (SES)		
Low	231	15.1
Medium	741	48.4
High	560	36.6
Smoking in the last 30 days		
No	1090	71.1
Yes	441	28.8
Child's rank		
First	839	54.8
Second	496	32.4
Third and up	197	12.9
The child was born full-term		
At term	1377	89.9
Before term	155	10.1

Table I shows the frequencies and percentages of the characteristics of the entire sample of children and their mothers. Overall, out of 1,532 children, 819 (53.5%) were males, 593 (38.7%) were aged 6-11 months, and 789 (51.5%) resided with their mothers in urban locations.

Additionally, most of the participants (mothers) were Romanian (84.3%), married (81.4%), had high/technical school level education (42.6%), were characterized as having a medium socioeconomic status (48.4%), and smoked in the last 30 days prior to data collection (71.7%). Furthermore, more than half of children were first-born (54.8%), as well as born at term (89.9%).

Prevalence of MAD, MDD, and MMF

Table II displays the frequencies and percentages of MAD, MDD, and MMF. Specifically, in infants 6-23 months of age, it was found that the rates of achieved minimum acceptable diet were relatively high (72.3%), as well as the minimum dietary diversity (76.1%), and minimum meal frequency (96.1%).

MAD, MDD, and MMF model predictors

The odds ratios, confidence intervals (odds ratio scale) and *p*-values, along with other parameters for the MAD, MDD, and MFF model predictors are shown in Tables III, IV, and V.

As shown in Table III, those infants living with their mothers in rural areas were 1.3 times more likely (95% CI; 1.033, 1.655) to meet the complementary feeding indicators compared to infants who lived with their mothers in urban areas. Additionally, infants 12-17 months old and 18-23 months old were 1.7 (95% CI; 1.338, 2.298) and 1.5 (95% CI; 1.126, 1.973) times more likely to meet the complementary feeding indicators compared to infants 6-11 months old. Our results also showed that infants born second in their families were 0.7 (95% CI; 0.580, 0.957) times less likely to meet the complementary feeding indicators compared to their counterparts who were born first. Additionally, infants whose mothers identified themselves as Roma were 0.6 (95% CI; 0.414, 0.965) times less likely to meet the complementary feeding indicators compared to their Romanian counterparts.

As seen in Table IV, those infants living with their mothers in rural areas were 1.4 times more likely (95% CI; 1.070, 1.748) to meet the complementary feeding indicator MDD compared to infants who lived with their mothers in urban areas. Additionally, infants 12-17 months old and 18-23 months old were 2 (95% CI; 1.523, 2.674) and 2 (95% CI; 1.649, 3.037) times more likely to meet the complementary feeding indicators compared to infants 6-11 months old. Our results also showed that infants born at term were 0.6 (95% CI; 0.438, 0.900) times less likely to meet the complementary feeding indicator MDD compared to their counterparts who were born prematurely. Additionally, infants whose mothers identified themselves as Hungarian were 0.7 (95% CI; 0.422, 1.011), times less likely than their Romanian counterparts to meet the complementary feeding indicator MDD; this outcome was statistically marginally significant. In relation to this variable, mothers who identified themselves as Roma were 0.5 (95% CI; 0.347, 0.798) times less likely to meet the complementary feeding indicator MDD compared to their Romanian counterparts.

Finally, as seen in Table V, the results showed that infants with severe anemia were 0.2 (95% CI; 0.049, 1.170) times less likely to meet the complementary feeding indicator MMF compared to those with no anemia. Additionally, infants 12-17 months old and 18-23 months old were 0.4 (95% CI; 0.193, 0.982) and 0.2 (95% CI; 0.090, 0.393) times less likely to meet the complementary feeding indicators compared to infants 6-11 months old.

Table II

Frequencies and percentages of MAD, MDD, and MMF (N = 1,532).

MAD	Frequency	Percent	MDD	Frequency	Percent	MMF	Frequency	Percent
Inadequate	424	27.67	No	366	23.89	Inadequate	59	3.85
Adequate	1108	72.32	Yes	1166	76.11	Adequate	1473	96.15

Table III

Multiple logistic regression analysis summary for various infant and mother variables predicting infant's minimum acceptable diet (MAD; N = 1,532).

Indicator	Estimate	Robust standard error	Odds ratio	z	p	95% confidence interval (odds ratio scale)	
						Lower bound	Upper bound
Mother's domicile (urban vs. rural)	0.268	0.120	1.308	2.229	0.026 *	1.033	1.655
Infant's age (6-11 months vs. 12-17 months)	0.561	0.138	1.753	4.068	< .001***	1.338	2.298
Infant's age (6-11 months vs. 18-23 months)	0.399	0.143	1.491	2.793	0.005**	1.126	1.973
Infant's gender (male vs. female)	-0.142	0.116	0.868	1.221	0.222	0.691	1.090
Infant's rank (first born vs. second born)	-0.294	0.128	0.745	2.301	0.021*	0.580	0.957
Infant's rank (first born vs. third born and up)	-0.189	0.187	0.828	1.011	0.312	0.574	1.194
Infant's birth (before term vs. at term)[1]	-0.312	0.179	0.732	1.743	0.081	0.516	1.039
Mother's marital status (married vs. other)[2]	-0.148	0.154	0.862	0.965	0.335	0.638	1.165
Mother's ethnicity (Romanian vs. Hungarian)	-0.249	0.220	0.780	1.133	0.257	0.507	1.199
Mother's ethnicity (Romanian vs. German)	-0.158	0.752	0.854	0.210	0.834	0.196*	3.729
Mother's ethnicity (Romanian vs. Roma)	-0.458	0.216	0.632	2.126	0.034	0.414	0.965

Note: MAD was expressed as a dichotomous variable with category 1 for meeting the complementary feeding indicators (adequate) and category 2 for not meeting those indicators (inadequate), which was the baseline group.

*p < 0.05; **p < 0.01; ***p < 0.001.

[1]Infant's birth at term (37-40 weeks) vs. before term (27-36 weeks).

[2]The "other" category included cohabitation, divorced/separated/widow, and unmarried.

Table IV
Multiple logistic regression analysis summary for various infant and mother variables predicting infant's minimum dietary diversity (MDD; N = 1,532).

Indicator	Estimate	Robust standard error	Odds ratio	z	p	95% confidence interval (odds ratio scale)	
						Lower bound	Upper bound
Mother's domicile (urban vs. rural)	0.313	0.125	1.368	2.499	0.012*	1.070	1.748
Infant's age (6-11 months vs. 12-17 months)	0.702	0.144	2.018	4.893	< .001***	1.523	2.674
Infant's age (6-11 months vs. 18-23 months)	0.805	0.156	2.238	5.171	< .001***	1.649	3.037
Infant's gender (male vs. female)	-0.146	0.123	0.864	-1.188	0.235	0.680	1.099
Infant's birth (before term vs. at term)[1]	-0.465	0.184	0.628	-2.532	0.011*	0.438	0.900
Mother's ethnicity (Romanian vs. Hungarian)	-0.426	0.223	0.653	-1.912	0.056 †	0.422	1.011
Mother's ethnicity (Romanian vs. German)	-0.396	0.762	0.673	-0.519	0.604	0.151	2.998
Mother's ethnicity (Romanian vs. Roma)	-0.641	0.212	0.527	-3.019	0.003**	0.347	0.798

Note: MDD was expressed as a dichotomous variable with category 1 for meeting the complementary feeding indicators (yes) and category 2 for not meeting those indicators (no), which was the baseline group.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. † represents a marginally significant outcome.
[1] Infant's birth at term (37-40 weeks) vs. before term (27-36 weeks).

Table V
Multiple logistic regression analysis summary for various infant and mother variables predicting infant's minimum meal frequency (MMF; N = 1,532).

Indicator	Estimate	Robust standard error	Odds ratio	z	p	95% confidence interval (odds ratio scale)	
						Lower bound	Upper bound
Infant's hemoglobin level (no anemia vs. mild anemia)[1]	0.289	0.296	1.335	0.975	0.329	0.747	2.388
Infant's hemoglobin level (no anemia vs. moderate anemia)	-0.456	0.481	0.634	-0.947	0.344	0.247	1.628
Infant's hemoglobin level (no anemia vs. severe anemia)	-1.429	0.809	0.239	-1.766	0.077 †	0.049	1.170
Infant's age (6-11 months vs. 12-17 months)	-0.831	0.415	0.436	-2.004	0.045*	0.193	0.982
Infant's age (6-11 months vs. 18-23 months)	-1.669	0.375	0.188	-4.446	< .001***	0.090	0.393
Infant's rank (first born vs. second born)	-0.359	0.305	0.698	-1.178	0.239	0.384	1.269
Infant's rank (first born vs. third born and up)	-0.602	0.378	0.548	-1.594	0.111	0.261	1.148
Mother's marital status (married vs. other)[2]	-0.483	0.322	0.617	-1.500	0.134	0.328	1.160

Note: MMF was expressed as a dichotomous variable with category 1 for meeting the complementary feeding indicators (adequate) and category 2 for not meeting those indicators (inadequate), which was the baseline group.
[1]Four levels were established to categorize hemoglobin concentration (Hb), namely Hb ≥ 11.0 g/dL (no anemia); Hb 9-10.9 g/dL (mild anemia); Hb 7-8.9 g/dL (moderate anemia), and Hb <7.0 g/dL (severe anemia).
[2]The "other" category included cohabitation, divorced/separated/widow, and unmarried.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. † represents a marginally significant outcome.

Discussions

Importantly, this is the first study that describes infants' complementary feeding patterns in Romania, based on the relatively newly developed WHO infant feeding indicators (5,12). This current investigation was conducted on a nationally representative sample (N = 1,532) and determined the prevalence of recommended minimum criteria for the complementary feeding indicators MAD, MDD, and MMF in infants 6 to 23 months of age.

Overall, as seen in Table II, in infants 6-23 months old, it was found that the rates of achieved minimum acceptable diet were relatively high (72.3%), as well as the minimum acceptable dietary diversity (76.1%), and minimum meal frequency (96.1%).

- *MAD*

Those infants living with their mothers in rural areas were more likely to meet the complementary feeding indicator MAD compared to infants who lived with their mothers in urban areas (Table III). Additionally, infants 12-17 months old and 18-23 months old were also more likely to meet the complementary feeding indicators compared to infants 6-11 months old. Our results also showed that infants born second in their families were less likely to meet the complementary feeding indicators compared to their counterparts who were born first. Additionally, infants whose mothers identified themselves as Roma were less likely to meet the complementary feeding indicators compared to those identifying themselves as Romanian.

- *MMD*

Those infants living with their mothers in rural areas were more likely to meet the complementary feeding indicator MDD compared to infants who lived with their mothers in urban areas (Table IV). Additionally, infants 12-17 months old and 18-23 months old were more likely to meet the complementary feeding indicators compared to infants 6-11 months old. Our results also showed that infants born at term were less likely to meet the complementary feeding indicator MDD compared to those born prematurely. Additionally, infants whose mothers identified themselves as Hungarian were less likely than their Romanian counterparts to achieve adequate MDD; this outcome was statistically marginally significant. In relation to this variable, mothers who identified themselves as Roma were less likely to meet the complementary feeding indicator MDD compared to those who identified themselves as Romanian.

This result can be attributed to the fact that in rural areas, children generally eat from adult food much earlier than in urban areas. Traditionally, rural mothers have the culture of accustoming the child to adult food as early as possible so that they can carry out household activities. Additionally, there are still many pediatricians who do not recommend the introduction of foods such as beans, lentils, green peas before 3 years of age, and mothers in urban areas are more likely to "benefit" from such recommendations.

- *MMF*

As seen in Table V, the results showed that infants with severe anemia were less likely to meet the complementary feeding indicator MMF compared to those without anemia. Additionally, infants 12-17 months old and 18-23 months old were less likely to meet the complementary feeding indicators compared to infants 6-11 months old.

Strengths and limitations

This cross-sectional survey utilized a national family physician database and stratified sampling across all eight macro-development regions of Romania to determine a large sample of children making the outcomes nationally representative. Although demographic factors may appear to have a causal relationship with children's nutritional patterns, the cross-sectional design of the present study does not allow such inferences to be made. Self-reporting bias could also be a factor that needs to be taken into consideration as a limitation of the study.

Conclusions

1. The present study provided detailed information on complementary feeding practices of infants aged 6-23 months in Romania. The assessment of infants' feeding practices based on the three indicators, MAD, MMF, MMD, provides for the first time in Romania information about the quality and quantity of food consumed by children after the first 6 months of life, at population level.

2. The results of the study showed that, overall, the prevalence of children who have an adequate complementary diet in terms of the three indicators exceeds 72%. However, there are also population groups that do not reach this prevalence.

3. Adequate complementary nutrition is generally achieved around the age of 1 year and less than 6-9 months, when the development needs of children already require animal foods rich in micronutrients.

4. Using these new indicators to measure infants' feeding practices allowed to more easily examine the influence of different social and demographic factors on adequate or inadequate dietary practices of children aged 6-23 months.

5. The results of this study are useful for developing policies to reduce health inequalities that affect vulnerable population groups.

Conflict of interests

The authors report no conflict of interest. The authors alone are responsible for the content and the writing of the paper.

Acknowledgments

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Exercises and physical procedures improve walking distance in peripheral artery disease - a randomized controlled trial

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Abstract

Background. Globally, in recent years the best methods have been sought for physical treatment, medication, revascularization in order to slow down or stop the progression of peripheral artery disease. Current treatment, along with the patient selection criteria are clearly standardized through treatment guidelines based on the results of many clinical trials.

Aims. The aim of this prospective, randomized, controlled clinical trial was to determine whether a rehabilitation program is more effective than usual care to improve ambulatory function in patients with peripheral arterial disease.

Methods. We randomized 111 patients into: the control group (which followed medication, hygienic and dietary recommendations), the exercise group, and the group with exercise and procedures. Patients were evaluated at baseline, after 12 weeks of rehabilitation and at the end of the study using the 6-minute walking distance.

Results. For both group 2 and group 3, the 6-minute walking distance values improved significantly as compared to control. We still registered after the first 12 weeks better values by 15% for the exercise group and by 18% for group 3. At the end of the study, the 6-minute walking distance values improved by 19% for the exercise group and by 22% for the group with exercises and procedures. No significant differences were found regarding the evolution of the 6-minute walking distance in females and males. The evolution of values under physical treatment is much less influenced by smoking.

Conclusions. Physical therapy is the object of more recent or older research through the great advantages it could offer in increased efficiency, low risks in relation to revascularization methods, high addressability, and lower costs.

Keywords: peripheral arterial disease, exercises, procedures, walking distance.

Introduction

While cardiovascular disease of atherosclerotic cause is the most common cause of death, chronic peripheral vascular disease, usually with a long evolution over time, is one of the most common causes of disability, thus with a negative impact on patient quality of life. Lower extremity peripheral artery disease (PAD) affects 8.5 million men and women in the United States and more than 200 million people worldwide (Benjamin et al., 2017). The number of patients with PAD is continuously increasing due to the aging population and the growing number of patients with diabetes (***, 2019).

Stage I of chronic peripheral artery disease is certainly the most favorable time to sustainably apply all means of therapy and secondary prophylaxis, but unfortunately this stage is less often found, and the patient is far from easily convinced of the future of his/her health. For this reason, stage II should not be missed either for complex assistance.

Adequate behavior of patients at home, in ordinary daily life, is more important for the evolution of the disease than most drug treatments.

Drug treatment and rehabilitation in peripheral artery disease are primarily aimed at the underlying disease and are indicated in patients whose ischemia does not threaten the integrity of the limbs, as it is not so severe as to affect their lifestyle or professional activity.

Only two medications, cilostazol and pentoxifylline, are Food and Drug Administration (FDA) approved for treating PAD-associated ischemic symptoms. However, benefits from cilostazol are modest and recent evidence suggests that pentoxifylline does not improve walking performance meaningfully more than placebo (McDermott, 2018). Cilostazol improves treadmill walking performance in people with PAD who have intermittent claudication symptoms by approximately

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25% to 40% (Gerhard-Herman et al., 2017).

The different means of kinetic physical therapy are the object of more recent or older research due to the great advantages they could offer: increased efficiency, low risks in relation to revascularization methods, high addressability, and lower costs (Treesak et al., 2004). By identifying the optimal exercise program to improve functional capacity, the results obtained will have substantial clinical and public health implications for millions of patients with PAD.

In 2012, a meta-analysis by Fakhry et al. summarized the results of 25 randomized clinical trials of supervised walking therapy in 1054 patients with PAD and claudication symptoms, and 15 (71%) reported between 50% and 99% improvement in maximal treadmill walking distance, while 5 (21%) reported more than 100% improvement in maximal treadmill walking distance in response to supervised walking exercise (Fakhry et al., 2012).

Gardner et al. randomized 180 participants with PAD and intermittent claudication to supervised treadmill exercise, home-based walking exercise and a control group that received light resistance training focused on the upper extremities, and demonstrated that walking exercise in a home setting significantly ameliorates the walking ability and improves the 6-min walk more than a supervised treadmill exercise program (Gardner et al., 2014).

Globally, in recent years, the best methods have been sought for physical treatment, medication, revascularization in order to slow down or stop the progression of PAD. Current treatments, along with the patient selection criteria are clearly standardized through treatment guidelines based on the results of many clinical trials. However, in Romania, the usual indication for physical therapy in patients with PAD is to walk a lot, without patients being focused at least on parameters such as intensity, duration, frequency, or without being called upon for check-ups, hence the very low compliance to this type of treatment (Pătru et al., 2020).

Hypothesis

The aim of this prospective, randomized, controlled clinical trial was to determine whether a rehabilitation program is more effective than regular medical care (medication, dietary measures) to improve outpatient function in patients with PAD and intermittent claudication.

Material and methods

The study was performed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice, and was approved by the Ethics Committee of the hospital. All patients provided a written informed consent.

Research protocol

a) Period and place of the research

We randomized 111 patients, 56 men and 55 women, diagnosed with PAD of the lower limbs and treated in the Physical Medicine and Rehabilitation Clinic of the Clinical Emergency County Hospital of Craiova, between February-December 2019.

b) Subjects and groups

The patients included in the study had to comply with the following inclusion criteria: diagnosis of PAD, with or without diabetes mellitus, positive Edinburgh Claudication Questionnaire, Fontaine stage IIa only (mild claudication, walking distance > 60 m), ambulatory without assistive devices, calf muscle claudication within 10 minutes of treadmill walking and calf muscle exercise. Exclusion criteria were: PAD secondary to Buerger's disease, autoimmune arteritis, fibromuscular dysplasia, chronic and repetitive occupational trauma, venous stasis, hypercoagulability disorder or arterial embolic disease, severe claudication, leg rest pain, skin ulceration, necrosis or gangrene, poorly controlled diabetes mellitus, poorly controlled hypertension, Raynaud's syndrome, exertional angina, dyspnea, fatigue or dizziness, severe coronary artery disease, congestive heart failure, exercise intolerance limited by leg pain of non-vascular origin, transmetatarsal or more proximal lower extremity amputation, unstable claudication symptoms, lower limb revascularization, major orthopedic or surgical interventions three months before the study inclusion, patient included in other current clinical studies, dementia.

Randomization was done into three groups in the order of inclusion. The control group, which throughout the study followed only the medication regimen along with hygienic and dietary recommendations (51 patients). To reduce adverse cardiovascular events associated with lower extremity PAD, our patients' treatment included modification or elimination of atherosclerotic risk factors such as: cigarette smoking, diabetes mellitus, dyslipidemia, hypertension and promotion of daily exercise and use of a non-atherogenic diet. The patients with dyslipidemia (36%) took lipid-lowering drugs (statins or fibric acid derivatives). Lifestyle interventions for PAD patients included smoking cessation, weight loss for obese patients, and intensive blood pressure and blood glucose control with antihypertensive drugs (17%) and diabetes therapies (28%). Some patients took antiplatelet therapy for reducing the risk of myocardial infarction, stroke, or vascular death, such as Aspirin 75-325 mg per day (23% patients) or Clopidogrel 75 mg per day (only 2%). Most patients took Pentoxifylline 400 mg TID (71%) and 46% patients took ginkgo biloba 120 mg per day. We encouraged proper foot care: daily foot inspection, skin cleansing, and topical moisturizing creams, urgently addressing skin lesions and ulcerations.

The exercise group (Ex group), which followed a supervised exercise programme for 12 weeks, then continued at home the exercise programme they had learnt for another 12 weeks (24 patients). The special kinesiotherapy program was easy to understand, easy to learn and especially easy to repeat at home, without requiring any special equipment. The training started with a 10-minute warm-up, consisting of exercises for mobility and respiration, followed by exercises of analytical gymnastics, Buerger gymnastics, exercises for increasing the cardiac flow and codified walking (15-60 minutes daily), ending with relaxation exercises (5-10 minutes). The exercises were chosen according to the location of the obliterations: exercises involving the muscles of the thigh and hip were chosen for upper obliterations, exercises involving the shank muscles were performed for middle obliterations (of femoral and popliteal arteries), and exercises involving the short muscles of the leg were preferred for distal obliterations. The number of exercise repetitions was established individually, according to the physical state of every patient, these being practiced up to the onset of moderate claudication, a moment followed by a short rest in orthostatic or sitting position, until the symptoms diminished. Initially, the sessions lasted for approx. 30 minutes and the training time gradually increased with every session up to approximately 60 minutes. The kinesiotherapy sessions took place 3 times a week.

The group with exercise and procedures (Ex +P group), which during the first 12 weeks, in addition to the supervised exercise programme also followed a predetermined set of procedures of electrotherapy, hydrotherapy, thermotherapy, massage, and afterwards, during the next 12 weeks they had to continue at home the exercise programme they had learnt (36 patients). We included different forms of currents for the reflex, remote, sympatholytic, vasodilator and collateral circulation promoting effect. For example, in this prospective, double-blind, multicenter, randomized, placebo-controlled trial, transcutaneous electrical nerve stimulation (TENS) significantly delayed pain onset and increased the pain-free walking distance in one hundred subjects with unilateral PAD Leriche-Fontaine stage II (Besnier et al., 2017). Thermotherapy procedures included heat applications on the reflex areas, abdominal, low back areas, also for the sympatholytic effect. Upward trophic massage was indicated, using techniques such as effleurage, kneading.

c) Applied tests

Peripheral artery disease is a highly prevalent disease that impairs the walking ability. Apart from the walking speed, another valuable parameter in assessing the severity of claudication and also in assessing the effects of applied therapies is the walking distance.

Walking tests, such as the 6-minute walking distance (6MWD) and the 4-meter walk test, are commonly used to assess exercise endurance and ambulatory function over a short distance, respectively (Xi et al., 2017). It is a parameter that is quite easy to measure primarily because it does not require any equipment, as it is simply the quantification of the distance that a subject can cover in 6 minutes. The relevance of the recorded values is very high, because claudication occurs during the 6 minutes in most patients with PAD and they stop walking until the pain goes away while the timer continues to run. Thus, in addition to the fact that 6MWD is an important functional quality of life parameter, we can say that its measurement also contains information about the duration of claudication.

Patients were evaluated at baseline, after 12 weeks of rehabilitation and at the end of the study, after 24 weeks.

d) Statistical processing

Statistical analysis was performed using SPSS 16.0 for Windows software. Descriptive statistics including frequencies and means and correlation analysis were conducted. The Student's t-test was used to compare our scores against published norms and between different patient groups. ANOVA and Post Hoc tests were applied to compare the course of walking distance between patient groups. A p-value < 0.05 was considered statistically significant.

Results

The clinical features upon study entry and the gait features were comparable in the three groups.

In our study, most patients were males (79.27%), the average age was 69 years, with the male/female ratio being about 3.8:1; an explanation for the fact that the male/female ratio was so different is the higher prevalence of PAD in men, as it clearly appears from the literature (Song et al., 2019; Srivaratharajah & Abramson, 2018).

The distribution by age groups shows that 82% of patients with PAD, who were covered by this study, were over 60 years old, thus confirming the literature data, which indicate the age of over 60-70 years as a potential risk factor in the development of peripheral ischemia (Fowkes et al., 2017).

Regarding the education level, the distribution of patients in the three groups was approximately uniform, with most of the subjects declaring that they had secondary/higher education, followed by patients with vocational school education. Patients who had completed only primary or secondary education were the fewest and there were no significant differences between the three groups.

For the patients enrolled in the study, we obtained an average body mass index (BMI) value of 27.16 (SD = 5.2), an average that is within the ideal weight limits, but towards the upper value of these limits.

The determination of the ankle-brachial index (ABI) in the patients from the studied group allowed the calculation of an average of 0.655 (SD = 0.094), with a minimum value of 0.469 and a maximum value of 0.827. Practically equal mean and median values show a quasi-asymmetric distribution of values.

In all three groups, the mean blood pressure, both systolic and diastolic, was normal, all patients enrolled in the study were balanced in cardiovascular terms, with hypertensive subjects taking the hypotensive treatment prescribed by the cardiologist prior to the study.

The first place among the diseases most frequently associated with PAD patients was occupied in all three groups by cardiovascular and cerebrovascular diseases, including a history of myocardial infarction, heart failure, stroke, coronary heart disease, with spinal and peripheral osteoarthritis coming second in terms of comorbidity.

To identify the associated risk factors in the patients enrolled in the study, diabetes mellitus was most common, 35% in the control group, 30.4% in the exercise group and to a lesser extent, 28%, in the exercise and procedure group.

The initial features differed significantly in the group of smokers compared to non-smokers; for example, the average age of smokers was more than 2 years lower than the average age of non-smokers, the onset of claudication symptoms occurred earlier in smokers, the average ABI was 16 percent lower compared to non-smokers.

The anamnesis conducted in patients upon inclusion in the study resulted in an average duration of 4 years elapsed since the onset of claudication, with the average values of this duration in the three groups being all close to this value.

The dynamics of the values under treatment with the increase of the walking distance and even with cases recorded in which claudication did not occur during the 6 minutes were an important motivator for patients and we could see that they proved a much better compliance when measuring the walking distance compared to the walking speed. How the 6MWD values changed in the exercise group and in the exercise and other physical procedures group is shown in the following table as compared to the control group (Table I).

Table I

6MWD values per groups.

Group		N	Min	Max	Mean	SD
Control	6MWD1	51	180	250	217.55	19.431
	6MWD2	51	181	250	214.90	18.241
	6MWD3	51	188	250	224.08	19.164
	Valid N (listwise)	51				
Exercises	6MWD1	24	181	247	210.67	23.070
	6MWD2	24	225	290	253.54	20.828
	6MWD3	24	260	298	278.38	11.620
	Valid N (listwise)	24				
Exercises Procedures	6MWD1	36	180	249	215.33	20.063
	6MWD2	36	227	298	260.86	20.993
	6MWD3	36	265	315	288.94	14.491
	Valid N (listwise)	36				

As can be seen, for both group 2 and group 3, 6MWD values improved significantly compared to group 1, the control group. We still registered after the first 12 weeks higher values by 15% for the exercise group and by 18% for the exercise and procedure group. At the end of the study, after 24 weeks, 6MWD values improved by 19% for the exercise group and by 22% for the exercise and procedure group.

The following chart shows the evolution of the average 6MWD values in the three groups (Fig. 1).

Unlike the control group, in the exercise group and the exercise and procedure group, we recorded a better grouping of the values around the average at both 12 and 24 weeks.

The following chart shows the values obtained for the separate walking distance for the two genders in the three groups; no significant differences were found regarding the evolution of 6MWD in females and males (Figs. 2 and 3).

When analyzing the 6MWD parameter in smokers and non-smokers, we obtained the average values shown in the following table (Table II).

Table II

6MWD – Smoking.

Group	Smokers		N	Min	Max	Mean	SD
Control	no	6MWD1	22	180	250	216.18	18.259
		6MWD2	22	182	250	216.14	18.602
		6MWD3	22	189	250	224.95	18.464
		Valid N (listwise)	22				
	yes	6MWD1	29	181	250	218.59	20.533
		6MWD2	29	181	246	213.97	18.236
		6MWD3	29	188	250	223.41	19.978
		Valid N (listwise)	29				
Exercises	no	6MWD1	7	198	247	226.14	21.737
		6MWD2	7	249	290	266.86	17.043
		6MWD3	7	276	298	287.43	8.923
		Valid N (listwise)	7				
	yes	6MWD1	17	181	242	204.29	20.975
		6MWD2	17	225	288	248.06	20.129
		6MWD3	17	260	297	274.65	10.659
		Valid N (listwise)	17				
Exercises Procedures	no	6MWD1	14	194	246	221.36	17.394
		6MWD2	14	240	297	267.93	20.243
		6MWD3	14	271	313	292.21	13.360
		Valid N (listwise)	14				
	yes	6MWD1	22	180	249	211.50	21.071
		6MWD2	22	227	298	256.36	20.546
		6MWD3	22	265	315	286.86	15.094
		Valid N (listwise)	22				

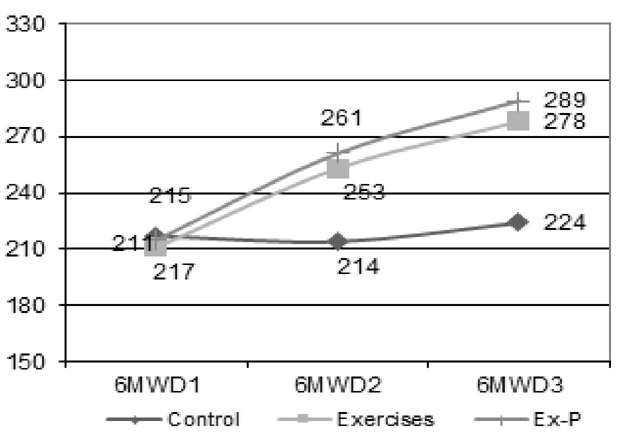

Fig. 1 – The evolution of average 6MWD values in the three groups.

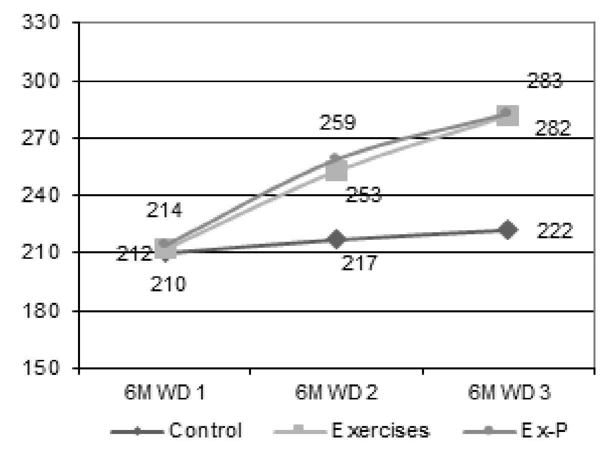

Fig. 2 – 6MWD-Females.

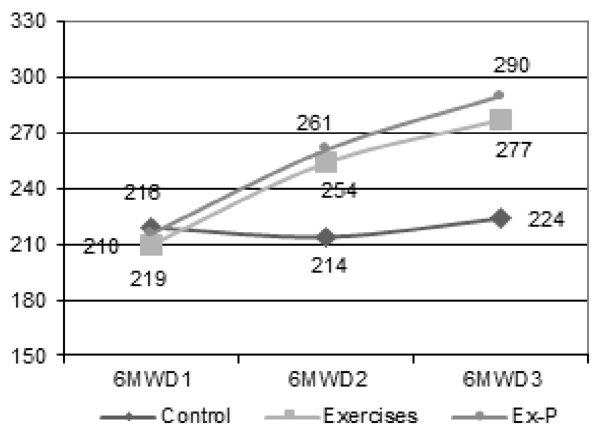

Fig. 3 – 6MWD-Males.

For the walking distance, we found that the evolution of values under physical treatment was much less influenced by smoking. Moreover, from the first determination of this parameter the values were about the same, and although they increased significantly at 12 and 24 weeks as can be seen in the following chart, the differences between smokers and non-smokers were statistically insignificant (Figs. 4 and 5).

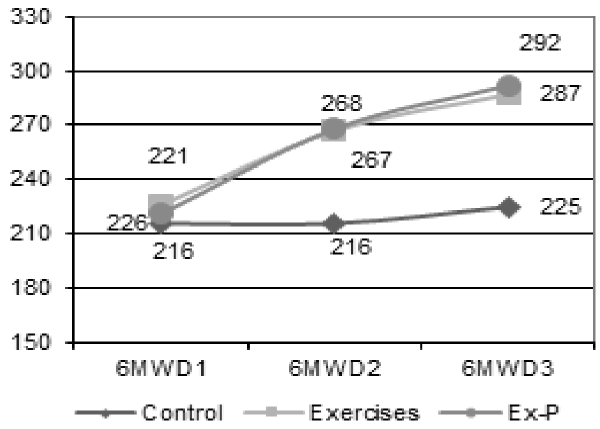

Fig. 4 – Non-smokers.

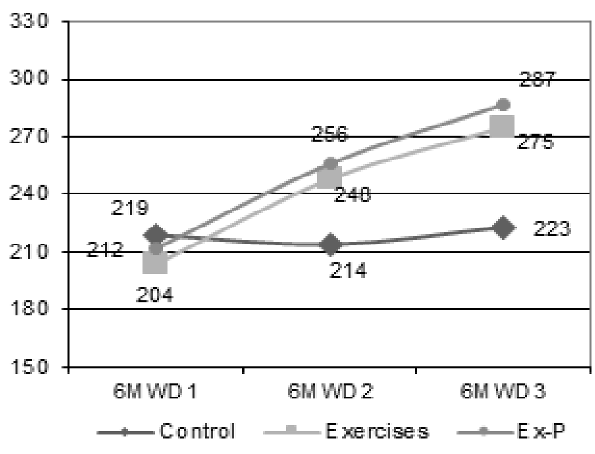

Fig. 5 – Smokers.

An interesting fact found in connection with the walking distance is its correlation with patients' age (Table III). Thus, a high correlation was noted for all three groups ever since the enrolment in the study, a correlation that increased more at the end of the 24 weeks for patients in groups 2 and 3 compared to those in the control group.

Table III
Age correlation.

Group	R	R Square	Adjusted R Square	Std. Error of the Estimate
Control	0.943[a]	0.888	0.886	6.469
Exercises	0.956[a]	0.913	0.909	3.499
Exercises Procedures	0.967[a]	0.935	0.933	3.739

a. Predictors: (Constant), age
Dependent Variable: 6MWD3

In patients with PAD, the same relationship between age and the ability to walk as that generally found in the population after a certain age was detected.

Discussions

In the presence of an atherothrombotic disease in one vascular bed (e.g., PAD), patients are at high risk of cardiovascular morbidity and mortality in other vascular beds (Cho et al., 2015; Steg et al., 2007). Regardless of the type, diabetes mellitus is associated with an increased risk of peripheral atherosclerosis. A systematic review of risk factors for PAD from 34 trials conducted since 1997 estimated the pooled relative risk of PAD due to diabetes mellitus with an odds ratio of 1.88 (95% CI: 1.66–2.14) (Fowkes et al., 2013). Diabetes increases the probability of distal disease in PAD and coronary artery disease (CAD), multi-vessel disease, which more frequently results in the need for coronary and/or peripheral bypass surgery compared to patients without diabetes (Ryden et al., 2014). Smoking is at present the most important risk factor for PAD. The corresponding amount of exposure (number of pack years) is associated with the severity of PAD, a higher amputation rate, peripheral prosthetic bypass occlusion and mortality (Willigendael et al., 2004).

The results obtained in our clinical study from the statistical analysis of the parameters were compared with the results of literature studies.

In a very recent clinical study from 2020, the outcome of multimodal supervised exercise training on walking performances and different hemodynamic parameters was evaluated in eighty-five patients with symptomatic lower extremity peripheral artery disease. Following a 3-month exercise program, 6MWD significantly increased (+14%; $P \leq .001$) (Calanca et al., 2020).

Recently, evidence has suggested that heated-water exercise therapy (HWET) is an effective intervention for PAD. PAD patients (n = 53) were recruited and randomly assigned to a land-based exercise training (LBET) group (n = 25) which performed treadmill walking, or a HWET group (n = 28) which performed walking in heated water for 12 weeks. Both groups had significantly increased 6MWD ($P < 0.05$) (Park et al., 2020).

In 2019, the American Journal of Physiology published the results of a 12-week randomized controlled trial of heat therapy vs. supervised exercise therapy for peripheral arterial disease. Following the interventions, the total walking distance during the 6-min walk test increased (from 350 m) by 41 m (95% CI: [13, 69], P = 0.006) regardless of the group, and the pain-free walking distance increased (from 170 m) by 43 m ([22, 63], P < 0.001) (Akerman et al., 2019).

A systematic review and meta-analysis including randomized controlled trials of exercise training versus usual medical care in persons with PAD concluded that exercise training produced significant 6-minute walk initial claudication improvements with mean difference (MD) 52.7 m (95% CI 24.7-80.6 m; p = 0.0002); total walking distance MD 34.9 m (95% CI 25.6-44.1 m; p < 0.00001) (Parmenter et al., 2015).

Conclusions

1. Physical exercise therapy is an important landmark in the medical treatment of intermittent claudication, through the regularity and not the intensity of exercises, a better use of energy resources in the muscles of the lower limbs, and it is a factor that contributes to slowing the evolution of claudication by increasing walking distance.
2. The beneficial effects of exercise and physical procedures on locomotion can be explained by various mechanisms, with improvements in gait economy and calf muscle perfusion being two of the mechanisms that act synergistically to improve claudication, decreasing metabolic demands and increasing oxygen supply.
3. All patients with PAD and intermittent claudication, who can perform an exercise program in complete clinical, cardiorespiratory and orthopedic conditions should be considered candidates for recovery with kinetic and physical means.
4. There were no complications during the physical therapy sessions or procedures and no complications in the control group, which could have been a consequence of enrolment in this study.

Conflict of interests

The authors declare that they have no conflict of interests.

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REVIEWS

Redox homeostasis and physical activity

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Abstract

Physical activity/exercise is a non-pharmacological treatment with a sanogenetic, antiaging and therapeutic role, depending on exercise intensity, duration, frequency and type.

Physical activity/exercise determines biochemical changes in the redox homeostasis of the O/AO balance: either generation of OS in acute exhausting exercise, high intensity and endurance exercise, and overtraining syndrome, or decreased OS and AOC generation in appropriate exercise during moderate training.

Controlling the oxidant/antioxidant balance during physical exercise through proper training and nutritional and non-nutritional supplementation of antioxidants can help reduce oxidative stress and increase performance.

Keywords: oxynitrosative stress, redox homeostasis, physical activity.

Physical inactivity

Physical inactivity is considered sedentariness, while sedentary people are those who have difficulties to leave their home, who do not exercise outside, whose professional activities are static and who perform minimal physical activity in general.

Physical inactivity has negative consequences, even anti-sanogenetic effects of causing or aggravating certain conditions (Lee et al., 2012; Cai et al., 2019; Moreira et al., 2014; Alberti et al., 2009; Lessiani et al., 2016):

- cardiovascular diseases (hypertension, coronary diseases, varices of the lower limbs, arteriosclerosis)
- respiratory diseases (chronic pulmonary diseases, infections of the airways)
- various digestive diseases, hemorrhoids, irritable bowel syndrome, colorectal cancer
- osteomuscular diseases, static disorders of the spine, arthroses, sarcopenia
- obesity, type 2 diabetes, metabolic syndrome
- psychic diseases (depression, anxiety)
- increase in the population risk of morbidity and mortality

Physical activity / Physical exercise

Automation, mechanization and robotisation of the contemporary society have led to a gradual decrease in physical activity, alongside the professional stress of underload and overload. In industrialized countries, more than 60% of the population do not engage in sufficient physical exercise.

WHO recommends 150 minutes of moderate intensity physical exercise a week.

Physical exercise represents a complex strain of the body from a physiological (neuromuscular, cardiorespiratory, endocrine metabolic), immunological, psycho-emotional and biochemical point of view. Correctly carried out, moderate intensity physical effort, either continuous or intermittent, has beneficial effects on the body: preventive sanogenetic role, curative and recovery role, pro-longevity role and active longevity role, as well as therapeutic role.

a) The sanogenetic role, of maintaining the health of the body, is achieved through (Joseph et al., 2016; Simioni at al., 2018; Sallam & Laher, 2016; Rezende Freitas et al., 2017; Daimiel et al., 2020; Dumitru, 1997):

- cardiovascular mechanisms, reducing the risk of cardiac diseases (ischemic cardiopathy), cerebrovascular accident, hypertension, increase of the good cholesterol (HDL)
- endocrine mechanisms of reducing increased hormone release (growth hormone, glucagon, testosterone, adrenaline)

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- digestive mechanisms (appetite control, improving digestion)
- respiratory mechanisms (reducing the decline of pulmonary activity, improving tissue oxygenation)
- maintaining the health of the myo-arthro-kinetic system (muscle mass and strength, joint mobility, right posture, minimizing the risk of osteoporosis and fractures)
- protection effect against breast cancer or colorectal cancer
- body weight control, through reducing the overall fat mass and obesity prevention
- reducing the occurence of infections and improving immunity
- maintaining and improving cognitive psychic functions (memory, attention, creativity, intellectual performance)
- metabolic mechanisms (reducing the glycemia level and increasing glucose use, prevention of diabetes, increasing lipid use and prevention of arteriosclerosis).

Other effects of physical exercise include:

- improvement of sleep
- body detoxification through sweating
- reducing the risk of premature birth and death by cardiovascular diseases
- prevention of sedentary behavior
- harmonious physical development.

b) The pro-longevity and active longevity role consists of:

- prolonging life expectancy and increasing survival through performing physical exercise and maintenance sports (30-40 minutes of jogging per day can delay aging by up to 9 years)
- reduction of the mortality rate.

c) The therapeutic role of physical activity consists of:

- increase in immunity
- normalization of glycemia
- stimulation of antioxidant defense mechanisms
- post-traumatic physical therapy and physical therapy of locomotor diseases
- treatment of cardiovascular diseases, coronary diseases and hypertension, as well as respiratory diseases by physical therapy
- treatment of psychic diseases (depression, schizophrenia, anxiety)
- improving psychosocial behavior

Oxidative stress

Oxygen (O_2) consumption in aerobic organisms leads to the formation of reactive O_2 species (ROS) or O_2 metabolites or catabolites, which according to Halliwel (2007) can be:

- radical species:
  - inorganic: superoxide (hyperoxide) – $O_2^{\bullet -}$; hydroxyl – $OH^{\bullet}$; hydroxyl radical – $RO^{\bullet}$;
  - organic: alkoxyl – RO; hydroperoxyl – $HO_2^{\bullet}$;
- non-radical species: perhydrol or oxygenated water – H_2O_2; hypochlorous acid – HOCl; singlet oxygen or molecular oxygen in activated state – $1O_2\,\Delta g$; ozone – O_3; dioxygen O_2.

ROS formation is tightly connected to the formation of reactive nitrogen species (RNS), while either antagonistic or synergistic relationships occur between them. RNS can be:

- radical species: nitrogen monoxide or nitric oxide – NO; nitrogen dioxide – NO_2; nitronium ion – NO_2^-;
- non-radical species: nitrous acid – HNO_2; peroxynitrous acid – ONOOH or HNO_3; dinitrogen trioxide – N_2O_3; dinitrogen tetraoxide – N_2O_4; nitronium ion – NO_2^+; alkyl-peroxynitrate – ROONO; nitroxyl – HNO; nitrite anions - NO_2^- and nitrate NO_3^-.

The interaction of oxygen-dependent processes with ROS and RNS is involved in:

- acute inflammatory response and phagocytosis
- anticoagulant, antifibrinolytic action
- procoagulant, antifibrinolytic, prothrombotic proaction.

At cellular level, as well as at the level of the entire organism, ROS determines a series of paradoxical effects, which can be either harmful or beneficial.

a) Harmful effects of ROS occur in the case of production of large quantities and lead to the destruction/deterioration of cellular structures, to malignant transformation, abnormal cell proliferation, cytotoxic cell aging, cell death (apoptosis). Major harmful prooxidant effects of ROS with OS production are due to the oxidative attack on nucleic acids, proteins, lipids and carbohydrates:

- DNA lesions, referring to thymine, cytosine, adenine, guanine and deoxyribose, followed by cellular injuries and mutations
- modifications of proteins and glycoproteins
- alterations of membrane proteins and transport disturbances through the membrane
- modification of enzyme activity and lipid metabolism
- lipid peroxidation, modifications of the structure and function of membranes
- carbohydrate damage, effects which can lead to apoptosis and necrosis (Evans et al., 2004; Bullone & Lavoie, 2017).

Oxidative stress (OS) was described as the total oxidative lesions caused by O&NS or, in terms of accumulation, modification and depletion:

- accumulation – refers to lipofuscin, lipoprotein pigments from the brain and myocardium
- modification – refers to nucleic acids, glycoproteins, proteins and lipids
- depletion – refers to the loss or reduction of the enzyme activity (Beckman & Ames, 1998).

Major intracellular sources of OS are: the mitochondrial transport chain, polymorphonuclears and xanthine oxidases (Sessa et al., 2020).

b) Beneficial effects of ROS occur in the case of production of small quantities:

- anti-infective defense through bactericidal activity in the course of phagocytosis and stimulation of the activation of lymphocytes
- control of normal vascular tone
- modification of the hydrosolubility of certain substances
- stimulation of cell growth, proliferation and transformation
- cellular signaling and regulation of gene expression
- stimulation of erythropoietin secretion

- learning and memory (Janssen et al., 1993; Ivanov et al., 2016; Faienza et al., 2020).

Normal aerobic life is constantly subject to an attack from ROS-RNS, which take part in oxidative and nitrosative stress (O&NS). The sources of ROS-RNS can be:

- endogenous, intracellular – mitochondria, microsomes, endoplasmic reticulum in neutrophils, eosinophils, monocytes, endothelial cells, myocytes
- exogenous – redox substances, UVR/IR radiation, pollution, lifestyle (for example physical activity and diet), alcohol and smoking (Riga & Riga, 2007; Rytz et al., 2020).

Antioxidant capacity of the body (AOC)

Aerobic life is characterized by the balance between ROS and the capacity of the antioxidant systems (AOS), both at cell level and at the entire body level, to counterattack ROS actions. AOS comprise all antioxidants (AO) that operate within the intracellular and extracellular compartment.

The body developed its own AOS, which can be classified according to different criteria as follows (Olinescu, 1994; Halliwell, 1990; Bonorden & Pariza, 1994):

- according to the moment of intervention:
  - primary, preventive, classical or true AO, which operate from the initiation stage of ROS, forming: thiols, sulfides, catalase, peroxidase, transferase, diaphorase, SOD, urate, ascorbate, isomers of the linoleic acid, chelating agents (peptides)
  - secondary AO, which fragment the oxidation chain: α-tocopherol, β-carotene
- according to the place where they operate:
  - intracellular AO in the membrane, cytoplasm and nucleus: vitamin E, β-carotene, vitamin C, GSH, CuZnSOD, GSH-Px, GSH-S-T, ferritin, metallothionein, carnosine, anserine, CAT
  - extracellular AO: CuZnSOD, transferrin, lactoferrin, haptoglobin, hemopexin, ceruloplasmin, albumin, vitamin C, uric acid, bilirubin, vitamin E
- according to the operating mechanism:
  - enzymatic AO: the SOD family (CuZnSOD, CuSOD), CAT, the glutathione redox cycle (GSH-Px, GSH-S-T, GSH-r, G-6-PDH)
  - non-enzymatic AO: GSH, vitamin E, vitamin C, carotenes and vitamin A, Se, uric acid, bilirubin, albumin, estrogens, metallothionein, polyamines, saturated fatty acids, quinones
- according to solubility:
  - hydrosoluble AO: vitamin C, uric acid, glucose, cysteine, GSH, Se, histidine, taurine, metal chelating proteins, heme fixation proteins
  - liposoluble AO: vitamin E, β-carotene, bilirubin, estrone, estradiol.

The antioxidant systems of the body comprise all AO and they control physiological processes, as well as prooxidant pathological systems.

The research of Olinescu et al. (1994) pointed out that the total AO status of the body shows variations according to gender, age and blood type. Cellular redox homeostasis is maintained and OS is prevented through:

- genetic control of the AO: CAT, SOD, NOS
- vitamin control through vitamins C and E
- myokine intervention.

Genetic control is achieved by nuclear factor-kappa B (NF-kappa B) and mitogen-activated protein kinase (MAPK), which are the signal transduction pathways in ONS, activating the genetic expression of a number of enzymes in O/AO homeostasis: MnSOD, NOSi and NOSe (Ji, 2008).

Vitamin C (ascorbic acid) is a hydrosoluble AO, present in intra- and extracellular fluids (plasma, synovial fluid, CSF), with multiple AO properties: direct scrubber for $^1O_2$, $O_2^{\bullet -}$, $OH^{\bullet}$; neutralizes the oxidants set free by neutrophils; helps regenerate vitamin E, a liposoluble AO; reduces the α-tocopheroxyl radical to α-tocopherol, has a synergistic action compared to vitamin E (α-tocopherol); reduces nitroxide radicals. When in excess it can have a prooxidant effect by Fe^{3+} in Fe^{2+}.

Myokines are cytokines produced in the scheletal muscles during physical effort, influencing the formation of ROS, RNS and AOC. The myokine family comprises: brain-derived neurotrophic factor (BDNF), cathepsin B, decorin, growth factors of the fibroblasts-2 and 21, follistatin and follistatin-like, growth factor insulin-like-1, interleukins 6, 7 and 15, irisin, leukemia inhibitory factor, meteorin-like, myonectin, musclin, myostatin and osteoglycin (Szabó et al., 2020; Ost et al., 2016).

Effort/exercise capacity

Exercise capacity is the ability of the active muscle system to release the energy required for mechanical work, in the highest possible amount and for as long as possible. Physical exercise is supported via two metabolic pathways: anaerobic and aerobic, the latter being 50 times more efficient than the former one. Predominantly aerobic exercises are characterized by:

- low, medium or submaximal intensity
- real or apparent balance between O_2 demand and intake
- duration of more than 3 minutes, up to a few hours (i.e. 2-3 hours), depending on intensity, maximum VO_2 used
- mechanical efficiency 23-26%
- energy source: 30% carbohydrates during endurance exercise; 70% lipids
- final catabolites from univalent reduction of O_2: ROS.

Aerobic training determines:

- central adaptive changes, which affect the cardiorespiratory activity (heart rate, beat volume, O_2 extraction and uptake, muscle blood flow and muscle metabolism)
- peripheral adaptive changes at the muscle level: number and size of mitochondria, capillary density, myoglobin content, oxidative enzyme activity (Tache & Staicu, 2010).

Skeletal muscles, which are the active organs of the locomotor system, are characterized by very large changes in O_2 metabolism at rest and in exertion, which can be considered normal; no other tissue in the body has such characteristics. During physical exercise, blood flow was found to increase by about 10-20 times, with hyperemia limits between 10-50 times, depending on exercise intensity and the type of muscle fibers; the O_2 influx in sarcosomes increased by about 100-200 and the O_2 arteriovenous difference increased by 3-4 times.

The increased O_2 consumption is determined by: particularities of the practiced exercise such as intensity, strength, endurance; aerobic, anaerobic or mixed nature; duration and speed of exercise; active muscle mass; body position; active and/or static components. In addition to these factors, the environmental circumstances in which exercise is carried out, such as atmospheric pressure, hypoxia, temperature, humidity, noise and adaptive or non-adaptive processes (training, acclimatization, fatigue, overtraining, emotions, etc.), also contribute to stress in sports, in its forms of eustress or distress (Tache et al., 2009).

Redox homeostasis during physical exercise

ROS and RNS production in muscle takes place continuously at a low level and increases during muscle activity. ROSs and RNSs have multiple direct and indirect effects on contractility, excitability, metabolism and calcium homeostasis.

a) Endogenous sources of ROSs and RNSs

Endogenous sources generating reactive species in the body can be: electron transport chains in mitochondria and microsomes; autoxidation reactions (ferrous ions, adrenaline); oxidative enzymes (oxidases - xanthine oxidase, galactosidase, monoamine oxidase, nitric oxide synthase - NOS, NADPH oxidase; oxygenases - tryptophan dioxygenase, indolamine dioxygenase, cyclooxygenase, lipoxygenase); blood phagocytic cells (neutrophils, eosinophils, monocytes, macrophages) and vascular (endothelial) cells (Riga & Riga, 2007).

The intracellular sources of ROS generation in striated muscle fiber are:

- sarcolemma (membrane), with the help of the NADPH-oxidase enzyme
- sarcosomes (mitochondria) (2-5%), with the participation of phospholipase A_2 (PLA_2) and the electron transfer respiratory chain, especially in stage 4
- microsomes (sarcoplasmic reticulum) in the electron transport chain
- sarcoplasm, with the help of oxidative enzymes (oxidases and oxygenases)
- interconversion of RNSs to ROSs
- transsarcolemmal diffusion of extracellular ROSs.

The major intracellular source of ROSs and RNSs is considered to be sarcosomes. NO in turn modulates the production of ROSs in sarcosomes, and the effects are reversible in the presence of oxymyoglobin (Sarkela et al., 2001; Di Meo & Venditti, 2001).

The extracellular sources of ROSs at the musculoskeletal level are the transsarcolemmal efflux of intracellularly formed ROSs and the extracellular interconversion of RNSs to ROSs. The extracellular sources of RNSs at the musculoskeletal level are: transsarcolemmal efflux of RNSs formed intracellularly with the help of eNOS, subsarcolemmal nNOS, and extracellular interconversion of ROSs to RNSs (Murrant & Reid, 2001).

Oxidative stress (OS) and nitrosative stress (NS) are generated by excess production of ROSs and RNSs. OS and NS are caused by divergent disruption: demands/ resources, i.e. by the double imbalance between the increasing oxidizing aggression and the decreasing AO defense (Riga & Riga, 2007).

The term currently in use is oxynitrosative stress (ONS). The evaluation of ONS at the biological level, which is a process involved in the etiopathogenesis of over 100 human and animal diseases, is carried out in two opposite directions:

- measurement of aggressor factors (O_2 and N_2 catabolites or ROSs and RNSs) and their effects
- quantification of the body's AO defense and prooxidant enzyme activity.

ONS includes all oxidative chain damage caused by ROSs and RNSs in biological molecules of proteins, carbohydrates, DNA and lipids: oxidation, peroxidation, autoxidation, cooxidation. O_2 activation - a process which is considered to be fundamental and characteristic of the living world - generates mainly free radicals (FR) of O_2: singlet oxygen and free radicals - superoxide, perhydroxyl and hydroxyl. FRs are molecules or molecular fragments that contain an odd electron, have the property of being highly reactive and cause OS and NS (under conditions of imbalance with AO factors). They are themselves the main amplifying factor in the generation of "oxidative lesions": peroxides, hyperoxides, endoperoxides and epoxides, in addition to a new amplification resulting from balance disruption: excess of oxidants, doubled by AO deficiency (Riga & Riga, 2007).

ROS and RNS generation occurs in: muscle vascular endothelial cells (Mitchell & Tyml, 1996), vascular smooth muscle fibers (Charpie & Webb, 1993), inflamed joint cells, motor neurons, astrocytes, neutrophil leukocytes and lymphocytes (Suzuki & Machida, 1996), and red blood cells (Slater, 1987; Murell et al., 1990).

b) Effects of ROSs and RNSs

The direct effects of ROSs and RNSs on skeletal muscles involve the modulation of normal contractile processes, by alteration of the excitation-contraction coupling; decreased muscle metabolism and, indirectly, decreased contractility; influencing cellular redox status, which may frequently precede OS and NS (Kehrer & Lund, 1994; Li et al., 2003).

Other effects are: mediation of intercellular interactions, control of vascular tone and blood flow in large and small vessels of resistance ($NO^{\bullet}$ and $OH^{\bullet}$ - vasoconstriction/ vasodilation and hyperemia) (Prior et al, 2003); neuromuscular transmission; fusion of myoblasts; satellite cell activation; invasion of neutrophils, depolarization of related nerve endings (Murrant & Reid, 2001).

NS is associated with OS and causes damage or destruction of lipids, proteins and nucleic acids; decreased physical performance, muscle fatigue, muscle injuries and overtraining (König et al., 2001).

c) AO defense during physical exercise

ROS generation has a dual effect: it causes OS and oxidative damage, and it stimulates adaptive responses for long-term AO protection and increased resistance to OS.

AO defense, effort-induced OS limitation and increased tolerance to effort-induced OS are the result of repeated moderate aerobic physical exercise, long low-intensity training, and detraining.

The AO defense mechanism at muscle level is supposed to be based on the hyperregulation of AO defense systems in muscle. Regular moderate physical exercise reduces OS. Moderate OS may produce a hormesis effect in non-muscular tissues, thus representing a beneficial mechanism of physical exercise by hyperregulating various AO mechanisms, including AO enzymes and degraded molecular repair enzymes (Goto et al., 2007; Radak et al., 2008).

ROSs play the role of signaling molecules that modulate both the contractile function in tired and non-tired skeletal muscles and the gene expression via redox-sensitive transcription pathways, which is an important mechanism in the adaptation to training and AO defense processes. In this context, the adaptation of endogenous AO systems to regular training reflects a potential mechanism for increasing the tolerance of skeletal muscles to exercise-induced OS (Niess & Simon, 2007).

Changes in redox homeostasis during exercise depend on physical exercise frequency, duration, intensity, and type. Such changes consist of homeostasis alteration and homeostasis regulation. Some authors have recommended a practical investigation of the level of prooxidants-antioxidants and their ratio (PO/AO) or the Loverro coefficient in order to determine the OS risk (level of lipid peroxidation products/SOD, CAT and erythrocyte GSHPx) (Zembron-Lacny et al., 2008). The PO/AO ratio is influenced by factors + processes + mechanisms / resources + protection + defense (Riga & Riga, 2007).

Redox homeostasis alteration consists of the generation of ONS in acute exhausting exercise, endurance training and high intensity training, or overtraining syndrome (Kruk et al., 2019; Sessa et al., 2020; Navarro-Ibarra et al., 2019; Neves et al., 2018; Thirupathi & Pinho, 2018; Powers et al., 2020).

ONS caused by intense physical exercise induces an increase of oxidative indicators in serum and muscle (peroxidated lipids, expired ethane, MDA, F2-isoprostanes, conjugated dienes, 8-hydroxy-2 deoxyguanosine), which recommends AO supplementation (Urso & Clarkson, 2003).

Redox homeostasis regulation occurs in moderate, regular exercise, in long low-intensity training, in combined physical exercise (aerobic + strength training) and in fractional training (Tromm et al., 2016).

Adaptive changes consist of:

- lower ONS (limitation of ROS and RNS generation)
- increased AO defense capacity (Kruk et al., 2019; Alikhani & Sheikholeslami-Vatani, 2019; Lamarão-Vieira et al., 2019; Thirupathi et al., 2020; Radak et al., 2005; Lee et al., 2017; Mota et al., 2019; Rytz et al., 2020)
- lower prooxidant parameters (de Sousa et al., 2017)
- increased activity of AO enzymes (Tromm et al., 2016).

Training causes similar changes in young people and the elderly (Alikhani & Sheikholeslami-Vatani, 2019), and also gender-dependent changes (Rytz et al., 2020).

ROS generation in moderate exercise and low-intensity training plays a role in:

- induction of AO defense, DNA repair and antioxidant enzyme repair (Angulo et al., 2020) and adaptation to exercise (Elejade et al., 2021; Ismaeel et al., 2019; Angulo et al., 2020)
- redox intracellular signaling, acting as a signaling molecule (Ismaeel et al., 2019; Thirupathi & Pinho, 2018)
- hyperrelation of AO gene expression involved in redox homeostasis (Ji et al., 2007).

Muscular AO defense systems are hyper-regulated during exercise. Nuclear factor-kappaB (NF- kappaB) and mitogen-activated protein kinase (MAPK) are the signal transduction pathways in OS, which activate the gene expression of a number of enzymes and proteins that play an important role in maintaining intracellular O/AO homeostasis; this idea is supported by numerous recent studies (Ji, 2007; Ji, 2008). NF-KappaB and MAPK intervene in skeletal muscles in the changes occurring in gene expression hyperregulation of enzymes involved in O/AO homeostasis: MnSOD and iNOS and eNOS in mitochondria (Ji et al., 2007). MAPK and NF-kappaB are the two major regulators of gene transcription and metabolism in response to oxidative, energetic and mechanical stress in skeletal muscles. The activation of these factors is stimulated by exercise (Kramer & Goodyear, 2007).

Conclusions

1. Physical activity/exercise is a non-pharmacological treatment with a sanogenetic, antiaging and therapeutic role, depending on exercise intensity, duration, frequency and type.
2. Physical activity/exercise determines biochemical changes in the redox homeostasis of the O/AO balance: either generation of OS in acute exhausting exercise, high intensity and endurance exercise, and overtraining syndrome, or decreased OS and AOC generation in appropriate exercise during moderate training.
3. Controlling the oxidant/antioxidant balance during physical exercise through proper training and nutritional and non-nutritional supplementation of antioxidants can help reduce oxidative stress and increase performance.
4. Anti-stress measures taken during physical exercise aim to overcome the stress caused by physical exercise, reduce systemic physiological stress, reduce oxidative stress, overcome and reduce psycho-emotional stress. Controlling and overcoming the stress caused by physical exercise can contribute to athletic success.

Conflicts of interests

The authors declare no conflict of interest.

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Could antioxidants play an important role in the prevention and treatment of COVID-19 infection?

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Abstract
COVID-19 is a global public health problem for which no specific treatment has yet been discovered. Prevention recommendations issued by officials such as strict hand hygiene, wearing a mask, social distancing should also include recommendations for a diet rich in antioxidants and regular exercise, measures meant to increase the body's resistance to this new virus. Excessive reactive oxygen species play an important role in acute respiratory failure or multiple organ dysfunction syndrome, complications often encountered in severe forms of COVID-19 infection. It is thus very important to maintain the redox balance and prevent cellular damage. Vitamins such as vitamin D, C, A and E, minerals such as magnesium, zinc, copper, enzymes such as superoxide dismutase, hormones such as melatonin and multiple polyphenols and phytotherapeutics are known in literature for their antioxidant, anti-inflammatory and immunomodulatory effects. Vitamin C, zinc, Sambucus nigra extract and others are also known for their direct antiviral effects which prevent viral cell adhesion and replication, including viruses from the Corona family. There are many studies that indicate a beneficial effect of the antioxidants listed above. We believe they should be used more for prevention, but also for treating viral infections as they have been shown to shorten disease duration, lower tissue damage due to inflammation and also protect against the possible side effects of pharmaceutical medication.
Keywords: corona viruses, COVID-19 disease, antioxidants, antiviral, anti-inflammatory, immunomodulation, vitamins, minerals, polyphenols, phytotherapy, exercise, diet.

Introduction

Coronaviruses contain various proteins in their structure, such as surface proteins (so-called spike proteins), coating proteins, membrane proteins and nucleocapsids. Many cell membranes of the oral mucosa, alveolar mucosa, upper esophagus and intestine, and also the vascular endothelium have on the surface a receptor for viral S glycoprotein called angiotensin convertase 2 (ACE2), which allows the virus to penetrate the cell (Jena et al., 2021; Wallace, 2020). Thus, SARS CoV-2 enters the cells of the epithelium lining the alveoli through ACE2, causing destruction which increases the permeability of cell membranes releasing the virus into the extracellular space. A strong immune response develops and an inflammatory exudate rich in interleukin 6 (IL-6) and C-reactive protein (CRP) floods the alveoli, generating dyspnea and finally, respiratory failure. Just as pharmaceutical agents that block the pro-inflammatory action of IL-6 such as tocilizumab have been shown to be effective in treating COVID-19 infection, vitamins and minerals effective in lowering IL-6 levels, with anti-inflammatory, antioxidant and antiviral properties, may play an important role in the treatment of COVID-19 (Wallace, 2020; Kassi et al., 2020).

a) Zinc

Zinc can be an ally in the fight against SARS-CoV2 by its direct activity of inhibiting viral RNA polymerase and by decreasing the activity of its main cellular receptor ACE2. Zn stimulates antiviral immunity by increasing the production of interferon alpha, modulating the immune response of T cells, and by inhibiting the activity of NF-kB chemokines. Zn can also affect mucociliary clearance by making it more efficient, thus preventing bacterial and viral

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infections. Studies on the direct antibacterial effect of Zn on *S. pneumoniae* have already been published. Foods rich in Zn that should be consumed to ensure a sufficient intake of this micronutrient are beef, pork, lamb, dairy products, legumes (chickpeas, lentils, beans), nuts (cashews, almonds, hazelnuts), seeds (pine, hemp, sesame, pumpkin), eggs, dark chocolate, whole grains, potatoes and seafood, or Zn supplements can be taken when feeding is not possible (Skalny et al., 2020). In children, Zn supplements have been shown to reduce the number of upper respiratory tract infections and also shorten their duration. In adults, a daily dose of 30-50 mg Zn may be useful in limiting viral replication when it comes to coronaviruses (Zabetakis et al., 2020).

b) Magnesium

Magnesium (Mg) is one of the most abundant intracellular cations. Mg is involved in over 600 enzymatic reactions and is an important transporter of K and calcium ions. It has a known anti-inflammatory, antioxidant and muscle relaxant action (Wallace, 2020; Tang et al., 2020). Foods rich in magnesium are bananas, sesame and pumpkin seeds, cashew nuts and almonds. In the human body, only 1% of Mg is found in serum, the rest being stored in bone and muscle, and only about half of it circulates in the bioactive cationic free form. Determining bioactive free Mg values may be a superior marker of evaluation compared to determining total serum Mg or urinary Mg. An inversely proportional relationship between serum inflammation markers and oral Mg supplementation was observed, including a decrease of IL-6. Mg supplements can be administered orally, especially when there are nutritional deficits, at a dose of 350 mg/day, and could be useful for preventing COVID-19 infection, especially in diabetics, hypertensives or pregnancy, in addition to vitamin D supplementation. For patients with COVID-19 infection, hypomagnesemia and hypokalemia, intravenous administration of magnesium sulfate should be considered (Wallace, 2020). Hypokalemia is also aggravated by hypomagnesemia and is often refractory to potassium supplementation (Alfano et al., 2021). When treating COVID-19 infection, Mg supplements could prevent cytokine storm and side effects of other pharmacological medications such as hepatotoxicity, cardiotoxicity and neurotoxicity (Tang et al., 2020).

c) Copper

Copper (Cu) is an essential component of protection against oxidative stress, its deficiency resulting in low SOD activity and excessive accumulation of reactive oxygen species that cause injury to lipids, proteins and can affect DNA integrity (Uriu-Adams & Keen, 2005). Also, when there is a deficiency of Cu, an increase in the frequency of infections and a low immune response have been observed. Similarly to Cu deficiency, excess Cu can cause tissue damage by increased oxidative stress, especially in the lungs. Cu supplements can be administered in doses of 7.8 mg/day without side effects, which can beneficially influence the outcome of COVID-19 infection by reducing oxidative stress and its immunomodulation activity (Zabetakis et al., 2020).

d) Vitamin C

Studies on chicken embryos have shown that vitamin C is found in large quantities in the structure of the mucosa lining the airways, which prevents the attachment and penetration of microorganisms into the cells and has a strong antioxidant effect (Atherton et al., 1978; Hemilä, 2003). The daily requirements of vitamin C can be met from a diet rich in fresh fruits (citrus fruits, berries) and vegetables (leafy greens, tomatoes) (Zabetakis et al., 2020). Previous studies have proven that vitamin C supplements can shorten the duration of viral infections and reduce the severity of symptoms (Zabetakis et al., 2020; Alschuler et al., 2020; Hemilä H, 2003).

The recommended daily dose of vitamin C can vary between 500 mg and 3000 mg, depending on the purpose of treatment, preventive or curative (Alschuler et al., 2020).

Vitamin C is known for its immunomodulatory effects, having the ability to increase the production of interferon alpha and beta and also to decrease pro-inflammatory cytokines (Hemilä H, 2003). Some studies indicate increased in vitro virucidal activity of vitamin C in the presence of Cu and/or iron. There are already published studies that reveal the effectiveness of vitamin C in COVID-19 infection when administered in high intravenous doses. In Saudi Arabia, the National Institute of Health states that vitamin C infusions of 1.5 g/kg body weight are beneficial and without risks (Boretti & Banik, 2020).

e) Vitamin D

Vitamin D is known for its anti-inflammatory and immunomodulatory role, but it can also act as an antiviral agent by interfering with viral replication, as studies have shown. Important dietary sources of vitamin D are eggs, salmon, mushrooms and dairy products (Zabetakis et al., 2020).

Due to the already known ability of 1.25(OH)vitamin D to increase IL-1b, current recommendations state that it should be used with caution in COVID-19 infections, avoiding high doses to prevent the development of cytokine storms (Alschuler et al., 2020).

f) Vitamin A

Studies performed on retinol show a possible anti-inflammatory effect by decreasing serum levels of interleukins (IL-1B). Vitamin A can be administered both preventively and curatively in COVID-19 infection. The possible hepatotoxic effects of vitamin A should be mentioned even at low doses, requiring monitoring of liver enzymes during treatment (Alschuler et al., 2020).

g) Vitamin E

Vitamin E is found in vegetable oils, nuts, seeds, cereals and leafy greens. It has an anti-inflammatory and antioxidant effect and plays an important role in cellular and humoral immunity. Studies suggest the possibility of combining it with vitamin C in doses from 15 mg to 1000 mg/day for the prevention and treatment of heart complications in COVID-19 infection (Zabetakis et al., 2020).

h) Melatonin

There seems to be an important correlation between the course of respiratory viral infections and melatonin levels in adults and children. Adults generally have lower melatonin levels compared to children, which could be the reason why adults also more often develop severe symptoms during viral infections. A daily dose of 0.3 mg to a maximum of 20 mg can reduce lung inflammation and oxidative damage at this level and can lead to a faster resolution with fewer complications of COVID-19 infection (Alschuler et al., 2020).

i) Polyphenols and phytotherapeutics

Phytotherapeutics from traditional Chinese and Indian medicinal plants have already proven their efficiency in Coronavirus infections and other viral infections in scientific studies (Lin L-T et al., 2014; Vellingiri et al., 2020). Extracts from African plants, containing alkaloids and terpenoids which are known to have high affinity for 3-chymotrypsin-like proteases with a key role in the replication of viruses from the Corona family, could exhibit antiviral efficacy. These extracts represent a promising option in the therapy of COVID-19 infection, especially since there is already evidence that some patients have shown a favorable therapeutic response to treatment with other antimalarials such as hydroxychloroquine (Gyebi et al., 2020). Ongoing studies in China, with promising results so far, have administered a lung detoxifying decoction made of 21 medicinal plants with over 90% efficacy in the treatment of moderate and severe forms of SARS CoV-2 infection (Weng, 2020).

Sambucus nigra extract could have an important role in preventing viral infections, including infection with viruses from the Corona family, by inhibiting their attachment to cellular receptors and stopping their replication, but due to its cytokine stimulation effect, administration should be discontinued in case of specific symptoms of COVID-19 infection. In addition to Sambucus nigra, there are other extracts that should be used with caution in COVID-19 infection due to their immunostimulatory effect, increasing the levels of interleukin-1b and IL-18, such as extracts from Echinacea angustifolia and E. purpurea commonly used in treating symptoms in other viral infections (Alschuler et al., 2020).

Polyphenols are substances with strong anti-inflammatory effects that act at the cytoplasmic level by reducing the number of inflammasomes from macrophages and the number of T1 helper cells that once activated, release pro-inflammatory cytokines. They may play an important role in the prevention and treatment of COVID-19 infection. Bioflavonoids can be isolated from fruits and vegetables, some examples being dihydroquercetin and quercetin found in onions and apples; myricetin from oranges, berries, tomatoes and nuts; apigenin from celery, chamomile and parsley. Catechin found in green tea is a powerful inhibitor of the virus's penetration into the cell and its replication. Curcumin found in turmeric inhibits monophosphate dehydrogenase, the enzyme needed in the de novo synthesis of guanine nucleotides (Alschuler et al., 2020). Both have the capacity to bind to cell receptors ACE2 of the host and viral protein S, but studies show a slightly greater affinity of catechin vs. curcumin. They also enhance the antiviral activity of zinc (Jena et al., 2021). Resveratrol found in *Vitis vinifera* is known for inhibiting viral replication and is thought to have a synergistic antiviral effect with catechins (Annunziata et al., 2020). To ensure an optimal intake of bioflavonoids, at least 5-7 servings of vegetables/day and 2-3 servings of fruit are needed in diet (Alschuler et al., 2020).

j) SOD

Oxidative stress plays an important role in many life threatening conditions such as acute respiratory failure or multiple organ dysfunction syndrome, which is why enzymes that protect against excessive reactive oxygen species (ROS) are necessary to maintain the redox balance and prevent cellular damage.

The superoxide dismutase (SOD) enzymes are three isoenzymes with distinct locations and with antioxidant effect; CuZnSOD known as SOD1 is located in the cytoplasm, MnSOD known as SOD2 is found in the matrix of mitochondria, and SOD3 or EcSOD also contains Cu and Zn and can be found in the extracellular space due to its heparin binding domain (Yan et al., 2020; Uriu-Adams & Keen, 2005).

EcSOD is found in high concentrations in the lungs and kidneys, but studies have shown that it can be produced in skeletal muscle during endurance exercise, from where it reaches the vascular system in the heart and lungs, providing increased protection through the anti-inflammatory effect exerted. EcSOD protein therapy could have a major benefit in diseases such as COVID-19 infection, where the injury caused by the exaggerated inflammatory response underlies the symptoms. Active people with a regular endurance exercise program benefit from an increased amount of protective EcSOD, which could prevent the occurrence of respiratory failure as a complication in case of an infection with the new COVID-19 virus (Yan & Spaulding, 2020).

Studies have also found increased SOD levels and reduced ROS levels when using alkaline water supplementation (Logozzi et al., 2020) and coenzyme Q10 supplements (Sangsefidi et al., 2020).

Conclusions

When fighting infectious diseases, in addition to applying the right treatment, the patient's immune and nutritional status plays an essential role.

COVID-19 infection does not yet have a specific treatment, protocols vary from one country to another, new possible effective treatments emerge every week, and there are not many certainties in this area; therefore, it is essential to support our natural defense system and help it regulate itself with anti-inflammatory, antioxidant and immunomodulatory nutrients, as well as by an active lifestyle, in order to increase the chances of a favorable outcome in COVID-19 infection and to prevent post-infectious sequelae.

Conflict of interests
There is no conflict of interests.

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Rehabilitation in knee osteoarthritis patients in 2020. Narrative review

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Abstract

There are a multitude and variety of treatment options available for patients with knee osteoarthritis, which can be overwhelming for rehabilitation and physiotherapy healthcare professionals.

The basis of the 2020 review of rehabilitation in KOA patients was performed by our team selecting systematic reviews from Medline via Ovid, PubMed, CINAHL and Google Scholar in regard to trends and recommendations in rehabilitation / physical therapy programs in people diagnosed with KOA.

In our descriptive research, we used combinations of “osteoarthritis” and “knee”, “rehabilitation” “physical therapy”, “exercises”, “kinetic program”, “balneotherapy”, yielding a total of 965 publications. This was reduced to just 62 papers after the removal of publications dealing with clinical trials, imaging, biomechanics, biomarkers and genetics, medications, knee replacement, which are dealt with elsewhere in this rich medical literature.

The objective of our study is to assess and review the effectiveness of current available rehabilitation options for knee osteoarthritis to guide all practitioners in physical medicine and rehabilitation, for ensuring that the care they provide is safe and aligns with best practices.

Keywords: knee osteoarthritis, rehabilitation, physical therapy, exercises, kinetic program, balneotherapy.

Introduction

One of the most common subjects in the medical literature worldwide is osteoarthritis (OA) – the most prevalent chronic degenerative musculoskeletal and joint disorder, defined as the deterioration of cartilage in joints, which results in stiffness, pain and impaired movement (Lau et al., 2021), disability and decreased quality of life (Vos et al., 2012). Its definitions refer to epidemiological, pathogenic, clinical, imaging and functional data. According to this aspect, the management of OA requires a major interest in the medical fields, especially in rehabilitation and physiotherapy. Moreover, it is unanimously recognized that OA has no cure, and self-management with exercise and physical activity is a main strategy in the complex management of OA patients (Quicke et al., 2020).

Knee osteoarthritis (KOA) is the most common OA localization (Teo et al., 2020).

The dynamic process of modernization of electric and physical modalities used in physical medicine and rehabilitation characterizes the last years. Over the last few years, systematic reviews (SRs) with or without meta-analyses (MAs) have been widely used in resolving questions in various compartments of KOA management. According to the Joanna Briggs Institute (JBI), scoping reviews are useful for effectively and rigorously examining emerging evidence (Peters et al., 2020). Research mentioned in these SRs has focused especially on determining the underlying mechanisms, the health benefits of exercise and physical activity, mediation of knee state, and less on the role of physiotherapy in KOA. So, we consider that a multidisciplinary team who believes

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that KOA patients should be informed by updated evidence from systemic reviews on the effectiveness of all physical therapies indicated for these patients is necessary.

We performed, to our knowledge, the first Romanian narrative overview of systematic review articles to comprehensively analyze various rehabilitation (kinetic and physiotherapeutic) programs in KOA. Based on the available English language documents published only in 2020 in four important databases - Medline via Ovid, PubMed, CINAHL and Google Scholar, we aimed to assess and perform a narrative summary of the effectiveness of all physical, kinetic and alternative interventions for KOA, in the complex management of this disease. The mentioned systematic literature reviews were hand-researched. We performed our search strategy using combinations of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords - "osteoarthritis" and "knee", "rehabilitation" "physical therapy", "exercises", "kinetic program", "balneotherapy", yielding a total of 965 publications (Fig. 1). This was reduced to 62 papers, abstracts and full texts. All studied SRs are based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and included randomized controlled trials (RCTs).

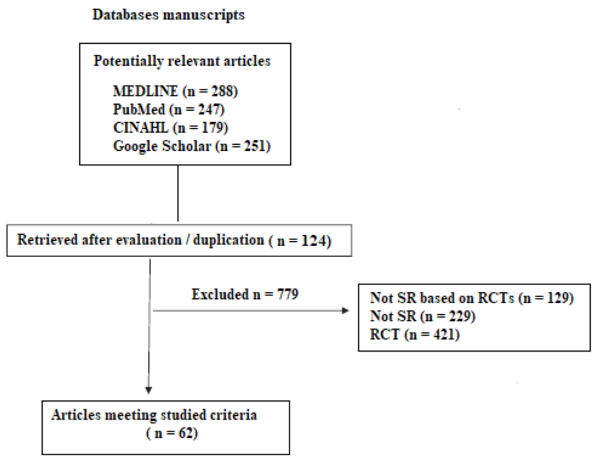

Fig. 1 – Flowchart of our narrative review

Initial literature search was performed by **FOF** and screening for relevance was performed by all authors, based on the authors' clinical and research expertise in the field of KOA rehabilitation. Here, we will review the current state of KOA rehabilitation in this field from a biological, clinical, and functional perspective and in terms of outcomes for pain, knee physical function and quality of life after the rehabilitation program.

Knee osteoarthritis definitions

The knee is identified as one of the most commonly affected joints in OA, being followed by the hand and hip. Described as a complex multifactorial and polygenetic disease involving structural and functional alterations of the entire joint (articular cartilage, menisci, subchondral bone, capsule, synovium, ligaments, and periarticular muscles) (Byra & Czernicki, 2020) and one of the leading contributors to global chronic disability, KOA is characterized by joint pain and stiffness leading to functional limitations and loss in participation and quality of life (Zhou et al., 2020).

The prevalence of KOA is increasing worldwide, has an enormous health care impact, and entails a high cost to society. Although it is most prevalent in the elderly population (>65 years old, more than 70% of this population has symptomatic KOA) (Zhang et al, 2020), particularly overweight elderly people, and in persons with traumatic joint injuries (Smith, 2020), there is an increasing trend of young adults (under 55 years old) being diagnosed with KOA, estimated to affect one in eight adults. KOA now represents one of the major causes of disability worldwide, with reduced mobility of the entire population, women being twice as affected compared to men (Lau et al., 2021).

Complete diagnosis

Before considering rehabilitation for knee osteoarthritis, a complete assessment (pathogenic, clinical, paraclinical and functional evaluation) is needed, both for the joint and the patient as a whole.

The knee is a complex joint, with mechanical and biological functionalities that can be difficult to separate. The cellular and molecular events from chondrocytes which lead to KOA signs and symptoms are neither well understood nor easily measurable (Kanamoto et al., 2020).

The pathogenesis of OA disease is unclear, but studies have indicated several factors which include: articular cartilage degeneration (partial-thickness and full-thickness focal cartilage defects seem to contribute equally to the development of new cartilage damage in knee OA), subchondral bone thickening, osteophyte formation, synovium inflammation (synovitis), degradation of ligaments and menisci, and joint capsule hypertrophy (Smith, 2020). The complex morphological and pathogenic knee disturbances cause clinical symptoms – various types of pain (dull or sharp, intermittent or persistent), crepitation, swelling, stiffness, muscle weakness (especially quadriceps), instability and a decline in range of motion due to pathogenic conditions that block normal synchronous movement; all these symptoms and signs decrease physical function and quality of life (Kawabata et al., 2020). Weight-bearing activities that involve large knee flexion are biomechanically and physiologically more challenging than level walking and are thought to be the first mobility limitation observed in KOA patients. End-stage KOA results in severe pain and remarkably limited functional activities (Hislop et al., 2020).

Among contributors to global disability, osteoarthritis is among the three most disabling conditions, having a remarkable public health impact in developed countries (1).

Today, complete diagnosis of KOA is established due to imaging investigations. The imaging hallmark of OA is plain film X-ray (for changes in subchondral bone). Early bone changes - bone marrow lesions - are detected by MRI exam. The whole-organ MRI scoring method (WORMS) is used in MRI for OA, assessing damage, providing a detailed analysis of the joint (Sandhar et al., 2020). Direct visualization of the cartilage phenotype, using 3D transport-based morphometry, defining predictive KOA, and possible diagnosis made at a potentially reversible stage will be very important in the future (Kundu et al., 2020).

Functional evaluation is important and represents one of the six domains that are mandatory in the assessment of KOA, including pain, physical function, quality of life, patient's global assessment of the target joint and adverse events including mortality and/or joint structure, depending on the intervention tested (Smith et al., 2019). Gait analysis is included as a target outcome measure in KOA patients, considering that gait is the essential function of the lower limbs (Sandhar et al., 2020). Functional examination is undertaken according to a standard evaluation form based on the International Classification of Functioning, Disability and Health (ICF) model (1) (Vongsirinavarat et al., 2020).

After complete diagnosis of KOA patients, it is important to mention the KOA phenotypes to better understand the individual patient's need. Until now, six distinct KOA phenotypes have been identified through a synthesis of 24 individual studies: chronic pain, inflammatory, metabolic syndrome, bone and cartilage metabolism, mechanical overload and minimal joint disease phenotypes. Also, the research of OA phenotypes is only beginning; this aspect permits to individualize treatment options and rehabilitation treatment protocols (Primorac et al., 2020).

Optimal rehabilitation program in KOA

OA is a progressive disorder, with different degrees of severity, which requires long-term management with various treatment options over the course of the disease. The goals of treatment are to reduce symptoms and ultimately slow disease progression, which may in turn reduce the impact of OA on patient's mobility and quality of life, with a consequent reduction in healthcare resource needs.

Improvement or compensation of impaired movement function remains key to the management of KOA and is the basic principle in the ESCEO algorithm (Economic Aspects of Osteoporosis and Osteoarthritis algorithm), which provides advice for treatment prioritization and possible combination (Whittaker et al., 2020).

Several professional recommendations for KOA care (EULAR - European League Against Rheumatism, ACR - American College of Rheumatology, OARSI - Osteoarthritis Research Society International) highlight the role of non-pharmacological and non-surgical approaches including education, and weight reduction, kinetic programs (aerobics, muscle strengthening and water-based exercises - recommended first-line treatment for people with KOA), and orthotic devices, heat and cooling packing, neuromuscular electrical stimulation and other electric interventions (for example transcutaneous electrical nerve stimulation, ultrasound and low-level laser therapy), acupuncture and spa therapy (Kolasinski et al., 2020; Holden et al, 2020).

It is important to take into consideration adapting all rehabilitation programs to comorbid populations, exercise behavior change, community-based self-management education and technology support, including alternative, low-cost, flexible delivery options, from online self-directed guides to low-tech phone contact and self-help program books and tool kits (Arden et al., 2021), as it is mentioned in several available updated guidelines for the management of KOA (Kolasinski et al., 2020).

These interventions can reduce pain and improve physical function in patients with KOA, in accordance with studies, reviews and meta-analyses published so far (Ferreira et al., 2018), with a seven-year-old remark that exercise is a key factor for managing OA (Nelson et al., 2014). The management of KOA depends on the severity of its clinical symptoms. Patients with mild KOA benefit from non-pharmacological interventions and topical non-steroidal anti-inflammatory drugs - NSAIDs. In moderate to severe cases, treatment and rehabilitation modalities include exercise, knee braces, walking aids, oral NSAIDs and surgery. Alternative treatment modalities to alleviate KOA symptoms are in high demand, because oral NSAIDs are often associated with cardiovascular diseases, kidney injury, gastrointestinal bleeding. Furthermore, rehabilitation measures may control the neuropathic pain components in KOA, especially in patients with minor bone and joint changes but with a high level of this symptom refractory to classical analgesic pharmacological treatment (Kanamoto et al., 2020; Peprah & Argáez, 2020; Rocha et al., 2020).

Pharmacotherapy measures

All rehabilitation team members have to know the recommended pharmacological measures for KOA patients. Relatively low-grade inflammation is present in the majority of OA patients, characterized by synovitis and a pro-inflammatory/ catabolic state of chondrocytes. So, non-steroidal anti-inflammatory drugs (NSAIDs), analgesic agents with topical and oral administration, and intra-articular injection of corticosteroids are indicated to control the inflammatory joint process and pain status (Nelson et al., 2014).

Recent studies have focused on new intra-articular injections of various agents which facilitate the delivery of growth factors, cytokines and morphogens, all of which have proven chondroprotective, anabolic, anti-inflammatory and immunomodulatory properties: hyaluronic acid, platelet-rich plasma, and plasma rich in growth factor articular injection, ozone therapy, prolotherapy, intra-articular botulinum toxin administration. These newer injectable therapies have safer side effect profiles (Billesberger et al., 2020; Tang et al., 2020), and research efforts to find the most effective injection therapy for knee OA continue, without a real standardization of the testing protocol (Saltzman et al., 2020).

In the last decade, the new pharmacological treatment has been focused on macrophages as key mediators in OA-associated inflammation and mesenchymal stem cells (MSCs), which have been predominantly tested with the aim to repair cartilage, in order to produce anti-inflammatory mediators and induce reparative properties in a paracrine manner (van den Bosch, 2020).

Also, multiple research groups have published their results regarding the possible protective effects of metformin on OA development (structural damage and progression) (van den Bosch, 2020), and there is evidence in recent SRs (Ma W et al., 2020) that curcuminoids relieve the symptoms of patients suffering from KOA.

In general, pharmaceutical treatment does not promote clinically important effects in time regarding improvements in pain and function. On the contrary, exercise and physical therapy show high-quality evidence of optimal effects for patients with KOA - significant reduction of pain, improved function and quality of life (Whittaker et al, 2020).

Education and dietary intake

Today, all medical literature mentions the importance of effective education of KOA patients for optimal management. All members of the rehabilitation team, including physiotherapists, provide information and advice regarding weight loss (Sprouse et al., 2020), pain medications, physical and kinetic measures, and behavior modification techniques which influence patients' experiences of KOA, aimed at learning to live and control this disorder. Care may be improved when KOA patients are fully informed about all their treatment options, as it is mentioned in a last year review (Teo et al., 2020).

Weight management and knee joint health are two educational objectives in KOA patient management. Patients with KOA who maintain an appropriate body weight can potentially slow progression of the disease, due to greater reductions in knee compression forces (Sprouse et al., 2020).

In a review by van den Bosch, it is mentioned that dietary intake and composition likely represent an important factor that lowers the threshold for OA development. So, future OA-preventing strategies may include an adapted diet, in accordance with the gastrointestinal microbiome so sensitive to therapeutic interventions (van den Bosch, 2020). Diet is very important for people with mild to severe knee OA, which are at a high risk of sarcopenia. Several recent studies have indicated physical activity, protein supplementation in daily nutrition and protein-based diet interventions as adequate methods to improve muscle mass, muscle strength, and functional outcomes, and to reduce pain in older adults with KOA (these persons are at a high risk of sarcopenia) (Liao et al., 2020; Lo et al., 2020).

In accordance with the electronic development of our society in recent years, education tools are currently adapted. So, podcasts (portable digital audio files) have become a powerful medium and an indispensable tool in higher education for disseminating research findings, providing continuing medical education for healthcare professionals and educating patients about self-managing their condition. These podcasts promote the dialogue between them using this increasingly popular platform (Mobasheri & Costello, 2021).

In their article, Karasavvidis A. and colleagues mentioned the importance of education in KOA, even in pandemic conditions. Education on OA management along with information about physical exercises and weight loss by virtual visits to the physician could reinforce the effectiveness of exercise and weight loss programs when implemented simultaneously. The results were promising in WOMAC pain scores and IL-6 levels (Karasavvidis et al., 2020).

Today, all researchers agree with the cost-effective or cost-saving dimension of education or diet with a kinetic program, comparatively with the well mentioned aspect that education interventions were not cost-effective compared to usual care or placebo at conventional willingness-to-pay thresholds in 2020 medical databases (Mazzei et al., 2020).

Physiotherapy

The term physiotherapy was used for any supervised, physiotherapist-led, non-invasive treatment (mobilizations and massage / manual therapy, application of ice and heat, diathermy, electrotherapy modalities) (3).

In the Romanian Physiotherapy High School, it is considered that therapy with physical agents is recommended to assist kinetic programs in the management of KOA patients.

All studied SRs mentioned that physical agents improve pain and function, increase the strength of the knee extensors, and include: thermal interventions (locally applied heat / paraffin or cold), electrical (transcutaneous electrical nerve stimulation - TENS, neuromuscular electrical stimulation - NMES, interferential current therapy - ICT), electromagnetic (pulsed electromagnetic field - PEMF, classical magnet therapy) and phototherapeutic procedures (shortwave diathermy therapy - SDT, iontophoresis, low-level laser therapy - LLLT, non-selective chromotherapy with Bioptron), extracorporeal shock wave therapy (ESWT), acupuncture (Bierma-Zeinstra et al., 2020).

The effects of various physical therapies on temporal summation and conditioned pain modulation in KOA patients with chronic musculoskeletal pain are mentioned in a systematic review and meta-analysis (Arribas-Romano et al., 2020).

So, we consider that patients with chronic pain and KOA really benefit from the process of central sensitization after physical therapy, based on various types of electrical and magnetic procedures. The most effective therapeutic modalities for KOA seem to be magnet therapy and ultrasound, and cold therapy. It is not yet known which physical resources promote the greatest improvement in clinical variables when added to exercise therapy. Probably, multimodal strategies are optimal to control / reduce the signs and symptoms of KOA (Chen AT et al., 2020).

Choosing a physical agent in the rehabilitation program for a patient with KOA depends on the equipment, the experience of the team and the particularities of the patient. After examining the published reviews in 2020 for the physical therapy of patients with KOA, we can determine the following:

- TENS – a non-pharmacological pain-reduction intervention in KOA patients is efficient (in order to best control pain and maximize functional status, *12-15 sessions over 4-6 weeks,* measured using instruments such as the visual analog scale or the Western Ontario and McMaster Universities Arthritis Index scale and *it lasts about 2 weeks*) in all patients, but with special genotyped COMT and EDNRA genes implicated in central and peripheral pain pathways. The pathogenic theories for TENS pain control are mentioned in a recent systematic review: the gait control theory of pain and activation of endogenous opioids for nociceptive pain mechanisms, the increasing of neural drive and diminishing the excitatory effect upon removal, providing increased afferent stimuli interpreted by the central nervous system as excitatory resulting in the facilitation of inhibited motor neuron pools (Lee et al., 2020). When TENS is applied in conjunction with exercise, the results are better. TENS after exercise was proved to be more effective in increasing function and reducing disability in knee OA patients (Shamsi et al., 2020). Other researchers mentioned that TENS was not beneficial for KOA, but in small size studies with variable controls (Kolasinski et al., 2020).

- NMES - produces high muscle force at a relatively low intensity; it occurs non-selectively with regard to the type of motor unit and synchrony, and it preferentially activates type II fibers as compared with voluntary muscle contraction (Gregory & Bickel, 2005). In 2020, an interesting review was performed to provide guidelines - standardized clinical treatment parameters for neuromuscular electrical stimulation (frequency of at least 50 Hz and no more than 75 Hz with a pulse duration between 200 and 400 μs, and a treatment duration of 20 mins) - by researching its efficacy in improving muscle strength and decreasing pain in patients with knee osteoarthritis (Novak et al., 2020). Conventional NMES can train both quadriceps and hamstring at the same time if electrodes are placed on both muscles. A higher intensity NMES is more effective but causes discomfort. In rehabilitation, electrical stimulation of quadriceps and hamstring is preferred, which are alternate and intermittent during hybrid training system, a technique to combine the application of electrical stimulation and volitional contractions (Gregory & Bickel, 2005).

- ICT – despite its widespread use, information about it is limited, and the heterogeneity across studies and methodological limitations prevent conclusive statements regarding analgesic efficacy. There is a lack of ICT specific research compared with TENS. Classically, four electrodes were placed around the affected knee joint, the intensity adopted by the stimulator was kept at a level considered strong but comfortable, throughout the treatment (Whittaker et al., 2021).

- PEMF therapy - the effects on KOA patients are still unclear, because the underlying mechanism of action of PEMFs in OA is not entirely understood; probably, the clinical results may be explained through a significant reduction in some of the most relevant pro-inflammatory cytokines in human chondrocytes; today, PEMFs are effective in preventing OA development and progression and have beneficial effects on pain, stiffness, and physical function in patients with OA. Duration of treatment may not be a critical factor in pain management. Further studies are required to confirm the effects of PEMF therapy on QOL (Yang et al., 2020).

- LLLT – is an effective modality for short-term pain relief, function improvement and disability control in patients with chronic KOA, as mentioned in the systematic reviews (Ganjeh et al., 2020).

- ESWT using medium energetic density is an effective treatment for improving pain and functionality in patients with KOA (Avendano-Coy et al., 2020). The conclusion of last year reviews mentioned the efficacy and safety of ESWT for KOA; physical measure was efficacious and safe for reducing pain and improving knee function (in terms of the Western Ontario and McMaster Universities Osteoarthritis Index at 4-12 weeks), without increasing the risk of adverse effects (Wei et al., 2020; Ma H et al., 2020).

- acupuncture - is one of the most popular treatment modalities to control KOA symptoms; it has similar mechanisms to relieve pain without serious adverse effects like TENS. Electroacupuncture (a combination of acupuncture and transcutaneous electrical nerve stimulation) and laser acupuncture (a form of low-level laser therapy) have become popular treatments for KOA and are associated with a low risk of adverse reactions (Wu SY et al., 2020).

There is little evidence to support the use of thermal packs (used at the same time as stretching during painful episodes) or ice packs (for managing acute episodes) or alternation between heat and cold therapies. However, due to the fact that they are accessible and affordable for most patients, thermal modalities are included in OA treatment guidelines for managing pain (Whittaker et al., 2021)

Kinetic program in KOA patients

More recent reviews have pointed out the complex and complete role of therapeutic exercise (TE) in the management of KOA patients. Physical exercise appears to be the most effective therapy for controlling symptoms and can delay disease progression and thus the need for joint replacement. Exercise therapy may be recommended as a relatively safe intervention in all KOA patients (Niemeijer et al., 2020) and has beneficial effects on physical and psychosocial health in people with multimorbidities (Bricca et al., 2020). After their investigation about the role of physical activity as a conservative treatment for older KOA people, the authors of SRs mentioned that active exercise and sport are effective to improve pain and physical function; for validating the use of physical activity to control stiffness, quality of life, and dynamic balance, further studies are required (Zampogna et al., 2020).

a) The pathogenic impact of TE in KOA patients

In their review, Dalle and Koppo presented the evidence so far that describes the involvement of inflammatory signaling in pathology-related muscle wasting in KOA patients. More exactly, this disease induces morphological changes in skeletal muscle tissue in end-stage patients, including neurogenic muscular atrophy and muscle fiber degeneration. Because the changes in systemic and muscle inflammation are connected to changes in muscle molecular signaling (anabolic, catabolic, oxidative stress, etc.), muscle mass and muscle strength, it is important to include physical activity as a modulating variable when studying muscle function (Dalle & Koppo, 2020).

In 2020, Smith explained the beneficial effect of TE on the skeletal system and its role as an adjuvant to cartilage regeneration therapy. TE decreases immune cell production of osteoclastogenic cytokines and increases the production of anti-osteoclastogenic cytokines (Smith, 2020).

Other authors consider that there was no decrease in systemic inflammation markers (interleukin-6, tumor necrosis factor-alpha) and small to moderate changes in markers of cardiovascular health (heart rate, systolic and diastolic blood pressure) occurred when KOA patients performed aerobic exercise (Schulz et al., 2020).

Some authors observed that resistance exercise training exerted benefits on lean mass or muscle hypertrophy in patients with OA, whereas others indicated no significant effects of strength training exercise on muscle mass and muscle volume. Controlling the decline in muscle mass, a risk factor for KOA, allows limiting KOA progression (Aguiar et al., 2016).

Muscle strength exercise training (MSET) is effective in increasing lean mass and muscle size in older adults with OA. Clinicians should incorporate MSET into their management of patients at risk of low muscle mass to maximize health status, particularly for older individuals with OA (Liao et al., 2020).

Knee sagittal dynamic joint stiffness may be a potentially modifiable risk factor for patellofemoral cartilage damage worsening over 2 years (Haj-Mirzaian et al., 2020). So, novel insights into kinetic programs in KOA take into consideration the prevention of patellofemoral cartilage loss through maintenance of adequate extensor/flexor muscle balance in the knee joint.

Combining exercise and cognitive behavior therapy seems to be an effective method to reduce KOA pain, even though it is based on a small number of studies. Although it is known that KOA chronic pain can result in brain structural and organizational changes, and patients' pain level, emotional status, and perception of their condition might be negatively altered, further studies are needed to reveal any differences when each intervention is applied separately (Pitsillides et al., 2021).

Although the taping technique did not produce better results in mobility and functioning improvement over non-specific knee taping, it had a higher patient-reported subjective value for symptom attenuation and experienced mobility enhancement. The pathogenic support for this functional improvement would be the neurophysiological effects due to the irritation of skin receptors and sensory neurons evoked by the tapes attached to the knee skin. The elastic taping, which applies appropriate tension along the tape and places the target muscle in a stretched position, may improve mechanoreceptors and proprioceptive input causing central inhibition of nociceptive transmission and hence modulation of pain, in line with the gate control theory of pain (Banerjee & Johnson, 2020).

b) Clinical and functional effects of TE in KOA patients

- *Pain*

Until now, it has been established that TE may be effective in reducing pain in people with knee OA and neutral alignment. The reviews and meta-analyses of randomized controlled trials (RCTs) of TE interventions in people with KOA provide strong evidence of, on average, small-to-medium effects on pain and function compared to non-exercise controls. These results depend on some factors, named moderators, such as socio-demographics (age), clinical assessment findings (the presence of comorbidity – obesity, cardiac problems, vascular lower limb disease), or biomechanical factors (joint malalignment) (Quicke et al., 2020). Future research is needed to increase statistical power for moderator analyses before drawing firm conclusions about how TE controls pain in different clinical subgroups of KOA patients.

The effect size on pain is variable. Strength training or exercise therapy alone showed a small effect size on pain compared to the moderate effect of exercise therapy plus manual mobilization. In the short term, non-weight-bearing hip and knee strengthening exercises were recommended to reduce pain in people with knee osteoarthritis (Hislop et al., 2020).

A systematic search conducted in seven databases concluded that stationary cycling exercise relieves pain and improves sport function in KOA patients, but may not be as clinically effective for improving stiffness, daily activity, and quality of life (Luan et al., 2020).

Resistance training improves pain and physical function in knee osteoarthritis. Greater improvements in pain tend to be associated with higher functional levels. Large effect sizes were associated with 24 total sessions and 8- to 12-week duration. No optimal number of repetitions, maximum strength, or frequency of sets or repetitions was found. The most common regimen was a 30- to 60-minute session of 2 to 3 sets of 8 to 12 repetitions with an initial resistance of 50% to 60% of maximum resistance that progressed over 3 sessions per week for 24 weeks (Turner et al., 2020).

Pain in KOA patients has a multidimensional aspect, so various types of physical therapy are available and applied. One of these is kinesiology taping. When comparing the therapeutic effects between physical therapy (PT) combined with kinesio-taping (KT) and PT alone in knee osteoarthritis treatment, the authors of a systematic review established that PT combined with KT provided a better therapeutic effect regarding pain reduction and functional improvement in patients with knee osteoarthritis (Lin et al., 2020). The results could last at least six weeks after initial treatments.

Xie and colleagues conducted a systematic review and meta-analysis to assess the effect of internet-based rehabilitation programs on pain and physical function in patients with knee OA. The results showed that internet-based rehabilitation programs could improve pain, but not physical function for KOA patients (Xie SH et al., 2021).

- *Muscle strength*

Pain was considered to be a limiting factor for physical function (strength and range of motion), and a pain–weakness–pain vicious circle would be formed in the progression of KOA. Most of the exercise programs had a significantly positive outcome result in both criteria (pain and muscle strength), but mainly for pain relief (Rocha et al., 2020). So, the common denominator in all articles that performed muscle strengthening, regardless of the kinetic protocols used, is the improvement of pain.

A physical method for increasing the muscular strength of the quadriceps for patients with painful KOA is blood-flow restriction (BFR). Because quadriceps strengthening requires heavy resistance that can increase knee pain, BFR (which involves placing a pneumatic cuff proximal to the muscle to limit blood flow during exercise; based on brief periods of vascular occlusion which cause muscle hypertrophy and increased strength) may be a low-load alternative to increase quadriceps strength in people with pain KOA, as concluded by Cant and colleagues (Cant et al., 2020).

An ideal kinetic program for the treatment of pain and muscle strength in KOA patients would include isometric and quadriceps femoris and crural ischial muscle isotonic strengthening exercises, especially quadriceps isotonic strengthening, crural and gastrocnemius ischial muscle dynamic stretching and other proprioception and balance exercises. The duration of the intervention was very variable (Rocha et al., 2020).

- *Joint instability*

While in general, previous reports of common exercise treatment of age-related OA showed functional improvements, exercise therapy focusing on knee joint stabilization tended to be effective for patients with knee OA and many instability episodes. So, prior to exercise therapy for knee joint instability, evaluation of muscle strength and knee joint instability, and appropriate treatment protocols (education, medication, physical therapy), may improve the treatment for knee joint instability.

One review conducted after searches in three databases concluded that exercise therapy focusing on joint instability, including muscle maintenance and strength training, and specific training targeting knee instability have no additional beneficial effects on knee joint instability (Kawabata et al, 2020).

- *Proprioceptive acuity and motor control*

Theoretically, osteoarthritis may lead to a decrease of proprioceptive function and sensory input, thus affecting patients' ability to maintain balance. There is a lot of evidence of the effects of cognitive tasks on motor performance in patients with knee conditions (Abdallat et al., 2020). Alterations in neuromuscular control of the knee joint are common in knee osteoarthritis, but there have been conflicting results in terms of proprioceptive deficit in osteoarthritic knees. Studies comparing proprioception in osteoarthritic and healthy knees of an age-matched control group using thresholds to detect passive motion or joint position sense tests were reviewed in 2020 and published in 2021 (Lee et al., 2021). The conclusion was that the knee proprioceptive acuity of patients with KOA was poorer than that of patients with unaffected knees.

Quadriceps weakness is also a risk factor for early-onset post-traumatic knee osteoarthritis (PTOA). Identifying the strength, control and timing of muscle force deficits in accordance with neural adaptations in the PTOA population justifies targeted rehabilitation strategies and optimal recovery based on adapted kinetic measures (Tayfur et al., 2021).

A review of studies on how exercise affects measures of pain processing and motor function in KOA concluded that following an exercise program (range 5-12 weeks), there were no statistically significant changes in pressure pain threshold, temporal pain summation and voluntary quadriceps muscle activation (Hall et al., 2020).

In 2020, Xie C and colleagues reported a higher methodological quality and more rigorous reporting quality for the effects of Otago exercise on falls and balance in patients suffering from OA (Xie C et al., 2020).

A narrative review was aimed at investigating the effectiveness of virtual reality (VR) in the rehabilitation of elderly patients with knee or hip osteoarthritis, but the conclusion was that effectiveness of VR-based rehabilitation is unclear and not sufficient to create clinical guidelines, although interventions based on VR are promising in view of postural and proprioception training and pain management (Byra & Czernicki, 2020).

- *Quality of life*

Worldwide, the benefit of physical activity on function and quality of life is recognized (QOL) in osteoarthritis patients. How the relief of pain has a direct favorable impact on QOL will be mentioned here, as well as other conclusions of review studies for QOL, besides the ones mentioned before, in the *Pain* subchapter. A systematic review included in the study randomized controlled trials investigating the effect of adding hip exercises to quadriceps exercises in KOA people on pain, function and QOL (Hislop et al., 2019). The conclusion was that this addition resulted in greater improvements in patient-reported pain, walking and QOL.

Zampogna et al. reported no significant differences in improvements in pain, physical function, and QOL between aquatic and land-based exercise; when analyzing sports, such as Baduanjin, Tai Chi, or yoga, all the studies presented significant improvements in pain, stiffness, physical function, and QOL after the rehabilitation program (Zampogna et al., 2020).

A systematic review examined the effects of technology-supported exercise programs on knee pain, physical function, and QOL of individuals with KOA and/or chronic knee pain. The technology types and program features that were associated with health values were identified, so this kind of delivering the exercise programs appears to offer benefits (Chen et al., 2021).

c) The TE types indicated in KOA

The unanimously accepted definition of TE is - a physical activity that involves repetitive voluntary contractions of limb, back, or abdominal muscles that are of sufficient force to maintain or improve physical conditioning (Smith, 2020); it is planned, structured, repetitive and purposeful for the improvement or maintenance of a specific health condition. TE has great potential to reduce pain and improve muscular strength, balance, and range of motion in individuals with osteoarthritis (Bielecki & Tadi, 2021). Dosing parameters are needed to ensure the best practice guidelines for knee osteoarthritis. Exercise is associated with better outcomes (pain perception, knee function recovery, mobility, improvement of the movable degree of the knee joint, quadriceps strength and adverse events: increase of pain or disease activity, various dysfunctions of the knee joint) when supervised (Chen L et al., 2020).

Evidence exists to support the utilization of various forms of exercise.

Both traditional (for example – strengthening, resistance and endurance, flexibility, aerobic / walking and proprioceptive based exercises / balance training) and non-traditional exercises (for example - mind-body exercise, Tai Chi, yoga, and aquatic exercise) have been shown to be effective in the management of KOA (Li R et al., 2020).

Land-based exercise and strength training are recommended as core treatments for all patients with KOA. Exercises were performed to enhance muscle strength, mainly the gluteus medius, maximus and quadriceps. Various procedures are mentioned for use of loads, repetitions and implementations of loads over time. The maximum load was defined before the first treatment session and, when necessary, reviewed at the end of each week (Hislop et al., 2020). The recent systematic review of Hislop AC and collegaues demonstrated greater gains in quadriceps strength with high-intensity compared to low-intensity resistance training in people with KOA, associated with greater improvements in symptoms and disability. Strengthening of the upper leg muscles is thought to be one of the factors involved in reducing pain associated with knee OA. The benefits often last less than one year because people often fail to maintain exercises in the long term (Li R et al., 2020).

In general, lower impact activities (walking, swimming, biking, yoga) are preferred over higher impact activities (running, jumping) in order to lessen pain with exercise. Weight-bearing strength training, non-weight-bearing strength training, and aerobic exercise have all been shown to be effective for short-term pain relief in knee OA, with non-weight-bearing strength training being the most effective (Shamsi et al., 2020).

Resistance training exercises involve muscle actions that are concentric and eccentric. Concentric actions are vital in stair ascent, standing up, and rising from a chair. Eccentric exercise actions, essential in daily activities, such as descent, squatting or sitting into a chair, are characterized by low energy cost, high force production, hypertrophic impact and favorable effect on fall risk and physical function and mobility. Resistance training and endurance training are especially beneficial for pain and balance in osteoarthritis of large joints such as the knee (Bielecki & Tadi, 2021).

Many recent available studies have concluded that backward walking or retrowalking can improve the symptoms of KOA patients and represents one of the kinetic choices, but there is a lack of evidence-based medical research. As opposed to forward walking, retrowalking is a counter sequential exercise and has a helpful effect on improving lower limb proprioception, gait synergy and limb balance (Wu Y et al., 2020).

The Otago exercise program, formulated in 1997, is a home-based fall prevention program, to target the modifiable fall risk factors of lower limb weakness and impaired balance of old people, by guiding the elderly to carry out individual and step-by-step muscle strength and balance function exercise. Otago exercise consists of 2 parts of training, with clear indications for the time, intensity and frequency of the exercise. The first part includes flexibility training, lower limb muscle strength training, and balance function training. The second part is walking training (Punlomso et al., 2020). A single recent review reports the evidence of higher methodological quality for the effects of Otago exercise on falls and balance in patients suffering from OA (Xie C et al., 2020).

Tai Chi is a form of mind-body therapy and low impact and aerobic exercises. Previous biomechanical studies of Tai Chi only focus on pain, physical function, kinematics and kinetics of the knee joint for KOA. This type of kinetic program includes many fundamental postures that flow smoothly from one to another, and it is an effective management for individuals with KOA because it can reduce pain and promote muscle endurance, motor control and postural stability (Zhang et al., 2020). It can be an appropriate and safe therapy for old-aged people (Ren et al., 2020).

Baduanjin kinetic therapy is a Chinese form of low-intensity aerobic exercise, containing eight movements, with a real benefit on reducing pain and improving physical function in KOA patients (Li J et al., 2020). One review was performed based on a literature search conducted in 10 databases and included eligible trials in which Baduanjin was applied either alone or as an adjuvant treatment for baseline pharmacological measures in patients with KOA. The results proved that this Chinese type of kinetic program could improve physical function and pain in KOA (Zeng et al., 2020).

Also, proprioceptive neuromuscular facilitation and static stretching show excellent results as an adjunctive treatment in an exercise program for OA management; only a few studies included that therapy as a favorable technique in the rehabilitation program of osteoarthritic patients (Rocha et al., 2020).

Elastic taping has significant effects on pain, physical function, range of motion, and quadriceps muscle strength in KOA patients. The elastic bands used had 8 levels of resistance divided by colors, in which the more intense coloring indicated greater resistance. The sessions were held three times a week, over 8-10-12 weeks, on alternate days, lasting approximately 90 min each. The current evidence is insufficient to draw conclusions on the effects of elastic taping combined with other physiotherapy procedures for KOA. Further studies are needed to investigate the long-term effects of elastic taping combined with other forms of physiotherapy (Ye et al., 2020).

Of the exercise types available for physical therapy, the most effective appear to be strengthening and aerobic exercises, although proprioceptive exercises can also be beneficial. Backward walking, blood flow restriction, and hydrotherapy can increase tolerance to training. Physical exercise should be combined with educational and habit change measures. Today, self-efficacy and self-management kinetic programs are promoted. A novel finding is the conceptual link of self-determination to high adherence to strength-training exercises over 2 years among adults with KOA (Kamsan et al., 2020).

d) The rehabilitation exercise program

The SRs in 2020 performed for KOA rehabilitation are focused on three aspects: exercise-therapy, methods to deliver exercise-therapy remotely, and approaches to facilitate exercise-therapy behavior change (Whittaker et al., 2020).

In designing a rehabilitation program, consideration should be given to exercises that simulate the type of muscle activity that patients use in their daily routines.

The pathogenic knowledge of KOA allows the election and performance of an optimal rehabilitation program. Each method of rehabilitation justifies its choice by its effects on the physiology of the organism, especially on the components of the neuromyoarthrokinetic system (Hislop et al., 2020). Holden and colleagues mentioned in their narrative review that numerous types of therapeutic exercise may be utilized at varying doses and in different settings to improve pain and function for people with knee and hip osteoarthritis. Moreover, this review informs us how to implement best practice therapeutic exercise, at a sufficient and appropriate dose (Holden et al., 2020). Active exercise and sport are effective to improve pain and physical function in elderly people with osteoarthritis. However, the benefit seems to be short (< 6 months) and most clinical trials assessing the impact of physical activity, especially land-based exercises, have a short-term follow-up ranging from 6 to 12 weeks (Zampogna et al., 2020).

Most SRs promote low-impact, moderate-intensity physical activity for adults with KOA, which includes aerobic, balance, and muscle strengthening components. Until now, no optimal dose of therapeutic exercise (intensity, frequency, duration) that produces improvements in clinically and person-relevant KOA outcomes has been identified (2). Exercise regimens (different protocols used, optimal combination) may be adapted according to the clinical and functional KOA patient status (Table I).

Table I

Types of physical therapy / exercises recommended in KOA in accordance with 2019 ACR Guidelines published in 2020.

Types of exercises	Description	References
Strengthening exercises (land-based) (for any type of KOA) **Strongly recommended**	Muscle strengthening in their daily schedule / resistance training (high-intensity / low-intensity) - improves symptoms (patient-reported pain) and physical function For resistance training, two sessions per week, with two sets of 8 to 12 repetitions at a load of 60% to 70% of one repetition maximum with a rest period of 48 h between resistance training sessions are indicated. Resistance training can produce favorable responses independently of the type of equipment (dynamometers, weights, bands) utilized, the type of exercise (e.g., isokinetic, isotonic), and the muscle action (i.e., isometric, eccentric, concentric) performed. Mixed program - strengthening and endurance training / aerobic exercise - reduces pain, relieves stiffness, and improves physical function; it should include low impact like walking or preferably cycling, daily, and a minimum of 150 min of moderate intensity or 75 min of vigorous intensity aerobic exercise per week in sessions of at least 10 min	Shamsi et al., 2020 Smith, 2020 Hislop et al., 2020 Rocha et al., 2020
Functional neuromuscular exercises (land-based) **Strongly recommended**	Stepping, single-leg squat, step-downs. Effects on psychosocial characteristics such as kinesiophobia or self-efficacy. Adding resistance hip exercises to quadriceps exercises is beneficial for patient-reported outcomes and physical function in the short-term. Functional neuromuscular hip exercises combined with quadriceps exercises improved physical function (walking)	Hislop et al., 2020
Aquatic cycling (for any type of KOA) **Strongly recommended**	Improves knee stiffness and pain, and physical functioning. An intensive aquatic resistance training program had a small short-term impact on knee stiffness.	Zampogna et al., 2020
Home exercise program (especially for severe KOA) **Strongly recommended**	Exercise is highly recommended (walking, stretching, home cycling and muscle strengthening, gymnastics), alongside: • proper nutrition • virtual education on self-management strategies • range of motion activities in their daily schedule • use of corrective and assistive orthotics In accordance with various exercise protocols, each training session comprised a 10-min warm-up, a 40 min period of elastic resistance exercises and a 10-min cooldown period. The following exercises have to incorporate into the training design: seated chest press, seated now, seated shoulder press, hip circumduction, leg press, leg curl.	Karasavvidis et al., 2020
Tai-chi **Strongly recommended**	These non-traditional exercises have been shown to be effective in the management of KOA, because they can reduce pain and promote muscle endurance, motor control and postural stability.	Li Ret al., 2020
Cognitive behavioral therapy **Conditionally recommended**	It is important to control the emotional, cognitive and behavioral outcomes that contribute to KOA pain. The cognitive behavioral sessions ended with exercises, diaphragmatic breathing, knee muscle relaxation and walking.	Pitsillides et al., 2021
Kinesiotaping **Conditionally recommended**	Theraband products, whose colors denote the degree of elasticity and indicate the corresponding resistance level (yellow, red, green, blue, black or gray) Kinesiotaping combined with physical therapy provided better therapeutic effects regarding pain reduction and functional improvement in KOA patients	Banerjee et al., 2020
Balance training **Conditionally recommended**	Otago exercise has effects on falls and balance in patients suffering from OA.	Xie et al, 2020
Telecare (for any type of KOA) **Significance uncertain**	Telephone delivered physiotherapist-led exercises advice and support modestly improved physical function but not the co-primary outcome of knee pain at 6 months. Functional benefits were not sustained at 12 months.	Chen T et al., 2021

Balneotherapy

Balneotherapy, involving immersion in mineral and/ or thermal waters from natural springs, interventions with natural gases, peloids / mud, and other traditional remedies (spa-therapy), has been frequently used in rehabilitation of KOA patients as a complementary and/or alternative therapy. The complete effects (mechanical, thermal, and chemical) of mineral water (sulfur and sodium chloride mineral baths) and mud on changes in pain, stiffness and the functional state (walking speed, flexion and extension range, flexor and extensor strength) of patients with KOA are mentioned in the medical literature (Varzaityte et al., 2020; Raza et al., 2020).

These mineral baths, peat mud applications alongside physiotherapy were more effective than physiotherapeutic treatment alone (Karagulle & Karagulle, 2015). Future studies will be able to determine the role of mineral water ingestion on human microbiome dynamics, with a subsequent impact on the general status of the human body.

In their review, Kamioka and colleagues set themselves the goal to summarize systematic reviews with meta-analyses of balneotherapy and spa therapy based on randomized controlled trials, and to provide a perspective for future research. They concluded that both balneotherapy and spa therapy, especially exercises under mineral water, provided significant pain relief and improved physical fitness and quality of life in chronic diseases of the musculoskeletal system and connective tissues (Kamioka et al., 2020).

Psychosocial interventions

Cognitive behavioral therapy (CBT) is important to control the emotional, cognitive and behavioral outcomes that contribute to KOA pain. Its goal is to change the patterns of thinking, behavior and attitude underlying the disorder and pathologies. It helps in relief of knee pain, improvement in functional ability when performing activities of daily living and improved ability to cope with depression and anxiety as well as to better respond to pain catastrophizing. In the last years, it has been mentioned that chronic KOA pain can result in brain structural and organizational changes, with a negative impact on patients' perception of their condition (Pitsillides et al., 2021). So, based on a small number of studies, combining exercise with CBT may enhance the therapy for patient`s pain level and emotional status.

External devices

Walking aids, knee braces and modified shoes, with lateral and medial wedged insoles for patients with KOA, have a sufficiently large impact on ambulation, joint stability and/or pain to warrant use of an assistive device, and are able to tolerate the associated inconvenience. Knee bracing and foot orthoses are effective by either correcting the knee position or providing shock absorption, and may contribute to countering the pain coming from excessive knee adduction moment during walking (Zafar et al., 2020).

Various walking aids (cane, crutch, walking frame / walker) and assistive technology play a crucial role in the management of knee OA, since 90% of adult people suffering from severe knee pain report the use of canes. Reduction of pain can be achieved by using walking aids, and patients should be taught the optimal use of a cane or crutch in the contralateral hand, while wheeled walkers are ideal for those suffering from bilateral pathologies and require maximum assistance, particularly for the elderly (Karasavvidis et al., 2020).

The monitoring of patients with KOA in the rehabilitation program is done especially for two parameters - pain and function, with the help of evaluation scales (Table II). Different generic scales are also used for quality of life. Through the variation of the score, results are obtained which allow the suited studies to be carried on, in conformity with evidence-based medicine, a long-debated feature for physical and rehabilitation medicine.

Table II

Tools/Questionnaires for Outcome Measures in KOA rehabilitation program.

Parameter		Scales
Pain		AIMS (pain subscale) Global knee pain (VAS) HAQ (pain subscale) Knee-Specific Pain Scale (KSPS) Lequesne algofunctional index (pain subscale) McGill Pain Questionnaire (pain intensity) Number of painful days (days) Pain during activity (VAS or NRS) Pain during walking (VAS or NRS) Pain at night (VAS) Pain at rest (VAS) SF-36 (bodily pain (BP) subscale) WOMAC pain subscale (Likert/100mm) or KOOS or HOOS
Stiffness		WOMAC stiffness scale
Function	Self Reported	ASES (disability subscale) HAQ (disability subscale) PDI (pain disability index) Physical composite score (PCS) based on SF-36, SF-12 SF-36 (subscale physical function (PF) WOMAC subscale Function (Likert/100mm) or KOOS or HOOS
	Performance Based	Aerobic capacity/walking long distances (6-min walk test) Ambulatory transitions (timed up and go) Sit-to-stand (30-sec chair stand test) Walking short distances (4x10m fast paced walk)
Quality of life		SF-36 / SF-12 KOOS QOL

Legend: KOA = knee osteoarthritis; AIMS = Arthritis Impact Measurement Scale; ASES = Arthritis Self Efficacy Scale; HAQ = Health Assessment Questionnaire; HOOS = Hip Disability and Osteoarthritis Outcome Score; KOOS = Knee Injury and Osteoarthritis Outcome Score; NRS = Numerical Rating Scale; SF-36 / SF-12 = 36-Item Short Form Health Survey / 12-Item Short Form Health Survey; VAS = Visual Analog Scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

Discussions

Our review does not detail all the remarkable work that has been published over the last year, but we intended to highlight common research topics that were studied by multidisciplinary medical teams and significant breakthroughs in the field of KOA rehabilitation international research.

A review of the reviews since at least the late 1980s, proposed by the National Institute on Disability, Independent Living and Rehabilitation Research, has proven that Clinical Practice Guidelines (CPGs) in principle are an ideal means to move the knowledge obtained from clinical research to practice, but all CPGs commonly have deficits, especially in terms of applicability (Dijkers et al., 2020).

Despite some guideline recommendations for physical therapy and lifestyle changes as primary treatments, the use of physical therapy for KOA declined between 2007 and 2015. In practice, non-pharmacological treatments are under-utilized (Khoja et al., 2020).

After 2015, the worldwide attitude towards KOA rehabilitation in complete management was reconsidered. We took into consideration only SRs focusing on RCTs with critical information for the formulation of a recommendation, because SRs of observational studies unrelated to adverse effects and the subsequent updates of their guidelines did not evidence critical information about how to best use and implement the recommendations in physical or kinetic therapy clinical practice for KOA patients. There was minimal overlap of the primary studies that were included in the systematic reviews. Thus, the estimates pooled separately from these systematic reviews contain some of the same data.

All included SRs reported substantial heterogeneity in their included studies due to variations in patient characteristics, disease severity, co-morbidity status, types of interventions used and choice of controls, and methodological characteristics. The heterogeneity potential of the results of studied SRs limits the generalization of results. It was unclear whether the observed outcomes were entirely due to the interventions and controls of interest, or the results were influenced by other factors. Also, none of the included SRs provided enough information about the type, intensity, duration, or frequency of physical activity to achieve optimal clinical effectiveness for KOA patients.

Furthermore, information about adherence to exercise programs and adverse events associated with exercise in patients with KOA was limited.

Based on the studied SRs, it could be concluded that there is high-quality evidence that exercise and weight loss reduce pain and improve physical function in patients with KOA. There is moderate-quality evidence that acupuncture, TENS stimulation and low-level laser therapy reduce pain and that psychoeducational interventions improve psychological outcomes. For other interventions and outcomes, the quality of evidence is low or there is no evidence from SRs (Kolasinski et al., 2020).

Physical therapy confers various term-related results (short-term <6 months, intermediate-term ≥6 to <12 months and long-term ≥12 months) for relief of symptoms, a decreased need for pain medications, functional improvements (possible articular malalignments, range of motion, aerobic capacity, quadriceps muscle strength, flexibility and lower extremity stability and performance, gait pattern), physiological well-being (Rat et al, 2020).

There is no consensus on what represents an optimal rehabilitation exercise program for KOA patients with one exception - regularly performed physical exercise should become a lifetime commitment and should be done in sufficient volume to relieve pain and improve function.

Methods to determine and promote ideal exercise-therapy prescription are needed in the future (Whittaker et al., 2020).

After all SRs, we consider the two following fundamental aspects correlated with the kinetic program in KOA patient rehabilitation:

- a variety of choices for exercise programs with positive recommendations for strengthening, without standard protocols, probably due to co-morbidities;
- the necessity to develop combined exercise protocols, both in supervised and home-based exercise programs, to preserve patient compliance and sustain long-term outcomes for pain, function and quality of life.

To increase the value of rehabilitation scoping reviews, rehabilitation stakeholders need to use existing methodological standards for the conduct, reporting, and appraisal of scoping reviews. Much work needs to be done by guideline developers to make it easier for the average rehabilitation organization and clinician to implement CPGs in daily practice. Optimal evidence-based models may use the PICO (Population, Intervention, Comparison, and Outcome) process for the management of KOA (Colquhoun et al., 2020). In the future, all rehabilitation medical professionals focused on KOA patients have to solve the debate regarding the optimal electric, thermal and kinetic modalities and their real effect on symptoms, joint function and quality of life, as well as their feasibility in the long term in accordance with KOA phenotypes (Fig. 2).

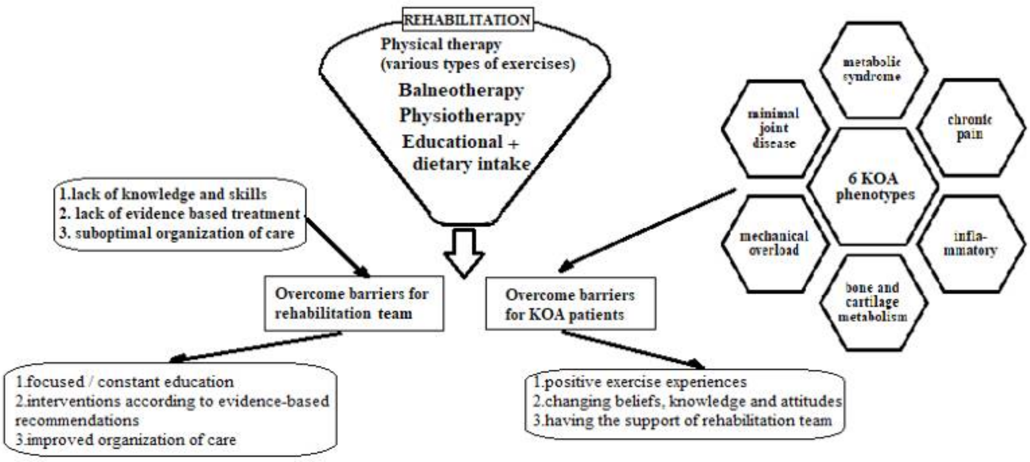

Fig. 2 – Rehabilitation in patients with KOA.

Conclusions

Our narrative review allows all members of the KOA rehabilitation team to improve and upgrade the synoptic knowledge about KOA patients.

We consider that an optimal rehabilitation program for KOA patients is possible only with the involvement of the entire team.

The role of the physiotherapist is well established in non-pharmacological management and to evaluate its effectiveness in treating pain, functional disability and the psychological outcomes of KOA patients. Also, the physiotherapist may overcome the problem of the lack of clinical psychologists to advise patients in self-managing their own conditions.

Conflict of interests

There are no conflicts of interests.

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Is physical activity safe and beneficial for patients with juvenile idiopathic arthritis?

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Abstract

Juvenile idiopathic arthritis is one of the most common physically disabling conditions of childhood and its cause is unknown. Untreated, the disease has a natural oscillating evolution, with exacerbations and periods of low activity and, less frequently, episodes of spontaneous remission. Over time, the disease affects the body's functionality and greatly reduces its adaptation to the environment and quality of life.

The treatment used addresses both symptoms and structural and functional changes so that, along with anti-inflammatory and disease-modifying substances (synthetic or biological), regular physical exercise can be a form of prophylactic treatment of long-term complications.

In this regard, we set out to review a series of articles to highlight the impact of physical activity on children affected by juvenile idiopathic arthritis. Physical activity has been shown to have an impact not only on functional capacity, but also on a cellular level, with the final result of reducing inflammation and promoting a healthier intestinal environment by diversifying the intestinal microbiome.

In conclusion, physical activity is safe for children with juvenile idiopathic arthritis. Keeping a physical activity regimen brings benefits both at the systemic level, through cellular mediation, and at the musculoskeletal level.

Keywords: juvenile idiopathic arthritis, physical activity, functionality, quality of life, cellular impact, impact on intestinal microbiome.

Introduction

Data from the specialized literature emphasize that regular physical activity sustained by patients who are diagnosed with juvenile idiopathic arthritis (JIA) is an important element in the therapeutic management of the disease. However, at present in the medical world there are still delays in prescribing exercise to patients with JIA mainly for safety reasons. In this article we aim to review some data about the impact that exercise has on the evolution of the disease both clinically and biohumorally.

JIA is the most common chronic rheumatic disease in children and adolescents, and is characterized by the presence of arthritis of unknown etiology persisting for at least 6 weeks, which occurs before the age of 16 years (***, 2018).

Both endogenous and exogenous factors have been linked to the pathophysiological mechanism of the disease; at present, the disease is considered to be the result of the interaction between genetic and infectious factors (Takken, 2010).

From a genetic point of view, JIA is considered a polygenic disease, the HLA region being the major locus of susceptibility which explains 13% of the genetic risk for JIA (Ravelli & Martini, 2007).

From a clinical point of view, JIA can manifest in several forms. There are 7 categories of JIA (Melson et al., 2005):

a) Systemic arthritis
b) Oligoarthritis
- Persistent oligoarthritis
- Extended oligoarthritis
c) Polyarthritis (rheumatoid factor negative)
d) Polyarthritis (rheumatoid factor positive)
e) Psoriatic arthritis
f) Enthesitis-related arthritis
g) Undifferentiated arthritis

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The treatment of the disease is a multidisciplinary one. Along with medication with disease-modifying anti-rheumatic drugs (DMARDs) – conventional and biological, rehabilitation by physical therapy and psychotherapy have an important role.

JIA is a disease in which by careful management, patients diagnosed at childhood will not experience disabilities during adulthood. Early diagnosis, proper treatment, education and teamwork that includes family, patient and medical staff are factors that increase the success rate.

The objectives of rehabilitation in JIA include: controlling pain, preventing the development of mobility limitations, and improving ROM in the affected joints, improving and maintaining muscle tone, increasing and maintaining endurance for daily activities, minimizing the effects of inflammation, ensuring growth and development within normal parameters (Cakmak & Bolukbas, 2005).

The inability to perform normal movement can influence physical training, school performance, family life, recreational activities (social integration).

Unlike healthy children, children diagnosed with a chronic illness are most often absent from physical activities or sports programs (Apti et al., 2014). The altered general condition of children with a chronic inflammatory disease causes hypoactivity, which leads to a decrease in physical condition and enhances functional impotence, which generates a vicious circle (Metin et al., 2004).

The level of physical activity and cardiopulmonary capacity of patients with JIA is significantly lower compared to healthy children. A meta-analysis (Metin et al., 2004) shows that the maximum oxygen consumption (VO_2 peak) was 21.8% lower in patients with JIA than in healthy subjects. The reduced cardiopulmonary capacity of children with JIA does not appear to be directly related to its status, whether the disease is active or in remission (Lelieveld et al., 2007). Melson et al. found small differences in physical capacity between subjects who had disease activity and were taking medication and those who were in remission and not taking medication (Melson et al., 2005).

Inactivity is also strengthened by the fear of physical exertion, the belief that physical exertion is harmful (Apti et al., 2014), or by the postponement of physical exertion during periods of increased disease activity (Kirchheimer et al., 1993).

Over time, numerous studies have looked at the relationship between physical exertion and pain in patients with JIA. A randomized, controlled, single-blind study in which the control group was placed on a waiting list by the end of the study showed significant differences in pain level (measured by VAS) in favor of the study group, who practiced physical exercise (Houghton et al., 2018; Tarakci et al., 2012). On the other hand, on a smaller scale, there are exceptions: in a pilot study, Singh-Grewal states that subjects with severe hip impairment gave up the exercise program due to worsening pain during exercise (Singh-Grewal et al., 2006). Other studies show that pain levels are correlated with disease activity rather than exercise (Atwood, 2007).

Regarding the relationship between physical exertion and disease activity, Takken et al., through a meta-analysis conducted in 2008, evaluated the safety of exercise in patients with JIA and concluded that physical exertion does not appear to be directly responsible for exacerbations of arthritis (Takken et al., 2008). The results of a meta-analysis conducted by Kuntze in 2018 also advocate the safety of physical exercise by patients with JIA (Kuntze et al., 2018).

Thus, the main problems faced by patients with JIA are reduced exercise tolerance, reduced physical activity and disability due to joint damage (swelling, stiffness, reduced mobility, joint deformity), muscle (decreased strength, decreased motor performance), bone (fragility, damage to the growth cartilage with consecutive growth disorders), as well as emotional problems caused by the disease or the attitude of people with whom patients with AJI interact (parents, teachers, doctors).

A series of studies show that the prescription of physical exercise practiced either at home or in a specialized center, in aquatic environment or on land by patients with JIA has a positive impact both in the secondary prophylaxis of the disease and in the primary prophylaxis of the main comorbidities accompanying JIA (metabolic, endocrine, respiratory, cardiovascular, depressive syndromes) (Basile, 2017; Klepper, 2001; Long & Rouster-Stevens, 2010).

The types of physical activity proposed in the studies vary depending on the environment in which they are practiced (water, soil), depending on the intensity of the effort (from Pilates, Thai Chi to cardio exercises) and the goal (impact on joint mobility, strength, pain relief, increased quality of life, etc.). Lelieveld points out that a child's daily activities are generally anaerobic (jumping, throwing and catching objects, running short distances), which means a high energy requirement over a short period of time (Lelieveld et al., 2007).

The most suitable physical training program for patients with JIA is the one that targets the patient's posture, joint mobility problems, their physical capacity and muscular strength. It is recommended, depending on the patient's needs, to set the goals to be reached after exercise.

The most commonly monitored indices in clinical practice are: pain level, degree of joint mobility (ROM), number of affected joints, muscle strength, oxygen requirements and quality of life.

Decreased muscle strength in adolescents with JIA is another problematic issue. Exercises to increase muscle strength require extra attention and involvement from both the therapist and the patient and his/her family.

In a randomized controlled trial that included subjects with extended polyarticular or oligoarticular JIA, Eva Sandstedt observed a statistically significant increase in muscle strength after 12 weeks in subjects who performed exercises involving jumping or weightlifting compared to those who performed classic exercises. At the same time, the study shows that exercises involving weights or jumps can be performed safely, without significantly increasing pain, by patients with JIA (Sandstedt et al., 2013).

Following a prospective study evaluating 62 patients with JIA, Kirchheimer concluded that sports activities such as swimming or cycling do not adversely affect the upper or lower limb joints (Kirchheimer et al., 1993).

Takken et al., in a Cochrane review conducted in 2008, show that there was no clinically important or statistically significant evidence that exercise therapy can improve functional capacity, quality of life, aerobic capacity, or pain. At the same time, no short-term negative effects of exercise therapy were found, and the data show that exercise does not exacerbate arthritis and that the short-term effects of exercise in patients with JIA seem promising, but the long-term effects remain unclear (Takken et al., 2008).

Why and how does physical therapy improve the course of the disease and improve the quality of life in patients with JIA? We find the answer at the cellular level.

JIA is currently classified as an autoimmune disease, being predominantly characterized by the activation of the innate immune system. However, for this to happen it is necessary to involve the adaptive immune system (Rochettea et al., 2015). The antigen is presented to T cells by macrophages, B cells, dendritic cells, fibroblasts, endothelial cells, and the activation of T lymphocytes takes place which stimulate the production of Th1 lymphocytes and B lymphocytes following the activation of Th17 cells. Pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α play a central role in the differentiation of naive T lymphocytes into effector T lymphocytes (Th1/Th17) (Mellins et al., 2011). Subsequently, innate immunity is activated - effector cells - macrophages, mast cells, NK cells, which leads to an even greater release of cytokines. Inflammation of non-lymphoid tissues can induce the differentiation of T lymphocytes into activated, specialized, memory-based subsets (eTreg) (Kim & Moudgil, 2017).

Data from the literature show that exercise can help reduce the effect of inflammation both by regulating the lymphocyte population by apoptosis correlated with increased plasma cortisol levels through exercise, and by quantitatively decreasing pro-inflammatory cytokines and increasing anti-inflammatory mediators (Gordon-Smith et al., 2015).

While the pro-inflammatory cytokines TNF-α and IL-1β may show a slight decrease after physical training, IL-6 appears to decrease in prolonged training, but has a privileged anti-inflammatory pathway through both short-term exercise and prolonged training (Takken, 2003).

Anti-inflammatory mediators such as the IL-1 receptor antagonist (IL-1Ra), IL-10, the soluble receptor for TNF (TNF-R) increase after endurance exercise and resistance exercise. Exercise also has an effect on mi-RNA. There has been an increase in the circulating level of miR-146a, a molecule with anti-inflammatory effect, in trained people who perform episodic exercise (Rochettea et al., 2015).

It is known that during physical exertion the release of AMP is increased and the affinity of ecto-5'-nucleotidase for AMP increases. This causes an increase in the amount of adenosine released in the striated muscles, vessels, sympathetic nerve fibers, motor fibers.

A correlation was found in JIA between decreased adenosine production and disease severity. At the same time, the anti-inflammatory actions of methotrexate are mediated by the release of adenosine (from ATP molecules by ectonucleotidases CD39 and CD73). Serum levels of adenosine deaminase (the inosin-converting enzyme) may serve as a marker of JIA activity (Mendonca et al., 2013; Ravelli & Martini, 2007).

Thermal shock protein 60 (HSP60) appears to be involved in disease remission in JIA. In experimental models, immunization with HSP10, HSP60, HSP70 or HSP90 can suppress arthritis in laboratory animals. This is possible because HSP60 plays a key role in modulating the interaction between the inflammatory process and cellular stress. The reduction of HSP60 correlates with the increase in the expression of inflammatory tissue cytokines produced by macrophages, such as IL-6 and TNF-α (Khadir et al., 2018). Sustained training programs can increase the level of HSP60: 3 months, three times a week: 10 minutes of warm-up, 10 minutes of cooling to a frequency of 50-60% maximum heart rate (MHR) and 40 minutes of intense exercise at a frequency of 65-80% MHR (Kim & Moudgil, 2017).

The intestinal microbiota is an important part of the human body and it is increasingly brought to the attention of scientific researchers. It seems that the intestinal microbiota plays an important role in inflammation. The microbiota intervenes, among other things, in the maturation of the immune system, helping to develop the lymphoid tissue associated with the intestine (Yuliaxis Ramayo-Caldas et al., 2016). By continuously stimulating the immune system, a physiological state of inflammation is maintained at a low level, which helps to better defend against other microorganisms (Cassidy & Petty, 2005).

In patients with JIA, intestinal permeability is increased compared to children who do not have a chronic inflammatory disease, being disrupted by the role of mechanical barrier and leading to changes in the composition of the intestinal microbiome. The composition of the intestinal microbiome in children with JIA is different from that of healthy children, as they have high concentrations of Bacteroides species and high concentrations of Firmicutes species. Actinobacteria and Fusobacteria are present only in patients with JIA, while the genus Lentisphaerae is missing (Ramayo-Caldas et al., 2016).

Studies show that the intestinal microbiome can be modulated by physical activity. The effect of exercise on the modulation of the intestinal microbiome varies depending on the intensity of the physical effort practiced, the level of training and the level of fitness.

Moderate exercise results in a diversification of the Firmicutes phylum species (including Faecalibacterium prausnitzii, species of the genus Oscillospira, Lachnospira, and Coprococcus), which contributes to a healthier intestinal environment (Sule & Fontaine, 2019).

Regarding the implementation of exercise therapy, a strategy is needed for the clinician. Given that there is no consensus in the medical world about how to perform exercise, some basic rules that can be derived from studies conducted so far can be followed.

The recent literature supports the importance of combining: stretching exercises, muscle toning, proprioceptive reeducation and balance reeducation and underwater activities. Numerous studies propose an intensive program of physical activity and exercise therapy, performed 3 times a week for 12 weeks.

The difference between physical activity and therapeutic physical exercises is given by the purpose and ways used to practice the form of movement.

Therapeutic exercise consists of a set of activities designed and prescribed for specific therapeutic purposes such as restoring normal musculoskeletal function and reducing pain (Lelieveld et al., 2007).

Physical activity is any bodily movement produced by skeletal muscles and performed with energy consumption. It includes non-therapeutic activities (domestic, professional, sports) and the main goal is to increase the level of fitness (Cassidy & Petty, 2005).

Physical activity can turn into therapeutic exercise when the activities become planned and structured for people with medical conditions (occupational therapy).

For home exercise programs, 3 basic rules related to cost, customization and quality can be taken into account. First of all, the most convenient treatment is the simplest, least painful and cheapest; secondly, stretching and muscle toning exercises should be customized according to the daily activities which the patient has difficulty performing; thirdly, all treatment measures must be done under the careful guidance of a medical professional (Cakmak & Bolukbas, 2005).

The contraindications to exercise are fever, severe anemia, acute renal failure, heart failure, serositis, uncontrolled arrhythmias, uncontrolled hypertension, severe malnutrition (with a body weight loss of over 35%), joint pain and excessive swelling.

Ideally, children and adolescents would need more than one hour of moderate-intensity physical activity each day and more than one hour of high-intensity physical activity for at least 3 days each week.

Conclusions

1. The literature supports the importance of practicing physical exercise by patients with JIA. Moreover, data shows that physical exertion can be practiced safely, that it does not contribute to the exacerbation of the disease activity or to the increase of the perceived pain level.

2. Physical effort is worth considering in the therapeutic management of children and adolescents with JIA. Regular exercise can help improve the range of motion, increase muscle strength, decrease pain intensity and increase quality of life. Moreover, it can improve the intestinal microbial flora and has a positive impact on modulating the inflammatory process.

3. The concrete objectives of practicing physical exercise are managing pain and inflammation, maintaining range of motion, maintaining muscle strength and coordination, limiting strain on inflamed joints, increasing fitness, controlling disease activity, maintaining the physical and mental integrity of the child / adolescent, and increasing quality of life.

4. Ideally, children and adolescents would need more than one hour of moderate-intensity physical activity each day and more than one hour of high-intensity physical activity for at least 3 days each week.

Conflict of interests

There are no conflicts of interests.

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Physical activity and maintaining of the proteome in the aging process - are these footsteps on the way to longevity?

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Abstract

Accumulation of dysfunctional and damaged cellular proteins and organelles occurs during aging, resulting in a perturbation of cell homeostasis and inexorable degeneration up to cellular death. Therefore, moderating these components may be a key in the promotion of longevity. Exercise is known to promote healthy aging and mitigate age-related pathologies, and recent studies suggest that exercise modulates the proteome. Autophagy is an evolutionary conserved recycling pathway managing degradation, and it declines during aging. The target of rapamycin complex 1 (TORC1), a central kinase involved in protein translation, is a negative regulator of autophagy, and inhibition of TORC1 enhances lifespan. As a consequence, the longevity effects of exercise may stem from the maintenance of the proteome by balancing the synthesis and recycling of intracellular proteins, and thus may promote longevity.

Participation in vigorous physical activity at a specific time point is an indicator of good fitness and health and is associated with a reduced risk of death. However, randomized controlled trials (RCTs) and translational models have not provided strong evidence to show that physical activity started during adulthood extends lifespan and promotes longevity. Physical activity improves fitness and physical function, and confers other health-related effects.

Keywords: harmful binomial distress - aging, movement and physical activity, mTOR, stress, muscular contraction, autophagy, longevity.

Introduction

Aging is a biological process characterized at the cellular level by a progressive accumulation of dysfunctional proteins and damaged cell compartments. Accumulation and aggregation of these impaired components disrupt cellular homeostasis, progressive degeneration may appear, and the risk of cell death is increased (López-Otín et al., 2013).

Intracellular protein quality concurrently depends upon protein synthesis (Salminen & Kaarniranta, 2009). As such, the degradation of unnecessary and dysfunctional cytosolic elements, occurring through the autophagy process, represents only one aspect of intracellular protein deposits, which is counterbalanced by the regulatory components managing the synthesis of new cellular proteins.

The target of rapamycin complex 1 (TORC1; known as mTORC1 in mammalian species) is a central regulatory kinase that regulates cellular growth and protein synthesis. This complex is stimulated by nutrient availability (i.e. amino acids, ions), mechanical stress, and growth factors (i.e. insulin-like growth factor 1 – IGF-1) and is inhibited by nutrient starvation, energetic stress, and the macrocyclic polyketide *rapamycin* (Jung et al., 2010).

Recently, TORC1 activity has been linked to lifespan and the aging process in a variety of model organisms, whereby inhibition of the TORC1 pathway is consistently observed to enhance longevity in animal and cellular models (Lamming et al, 2013). TORC1 also serves as an inhibitor of autophagy, thus suggesting that autophagy represents a key link between TORC1 activity and the aging process (Xu et al., 2013).

Neither randomized controlled trials (RCTs) nor experimental animal studies have provided good evidence that *physical activity* initiated during adulthood prolongs lifespan, but on the other hand it was demonstrated that physical activity improves fitness and physical function and helps in the prevention of disability (Pasanen et al., 2017). The risk of death during exercise is low and the risk of sudden cardiac death is increased during episodic physical

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activity (Dahabreh & Paulus, 2017). People who usually exercised fewer times per week (once instead of four or five times) had higher relative health risks (Dahabreh & Paulus, 2017). Therefore, increasing levels of habitual physical activity were associated with progressively lower relative risks of myocardial infarction during episodic heavy physical activity (Mittleman et al., 1993). Plaque rupture represents one of the most unpredictable mechanistic causes for sudden death during or after physical exercise among individuals with coronary artery disease, as well as in apparently healthy individuals (Ciampricotti et al., 1990; Burke et al., 1993).

The correlation between the TOR pathway and the aging process

A less researched aspect in recent years has been the role of aging (Meijer et al., 2015). It is not due to the chance that chronic diseases occur simultaneously in most species when individuals reach two thirds of their lifespan, for example at about 60 years in humans. In conclusion, it is not time itself that becomes a variable, but the aging process and *the quality of the components* that are part of it. Thus, the causality of the disease is not given as in the previous century by pathogens or precarious environmental factors. Researchers have identified molecular and cellular mechanisms / pathways that inexorably lead to aging (Bjedov et al., 2010; Vellai et al., 2003). Thus, new pharmacological therapeutic options and dietary supplements such as rapamycin (Wu et al., 2013) and senolytics have been made available (Harrison et al., 2016).

It was predicted in 2003 that the irreversible transformation from cell maturation arrest to senescence (geroconversion) is determined by growth-promoting mediators, such as mTOR, when the cell cycle is blocked (Bitto et al., 2016). Figuratively, geroconversion is "tangled" growth, which occurs only when maturation is complete (Lee et al., 2010; Vincze & Vincze-Tiszay, 2020). In cell cultures, mTOR is activated to the maximum and geroconversion lasts 3-6 days, while in the human body it can take up to a few decades. MTOR drives geroconversion, making cells hypertrophic and hyperfunctional (e.g., secretory phenotype associated with senescence), leading to the development of age-related pathologies. Human fibroblasts, either presenescent (PRE) or senescent (SEN), have been immunostained for inflammatory cytokines such as IL-6 and IL-8 and the senescence marker p16 (Colhero et al., 2016). Various natural compounds have been reported, including epigallocatechin gallate (EGCG), caffeine, curcumin and resveratrol or berberine which inhibit mTOR when applied on cells isolated in cultures, or even diets have been proposed with modest results (Vaupel, 2010) (Fig. 1).

It is known that meclofenoxate (also known as centrophenoxine) is a cholinergic nootropic used as a dietary supplement. Chemically, it is an ester of dimethylethanolamine (DMAE) and 4-chlorophenoxyacetic acid (pCPA). In elderly patients, meclofenoxate has been shown to improve performance on certain memory tests. Meclofenoxate also increases cell membrane phospholipids (Stringhini et al., 2017). Meclofenoxate, as well as DMAE, has been shown to increase the lifespan of mice by 30–50% (Karvinen et al., 2015).

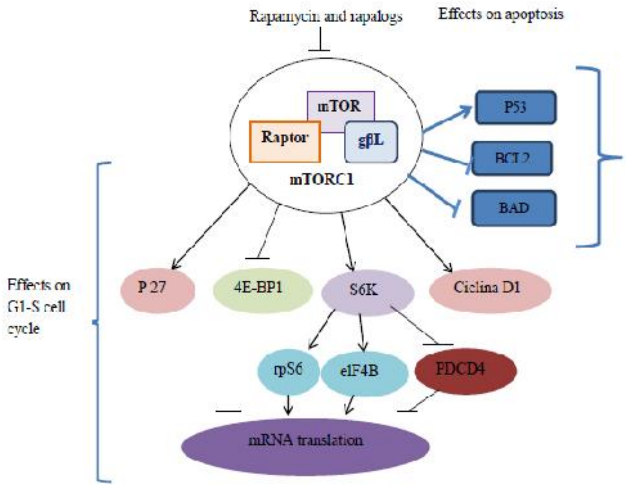

Fig. 1 – Effects of rapamycin and rapalogs on neoplastic cells.

Target of mTORC1 is one of two functionally distinct multi-protein TOR complexes, the second being TOR complex 2 (TORC2). Both complexes are highly conserved in all known eukaryotic cells. TORC1 is a primary mediator of protein synthesis and cell growth, whereas TORC2 remains less understood. TORC2 has been suggested to regulate spatial coordination of the cytoskeleton (Xu et al., 2013), while also being involved in TORC1 activation via the Akt pathway (Jung et al., 2010). Acute rapamycin treatment strongly inhibits TORC1 activity, but the effects of TORC2 are not fully characterized; as rapamycin cannot bind to the fully assembled TORC2, complex chronic rapamycin treatment can also disrupt TORC2 activity. Knowing that inhibition of TORC1 pathway extends lifespan and promotes healthy aging in multiple model species (Laplante & Sabatini, 2012) and that TORC1 also acts as an *inhibitor of autophagy*, we could presume that the lifespan-extending effects of TORC1 inhibition will directly and partially increase autophagic activity, reduce the synthesis of new intracellular proteins, or may be some combination of the two (Xu et al., 2013; Meijer et al., 2015).

It is a plausible hypothesis that increasing protein synthetic activity via TORC1 in post-mitotic cells (i.e. mature cells which have entered cell cycle arrest and no longer split) leads to less autophagy, and consequently the accumulation of superfluous organelles (Xu et al., 2013). What is interesting is that knockdown of *Atg genes* is critical to autophagic function, because it reverses the life-extending effects of rapamycin, allowing to conclude that autophagy does play a key role in TORC1-mediated life extension (Bjedov et al., 2010).

The first observation of extended lifespan due to TORC1 inhibition was made in *Caenorhabditis elegans*, where reducing TORC1 increased lifespan more than twofold (Vellai et al, 2003). In mice, the direct genetic knockdown of mTORC1 resulted in a 20% lifespan extension and a prominent reduction in age-associated pathologies (Wu et al., 2013). Administration of rapamycin at 600 days in mice (equivalent to 50 years in homo sapiens) extended lifespan up to 14% in female and only 9% in male animals (Harrison et al., 2009). Additionally, 3 months of rapamycin treatment increased life expectancy by up to 60% in middle-aged mice (Bitto et al., 2016). In contrast, silencing expression of *Sestrin*, a TORC1 inhibitor, has been shown to instigate numerous age-related pathologies (Lee et al., 2010).

Movement and physical activity – anti-aging factors

Distress, vulnerability and adaptation are studied comparatively in human ontogenesis during young, adult and old stages of life. The analysis of the negative temporal interrelationships between distress, the exhaustion phase of General Adaptation Syndrome (GAS) originally described by Selye and aging leads to the concept of harmful binomial distress ↔ aging (Riga & Riga, 2009).

This binomial manifests its adverse consequences through muscle hypokinesia or lack of movement of the individual. In addition to well known risk factors such as obesity, lack of physical activity and the inflammatory effect of oxidative stress, it will add exponentially decreased muscle mass and physiological malfunction (sarcopenia), osteoporosis and an increased risk of fractures.

a) Emergence of longevity

Some individuals can survive to old age, even in populations with a relatively low mean life expectancy. In human and animal populations, a low mean life expectancy is associated with low lifespan *equality* (Colhero et al., 2016).

Progress made in lengthening the human lifespan reflects contemporary medical practice and good public health systems, combined with rising standards of living, superior education and healthier nutrition and lifestyle (Vaupel, 2010). Interestingly, the association between socioeconomic status and mortality is comparable in strength and consistency to that of tobacco use, alcohol misuse, sedentariness, hypertension, obesity and diabetes, with smoking having the highest risk estimate (Stringhini, 2017).

b) Bias in interpretation of observational data and risk of death

Unfortunately, a causal relationship between adulthood physical activity and mortality/lifespan has neither been confirmed in randomized controlled intervention studies with initially healthy individuals (Karvinen et al., 2015) nor in animal experiments (Garcia-Valles et al., 2013).

In the first place, selection bias in the population is an alternative explanation. Aged individuals who are healthy enough to exercise (without any chronic disease) will manifest a reduced risk of death irrelevant of their physical activity level. Secondly, studies comparing the predictive role of physical activity at younger versus older age show that older age physical activity is a stronger predictor of death (Bijnen et al., 1999). High cardiorespiratory fitness, as an integrated measure of body function, together with neuromuscular and metabolic function, is a strong predictor of reduced mortality in humans (Kodama et al., 2015) and in rats (Koch et al., 2011). Low cardiorespiratory fitness is associated with an increased risk of multiple chronic diseases and death (Ross et al., 2016).

To increase our understanding of the associations between genes, physical activity and mortality, a study was carried out on separated human dizygotic (DZ) and monozygotic (MZ) twin pairs who were long-term discordant for vigorous physical activity. High heritability of physical activity reduced the number of MZ pairs discordant for physical activity and thus contributed to the only moderate statistical power in analyzing pairwise risk differences among MZ pairs (Karvinen et al., 2015). Therefore, genetic pleiotropy may partly explain the associations observed between high physical activity and mortality in epidemiological studies, and secondly, the inherited aerobic capacity is a predictor of longevity (Kujala et al., 2003). In rodents, physical activity initiated during adulthood (in twins after moving from the childhood home environment or in full-grown animals) did not improve longevity.

Physical activity mismatches in results among DZ pairs may occur due to genetic differences and only findings from MZ pairs control for genes at sequence level. Mendelian randomization analyses (Kennedy et al., 2014) and studies on genetic pleiotropy (Mannick et al., 2014) could also help in clarifying the role of genetic factors. Researchers have tried to develop useful biomarkers of aging to investigate which factors play a role in accelerating or decelerating the inexorable aging process. Biomarkers such as measuring telomere length (Justice et al., 2019) or DNA methylation age (epigenetic clock) could be the answers (Demidenko & Blagosklonny, 2008). Shortening of telomeres that induces cell senescence or apoptosis is associated with shortened life expectancy. Unfortunately, based on a recent meta-analysis, no consistent association has been found between physical activity and telomere length (Justice et al, 2019).

c) Evidence from randomized controlled trials

So far, RCTs have failed to provide conclusive evidence that exercise can extend lifespan/reduce premature deaths when individuals apparently healthy at baseline are randomized to physical activity/exercise versus control groups.

In the LIFE Study, a number of 1635 sedentary individuals aged 70-89 years were assessed (Newman et al., 2016). The intervention was aerobically-based, with a moderately intensive physical activity program, but the results showed no reduction of cardiovascular events although the intervention was effective in preventing mobility disability. Similarly, the Look AHEAD Study of 5145 overweight or obese patients with type 2 diabetes (Wing et al., 2013), including a combination of increased physical activity and improved diet intervention, demonstrated a difference in fitness between the intervention and control groups, but no difference in cardiovascular events.

d) Exercise may maintain the proteome

Exercise may increase autophagic activity in exercised muscle due to cellular mechanisms, including widespread protein or mitochondrial damage, increased mitochondrial respiration, high concentrations of reactive oxygen species (ROS), the presence of certain cytokines or other elements of the immune cascade (Vainshtein & Hood, 2016).

During physical exercise, autophagy mediates the clearance of proteins and organelles damaged by heat, pH changes or mechanical stress, which in fact acts against the accumulation of cytosolic components and maintains a good myocyte function (Schwalm et al., 2015). Moreover, alterations in calcium, NAD+, and ROS levels are also strong instigators of autophagic activity (Vainshtein & Hood, 2016). Unlike other tissues such as the liver and pancreas, upregulation of autophagy in skeletal muscle persists for days, rather than hours (pancreas or liver), following a period of energy insufficiency, indicating a greater importance of autophagic function in skeletal muscle proteostasis (Sandri, 2010).

Exercise seems to start autophagy in skeletal muscle through AMPK and SIRT1which are sensitive to alterations in AMP and NAD+, respectively. AMPK and SIRT1 actions are to upregulate expression of Atgs by increasing PGC1-α activity, activating FOXO1 and FOXO3 and inhibiting mTORC1 (Vainshtein & Hood, 2016). On the other hand, AMPK initiates autophagosome formation via ULK1 (Mooren & Kruger, 2015).

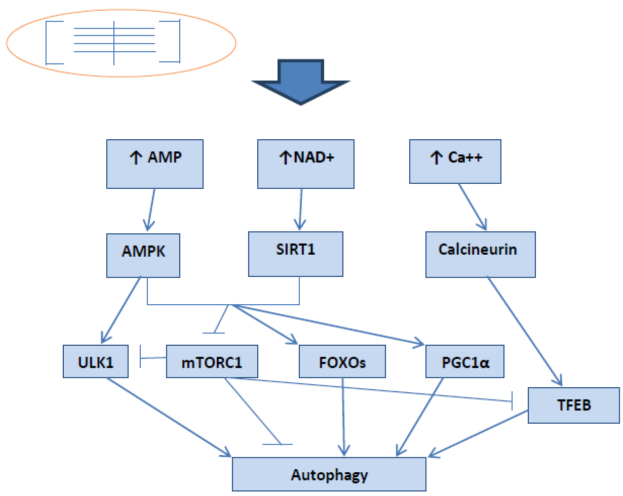

Fig. 2 – Skeletal muscle contraction.

AMPK is also sensitive to changes in the cellular AMP /ATP ratio and so it may be quite increased during exercise (Mooren & Kruger, 2015). The influence of exercise on mTORC1 activation also depends *on the type* of exercise performed, as mTORC1 *integrates* stimuli from growth factors, existing nutrients, and mechanical loading (i.e. resistance exercise type) (Watson & Baar, 2014). While energy demands induce a downregulation of mTORC1-mediated anabolism during exercise that is likely affected via AMPK activation, mTORC1 activity is upregulated in the adaptive post-exercise period, as opposed to a continuing high activity of AMPK (Rowlands et al., 2011) (Fig. 2).

Autophagy possesses a role in conferring the benefits of exercise, including enhanced endurance, mitochondrial biogenesis and angiogenesis (Lira et al., 2013). Chaperone-mediated selective autophagy has also been shown to be involved in skeletal muscle cytoskeleton maintenance and adaptation in response to resistance training (Ulbricht et al., 2015).

Also, exercise increased autophagic flux in the *anterior cerebral cortex* (He et al., 2012). The authors defined physical exercise as a newly created inducer of autophagy *in vivo* and they generated mice with a knock-in non-phosphorylatable mutation in BCL2 (BCL2 AAA), which are defective in exercise- and starvation-induced autophagy but not in basal autophagy (Yang et al., 2014). The results were that BCL2 AAA mice could not run on a treadmill as long as wild-type mice, and did not undergo exercise-mediated increases in skeletal muscle glucose uptake. Unlike wild-type mice, BCL2 AAA mice failed to reverse high-fat diet-induced glucose intolerance after 8 weeks of exercise training, possibly due to defects in signaling pathways that regulate myocyte glucose uptake and metabolism during exercise (He et al., 2012). Secondly, treadmill exercise also induces autophagy in the cerebral cortex of adult animals. Therefore, autophagy may mediate the beneficial effects of exercise in neurodegeneration, neurogenesis, and improve overall cognitive function (Ulbricht et al., 2015).

These mechanisms suggest that exercise has a role in modulating some of the age-related pathologies in which autophagy has been reported to be implicated, which include neurodegeneration (Yang et al., 2014), type 2 diabetes (Quan et al., 2013), neoplasm (Cecoconi & Levine, 2008) or cardiomyopathy (Nair & Ren, 2012), while improving muscle quality and overall function (Fan et al., 2016). Autophagy and mTORC1 represent a key in proteostatic pathways and are involved in aging phenotype (Rubinsztein et al., 2011; Wei et al., 2013). On the one hand, autophagic function declines during aging (Mejias-Pena et al., 2016) and on the other hand, there is empirical support for the important influence of autophagy on organismal lifespan (Martinez-Lopez et al., 2015; Jung et al., 2010).

MTORC1 inhibition is known to upregulate autophagic activity; therefore, there is good evidence of a potent role for autophagy in the aging process, and consequently, reductions in mTORC1 activity may also attenuate aging in an autophagy-independent manner (Xu et al., 2013).

In humans and rodents, acute exercise has been proved to promote autophagic activity in multiple tissues (He et al., 2012; Mooren et al., 2015; Schwalm et al., 2015), and chronic exercise may also induce upregulation of basal autophagy levels (Lira et al., 2015; Feng et al., 2011).

Conclusions

1. Based on observational population studies, high physical activity is associated with a reduced risk of premature death, but the causal relationship remains unproven. Participation in physical activity at a *specific time point* is an indicator of good fitness and health, and is associated with a reduced risk of death. Lifelong physical activity may extend lifespan, but evidence from interventional studies is limited and the potential effects of early adulthood physical activity versus inactivity on later health require more research. The possible life-shortening effects of vigorous physical activity are not completely demonstrated or understood.

2. Physical activity improves fitness and physical function, and confers other health-related benefits. These outcomes have a greater basis in terms of evidence-based data than any claims of a reduced risk of death, especially when recommending physical activity for previously

physically inactive middle-aged and elderly adults.

3. 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. Given that there is quite good evidence that regular exercise promotes healthy aging and mitigates age-related pathologies, it is possible to speculate that there is a common pathway in health and longevity which may be due to proteostatic maintenance. Currently, our understanding of the molecular mechanisms underlying cellular and biological aging and the interplay between physical activity and aging phenotype development requires further trials, especially in humans.

4. Movement, physical activity and sport are key sanogenetic factors in the bio-psycho-social activation context of the elderly. Therefore, physical activity as a goal for health is recommended to be implemented in the elderly population. At individual level, regular physical activity increases muscle mass and strength, improves the functioning of the cardiovascular system, and enhances cognition.

Conflict of interests

None declared.

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Vitamin K in sport activities: a less considered benefit for athletic training

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Abstract

Vitamin K is a family of different fat-soluble molecular compounds, represented by a single form synthesized by plants (vitamin K1), and multiple forms synthesized by bacteria (vitamins K2). Several vitamin K-dependent proteins are synthesized based on vitamin K co-enzymatic activity. The sources of vitamin K are mainly green and leafy vegetables, fruits, herbs, green and herbal teas and plant oils - for vitamin K1 and fermented animal foods - for vitamin K2.

Vitamin K and its dependent proteins have important roles in several physiological or tumoral processes: bone mineralization, blood clotting, metabolism of blood vessel walls, tumoral angiogenesis and even cell growth and nervous system biochemistry (aspects of behavior and cognition). Vitamin K deficiency is associated with several diseases, including osteoporosis, vascular calcification and even depression.

Through its involvement in cardiovascular and nervous system function, and bone metabolism, vitamin K supplementation could improve exercise capacity.

Keywords: vitamin K1, vitamin K2, diet, exercise capacity.

Biochemistry and metabolism of vitamin K

Vitamin K is known as a fat-soluble compound which has a common 2-methyl-1,4-naphthoquinone nucleus but differs in the structure of a side chain of the third position and is essential in the post-translational modification of a set of proteins which are called vitamin K-dependent proteins (Shearer & Newman, 2014). The discovery of vitamin K is related to different experiments which investigated the role of cholesterol in the diet of chicks – a curative factor present in vegetable and animal sources was a new fat-soluble vitamin, which was called vitamin K (Gröber et al., 2014). Phylloquinone is known as vitamin K_1 and has a phytyl side chain, menaquinones are known as vitamin K_2, and the synthetic compounds are named menadione and menadiol (Braasch-Turi & Crans, 2020). The natural nutritional sources of vitamin K1 are represented by fruits (e.g., avocado, kiwi, and green grapes), seeds, green and leafy vegetables (e.g., kale, Brussels sprouts, broccoli), herbs (e.g., cilantro, parsley), plant oils (soybean oil, canola, and olive oils), and the sources of vitamin K_2 are represented by bacterial fermented foods (fermented butter or cheese, curdled cheese), or foods of animal origin (egg yolk, foie gras, beef liver, poultry products) (Elder et al., 2009). We obtain by nutrition mostly vitamin K1 (phylloquinone), and intestinal bacteria synthesize K2 *de novo* and also convert vitamin K1 to vitamin K2 (menaquinones) (Kiela & Ghishan, 2016). The absorption of vitamin K depends on its incorporation into mixed micelles in the intestinal lumen. This process requires the presence of bile acids and the products of pancreatic enzymes (Iqbal & Hussain, 2009). Dietary vitamin K is absorbed in the proximal small intestine by active transport; then vitamin K is incorporated into chylomicrons which are then secreted into the lymph and pass into the blood (Kiela & Ghishan, 2016). Extrahepatic tissues use vitamin K_1 to synthesize menaquinone-4, from chylomicrons and

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very-low-density lipoproteins. Menaquinones are absorbed from the terminal ileum, and menadione is absorbed by way of the portal system and some of this compound is absorbed into the lymphatic system (Kulkarni, 2012). On the other hand, menadione is metabolized very fast and only a small proportion is converted to biologically active menaquinone-4. Because of the low levels of transporting lipoproteins, the transport of phylloquinone from maternal to fetal circulation is poor (Schurgers & Vermeer, 2002).

One of the most important metabolic functions of vitamin K is being a coenzyme in the carboxylation of protein-bound glutamate residues to yield gamma-carboxyglutamate residues. Vitamin K-dependent proteins refer to several proteins, especially the Gla proteins, and the enzymatic reaction is catalyzed by gamma-glutamyl or vitamin K-dependent carboxylase which is linked to a cyclic salvage pathway – the vitamin K epoxide cycle (Card et al., 2014).

The physiological roles of vitamin K

The role of vitamin K is very important and there are many vitamin K-dependent proteins that are found in bone tissues such as osteocalcin, matrix Gla protein also identified as MGP, Gas6 and protein S (1). The most important processes involving vitamin K are: blood-clotting, bone mineralization and density, cell growth, metabolism of blood vessel walls (Volpe, 2016), and even nervous system biochemistry (Bourre, 2006).

Table I
Vitamin K in human metabolism - activity and function (modified after Kulkarni, 2012).

Activity	Function
Blood clotting	Carboxylation of coagulation factors II, VII, IX, X
Bone metabolism	Carboxylation of osteocalcin Decreases urinary calcium excretion
Atherosclerosis	Carboxylation of matrix Gla protein
Nerve signaling	Carboxylation of growth arrest-specific protein
Kidney stones	Carboxylation of nephrocalcin

Vitamin K-dependent proteins

Many vitamin K-dependent proteins need gamma carboxylation to exercise their physiological activity. Vitamin K exerts its physiological activity by acting as a cofactor in the process of gamma carboxylation of its different dependent proteins (El Asmar et al., 2014; Schlieper et al., 2016).

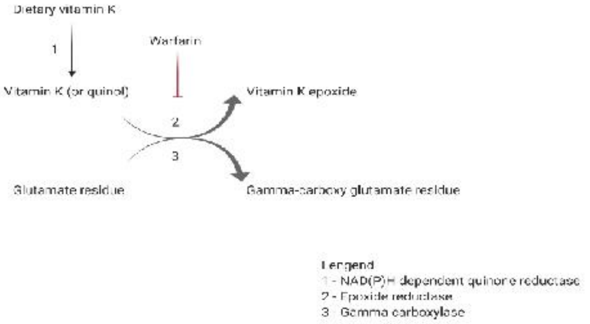

Fig. 1 – Vitamin K – mechanism of action.
Legend: 1 – NAD(P)H-dependent quinone reductase; 2 – Epoxide reductase; 3 – Gamma carboxylase.

According to Fig. 1, dietary vitamin K is transformed into quinol by NAD(P)H-dependent quinone reductase. The obtained compound is then utilized by a gamma-carboxylase to modify glutamate residue into gamma-carboxyglutamate residue in all vitamin K-dependent proteins, and the active form results. Vitamin K-dependent proteins such as the clotting factors II, VII, IX and X are gamma-carboxylated in the liver to obtain an active form; anticoagulant factors (protein C, protein S and protein Z) are gamma-carboxylated mostly in the liver and in extrahepatic tissues. Other well-known vitamin K-dependent proteins are represented by osteocalcin and matrix Gla protein. Carboxylation reaction is linked to the oxidation of vitamin K and obtaining vitamin K epoxide which is recycled back to the reduced form by epoxide reductase. Warfarin inhibits epoxide reductase and vitamin K stores are diminished, and the production of coagulation factors is inhibited (El Asmar et al., 2014; Danziger, 2008).

Two vitamin K-dependent proteins, Gas6, and to a lesser extent, protein S, are actively involved in the nervous system function. Gas6 is involved in neuron and glial cell mitogenesis, chemotaxis, growth and survival, playing key roles in the nervous system (Ferland, 2012). Protein S protects the brain through its antithrombotic and neuroprotective actions: in the brain of mice lacking protein S, severe thrombosis and necrosis were observed (Saller et al., 2009).

Gla proteins are present in the bone matrix and are named Gla proteins because their molecules contain gamma-carboxyglutamic acid. The most common Gla proteins are osteocalcin and matrix Gla protein.

Studies have indicated that osteocalcin is not the only protein present in bone, and substantial amounts of non-osteocalcin Gla were found in cartilage. Another protein capable of self-associating in solution was named matrix Gla protein, a single-chain polypeptide that contains five Gla residues at position 2, 37, 41, 48 and 52 of the 79 amino acid residues of human and bovine protein, which are stabilized by one intra-chain disulfide bond (Bjørklund et al., 2020).

Matrix Gla protein is a vitamin K-dependent and gamma-carboxyglutamic acid-containing protein and also a non-collagenous extracellular matrix protein. MGP contains post-translationally modified gamma-carboxyglutamic acid residue resulting from vitamin K-dependent carboxylation. This protein was first isolated and sequenced from bovine bone and cartilage, but in humans it is also found in tissues such as the lung, kidney, heart or others. Compared to osteocalcin, matrix Gla protein is more widely distributed in the body (Price, 1989; Yagami et al., 1999).

Using different techniques such as direct sequencing or cloning, many structures of matrix Gla protein are available. Even if matrix Gla protein was first isolated from bone, it has been shown to be expressed in different tissues, with a high level of expression in vascular smooth muscle cells, and the metabolic role of matrix Gla protein is very difficult to be clarified. Many experiments were conducted on mice, some of them informing about the development of spontaneous calcification of arteries (Wen et al., 2018; Lomashvili et al., 2011). Mutation in the MGP gene was associated with a rare human autosomal recessive condition named Keutel syndrome, which is characterized by midface hypoplasia and ectopic abnormal calcification (Munroe et al., 1999).

Vascular calcification is a passive event that occurs in the absence of functional inhibitors and it is also possible to demonstrate calcification of the elastic lamellae in the arteries and heart valves in a rat model using high concentrations of warfarin and also sufficient vitamin K to prevent hemorrhage. Even if the role of matrix Gla protein in preventing ectopic calcification is well established, the mechanisms that are involved in this response are less known. There are some possible roles of matrix Gla protein that can be summarized, such as binding calcium ions in the form of crystals in tissues or binding and inactivating bone morphogenic protein-2 and bone morphogenic protein-4. The capacity of matrix Gla protein to bind matrix components such as vitronectin or elastin and its influence on apoptosis of vascular smooth muscle cells suggested that this protein can be involved in ectopic mineralization (Fig. 2). There are a large number of genes that are known to be involved in the mineralization process of the extracellular matrix (El Asmar et al., 2014; Danziger, 2008; Bjørklund et al., 2020; Sterzyńska et al., 2018; Epstein, 2016; Jaminon et al., 2020).

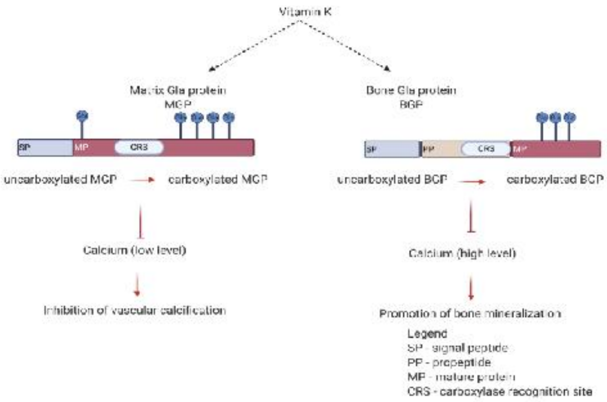

Fig. 2 – Effect of vitamin K on vascular and bone health. Structural organization of matrix Gla protein and bone Gla protein.
Legend: SP – signal peptide; PP – propeptide; MP – mature protein; CRS – carboxylase recognition site.

The physiological function of matrix Gla protein is to inhibit tissue calcification, pathological calcification or abnormal angiogenesis responsible for tumor progression. It is also known that matrix Gla protein expression is related to cellular differentiation and tumor progression, and it can be considered that matrix Gla protein expression could be tumor type dependent. Other important aspects are: a negative correlation between matrix Gla protein expression and tumor progression or metastasis in renal or prostate cancer, an up-regulation of matrix Gla protein transcript in breast cancer or glioblastomas associated with tumor progression and poor prognosis, and, the most important, the binding between matrix Gla protein and fibronectin, which enhances cell adhesion and spreads cancer cells (Sterzyńska et al., 2018; Jaminon et al., 2020; Graham & Miftahussurur, 2018).

Matrix Gla protein is also involved in lung development. Studies reported that a newly generated human MGP transgenic mouse suffers severe morphological defects in the pulmonary artery tree, considering that matrix Gla protein is involved in the development of lung vasculature and also in embryonic lung morphogenesis. Abnormal vascular development is correlated with abnormal morphology and cell differentiation in the terminal airways (Bjørklund et al., 2020; Yao et al., 2007; Pazhouhandeh et al., 2017).

Vitamin K supplementation

In adults, the average food intake of vitamin K is 122 mcg for women and 138 mcg for men daily. When both foods and supplements are considered, the average daily intake increases to 164 mcg for women and 182 mcg for men. The recommended intakes, depending on gender and age, are presented in table II (2).

Table II
Recommended intakes for vitamin K (after (3).

Age	Male	Female
Birth to 6 months	2.0 mcg	2.0 mcg
7–12 months	2.5 mcg	2.5 mcg
1–3 years	30 mcg	30 mcg
4–8 years	55 mcg	55 mcg
9–13 years	60 mcg	60 mcg
14–18 years	75 mcg	75 mcg
19+ years	120 mcg	90 mcg

In healthy people consuming a varied diet, vitamin K nutritional intake is sufficient and the clinical measures of blood coagulation will not be altered (3).

Deficiency of vitamin K can be caused by small bowel injury and malabsorption, chronic kidney disease and dialysis, and vitamin D deficiency, aging, or intake of broad-spectrum antibiotics, and this vitamin K deficiency can cause hypoprothrombinemia and hemorrhagic disorders (Kiela & Ghishan, 2016).

Several vitamin K forms can be used as dietary supplements: vitamin K1 as phylloquinone or phytonadione (a synthetic form of vitamin K1) and vitamin K2 as MK-4 (menaquinone-4) or MK-7 (menaquinone-7) (4).

Several studies showed the implication of vitamin K in chronic diseases (such as cardiovascular disease and osteoarthritis), and therefore, vitamin K deficiency can be associated with an increased risk for mobility disability, especially the disablement process in older age (Shea et al., 2020). In a study on knee osteoarthritis, a leading cause of lower extremity disability among older adults in the US, Misra et al. showed that vitamin K deficiency, even at a subclinical level, is associated with an increased risk of developing knee osteoarthritis and cartilage lesions (Misra et al., 2013). Therefore, considering its involvement in bone metabolism and mineralization (osteocalcin synthesis), vitamin K supplementation could improve the clinical condition of patients with osteoarthritis. In the case of this disease, with very limited treatment options, patients could greatly benefit from the prophylactic potential of vitamin

K supplementation, ensuring the recommended intakes for this micronutrient (Ishii et al., 2013; Thomas et al., 2018).

Vitamin K and exercise performance

The link between diet and exercise practice is clearly expressed at the bone tissue level: mechanical stimuli signal towards osteoblasts and osteoclasts, affect osteocyte function and remodel the bone architecture. The dietary modulators of bone metabolism, especially 1,25-dihydroxyvitamin D_3 and several forms of vitamin K, can improve bone health, when they act synergistically with an exercise regimen (Willems et al., 2017). Several studies, including a meta-analysis of randomized controlled trials, showed that oral supplementation with vitamin K (phytonadione and menaquinone) can reduce bone loss and prevent osteoporosis and fractures (Cockayne et al., 2006; Tamura et al., 2007; Lanham-New, 2008).

Also, important in the decision to perform constant physical exercise is the nervous system and cognition, and there is a strong relationship between vitamin K nutritional status and brain sphingolipids (neuronal membrane components). New researches highlighted important effects of vitamin K status, especially of MK-4, in the brain and other components of the nervous system, involving even aspects of behavior and cognition (Ferland, 2012). A cross-sectional analysis from a large cohort study showed that a higher dietary vitamin K intake was significantly associated with a lower presence of depressive symptoms (Bolzetta et al., 2019).

In practicing exercise, cardiovascular modifications should be taken into account. In a study on the effects of oral vitamin K2 supplementation during exercise, it was shown that an 8-week consumption was associated with increases in maximal cardiac output and heart rate, but not in stroke volume (McFarlin et al., 2017). Another study indicated that vitamin K2 supplementation for 4 weeks increased maximal cardiac output by 12% in aerobically trained male and female athletes, and also improved heart rate and lactate levels (5). Also, due to its protecting effect on arterial metabolism (through its action on matrix Gla protein) (Fusaro et al., 2020), it is possible that vitamin K nutritional status may improve exercise capacity.

Considering the involvement of vitamin K in bone and physical function, researchers have examined vitamin K status in athletes. In a study assessing the nutritional status correlated with bone metabolism in professional male baseball players, Iwamoto et al. showed that some athletes had low serum concentrations of vitamin K1, even if all athletes consumed the daily vitamin K requirements (Iwamoto et al., 2010). In female elite athletes, who use oral contraceptives or present amenorrhea induced by strenuous exercise, some bone mass can be lost rapidly, even in relatively young athletes, and low bone mass can lead to stress fractures (Braam et al., 2003). The study of Craciun et al. demonstrated that vitamin K supplementation decreases bone resorption markers and increases bone formation, improving the balance between bone formation and resorption (Crăciun et al., 1998).

Sumida et al., examining the nutritional status of Shorinji Kempo athletes (a Japanese martial art considered to be a modified version of Shaolin Kung Fu) who suffered from sports-related fractures, reported that 15 of 16 athletes had an insufficient vitamin K intake (Sumida et al., 2012). In a larger study (791 subjects) examining the correlation between vitamin K1 status and knee osteoarthritis in older athletes, Shea et al. reported that individuals with low plasma concentrations had a greater progression of knee articular cartilage damage (Shea et al., 2015).

Conclusions

1. Vitamin K and vitamin K-dependent proteins have important roles in several physiological and tumor processes: blood clotting, bone mineralization and density, cell growth and nervous system biochemistry, vascular wall development and metabolism, tumor angiogenesis, cancer cell spreading and metastasis formation.
2. Vitamin K status is related to pathological conditions such as osteoarthritis and osteoporosis.
3. More randomized controlled trials are needed to establish the pharmacological doses of vitamin K supplementation in order to ensure bone and vascular health, fracture prevention, and also to improve athletic performance.

Abbreviations

MGP: matrix Gla protein; TGF-β: transforming growth factor-β

Conflict of interests

The authors declare no conflict of interest.

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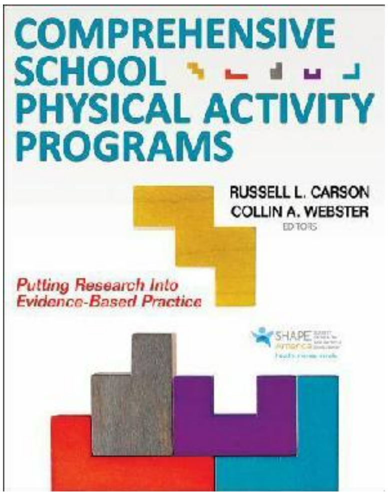

For the last decades, there has been no doubt that physical activity (PA) is critically important for children's physical, cognitive, social and emotional health, the current recommendations in the United States – as well as in many other developed countries - being for every youth, aged 6 to 17, to accumulate a minimum of 60 minutes of PA per day. However, despite the clarity of these minimum recommendations and the apparent ease to fulfill them, as well as despite the vast media attention worldwide, PA participation still declines as children move through their school years. And this even if the childhood and school period represents the best time for adopting behavioral patterns in general, and long-lasting PA habits that continue into adulthood, in particular.

The Comprehensive School Physical Activity Program, or CSPAP, emerged in USA as part of public health efforts to counteract the rising prevalence of chronic hypokinetic diseases such as obesity, heart disease and diabetes, and originated in a National Association for Sport and Physical Education (NASPE) position statement in 2008. At that moment, the launch of the CSPAP model was considered necessary because although the schools benefited from the most appropriate resources for daily PA routine implementation, they were still poorly prepared to generate a significant impact in this respect.

Taking note of the complex and pressing challenges of targeting schools and their professionals as change agents for public health initiatives, Russ Carson, a renowned leader of the CSPAP model, and Collin Webster, an internationally recognized expert in the field of youth PA promotion, have felt urged to finally offer a comprehensive up-to-date, all-in-one book dedicated to the promotion of PA in and through schools. A resource not only to bridge research and practice in one place, but also to summarize the vast experience of the national task forces mobilized by and within the respective model.

The book brings together a set of the most relevant texts written by pioneers and recognized practitioners in the CSPAP field, in order to accommodate the growing needs and questions of all those, not few in number, who want to learn more about CSPAP. Its 22 chapters are organized into six sections of different dimensions, but all the chapters use the same formal structure, with six subheadings: a review of the current research, succeeded by the knowledge claims (or "*what we know*"), knowledge gaps ("*what we need to know"*), evidence-based recommendations and applications ("*what we need to do"),* questions to consider for discussion, and case examples.

After the first part whose two chapters provide both the historical and foundational perspectives and the policy landscapes of the CSPAP model, the second part comes with three chapters from which we learn about the factors that need to be taken into account when designing, implementing, and estimating the program sustainability. Factors which can be of internal (within school) and external (beyond school), and also – in practice crucial – of psychological (within-individual) nature.

The next two parts with a total of ten chapters stand for the essential pillar of the book vision of the CSPAP model and its implementation. So, if the first five chapters of Part III focus on specific components of the CSPAP model - of which very important are PA during school (chapter 7), before and after school (8), along with staff involvement (9) and family and community engagement (10) - the last chapter (11) shows us why the complex multi-component approaches of the PA promoting programs through schools are the most effective and recommended. On the other hand, the first two chapters of Part IV provide comprehensive information and specific considerations for effectively promoting PA within urban and rural contexts, while chapters 14 and 15 refer to the ongoing international

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CSPAP initiatives and the model applications within other contexts than the school settings.

Part V also encompasses four chapters and is entitled *"Developing, measuring, and promoting CSAPs"*, and starts with information about the process and tools used to establish the real and specific PA promotion needs of each school community. Its last two chapters - 18 and 19 - deal with evaluating and advocating for CSPAPs, respectively. In the end, the three chapters within the last part help to make us look and see into the future of the field. In this attempt, their respective authors first examine the intended or already implemented reform efforts for the training of physical education teachers and other professionals (ch. 20), subsequently focusing on the possibilities to integrate new technologies into CSPAPs (ch. 21). The book concludes with a section within which the two editors not only summarize and synthesize all the previous content, but also "recommend strategies to advance and further coalesce the fields of practice where CSPAPs intersect, take root, and blossom".

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FOR THE ATTENTION OF CONTRIBUTORS

The subject of the journal

The journal has a multidisciplinary nature oriented toward biomedical, health, exercise, social sciences fields, applyable 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 methodo¬logy 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, trai¬ners, 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 Universitary 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.

The tables should be numbered consecutively in the text, with roman numbers, and sent as distinct files, accompanied by a legend that will be put above the table.

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 adress 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.

Conclusions. Conclusions that have a direct link with the presented study should be given.

Orientation articles and case studies should have an unstructured summary (without respecting the structure of experimental articles) to a limit of 150 words.

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:

For articles from journals or other periodical publications the international Vancouver Reference Style should be used: the name of all authors as initials and the surname, the year of publication, the title of the article in its original language, the title of the journal in its international abbreviation (italic characters), number of volume, pages.

Articles: Pop M, Albu VR, Vişan D et al. Probleme de pedagogie în sport. Educaţie Fizică şi 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).

Peer-review process

In the final stage all materials will be closely reviewed by at least two competent referees in the field (Professors, and Docent doctors) so as to correspond in content and form with the requirements of an international journal. After this stage, the materials will be sent to the journal's referees, according to their profiles. After receiving the observations from the referees, the editorial staff shall inform the authors of necessary corrections and the publishing requirements of the journal. This process (from receiving the article to transmitting the observations) should last about 4 weeks. The author will be informed if the article was accepted for publication or not. If it is accepted, the period of correction by the author will follow in order to correspond to the publishing requirements.

In order to check the quality of articles submitted for publication, the Health, Sports & Rehabilitation Medicine journal applies the method of single-blind peer review (the identity of reviewers, but not authors, is kept anonymous).

Conflict of interest

The authors must mention all possible conflicts of interest including financial and other types. If you are sure that there is no conflict of interest we ask you to mention this. The financing sources should be mentioned in your work too.

Specifications

The specifications must be made only linked to the people outside the study but which have had a substantial contribution, such as some statistical processing or review of the text in the English language. The authors have the responsibility to obtain the written permission from the mentioned persons with the name written within the respective chapter, in case the readers refer to the interpretation of results and conclusions of these persons. Also it should be specified if the article uses some partial results from certain projects or if these are based on master or doctoral theses sustained by the author.

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The Editors will notify authors in due time, whether their article is accepted or not or whether there is a need to modify texts. Also the Editors reserve the right to edit articles accordingly. Papers that have been printed or sent for publication to other journals will not be accepted. All authors should send a separate letter containing a written statement proposing the article for submission, pledging to observe the ethics of citation of sources used (bibliographic references, figures, tables, questionnaires).

For original papers, according to the requirements of the Helsinki Declaration, the Amsterdam Protocol, Directive 86/609/EEC, and the regulations of the Bioethical Committees from the locations where the studies were performed, the authors must provide the following:

- the informed consent of the family, for studies in children and juniors;
- 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;

certificate from the Bioethical Committees, for animal study protocols.

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.

Editorial submissions will be not returned to authors, whether published or not.

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