

The Effect of Whole-Body Electromyostimulation on Inflammatory Biomarkers and Adipokines in Overweight to Obese Adults with Knee Osteoarthritis: a Randomized Controlled Study

Ganzkörper-Elektromyostimulation, inflammatorische Biomarker und Adipokine bei übergewichtigen Erwachsenen mit Kniearthrose. Eine randomisierte kontrollierte Studie

Summary

- **Evidence of an anti-inflammatory effect of WB-EMS** is growing. However, applying comparable impulse-protocols, studies reporting positive effects on inflammatory markers, possibly including adipokines, used high volume, superimposed WB-EMS protocols that differ from the time-efficient, non-superimposed concepts mainly used in scientific and commercial settings. The aim of the present trial was to determine the effect of “standard WB-EMS” on inflammatory markers and adipokines in overweight to obese adults.
- **Seventy-two overweight to obese adults** 40–70 years old with osteoarthritis (OA) of the knee, were randomly allocated to a 29-week standard WB-EMS application 1.5x20min/week (WB-EMS) or to a usual care control groups (CG) with six sessions of physiotherapy. Study outcomes were changes of ultra-sensitive CRP, IL-1 β , adiponectin, leptin, total and LDL-cholesterol. Intention to treat analyses with multiple imputation with an ANCOVA adjusted for baseline group difference was applied.
- **Six participants** (WB-EMS=5) were lost to follow-up. Attendance rate averaged 88 \pm 10% in the WB-EMS group and >90% in the CG. After the intervention, we did not observe any significant change of usCRP, IL-1 β , adiponectin, leptin, total and LDL-cholesterol levels or significant between group differences (i.e. “effects”). Adverse effects related to the intervention were not observed or reported.
- **The present low-volume**, non-superimposed WB-EMS (standard) approach does not seem to have a significant effect on the analyzed inflammatory biomarkers and adipokines in overweight to obese adults with knee OA.

KEY WORDS:

Cardio Metabolic Risk Factors, Alternative training Technologies, Weight Loss, Protein Supplementation

Introduction

Due to its time efficiency, consistent supervision and joint friendliness Whole-body electromyostimulation (WB-EMS) is an attractive training technology for many patients unable or unmotivated to exercise conventionally (11). Particular due to its low mechanical stress, WB-EMS might be a suitable resistance-type exercise for knee osteoarthritis (OA). A current study provided evidence for positive effects of high-volume, superimposed WB-EMS on knee OA in older women (18), however the underlying mechanisms are still unclear. It has been shown that OA is often associated with obesity as well as with other metabolic diseases, such as insulin resistance, dyslipidemia or hypertension, together or separately (3). The so-called “metabolic” OA phenotype has emphasized the systemic role of adipose tissue distribution and of adipokines in OA pathophysiology (i.e., cartilage matrix degradation and joint inflammation). So far, a recent study (19) reported positive effects of WB-EMS on intra-abdominal fat mass in obese elderly women. However, it is not completely understood whether adipokines directly affect OA or whether this association is solely attributable to

an increased body fat mass as mediator creating a pro-inflammatory status (3). Therefore, the aim of our study was to determine the effects of non-superimposed WB-EMS applied 1.5x 20 min/week on adipokines and inflammatory markers in overweight to obese adults with moderate knee OA. Although not fully justified by the present literature on WB-EMS effects on inflammatory biomarkers and adipokines (7, 15, 18), we expected significant effects on ultra-sensitive C-reactive protein (CRP), interleukin-1 β (IL-1 β), adiponectin and leptin compared to a usual care control group.

Material and Methods

Study Design

The present WB-EMS randomized controlled trial (RCT) is part of the “electromyostimulation for the treatment of knee osteoarthritis (OA) (EMSOAT) study”. The present study focuses on WB-EMS effects on inflammatory markers and adipose tissue hormones. EMSOAT was planned, initiated and conducted by the Institute of Radiology, University Hospital >

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Table 1

Baseline characteristics of the study participants. ¹=as assessed by Bio Impedance Analysis (BIA), ²=Index from 1: very low to 7: very high.

VARIABLE	CG (N=36)	WB-EMS (N=36)	P
	MV±SD	MV±SD	
Gender (women/men) [n]	24/12	22/14	.624
Age [years]	57.9±7.0	58.3±7.2	.791
Body height [cm]	174.3±9.0	173.2±9.9	.621
Body mass [kg]	89.5±15.1	93.2±15.1	.309
Lean body mass (LBM) [kg] ¹	58.1±11.8	60.2±12.5	.454
Total body fat [%] ¹	35.0±7.7	35.2±9.2	.950
Waist circumference [cm]	100.7±11.5	102.7±10.9	.464
Obesity (BMI ≥30.0 kg/m ²) [n] ²	18	18	1000
Physical activity [Index] ²	3.7±1.1	3.6±1.3	.683
No exercise at all [n]	12	13	.804
Mean Arterial Pressure [mmHg]	104.8±9.5	103.6±9.4	.599
Number of diseases [n] ²	1.47±1.11	1.22±1.27	.507

Erlangen, Germany. The University Ethics Committee of the FAU gave official consent (Nr. 352_20 B) in complete adherence with the Helsinki Declaration “Ethical Principles for Medical Research Involving Human Subjects”. After detailed information, all study participants provided written approval. The project was registered under ClinicalTrials.gov (NCT05672264).

Participants

The full recruitment process of EMSOAT was described in another publication (5). Briefly, (figure 1) participants were included if they met the following inclusion criteria: (a) age 40-70 years old, (b) overweight/obesity (BMI>25 kg/m²), (c) ACR criteria for knee OA (1) with (d) radiographic or MRI-simulated Kellgren-Lawrence grades 2 and 3. Exclusions were (a) WB-EMS or resistance exercise (≥60 min/week) in the last 12 months, (b) glucocorticoid or opioid therapy, (c) trauma of the knee joint or (d) intra-articular injections in the last 12 weeks, (e) conditions, diseases and corresponding therapy with relevant impact on our study outcomes (e.g. rheumatoid arthritis, fibromyalgia), and (f) contraindications for WB-EMS (14). Finally, eligibility was confirmed by the study physician. Twelve people declined participation mainly because of the randomized assignment to the study groups (WB-EMS or control). In summary a total of 72 participants, 46 women and 26 men, 58±7 years old, were both eligible and willing to participate in the current study (figure 1).

Randomization and Blinding

Ensuring allocation concealment, participants assigned themselves to either the WB-EMS or control group by drawing lots. Assistants, testers and outcome assessors were blinded to the participants' group status (WB-EMS or CG).

Study Procedures

The WB-EMS training group (WB-EMS) underwent WB-EMS application while the control group (CG) received a “usual care” intervention (physiotherapy). Additionally, a self-management education program for knee OA was undertaken by both groups.

WB-EMS Intervention

We applied video-guided, consistently supervised WB-EMS (miha bodytec®, Type II, Gersthofen, Germany) 1.5x20 minu-

tes/week for 29 weeks. Both thighs and upper arms, gluteals, abdomen, chest, lower back, latissimus, and upper back were stimulated with bipolar current, 85Hz, 350 μs impulse width and a direct impulse boost. 6-seconds of EMS stimulation were interspersed by a 4-second impulse break. Impulse intensity was prescribed “6-7” (i.e., “hard+ to very hard”) on the Borg CR10 Scale. Low amplitude, low intensity movements were conducted in a standing position during the impulse phase. The approach fully respects the updated international guideline for safe and effective WB-EMS (10).

Control Intervention (Physiotherapy)

In accordance with standard care procedures for knee OA in Germany, the control group underwent six physiotherapy sessions, with a once weekly treatment frequency and a duration of 20 minutes/session. The physiotherapy session addressed the individual knee OA complaints of the participants. Correspondingly, the session focused on exercises and hand-on physiotherapeutic treatment aiming at pain reduction, muscle tissue flexibility, mobility of the knee joint and strengthening the lower muscle extremity. It was recommended that the therapy be carried out in one of three co-operating practices. All practices were informed about the study and the aims of the study in a letter accompanying the prescription.

Study Outcomes

As indicated, the EMSOAT study primarily concentrated on assessing outcomes linked to knee osteoarthritis. The current contribution focused on changes in markers of obesity in conjunction with fat metabolism biomarkers and hormones as well as inflammatory biomarkers.

Adipokines

- Changes in Leptin between baseline and 29-week follow-up (FU)
- Changes in Adiponectin between baseline and 29-week FU

Inflammatory Biomarkers

- Changes in ultrasensitive CRP between baseline and 29-week FU
- Changes in IL-1β between baseline and 29-week FU

Fat Metabolism (Subordinate Outcomes)

- Changes in Cholesterol between baseline and 29-week FU
- Changes in LDL-Cholesterol between baseline and 29-week FU

Assessments

Biomarkers: Blood was drawn one week prior to the WB-EMS intervention and 5 days following the completion of the intervention. After an overnight fast, blood was consistently sampled between 7:00 and 9:00 in the morning in a sitting position from an antecubital vein. Serum samples were centrifuged for 20 min at 3000 RPM and stored at -80°C. All biomarkers were measured in standard clinical laboratories. Ultra-sensitivity C-reactive protein (usCRP) was analyzed on an Alinity c system (Abbott Laboratories, Chicago, USA with manufacturer's reagents). For measurement of IL-1 β an Immulite 1000 (Siemens Healthineers AG, Forchheim, Germany) was used.

Baseline Characteristics and Confounding Factors

Body height was measured using a Holtain stadiometer (Crymych Dyfed., UK). Direct-segmental, multi-frequency Bio-Impedance-Analysis (DSM-BIA, InBody 770, Seoul, Korea) was utilized to assess body mass and body composition. Waist circumference was determined in a standing position as the minimum circumference between the distal end of the rib cage and the top of the iliac crest along the midaxillary line at the end of a normal expiration.

At baseline, a comprehensive standardized questionnaire gathered information on (a) demographic factors, (b) physical limitations, co-morbidities, history of surgeries, pharmacological treatment and dietary supplements, as well as (c) lifestyle aspects such as physical activity, exercise and diet. After 29 weeks of intervention, participants were asked to complete the FU questionnaire that aimed to identify changes in conditions/diseases, pharmacologic and physical therapy, exercise and diet i.e., factors that could potentially affect the present outcomes.

Sample Size Calculation

Sample size calculation was based on the primary outcome "pain of the knee joint" not addressed in the present contribution.

Statistical Analysis

Applying the Intention-to-Treat (ITT) principle with multiple imputation (R Development Core Team Vienna, Austria along with Amelia II) all participants included in the study were analyzed. T-test determined changes from baseline to 29-week FU within the groups, ANCOVA adjusted for baseline differences, was used to analyze corresponding between group differences (i.e. "effects"). Due to violation of normal distribution, IL-1 β was

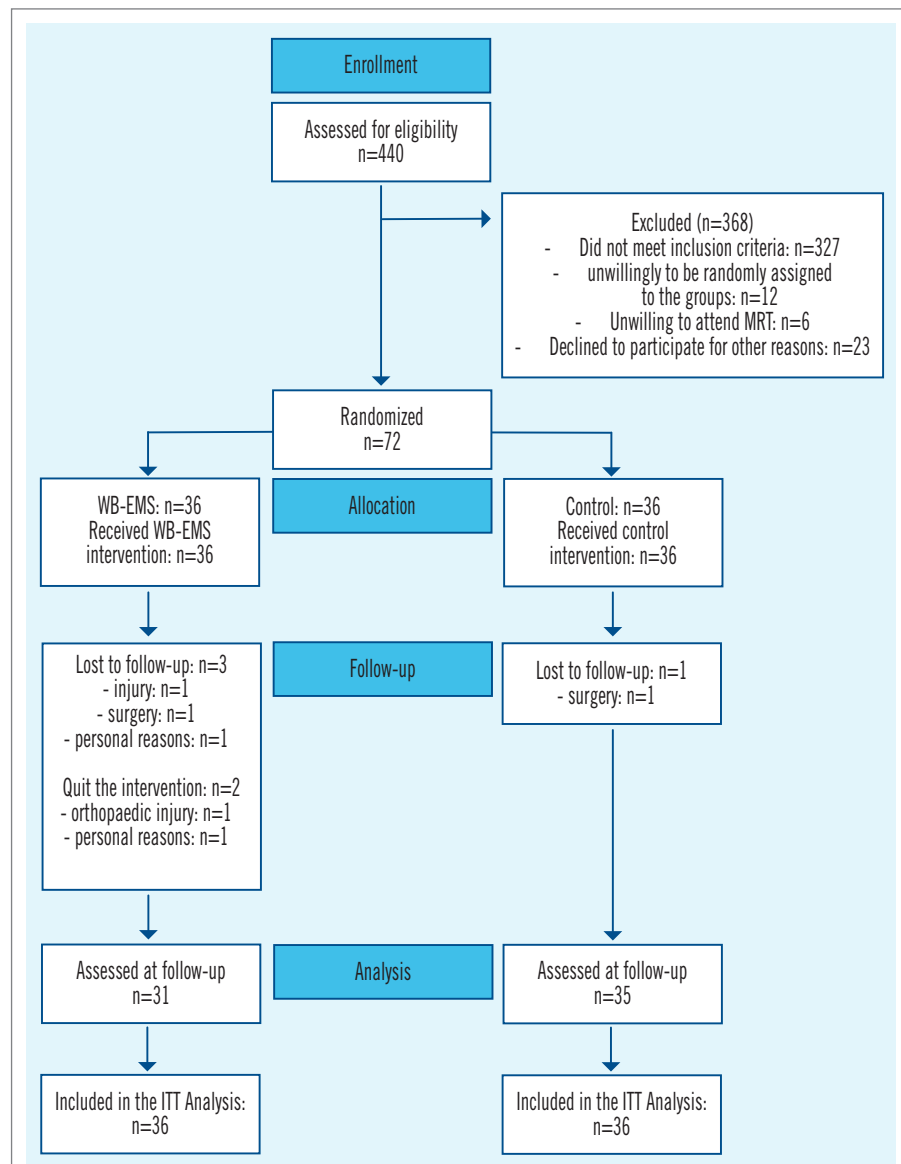


Figure 1

Participant flow through the study according to PRISMA.

log transformed before analysis. Pearson chi-square tests were used to analyze categorical variables. Standardized mean difference (SMD) was calculated according to Cohen's d). All tests were 2-tailed, significance was accepted at $p < 0.05$.

Results

Table 1 displays baseline results of the study cohort. In summary, no significant differences were observed between the WB-EMS and the CG at baseline.

Drop-out and loss to follow-up is displayed in figure 1. Apart from four participants who were unable to attend the FU assessment, two participants of the WB-EMS group quit the study because of personal or orthopedic reasons not related to the intervention. Attendance rate averaged $88 \pm 10\%$ in the WB-EMS group and $>90\%$ in the CG. No unintended adverse effects or injuries related to the WB-EMS application were observed or reported by the participants.

Study Outcomes

Tables 2 and 3 show results for biomarkers at baseline and the corresponding changes after 29 weeks of intervention. Ba- ➤

Table 2

Baseline data and changes of biomarkers of fat metabolism in the CG and WB-EMS groups with corresponding between group differences (ANCOVA). CG=control group; WB-EMS=Whole-Body Electromyostimulation.

	CG	WB-EMS	ADJUSTED DIFFERENCE	P-VALUE	EFFECT SIZE D
	MV±SD	MV±SD	MV (95% CI)		
LEPTIN [ng/ml]					
Baseline	23.9±15.7	24.0±17.6	-----	.990	----
Changes	1.11±8.93	1.90±9.24	.80 (-3.42 to .501)	.708	.09
ADIPONECTIN [µg/ml]					
Baseline	8.09±4.88	6.94±4.23	-----	.289	----
Changes	-.22±1.60	-.27±1.72	.19 (-.94 to .555)	.606	.03
CHOLESTEROL [mg/dl]					
Baseline	210.4±43.1	215.3±41.2	-----	.625	----
Changes	1.5±19.8	8.3±21.4	7.3 (-2.0 to 16.6)	.123	.33
LDL CHOLESTEROL [mg/dl]					
Baseline	138.5±40.5	146.3±37.9	-----	.406	----
Changes	2.3±16.2	2.8±16.8	1.6 (-5.9 to 9.1)	.668	.04

sed on minor intragroup changes without significant differences between CG and WB-EMS for body weight (CG: 0.78±0.47 kg vs. WB-EMS: 0.43±0.49 kg; $p=.736$), waist circumference (CG: 0.60±0.47 cm vs. WB-EMS: -0.20±0.48 cm; $p=.259$) and body fat percentage (CG: 1.21±0.33% vs. WB-EMS: 0.42±0.34%; $p=.098$), we determined only non-significant within as well as between group changes for leptin and adiponectin (table 2). In parallel, neither total nor LDL cholesterol levels were significantly altered in the WB-EMS intervention or the CG (table 2).

In a next step, it was tested whether inflammatory processes were suppressed by the WB-EMS training independently of alterations of adipose tissues. In summary, in comparison to the control group no significant WB-EMS-induced effects were determined for usCRP and IL-1 β (table 3). In addition, no significant changes within the WB-EMS or CG were observed for usCRP and IL-1 β (all $p > .05$) (table 3).

Confounding Factors

No significant changes within or between the groups were recorded for physical activity and exercise during the study period. Changes in dietary habits with lower carbohydrates/sugar and/or energy intake was reported by four participants of the WB-EMS and five participants of the CG respectively. No relevant changes of medication (e.g., glucocorticoids, statins), conditions (e.g. eating disorders) or diseases (e.g. thyroid function) with potential impact on the biomarkers addressed here were reported.

Discussion

Overweight and obesity is a strong predictor of knee OA incidence (16), not only due to the higher mechanical load but also to the pro-inflammatory effects particularly triggered by the visceral adipose tissue (VAT) fraction (9). Applying a joint friendly, time efficient WB-EMS protocol, we failed to determine significant positive effects on obesity, fat metabolism, leptin and adiponectin. Consistent with this, a meta-analysis of the efficacy of WB-EMS found no significant effect for reduction of body fat mass in 12 study groups (12). Additionally, only weak evidence (20) for positive effects of WB-EMS on adiponectin and leptin, as biomarkers of fat mass and metabolism has so

far been provided. However, in a prospective observational study baseline adiponectin and leptin levels were not associated to changes of cartilage and bone biomarkers (4). Hence, these adipokines do not seem to be involved in OA pathology, which might explain why their levels were not changed due to the WB-EMS intervention in our study. On the other hand, Resistin, an adipokine that is also considered as an inflammatory marker, seems to be more sensitive to super-imposed WB-EMS (15, 18, 23). This points to an effect of a pro-inflammatory body status on OA that is at least partly independent of obesity (21). However, we could not establish a down-regulation of the inflammatory biomarkers μ sCRP and IL-1 β due to the WB-EMS intervention. In contrast, Park et al. (18) reported positive effects on IL-6, TNF α , CRP and Resistin-levels after intense isometric exercise superimposed by WB-EMS 3x 30 min/week for 8 weeks. Apart from the higher exercise volume and intensity of the training protocol by the shorter intervention period that leading to acute adaptations to the WB-EMS stimulus that level out over longer periods. However, with respect to the latter speculation, at least no acute effects on inflammatory markers (hsTNF α , IL-6, IL-10, hsCRP) was reported after maximum intensity belt electrical stimulation (B-SES)(22), a technology closely related to WB-EMS (2). In parallel, there is a lack of evidence for leveling-off effects of WB-EMS-application on inflammatory biomarkers and adipokines.

Addressing limitations and particularities of the present trial, (a) the sample size analysis did not focus on the present biomarkers. Nevertheless, the sample size ($n=72$) exceeds the statistical power of most exercise studies with significant positive effects on inflammatory biomarkers (6, 17) or adiponectin and/or leptin (6, 17) and should therefore be adequate to address the present research question. (b) We established a usual care (physiotherapy) control group in order to create a real-world scenario that focuses on the treatment of knee OA however. Nevertheless, one may argue that the physiotherapy session and/or the self-management education program might have positively impacted the results of the CG. However, all the CG sessions were conducted during the first 3 months, thus it is unlikely that positive effects in the CG might have relevantly affected our 7-month findings. (c) The biomarker analysis was not stratified for sex, which might be an issue, since leptin levels

Table 3

Baseline data and changes of inflammatory biomarkers in the CG and WB-EMS groups with corresponding between group differences (ANCOVA). CG=control group; WB-EMS=Whole-Body Electromyostimulation.

	CG	WB-EMS	ADJUSTED DIFFERENCE	P-VALUE	EFFECT SIZE D
	MV±SD	MV±SD	MV (95% CI)		
ULTRA-SENSITIVE C-REACTIVE PROTEIN (usCRP) [mg/dl]					
Baseline	.304±.311	.313±.281	-	.899	-
Changes	-.042±.306	-.041±.312	.007 (-.09 to .11)	.886	.00
INTERLEUKIN 1β (IL-1β) [pg/ml]					
Baseline	.704±.029	0.781±.152			-
Changes	.005±.132	-.016±.138	.031 (-.030 to .091)	.196	.16

in particular are much higher in women than in men. However, we adjusted for baseline differences between the participants to make the results comparable without losing statistical power due to an analysis of smaller, stratified groups. (d) Several drugs like statins have been associated with changes of adipokine levels, which might have influenced our results. However, corresponding evidence is limited and effect sizes seem to be negligible (8). Additionally, no relevant changes of medication were recorded during our intervention. (e) Furthermore, it has to be noted that most participants exhibited biomarker levels that were within or near the reference values of a comparative healthy population. Hence, the limited possibility of improvements due to WB-EMS might have led to an underestimation of the positive intervention effects. Future studies in more vulnerable groups will be necessary to clarify this limitation.

Conclusion

Our study found that low frequency, non-superimposed WB-EMS protocols (i.e. the present standard protocols) was ineffective to significantly improve body fat metabolism and inflammatory biomarkers in overweight to obese adults. ■

Conflict of Interest

The authors have no conflict of interest.

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Ethical approval

Friedrich-Alexander-University of Erlangen Nürnberg, Ethics Committee Nr. 352_20 B

Summary Box

The aim of the present study was to evaluate the effect of WB-EMS, modifications of daily activity and diet on cardiometabolic risk in premenopausal overweight and obese women.

In summary, the WB-EMS intervention featured the lowest drop-out- and the highest compliance rate. While no significant between-group differences were determined, only in the WB-EMS group the MetS Z-score improved significantly ($p=.003$ vs. CG: $p=.647$ vs. PA: $p=.119$).

WB-EMS plus increased daily activity and dietary optimization seems to be a promising combination to improve the MetS in premenopausal overweight and obese women.

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