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ORIGINAL ARTICLE
VENOUS DISEASE

EDITOR'S CHOICE

Randomized controlled trial on occupational graduated compression clinical and cost-effectiveness

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ABSTRACT

Background: Subjects exposed to occupational standing are at risk of developing chronic venous disease. Graduated compression stockings (GCS) counteract venous hypertension. Aim of the present investigation was to assess GCS clinical and cost effectiveness in prolonged standing up workers.

Methods: Randomized controlled trial involving 75 healthy healthcare professionals working in 6 hours standing up shifts without or with GCS (group A and B, respectively). Outcome measures were performed before and after the shift, at baseline (T0), at 1 (T1), 6 (T6) and 12 (T12) months and included lower limb volume, air plethysmography (APG), quality of life, and dedicated cost-effectiveness questionnaires.

Results: Seventy-two subjects completed the data collection. Leg volume increased in group A and decreased in B at all assessment points (T0, 1, 6, 12) ($P<0.0001$). Venous filling index did not change within the 12 months, but, after every shift, its value was lower in B compared to A ($P<0.0001$). At 12 months, VVSymQ worsened in A and improved in B ($P<0.0001$) and CIVIQ significantly worsened in A ($P<0.0001$), while in B it significantly improved ($P<0.0001$). Perceived disability was higher in A at 12 months ($P<0.001$) and the cost calculation revealed a saving of 1510 euro per year in B.

Conclusions: GCS counteracted occupational oedema and positively influenced venous filling index, while improving vein specific quality of life measurements in addition to cost savings.

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Key words: Stockings, compression; Occupational medicine; Edema.

Working conditions requiring prolonged standing may lead to insufficient calf pump activity, lower limb venous stasis, valve incompetence, venous hypertension and sub-sequent inflammation. This patho-physiology phenomenon makes the prolonged occupational standing a recognized risk factor for chronic venous disease (CVD).[1, 2]

According to a 12 year Danish prospective study, occupational prolonged standing in healthy subjects was a risk factor for CVD, with a relative risk of 1.75 (95% CI 0.92 to 3.34) for men and 1.82 (95% CI 1.12 to 2.95) for women.[3]

The data were in-line with a Scandinavian investigation reporting a risk ratio for varicose veins of 1.85 for men and 2.63 for women, with results adjusted for age, social group, and smoking habits.[4]

In a similar investigation, spending more than 6 hours per day standing in the occupational setting led to an adjusted hazard ratio (HR) for varicose veins surgery of 3.17 and 2.34 for men and women, respectively, while high lifting exposures (≥1000 kg/day) showed a HR of 3.95 for men and 2.54 for women. The data pointed out how proper management and counteraction of prolonged occupational lower limb drainage overload could potentially reduce the clincal and economic burden of CVD.[5]

The clinical aspect of such burden was pointed out by Jo *et al.* demonstrating a higher odds ratio for lower extremity muscle pain in prolong standing up workers.[6]

Such phenomenon is complex and multi-factorial: there is no direct correlation between edema and symptoms development. Graduated compression stockings (GCS) reduced the edema in a dose-dependent way and can positively control related symptomatology not in a dose dependent way.[7]

Populations that had been investigated to better understanding the phenomenon were heterogenous in the few available scientific papers dealing with the topic.

Weiss *et al.* investigated on flight attendants using 8-15 mmHg GCS and demonstrated a significant improvement in swelling, fatigue, aching, and tightness, but no statistical difference by increasing the dose to 15-20 mmHg.[8]

Blazeck *et al.* reported an improvement in leg pain, feelings of swelling, heaviness and various other disturbing feelings in hairdressers wearing 15-20 mmHg GCS.[9]

Interestingly, one of the professions most exposed to CVD development is the health care profession. Ziegler *et al.* found venous hypertension in 34% of their dedicated study population, predominantly in women, utility workers and cleaners, and less prevalent in medical assistants, secretaries and scientific staff.[10]

A Korean study confirmed the role of standing posture in different kind of works,[11]in line with Kohno *et al.* investigation, which also suggested the concomitant role of obesity.[12]

A recent cross-over study explored the comparison between intermittent pneumatic compression and GCS for edema and pain control after prolonged standing. The results showed the potential benefits of both compression modalities and confirmed the patho-physiological complexity of the phenomenon considering extracellular fluids shifts did not correlate with edema and symptoms variations.[13]

Symptoms developed in working conditions represented a well-known cause of decreased productivity, but, up to our knowledge, literature is lacking in the analysis of venous hypertension symptomatology impact on work performance and related cost-analysis.[14]

Aim of this investigation was to assess the role of occupational venous hypertension and related GCS counteraction on both leg edema and symptomatology development, together with the economic consequences in terms of work disability and cost-analysis.

Materials and methods

Study design and population

A prospective parallel group randomized controlled trial was performed at the University Hospital, Ferrara Italy following a research grant supported by the Italian Ministry of Health awarding (project code: GR-2016-02364886). From December 2018 to December 2021, 100 healthy healthcare professionals (73 female and 27 male, mean age 42±11 y.o., BMI: 22±2) working for 6 hours standing up shifts were assessed for eligibility.

Inclusion criteria were:
- age between 18 and 65 years old;
- six hours standing up still working shifts;
- morning working shifts;
- employment with constant month workload along the year.

Exclusion criteria were:
- BMI>30;
- arterial, venous, or lymphatic disorders;
- sport activities or lifestyle requiring intense physical efforts;
- macroscopic postural defects;
- more than 3 pregnancies;
- previous major trauma or procedures on the leg, including aesthetic invasive treatments.

The study protocol was approved by Ferrara University Hospital Institutional Review Board (n° 98/2018/Sper/AOUFe). Before the enrollment, all the subjects were informed of the objective of the study and expressed written consent to participate.

Randomization

The randomization list was formulated using a computer system generating words in random order (https://www.blia.it/parolecasuali/), where the words “group-intervention” or “group-control” were inserted by the project manager (EM) who had no involvement in the subjects’ enrollment. The investigators involved in data collection were not aware of the allocation list until the assignment. The software randomly generated one of the two words, which was then matched to the subject’s ID. The study population was allocated in 1:1 fashion either to control group or intervention group using random block sizes of five or six.

Experimental design

All subjects underwent a detailed vascular specialist clinical visit and venous and arterial ultrasound scanning to exclude arterial, vein and lymphatic disorders. Within the same 6 hours working time, the control group (Group A) did not wear any kind of GCS, whereas the intervention group (Group B) worn 23-28 mmHg below-knee GCS. GCS were worn right at the beginning of the shift, removed immediately after, and were not used in between the shifts.

Clinical outcome measures

Outcome measures were performed before and after the shift, at baseline (T0), at 1 (T1), 6 (T6) and 12 (T12) months and they included:

- lower limb volume calculated by the mathematical truncated cone formula of Kuhnke (Vlimb=∑X2/π) assessing the leg circumference by a centimetered tape (Gulick Anthropometric Tape, Alimed), starting from above the malleolar level all the way up to the knee, every 4 cm, for a total of eight segments (sectors).[15, 16]
- air plethysmography (APG) measured venous filling index (VFI). APG test was performed according to the Christopoulos protocol.[17]
- quality of life (QoL) was measured by disease specific questionnaires VVSymQ and CIVIQ20.[18, 19]
- a dedicated cost-effectiveness questionnaire administered by the Department of Economics and Management of the University of Ferrara. In this regard, a questionnaire’s section was dedicated to detect the loss of efficacy experienced by both groups. In order to fulfill this aim, the Work Productivity & Activity Impairment questionnaire was used.[20]
- Furthermore, the questionnaire also contained a section aimed to determining the respondent’s tendency to buy products/services dedicated to vein symptomatology management. Statistical tests were then conducted in order to compare the intervention and control group in terms of disability costs and perception of lower limb fatigue; to establish whether the adoption of GCS was a cost-effective solution. The methodology used was detailed in the dedicated session.

Cost analysis methodology

The Mann-Whitney U Test for independent samples was conducted at time T0 and time T12 to examine the differences between those who used GCS to those who did not, and in regards to perception of disability due to the disease and the cost for loss of efficiency in carrying out activities. To calculate the disability coefficient (loss of efficiency), the respondent was asked to indicate on a scale from 0 to 10 to what extent her/his problem had an average effect on her/his daily working productivity in the last six months before the data collection, at T0 and at T12. The disability coefficient was calculated with the formula (Q/10)×100%, where Q was the value from 1 to 10 of perceived disability due to disease. The higher the value, the more the individual was less efficient in carrying out her/his work activities due to the disease. The costs of loss of efficiency were calculated by taking as a reference the coefficient of inability which was multiplied by the worked hours in the previous six months and the cost of hourly labor. The formula was then: ([Q/10]×100%) x amount of hours worked by the individual in the six months prior to the survey multiply cost of hourly labor. The formula refered to the Work Productivity and Activity Impairment Instrument (WPAI).[20]

The WPAI estimated the loss of efficiency in the week prior to the survey. We had extended the estimate to the loss of efficiency over the six months prior to the survey, coherently with the literature.[21]

The McNemar Test was also used to test if the purchasing volume of products and services to care for the disease has changed from t0 to t12 for each of the two groups. In this regard, healthcare professionals were asked to indicate whether they had purchased supplements, massages, and spa treatments to care for their disease symptomatology during the period under investigation.

Statistical analysis

The sample size calculation was done preliminary data on leg volume of 40 workers,[22] it was estimated a mean increase in lower limb volume of 89±47 mL. It was hypothesized that the use of elastic stocking would reduce the increase of the lower limb volume of 50% compared to the control group. A sample of 24 subjects for each group is required for a power of 90% with an α level of 0.05.

The statistical analysis was conducted using the software Instat GraphPad Inc. La Jolla, CA 92037 USA. The data were expressed as mean standard deviation. The Kolmogorov-Smirnov Test was used to verified the normal distribution of the data. Comparison between groups regarding the leg volumes, APG, and QoL questionnaire was performed using Mann-Whitney Test and/or the two-tailed Student's *t*-test, as appropriate. The data related to the right and left leg were averaged to obtain a single numerical value in order to simplify the analysis.

Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Results

Of a total of 100 eligible subjects, 25 were excluded as per figure 1 specification, while 75 were included and randomized in the study and 3 were lost during follow-up. Therefore 72 subjects were analyzed (Figure 1). Neither major nor minor complications were reported along the data collection. The clinical and demographic characteristics of the study participants were given in Table I.

Figure 2 showed the lower limb volume significantly increased in group A and reduced in group B, along all the T0, 1, 6, 12 observation time points (P<0.0001). Table II reported the detailed volume values at the beginning and at the end of the study.

The value of VFI at the end of each shift was significantly lower in Group B compared to A in all the assessment time points (T0 0.6±0.3 *vs.* 0.8±0.4, P<0.01; T1 0.7±0.3 *vs.* 0.8±0.3, P<0.03; T6 0.7±0.3 *vs.* 0.8±0.4, P<0.04; T12 0.6±0.3 *vs.* 1.1±0.3, P<0.0001) (Figure 3).

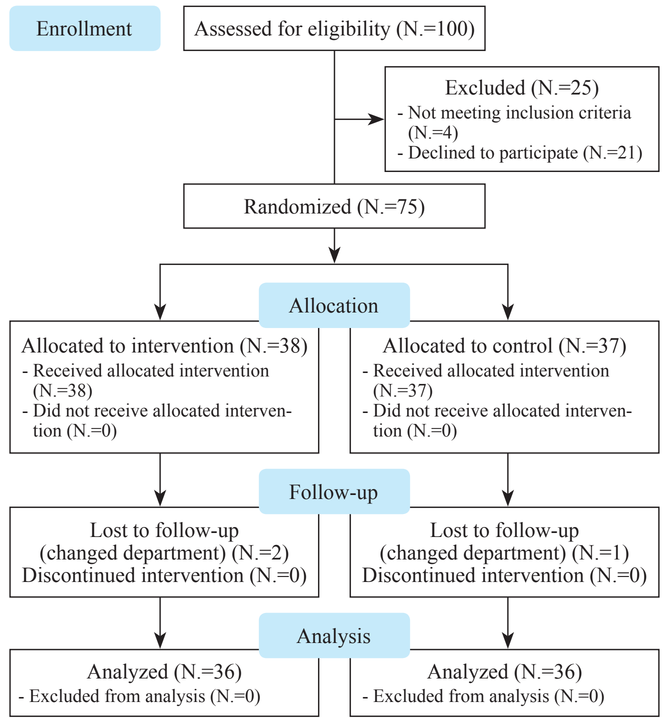

Figure 1.—Study flow diagram according to the CONSORT 2010 statement.

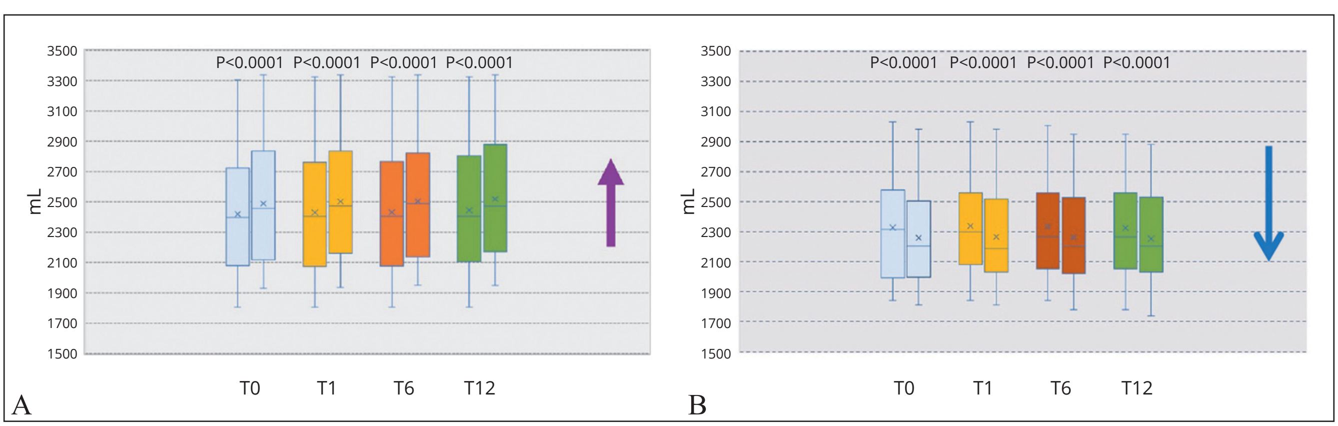

Figure 2.—After-shift lower limb volume variations at baseline, 1, 6 and 12 months in Group A (A) and B (B).

TABLE I.—*Clinical and demographics characteristics of the study participants at baseline.*

	Group A (36 subjects)	Group B (36 subjects)	P
Age (years)	39.7±11.8	44.9±9.9	0.1454
Gender (male out of female)	11/25	3/33	<0.03
BMI	21.9±1.7	22.1±2.4	0.6468
Main Veno-lymphatic Related Symptom (subjects out of total)			
• Heaviness	36/36	36/36	0.9999
• Achiness	20/36	27/36	0.1368
• Swelling	34/36	36/36	0.4930
• Itching	2/36	2/36	0.9999

TABLE II.—*Legs volume changed at baseline and 12 months follow-up measured before (pre) and after (post) working shift.*

	T0 pre (mL)	T0 post (mL)	P	T12 pre (mL)	T12 post (mL)	P
Group A	2420±393	2489±390	.0001	2445±404	2519±409	0.0001
Group B	2327±325	2259±319	.0001	2323±306	2252±305	0.0001

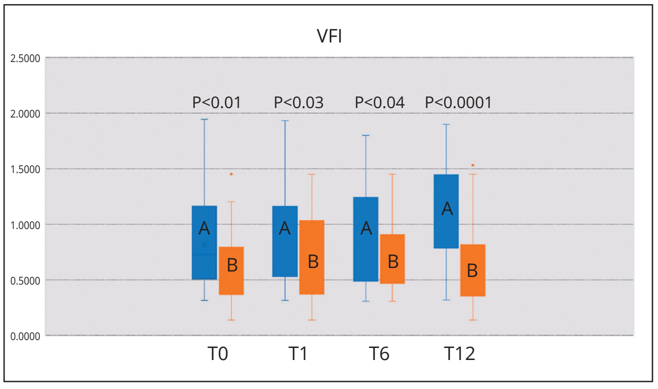

Figure 3.—After-shift VFI significantly differed between Group A (blue histograms) and Group B (orange histograms) at T0, T1, T6 and T12 months.

At 12 months, VVSymQ significantly worsened in Group A (from 4.8±1.4 to 6.1±1.1, P<0.0001) and improved in Group B (from 4.2±1.8 to 1.8±0.9, P<0.0001). At the same assessment time (T12), CIVIQ score significantly worsened in Group A (from 97.6±1.9 to 96.5±3.0, P<0.0001), while improved in Group B (from 96.4±3 to 97.8±2.4, P<0.0001).

The Mann-Whitney U Test for independent samples indicated that at T0 there was no differences between the two groups in terms of worked hours, perceived disability due to the symptomatology related to chronic venous insufficiency and the cost for loss of efficiency. In this regard, at T0 the compared samples were not significantly different. Conversely, at time T12 there were significant differences between those who used CGS (group B) and those who did not use them (group A) in regards to perception of disability due to the symptomatology and cost for loss of efficiency in carrying out work activities. We did not find significant differences between the two groups concerning the worked hours. Consequently, at T12 follow-up, those who wore GCS had a lower perceived disability (P<0.001) and a lower cost for loss of efficiency (P<0.0001) compared to those who did not use it (Table III). A beneficial effect of the GCS use was therefore deduced from results.

Working perceived disability assessed by the dedicated questionnaires was significantly higher in Group A compared to B at 12 months (disability coefficient: 19% *vs.* 12%, P<0.001) (Figure 4).

Concerning the results, the loss of efficiency for a healthcare professional who did not wear the compression stoking at time T12 was on average 3.452 euros, while for those who wore the compression stoking was 1.943 euros. Therefore, on average, not wearing GCS involved a loss of efficiency equal to €1.510 euros per healthcare professional (Figure 5).

TABLE III.—*Working hours, working perceived disability and cost for loss of efficiency at T12, differences between the two groups.*

	Working hours (six months)	Working perceived disability	Cost for loss of efficiency
U di Mann-Whitney	572.500	380.500	341.000
W di Wilcoxon	1238.500	1046.500	1007.000
Z	-0.860	-3.214	-3.465
Significance (at 2-Tailed)	0.394	.001	0.0001

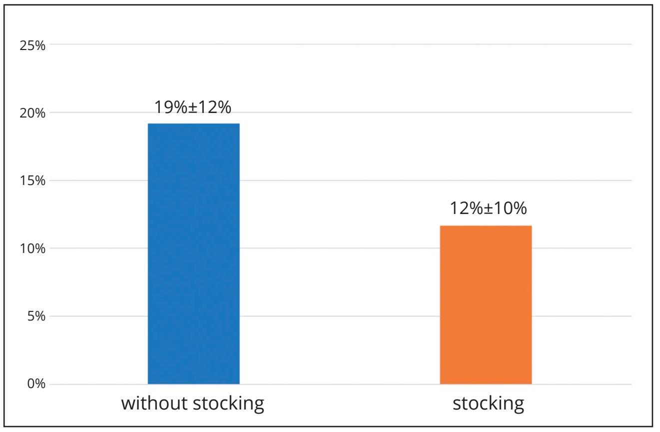

Figure 4.—Working perceived disability in Group A and B at 12 months follow-up.

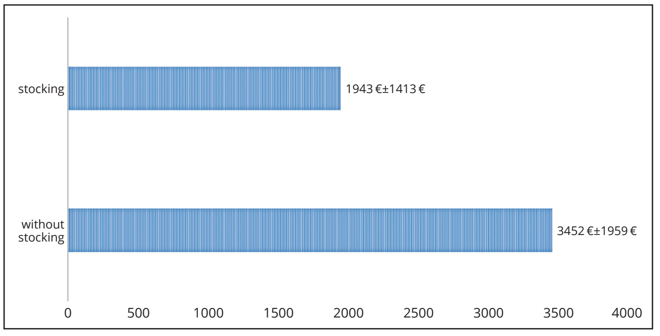

Figure 5.—Loss of efficiency cost (mean standard deviation) at time T12.

Table IV.—*Consumption of supplements not specific for venous diseases and self-managed by the subject itself, the group A significantly increase the use of supplements at T12 while group B did not.*

	Supplements purchase group A (change from time T0 to time T12)	Supplements purchase group B (change from time T0 to time T12)
N° of subjects	36	36
Significance (at 2-Tailed)	0.031	0.248

Regarding purchasing supplements (supplements with a price lower than 25 euros), the P value of the McNemar test was significant for those healthcare professionals who did not wear GCS (P<0.031), stating a change of behavior from T0 to T12 (Table IV). Specifically, 6 subjects who did not buy supplements at T0, started to buy them at T12, prospecting a worsening of symptomatology.

Finally, no significant differences were found at T12 in either group regarding changes in purchasing behavior for other self-care services and products.

Discussion

The impact of the amount of time spent in occupational lower limb drainage overload has been shown to increase the appearance of varicose veins, according to Shakya *et al.* the odds of having varicose veins was 27 times greater with every 1 hour increase in standing time per day.[23]

The present investigation confirmed the effect of long standing occupational time even in healthy subjects and it provided further insights on its negative impact on the vein disease specific quality of life scores and working performance, with a potential counteraction by means ofproper GCS. Even more, it pointed out the economic burden associated with the occupational condition and the possibility to better manage it by means of compression hosier.

Previous investigations demonstrated edema did not directly correlate with symptomatology, suggesting GCS of different dosage might not lead to difference in symptom control.[7]

Up to our knowledge, no data are available to significantly demonstrate the preference of below or above knee GCS.[24]

The VFI values assessed in Group B patients confirmed the venous hemodynamic role of GCS: an effect to be added to edema control, and the VVSymQ and CIVIQ quality of life scores improvement. This latte aspect was of great importance considering the known impact of CVD on quality of life.[25] We did not find significant VFI differences in the T0-12 range with a significant variation at the end of the shifts suggested the need of future investigations on the minimum daily time of compression use for longlasting hemodynamic effects.

The occupational burden was associated with a perceived disability and efficiency loss that was counteracted in the group wearing compression. The same subjects relied less on over the counter venous system supplements, which was a desirable attitude considering the lack of evidence in benefits delivered by inproperly validated products.[26, 27]

To the opposite, subjects not wearing GCS starting to use such supplements, indirectly indicating a progression of venous hypertension effect.

The fact no differences were reported in the use of services for lower limb wellness suggested a deeper analysis is needed for determining which factors may influence the use of such activity (costs, accessibility, time, etc).

Among the most valuable findings of the herein reported data was the translation into potential healthcare cost saving by the use of proper GCS in occupational prolonged standing posture.

This finding was in line with a previous study by Tabatabaeifar that highlighted a preventive potential of more than 60% of all cases in occupations to prolonged standing.[5]

Unfortunately, a significant heterogeneity existed among the different studies in terms of "prolonged standing" definition, for which a general agreement should be found.

Indeed, likely contradicting results among studies could be explained by heterogenous population analysis. For example, in a Taiwan study, varicose vein risk did not differ among physicians, non-physician healthcare professionals, and the general population.[28]

Overcoming this possible bias is fundamental to fulfil that literature improvement required by the 2013 Cochrane call about effectiveness of non-pharmacological interventions for preventing CVD in standing up workers.[29]

Further enhancement of the data collection should include appropriately sized study population in addition to objective health and patient reported outcomes.[30]

A specific research line should randomize prolonged standing *versus* sitting in order to better understand the related impact on lower limb venous-lymphatic drainage.[31, 32]

Limitations of the study

Limitations of our study included the lack of physical activity monitoring during resting time. This was considered non-feasible in light of the one year follow-up, yet future investigations should include a shorter analysis time focused on this aspect.

Different compression dosage should also be tested to identify the lowest pressure possible to obtain clinical and cost-effective results.

Conclusions

Prolonged occupational standing posture leads to lower limb edema and vein specific quality of life scores deterioration. Proper GCS can counteract the phenomenon. Up to our knowledge, this manuscript represents the first report related to prolonged occupational standing costs associated with venous disease management, and the possibility of health care cost savings when appropriate compression hosier are used in this setting.

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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions
Conceptualization, funding acquisition: Sergio Gianesini, Erica Menegatti; data curation and methodology: Sergio Gianesini, Erica Menegatti, Emidia Vagnoni; formal analysis: Sergio Gianesini, Emidia Vagnoni, Caterina Cavicchi, Yung-Wei Chi, Anselmo Pagani, Mirko Tessari, Paolo Zamboni, Erica Menegatti; investigation: Sergio Gianesini, Anselmo Pagani, Mirko Tessari, Caterina Cavicchi, Erica Menegatti; writing – original draft: Sergio Gianesini, Erica Menegatti, Emidia Vagnoni, Yung-Wei Chi; Writing – review and editing: Sergio Gianesini, Emidia Vagnoni, Caterina Cavicchi, Yung-Wei Chi, Anselmo Pagani, Mirko Tessari, Paolo Zamboni, Erica Menegatti. All authors read and approved the final version of the manuscript.

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