

## In this issue

### **Validation of a gravitational model to study local endogenous biomarkers in chronic venous insufficiency**

The present study was used to validate a gravity model for venous insufficiency, using two biomarkers for cell death and the matrix-metalloproteinases (MMP) as biomarkers for tissue remodelling. The study further underlines the importance of the gravity in the etiology of chronic venous insufficiency. It could be demonstrated that the use of medical compression stockings or lying for just one hour had a significant effect on local inflammatory parameters.

### **Graduated compression stockings for prevention of deep vein thrombosis**

With this Cochrane Review the authors wanted to evaluate the efficacy and safety of graduated compression stockings (GCS) in the prevention of deep venous thrombosis (DVT) in hospitalized patients. This meta-analysis shows that there is high-quality evidence available for the effectiveness of GCS, in reducing the incidence of DVT in hospitalized patients who have undergone surgery, with or without the use of other thromboprophylaxis.

### **Comparison of 15–20 mmHg versus 20–30 mmHg compression stockings in reducing occupational oedema in standing and seated healthy individuals**

The authors compared the efficacy of knee-high medical compression stockings (MCS) with different pressure profiles (15-20 mmHg and 20-30 mmHg) in healthy volunteers that are working in a seated, standing or a combined position. The treatment with MCS of both compression classes led to a reduction of the occupational oedema in the healthy study participants.

### **Treatment protocol on stasis edema in poorly mobile nursing home patients**

The present study investigated the reduction in leg volume after 15 days of initial treatment with a Velcro-Wrap (Circaid Juxtalite), followed by a comparison of the maintenance of the achieved reduction during a further 15 days with continued use of the Velcro wrap or a treatment with a medical compression stocking (MCS) with 15-20 mmHg compression.

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## Validation of a gravitational model to study local endogenous biomarkers in chronic venous insufficiency

*European Journal of Vascular and Endovascular Surgery 2018:1-9*

### Aim

The aim of this study was to validate a gravitational model of venous insufficiency using two biomarkers of cell damage and matrix metalloproteinases (MMPs), indicators of tissue remodelling.

### Methods

Both healthy volunteers and patients with chronic venous insufficiency (CVI) were recruited for this single-centre, prospective cohort study. Each participant acted as their own control. All patients had advanced CVI and were awaiting endovenous laser ablation for primary saphenous reflux with skin changes. Exclusion criteria included leg ulceration, previous venous intervention and history of deep vein thrombosis.

The gravitational model involved testing in three postures on three separate days. The three postures were:

- Standing: on a 40 x 40 cm space holding an orthopaedic support frame
- Lying down: both legs elevated at 20° with the knee joint supported
- Standing with compression: Standing as before with a knee-length, graduated compression stocking 23-32 mmHg

After 1 hour blood samples were taken from the ankle area. Samples were analysed for annexin V as a marker of apoptosis and microparticles as evidence of cells dying by blebbing. The presence of tissue repair was indicated by levels of MMPs. The primary outcome measure was a significant decrease in biomarker levels during lying and compression versus standing.

### Results

A group of 14 healthy volunteers and 14 patients were included in the study. There were no significant differences between the groups in BMI or age. Use of compression therapy or lying down significantly reduced levels of annexin V compared with those recorded after standing in both groups ( $p < 0.05$ ). A significant reduction in microparticles was also found with lying down versus standing for both groups ( $p < 0.05$ ), while compression had a significant impact on this biomarker in the volunteer group only.

In patients, evidence of tissue repair was significantly reduced with compression and lying down versus standing when all MMPs were considered together ( $p = 0.004$ ). When individual markers were considered the effect of lying down was greater than that of compression. In healthy volunteers there was a trend towards a reduction in MMP levels but the majority were not significant.

### Conclusions

This study reinforced the importance of gravity in the aetiology of chronic venous insufficiency. It also highlighted that compression or elevation can have a significant impact on local inflammatory biomarkers after only 1 hour. The authors recognise that further studies are needed to validate the gravitational model, including the effects of longer time periods, stronger compression and larger sample sizes.

### Comments of the Editors

This important study highlights the gravitational effect of standing for tissue damage in the legs as well in venous patients as in healthy volunteers. Standing and sitting belong to the risk factors for the development of chronic venous insufficiency but sitting more than 8-10 hours is also an independent risk factors for earlier

death in the general population<sup>1, 2</sup>. In this study the authors could demonstrate that leg elevation or standing with medical compression stockings (MCS) for one hour is associated with a significantly lower level of annexin V, claimed as a marker of apoptosis, in the ankle venous blood. After leg elevation the level of microparticles, claimed as a marker of cell death, was also significantly lower compared to one hour standing. MMPs as a marker of cell repair showed the opposite. In further studies a comparison of the one hour levels with baseline levels would be favourable. However these data suggest that inflammation and cell damage after standing or long term sitting may be reduced by compression stockings. If this can be reproduced in further studies, this would imply a far extended indication for compression not only in venous and lymphatic patients.

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Association between physical activity, occupational sitting time and mortality in a general population: An 18-year prospective survey in Tanushimaru, Japan.

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Physical Activity, Sitting Time, and Mortality From Inflammatory Diseases in Older Adults. *Front Physiol.* 2018 Jul 12;9:898. doi: 10.3389/fphys.2018.00898.

Sachdeva A, Dalton M, Lees T

## Graduated compression stockings for prevention of deep vein thrombosis

Cochrane Database of Systematic Reviews 2018, Issue 11. Art. No.: CD001484.

### Aim

The objective of this intervention review was to evaluate the effectiveness and safety of graduated compression stockings (GCS) in preventing deep vein thrombosis (DVT) in both surgically and medically hospitalised patients.

### Methods

Trial databases, including the Cochrane Central Register of Controlled Trials, were searched in both 2017 and 2018 for randomised controlled trials (RCTs) of GCS alone or GCS in combination with other DVT preventative methods. The quality of the trials was assessed using the Cochrane 'Risk of bias' tool, and data was extracted and cross checked by two of the authors.

### Results

Twenty RCTs were included in the meta-analysis, creating a total of 2853 analytic units (1681 individuals and 1172 individual legs), with 19 of the studies in patients undergoing surgery. All patients in the treatment groups received GCS (primarily thigh length), with

or without additional prophylaxis. Where used, concomitant preventative treatments included: dextran 70, subcutaneous heparin, aspirin, low molecular weight heparin and sequential compression. In the majority of trials, stockings were applied on the day prior to or of surgery and worn until discharge or until the patient became fully mobile. The studies were assessed as having an overall low risk of bias. Deep vein thrombosis Pooled data from all 20 studies showed an incidence of DVT of 9% (134 of 1445 units) in the GCS group vs 21% (290 of 1408 units) in the control group ( $P < 0.001$ ).

In surgical patients alone (19 trials), 9.8% (134 of 1365) developed DVT in the GCS group compared with 21.2% (282 of 1328) in controls ( $P < 0.001$ ). In the study of medical patients (those admitted following acute myocardial infarction), there were no incidences of DVT reported in the GCS group, vs 10% (8 of 80) in the control patients ( $P = 0.004$ ).

### Proximal DVT and pulmonary embolism

Due to the clinical significance of proximal DVT the authors also analysed data from trials that included its assessment. Based on eight studies, the incidence of proximal DVT was 1% (7 of 517) in the GCS treatment group and 5% (28 of 518) in the controls ( $P < 0.001$ ). Pulmonary embolism (PE) data was available from five studies, with an incidence of 2% (5 of 283) in patients receiving GCS vs 5% (14 of 286) in the controls ( $P = 0.04$ ). The quality of evidence for these results was downgraded to moderate for proximal DVT and low for PE due to the low event rate and lack of routine screening.

### Adverse effects

Reporting of adverse effects or complications of GCS varied significantly between trials - only seven studies including them in their analysis, but none specified in which group they occurred. One trial recorded patient experience of GCS, with 23% of those wearing above the knee stockings finding them uncomfortable and requesting removal.

### Conclusions

This meta-analysis shows that there is high-quality evidence for the effectiveness of GCS in reducing the incidence of DVT in hospitalised patients who have undergone surgery, with or without the use of other thromboprophylaxis. Further studies are needed to improve the quality of data available for prevention of proximal DVT and PE, as well as studies into specific treatment groups, such as those with a history of DVT and patients admitted for medical rather than surgical conditions. The duration of GCS use and incidence of adverse events or complications also require further investigation.

### Comments of the Editors

After the recommendations for prevention of thromboembolic events with thromboprophylactic compression stockings (TPS) was downgraded in recent guidelines because of the older database not fitting the actual situation, this Cochrane review shows a high-quality evidence for the effectiveness of TPS in surgical patients. This is true for compression alone or in combination with medical thromboprophylaxis. The term GCS in

the review is misleading as there is a difference between medical compression stockings (MCS) and thromboprophylactic stockings (TPS) in respect to material, stiffness, ankle pressure and methods of production. However both are graduated in their pressure. In most of the studies discussed here, TPS were used.

In this review TPS were also effective in preventing thrombotic events in medical ill patients and in the prevention of proximal DVT or pulmonary embolism. However the quality of evidence for these results was only moderate due to the low event rate and lack of routine screening. Nothing could also be concluded concerning better effectivity of thigh-long versus calf-long TPS.

As the rate of severe side effects of TPS is very low, TPS should be considered after surgery and in other patients on risk for thromboembolic events, in addition to other routine thromboprophylaxis management. More data is needed for high-quality evidence in medical ill patients and in the prevention of proximal thromboembolism.

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Belczak CEQ, de Godoy JMP, Seidel AC, Belczak S, Ramos RN, Caffaro RA

## Comparison of 15–20 mmHg versus 20–30 mmHg compression stockings in reducing occupational oedema in standing and seated healthy individuals

*International Journal of Vascular Medicine 2018:2053985*

### Aim

The aim of this study was to compare the effectiveness of knee-length elastic compression stockings (ECS) with different pressures (15-20 mmHg and 20-30 mmHg) in healthy individuals working for prolonged periods sitting, standing or a combination of both.

### Methods

This observational, cross-sectional study was carried out in Brazil between 2014 and 2015. Healthy volunteers were classified by their predominant posture during the working day; sitting, standing or a combination of sitting, standing and walking. Exclusion criteria included ischaemia, hypertension, diabetes and use of diuretic or hormonal medication. The volume

of both legs was measured by the same physical therapist at the same time at the beginning and end of each day using the water displacement technique. All subjects used no stockings on the first day, wore 15-20 mmHg ECS on the second, and 20-30 mmHg ECS on the third.

### Results

A total of 58 volunteers were enrolled in the study. Baseline characteristics were similar across the posture groups, except for body mass index which was significantly higher in those who spent the majority of the day sitting compared to those using a combination of postures. There were no significant differences between legs so analysis was performed on all lower limbs; 40 in the sitting group, 36 in the standing group, and 40 in the combination group.

Occupational oedema was present in all groups on the first day (no stockings). Mean volume at both morning and evening measurements were significantly higher in the sitting group than the other groups, and in the standing vs combination groups.

All groups had a significant reduction in their oedema with ECS 15-20 mmHg use compared to no compression ( $p < 0.001$ ). The use of ECS 20-30 mmHg caused a greater reduction in leg volume than no compression, an effect which was more significant for those subjects sitting all day ( $p < 0.001$ ) than for those standing ( $p < 0.05$ ) or able to combine postures ( $p < 0.05$ ).

**Conclusions**

The use of ECS reduced occupational oedema in healthy subjects who spent their working day in a particular posture; sitting, standing or both in combination with walking. Greater compression lead to greater protection against oedema, the most significant impact being in those sitting all day.

**Comments of the Editors**

This paper confirms the results of some previous publications that even low pressure graduated ECS are able to prevent occupational edema. Two points are emphasized by the authors of this article:

1. People in the sitting position show a higher amount of leg-edema in the evening than those who are standing or have a profession with changing body positions.

2. It was especially this group of sitting occupation who had the highest benefit from 20-30 mmHg stockings.

However, 15-20 mmHg stockings revealed excellent results in all three groups of different working positions, all showing no or only slightly greater lower leg volume in the evening than in the morning. Unfortunately, people were not asked about their subjective feelings with the applied stockings, but it may be assumed that 15-20 mmHg stockings would have been preferred by most test persons.

Benigni J-P, Uhl JF, Balet F, Chahim M

## Treatment protocol on stasis edema in poorly mobile nursing home patients

*International Angiology 2018;37(5):396-399*

### Aim

The aims of this study were to quantify the reduction in leg volume achieved with an adjustable compression Velcro wrap (Circaid Juxtalite) after 15 days, and compare maintenance of that reduction after a further 15 days with continued use of the Velcro wrap or a change to 15-20 mmHg compression stockings.

### Methods

Included in this randomised, comparative, prospective pilot study were 30 patients resident in a nursing home for over one month and diagnosed with stasis oedema CEAP C3-C5. Patients were defined as having poor mobility, be unable to walk independently, or at all. Ex-

clusion criteria included bedridden patients unable to sit, those with an ankle brachial index < 0.6 and those with macerated or exudative skin lesions.

Eligible patients were randomised to receive either 30 days treatment with Circaid applied to achieve a pressure of 40 mmHg, or 15 days treatment with Circaid followed by 15 days with a 15-20 mmHg compression stocking. Compression was applied for a minimum of 8 hours each day.

Leg volume was calculated using six circumference measurements taken lying down, and assessed at baseline, days 15 and 30.

### Results

The majority of subjects were female (28) and were classified as CEAP C3 (80%). Data for 26 patients (52 legs) was available for the final analysis. After 15 days, leg volume was found to have decreased from a mean of 1355.8 ml to 1210.3 ml (a reduction of 10.8%,  $p < 0.001$ ). During the maintenance phase, days 15-30, patients who switched to compression stockings experienced an increase in leg volume of 1.3%, while those who continued to use Circaid had a further decrease in volume of 1%, although the difference between groups at day 30 was not significant.



**Conclusions**

This study provides further support for the use of Circaid Juxtalite in reducing stasis oedema in elderly patients. Application of a Velcro wrap was felt by the authors to be quicker and easier than stockings or bandages, and can be administered by trained nursing home staff without the need for nursing assistance. The authors suggest that, as leg volume reduction could be maintained by a low pressure compression stocking (15-20 mmHg), the need for higher pressure compression could be unnecessary.

**Comments of the Editors**

These were patients who are unable to walk and that spend the main part of their life in a wheel chair.

Usually these patients will get compression stockings which are difficult to put on and off, which explains the high level of non-compliance. Sometimes bandages are used which require frequent bandage changes performed by experienced staff.

Benigni and coworkers have shown in their paper that adjustable compression wraps (ACW) may be an excellent alternative for this group of patients (mean age of the study population was 89 years!)

They showed that after 2 weeks of treatment with ACW, applied with a pressure of 40 mmHg, a dramatic

reduction of leg edema could be achieved which was maintained with continuous use of ACW for the following 14 days, while switching to light stockings (15-20, mmHg) resulted in a slight refilling of edema. However, it is emphasized that daily application of low pressure medical compression stockings seems to be enough to maintain the medium-term results achieved by ACW.

One major advantage of ACW is that these inelastic wraps can be handled by the patients after short demonstration. By using a "calibration card" patients can choose a pressure range (e.g. 40 mmHg).

The paper does not tell us how many patients were able to self-manage their condition.

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