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# Reduction of Body Fat Mass by Cryolipolysis without Changes in Clinical Biomarkers Levels

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**Abstract...**

**Background:** Cryolipolysis is a non-invasive cooling technique used to reduce localized body fat mass. The changes in fat percentage composition have been assessed by many analytical methods, including bioelectrical impedance analysis. The most common effects of cryolipolysis on reducing subcutaneous of visceral fat tissue have been addressed but biochemical parameters to safely evaluated its systemic effects have been not fully understood.

**Objective:** This study aims to systematically analyze potential changes in hematological and inflammatory biomarkers following the reduction of body fat mass.

**Methods:** A prospective longitudinal approach included a total of 20 participants divided into groups of 5 men and women in each with ages between 25 and 45 years. They were submitted to standard cooling exposure for 60 minutes at -5°C and -10°C with 360° and "shielded" equipment, respectively. The blood samples were analyzed at times T0 (baseline), T1 (2 days), T2 (14 days), T3 (30 days) and T4 (60 days) after the procedure. The percentage of body fat mass were analyzed by bioimpedance at times T0 (baseline), T1 (30 days), T2 (60 days), T3 (90 days) and T4 (120 days).

**Results:** No changes in hematological and inflammatory biomarkers serum levels were observed in both temperatures. However, bioimpedance analysis revealed a significant reduction in the percentage of body fat mass only in men participants, with a decrease of 28 (24.5/29.9) compared to 30 (26.2/33.30) when submitted to -5°C after 120 days.

**Conclusion:** These findings support cryolipolysis can be considered an effective and safe method for localized body fat reduction without significant changes in blood biochemical parameters.

***Keywords:*** Biomarkers; Inflammation; Lipids; Body fat; Cryolipolysis; Bio impedance.

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## Introduction

Cryolipolysis is an adipose tissue cooling technique designed to reduce the localized adipose tissue. In fact, subcutaneous fat tissue may be considered a risk factor for cardiovascular diseases. Its principle consists of low temperatures exposure to cause intentional damage to the adipose tissue and preserve adjacent tissues. Fat tissues are more susceptible to cold as demonstrated by the decrease of cheeks of children who consumed popsicles, called "popsicle panniculitis" as a result of oral inflammation at low temperatures [1] Zelickson et al. (2009) [2] used Yucatan and Yorkshire pigs to test a prototype cooling device designed to determine the selective destruction of fat cells with no damage to surrounding tissues. Furthermore, the analysis of serum lipids demonstrated no changes in the animal's lipid profile. In vitro, adipocytes underwent necrosis at temperatures ranging from -2° to 2°C and markedly increased apoptosis over 7°C [3].

Clinical studies also showed cryolipolysis did not affect serum lipids and liver function as revealed by no significant changes in the lipid profile of liver biomarkers [4]. However, the local injury after the freezing application may cause systemic changes in the body by affecting body thermal balance. Tissue response includes the increase in energy metabolic rate to maintain its thermoregulation [5].

Increased mitochondrial energy metabolism generates reactive oxygen species, which may activate proteolytic caspases enzymes in the apoptosis cascade signaling [6]. Other intracellular disturbances caused by ice-induced tissue ischemia affect osmoregulation by changing Na-K-ATPase activity, adenosine triphosphate (ATP) levels and lactic acid acidosis [7].

Despite the fact that more than 650,000 procedures have been performed worldwide since its inception, cryolipolysis remains unstandardized, with few physiopathological approaches [8]. The current scientific basis outlines the equipment used, as well as the location, exposure period and temperature. Inflammation that occurs as a result of adipose tissue cooling injury has not been addressed. In this context, the use of peripheral blood biomarkers might be useful in ensuring patient safety when applying the technique. These findings contribute to maximize the safe use of cryolipolysis technique while achieving the most desirable results.

## Material and methods

### Study design

In this prospective and open label clinical study, the participants were selected according to the inclusion criteria that included healthy individuals, with adipose tissue deposits in the abdomen greater than 2.0 mm as measured by the Lafayette Adipometer and a body mass index between 21.0 and 33.6 in men and 22.9 and 45.8 kg/m in women. A total of 20 participants were divided by computer-generated simple randomization into two groups, A and B, with each group consisting of 10 participants (5 men and 5 women). Body fat mass was measured and blood samples were collected at time zero (baseline), time one (2 days), time two (30 days), time three (60 days), and time four (90 days) after the procedure.

### Cryolipolysis procedure and body fat assessment

Cryolipolysis technique was applied to the lower and upper abdomen. During the 60-minute experiment, the temperature was -5°C for group A and -10°C for group B. Applications were performed in the upper abdomen (above the navel) and lower abdomen (below the navel) in a single application. The Dermasul company supplied the Adoxy Medical, Asgard VC10 model equipment to carry out the procedure. Two types of handles, 360° conventional "shielded" models were used. Before being exposed to low temperatures, the skin was protected with an anti-freeze membrane. Diuretic drugs were not taken for at least 24 hours before tests, food and beverages were not consumed was avoided up to 4 hours before tests, and patient was kept at rest. Body fat mass was measured using the Bioelectrical Impedance Analysis (BIA), following of the Brazilian Medical Association (AMB) and the Federal Council of Medicine (CFM) guidelines (2009).

### Cryolipolysis procedure steps

1. Installation of equipment before the activities.
2. Acclimatize room at 17°C before starting the application.
3. Setup the equipment.
4. Skin protection of participants with anti-freeze membrane.
5. Start application, reduce the vacuum to 10% after 5 minutes and proceed for 60 minutes.
6. Remove the handles from the applied area.
7. Remove and discard the used antifreeze membrane.

### Hematological and inflammatory parameters

Each study participant had 3 mL of venous blood drawn into an EDTA tube via venin puncture. A blood liquate was extracted from the whole blood sample for hematological analysis. Hematological parameters such as white blood cells (WBC) and red blood cells (RBC), hematimetric indices and platelets, were determined using an automated hematology analyzer, the ADVIA 120 (Siemens Healthcare, Berlim, Germany), a hematology analyzer that performs a complete blood count and provides results in printouts. An experienced Senior Laboratory Technologist who had special training and was certified on the automated hematology analyzer performed hematological analysis in accordance with the standard protocol and manufacturer instructions of the hematology analyzer machine and the Clinical and Laboratory Standards Institute (CLSI) guideline. Inflammatory biomarkers such as mean platelet volume (MPV), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR) and the immune inflammation index (SII) were calculated as described previously [9-11].

## Statistical analysis

Quantitative variables were expressed as mean ± standard deviation. Gaussian distribution (i.e., normality) were analyzed by the Shapiro-Wilk test. The levels in biomarkers and percentage of body fat mass between groups were performed using analysis of variance (ANOVA) followed by Holm-Sidak post hoc test or Friedman´s test followed by Dunn´s pos hoc test for multiple comparisons. All tests were two-tailed, with a value of $p<0.05$ considered statistically significant. All statistical analyzes were performed using GraphPad Prism 9.2.0 software (Graph-

Pad Software, Inc., La Jolla, California, USA).

## Results

### Subject demographics

In this study, 20 participants were included and allocated into two experimental groups, namely: group A (n=10) and group B (n=10), according to the protocol of intervention described early. Their age ranged from 25 to 45 years (man 35 ± 5 and women 35 ± 8 years old). The mean age was 36 ± 8 for group A and 35 ± 5 for group B. Within group A, the mean age for women was 35 ± 10, and for men it was 36 ± 7. Considering group B, women had a mean age of 36 ± 7, and men had a mean age of 34 ± 5.

### Determination of changes in hemogram after cryolipolysis

The effects of cryolipolysis application on hemogram showed no differences in both temperatures over time (Tables 1 and 2). All measure values were kept stable with means not exceeding the reference value established by the National Quality Control Program guidelines.

**Table 1:** Analysis of hemogram in patients submitted to cryolipolysis at -5°C.

| CRYOLIPOLISYS AT -5° C | | | | | |
|---|---|---|---|---|---|
| **Parameter** | ***Baseline*** | **2 days** | **14 days** | **30 days** | **60 days** |
| **HT (%)** | 41.2 (3.2) | 40.9 (3.3) | 41.4 (3.6) | 42.4 (3.3) | 42.2 (3.5) |
| **HB (g/dL)** | 14.7 (1.4) | 14.4 (1.5) | 14.3 (1.4) | 14.9 (1.3) | 14.8 (1.5) |
| **MCV (fL)** | 86.5 (3.8) | 86.6 (2.9) | 87.0 (3.8) | 89.6 (3.7) | 89.4 (4.0) |
| **MCH (pg)** | 30.8 (1.4) | 30.5 (0.9) | 30.1 (1.2) | 31.7 (1.4) | 31.4 (1.3) |
| **MCHC (%)** | 35.6 (0.9) | 35.3 (0.8) | 34.6 (0.6) | 35.3 (0.8) | 35.1 (1.1) |
| **RBC (mil/µL)** | 4.7 (0.4) | 4.6 (0.4) | 4.7 (0.4) | 4.7 (0.4) | 4.7 (0.5) |
| **RDW (%)** | 10.9 (0.5) | 10.9 (0.4) | 11.2 (0.2) | 11.0 (0.3) | 11.0 (0.3) |
| **LINF (mm³)** | 3145 (1378) | 2759 (745.7) | 2978 (1083) | 3156 (837.1) | 2575 (843.0) |
| **MONO (mm³)** | 550.3 (153.9) | 615.1 (170.8) | 489.3 (176.4) | 333.3 (238.3) | 597.3 (164.7) |
| **NEU (mm³)** | 4614 (1422) | 4380 (1941) | 4095 (1499) | 4619 (1130) | 4742 (1421) |
| **PLAT (mm³)** | 27250 (44733) | 279930 (62278) | 274288 (56847) | 276920 (48913) | 261620 (58986) |
| **LEU (mm³)** | 8806 (2381) | 7782 (2157) | 7967 (2157) | 8365 (1969) | 8350 (1732) |
| **EOS (mm³)[1]** | 147 (71.2/311.3) | 128 (79.7/189.5) | 115 (0/200.5) | 218 (0/431) | 128 (66.7/292.3) |

[1]Data are expressed as median and interquartile interval. Friedman´s test and Dunn´s pos test are used in multiple comparisons. HT: Hematocrit; HB : Hemoglobin; MCV : Mean Corpuscular Volume; MCH : Mean Corpuscular Hemoglobin; MCHC: Mean Corpuscular Hemoglogin Concentration; RBC: Red Blood Cells; RDW: Red Cell Distribution Width; LINF: Linfocytes; MONO: Monocytes; NEU: Neutrophils; ROD: Rod Cells; PLAT : Platelets; LEU: Leucocytes; EOS:Eosinophils.

**Table 2:** Analysis of hemogram in patients submitted to cryolipolysis at -10°C.

| CRYOLIPOLISYS AT -10° C | | | | | |
|---|---|---|---|---|---|
| **Parameter** | ***Baseline*** | **2 days** | **14 days** | **30 days** | **60 days** |
| **HT (%)** | 41.8 (3.3) | 41.7 (4.0) | 43.1 (4.3) | 43.6 (4.7) | 43.0 (4.2) |
| **HB (g/dL)** | 14.5 (1.4) | 14.2 (1.7) | 14.7 (1.7) | 15.0 (1.8) | 14.9 (1.9) |
| **MCV (fL)** | 84.3 (4.6) | 83.3 (4.2) | 84.9 (4.1) | 86.3 (4.5) | 86.7 (5.3) |
| **MCH (pg)** | 29.3 (2.1) | 28.4 (2.3) | 29.1 (2.2) | 29.7 (2.2) | 30.0 (2.8) |
| **MCHC (%)** | 34.8 (0.9) | 34.0 (1.1) | 34.2 (1.1) | 34.3 (0.9) | 34.5 (1.4) |
| **HE (mil µL)** | 4.9 (0.3) | 5.0 (0.3) | 5.0 (0.4) | 5.0 (0.4) | 4.9 (0.3) |
| **RDW (%)** | 11.7 (0.9) | 11.9 (0.9) | 11.8 (0.7) | 11.6 (0.7) | 11.4 (0.5) |
| **LINF (mm³)** | 2850 (445.7) | 2657 (826.3) | 2735 (689.3) | 2893 (572.1) | 2757 (788.0) |
| **MONO (mm³)** | 682.2 (163.4) | 602.7 (170.3) | 401.3 (244.5) | 565.0 (239.2) | 596.7 (171.9) |
| **NEU (mm³)** | 5626 (1931) | 5184 (1697) | 5464 (1984) | 5756 (1560) | 4812 (726.2) |
| **PLAT (mm³)** | 265080 (52307) | 265840 (59038) | 267730 (56270) | 264750 (50093) | 256910 (59208) |
| **LEU (mm³)** | 9455 (2270) | 8553 (2588) | 8996 (2118) | 9471 (2041) | 8475 (1252) |
| **EOS (mm³)[1]** | 216 (118.5/320.5) | 203 (124.8/254.5) | 105 (0/173.5) | 182 (111.5/248.8) | 153 (0/227.5) |

Data are expressed as mean ± standard deviation using ANOVA followed by Holm-Sidak post test.
[1]Data are expressed as median and interquartile interval. Friedman´s test and Dunn´s pos test are used in multiple comparisons.
HT: Hematocrit; HB : Hemoglobin; MCV : Mean Corpuscular Volume; MCH : Mean Corpuscular Hemoglobin; MCHC: Mean Corpuscular Hemoglogin Concentration; RBC: Red Blood Cells; RDW: Red Cell Distribution Width; LINF: Linfocytes; MONO: Monocytes; NEU: Neutrophils; ROD: Rod Cells; PLAT : Platelets; LEU: Leucocytes; EOS:Eosinophils; BAS: Basophils.

Further hemogram analysis was stratified by gender. Figure 1 shows RBC elements by sex submitted to -5°C. Men group showed a slight drop in hematocrit 2 days after the procedure as compared to baseline. An increase also could be seen from after 14 days. Changes in hemoglobin were minimal with a small decrease in hemoglobin in 14 days in men and no changes in RBC cells in both sexes.

Figure 2 depicts the levels of leukocytes, eosinophils, and platelets levels stratified by sex. Leukocytes and platelets remained stable with very similar levels in both sexes after 60 days after cryolipolysis (Figures 2A and 2B). In women, eosinophils tended to increase after 2 days (Figure 2C). Men showed a gradual increase in neutrophils when submitted to application, which could not be seen in women (Figure 2D). As part of the immune response as precursors of tissue macrophages, monocytes had a mild decrease in both sex 30 days after criolipolysis as compared to baseline (Figure 2E).

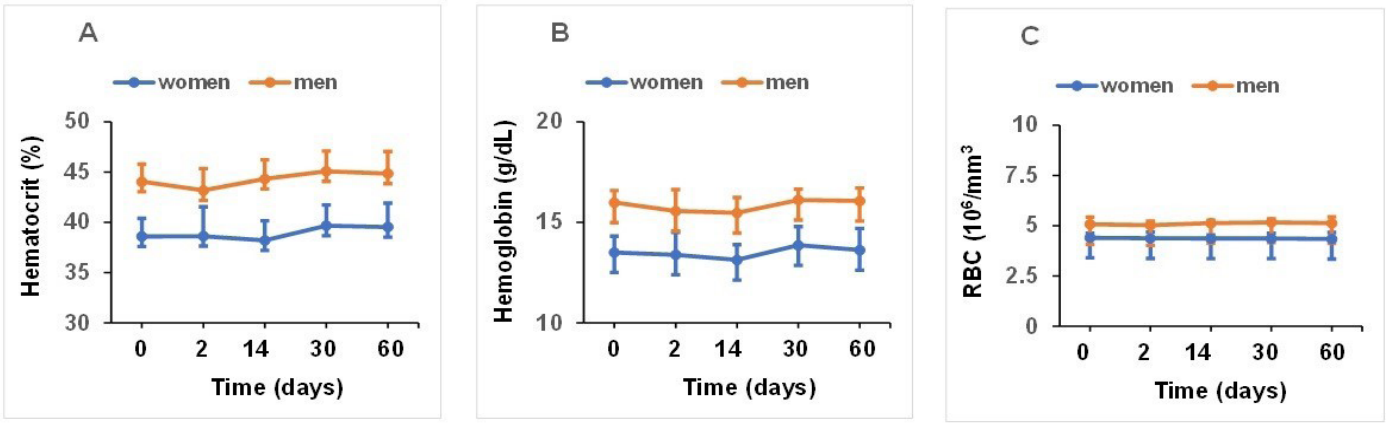


**Figure 1:** Analysis of hematological parameters in men and women after cryolipolysis at -5°C. Data are expressed as mean ± standard deviation. A) Hematocrit; B) Hemoglobin - men; C) Red blood cells.

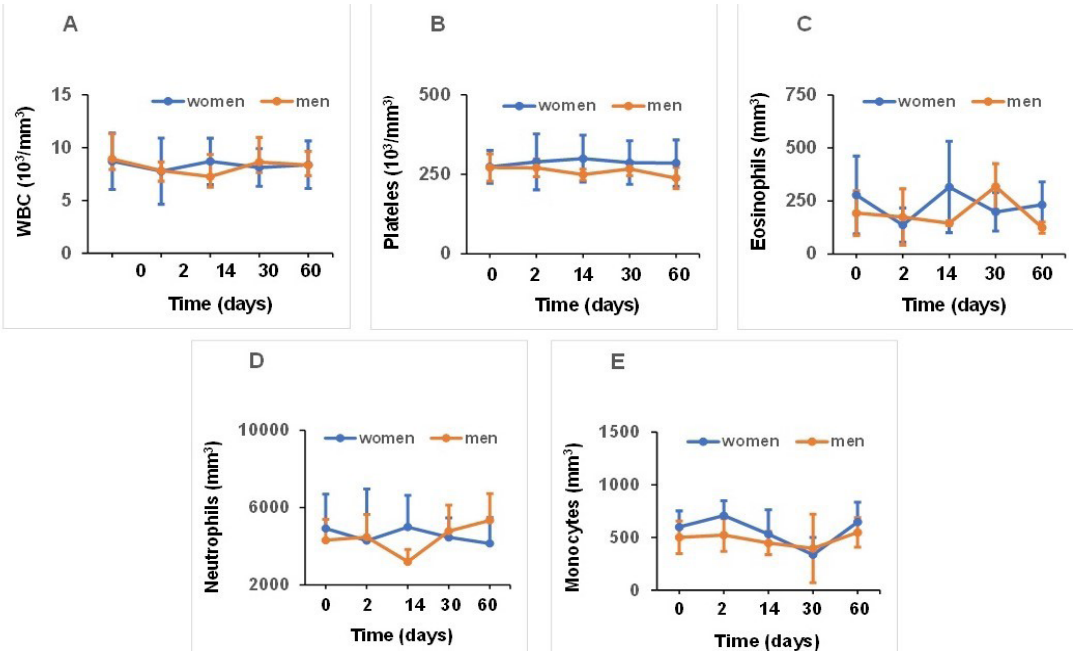


**Figure 2:** Analysis of white cells in men in women after cryolipolysis at -5°C. Data are expressed as mean ± standard deviation. A) Leukocytes; B) Platelets; C) Eosinophils D) Neutrophils; E) Monocytes.

### Body fat mass measurement

The changes in body fat mass were monitored during 120 days after the cryolipolysis at different temperatures. There were significant differences in man as revealed by BIA. The results showed a decrease in the percentage of fat mass after 120 days (28 – 24,45/29,85 vs 30 – 26,20/33,30) at -5°C with no significant changes at -10°C (Table 3 and 4). Surprisingly, the same effect could not be seen in women group with statistical significance. Tissue fat mass reduction by cryolipolysis stands for until 6 months after application, reaching up to 25% loss in total period [12]. DIERICKX et al. (2013) [13] also demonstrated the fat layer reduces up to 23% in 3 months.

### Determination of inflammatory biomarkers

Additional analysis was performed to assess potential changes from the baseline of plasma systemic inflammatory biomarkers during 60 days. The results of inflammatory parameters as MPV, NLR, PLR, SSI as well as CRP showed no changes circulating levels. PLR and LMR means had a slight increase after 2 and 30 days respectively at -5°C and CRP had a peak after 60 days at -10°C (Table 5 and 6).

**Table 3:** Analysis of percentage of body fat mass by BIA after criolipolysis at -5°C.

| CRYOLIPOLYSIS AT -5° C | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | MEN | | | | | WOMEN | | | | |
| DAYS | 0 | 30 | 60 | 90 | 120 | 0 | 30 | 60 | 90 | 120 |
| % | 30 (26.2/ 33.30) | 30 (22/ 31.95) | 28 (25/ 30.50) | 28 (24.6/29.95) | 28 (24.5/ 29.9)* | 43 (29.8/ 45.3) | 43 (28.9/ 44.3) | 42 (26.3/ 43.9) | 42 (25.9/ 43.5) | 42 (25.4/ 43.1) |

Data are expressed as median and interquartile interval. Friedman´s test following Dunn post test for multiple comparison. *p<0.05.

**Table 4:** Analysis of percentage of fat mass by sex submitted to cryolipolysis at -10°C.

| | CRYOLIPOLYSIS AT -10° C | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | MEN | | | | | WOMEN | | | | |
| Days | 0 | 30 | 60 | 90 | 120 | 0 | 30 | 60 | 90 | 120 |
| % | 28 (26.75/ 31.55) | 27 (26.35/ 31.25) | 27 (26/ 29.95) | 26 (25.60/ 29.85) | 26 (25.20/ 30.0) | 38 (38/ 42.10) | 37 (36.60/ 41.55) | 37 (35.60/ 40.95) | 37 (35.30/ 40.65) | 37 (35.20/40.80) |

Data are expressed as median and interquartile interval. Friedman´s test following Dunn post test for multiple comparison.

**Table 5:** Analysis of systemic inflammatory indexes after cryolipolysis at -5°C.

| CRYOLIPOLISYS AT -5°C | | | | | |
|---|---|---|---|---|---|
| Parameter | *Baseline* | 2 days | 14 days | 30 days | 60 days |
| MPV (fL) | 7.2 (0.9) | 7.1 (0.8) | 6.8 (0.7) | 6.9 (0.6) | 7.4 (1.3) |
| NLR (n/µL) | 1.6 (0.7) | 1.6 (0.7) | 1.5 (0.6) | 1.5 (0.2) | 2.1 (1.2) |
| PLR (n/µL) | 99.5 (35.7) | 104.4 (18.1) | 102.2(35.5) | 92.1 (22.6) | 109.2 (35.0) |
| LMR (n/µL) | 5.9 (2.4) | 4.8 (1.9) | 7.1 (3.8) | 13.9 (9.1) | 4.4 (1.4) |
| RCP (mg/L)[1] | 1.9 (0.65/3.55) | 1.5 (1.02/5.35) | 1.5 (0.87/3.67) | 2.1 (0.92/4.20) | 1.3 (0.92/6.27) |

Data are expressed as mean ± standard deviation using ANOVA followed by Holm-Sidak post test.

[1]Data are expressed as median and interquartile interval. Friedman´s test and Dunn´s pos test are used in multiple comparisons.

MPV: Mean Platelet Volume; NLR: Neutrophil Lymphocyte Ratio; PLR: Platelet Lymphocyte Ratio; LMR: Lymphocyte Monocyte Ratio; CRP: C Reactive Protein.

**Table 6:** Analysis of systemic inflammatory indexes after criolipolysis at -10°C.

| CRYOLIPOLISYS AT -10°C | | | | | |
|---|---|---|---|---|---|
| Parameter | *Baseline* | 2 days | 14 days | 30 days | 60 days |
| MPV (fL) | 8.0 (2.0) | 8.3 (1.5) | 7.6 (1.7) | 7.4 (1.5) | 7.9 (1.2) |
| NLR (n/µL) | 1.9 (0.6) | 1.9 (0.4) | 2.1 (1.0) | 2.0 (0.5) | 1.9 (0.8) |
| PLR (n/µL) | 94.8 (22.8) | 107.9 (36.3) | 105.4 (39.4) | 95.4 (28.5) | 107.6 (62.7) |
| LMR (n/µL)[1] | 4.3 (1.0) | 4.4 (1.1) | 9.6 (8.7) | 8.5 (11.5) | 5.0 (2.3) |
| RCP (mg/L)[1] | 1.6 (0.92/5.72) | 2.9 (1.00/11.05) | 2.9 (1.32/6.77) | 1.7 (0.77/6.27) | 4.5 (0.50/9.90) |

Data are expressed as mean ± standard deviation using ANOVA followed by Holm-Sidak post test.

[1]Data are expressed as median and interquartile interval. Friedman´s test and Dunn´s pos test are used in multiple comparisons.

MPV: Mean Platelet Volume; NLR: Neutrophil Lymphocyte Ratio; PLR: Platelet Lymphocyte Ratio; LMR: Lymphocyte Monocyte Ratio; CRP: C Reactive Protein.

## Discussion

The present work monitored body fat mass reduction and the potential changes in hematological and inflammatory parameters following cryolipolysis. We have not found effects on circulating inflammatory markers in the individuals submitted to the technique application. Also, for the first time, a clinical study systematically investigated the relationship between the reduction in fat body mass at different temperatures by gender.

The effects of cryolipolysis on body fat mass reduction remain controversial. Recent clinical studies examined the single-session effect of unilateral cryolipolysis on visceral and subcutaneous over a period of 12 weeks [14]. On the other hand, the fat percentage analyzed by BIA showed a decrease of 25% and 27% in abdomen and flanques after 6 months [15]. In our study, cryolipolysis reduced fat mass percentage significantly only in men group. By the methods employed, we could not see any significant change in these biochemical parameters, what reinforces cryolipolisys as safe technique. BIA measures the effect of electric current on body tissues. The method is precise and allows to determine body composition parameters.

The selective reduction in fat mass after cryolipolysis is ascribed to adipocyte cell death by apoptosis after cold exposure, which is then eliminated by macrophage engulfment as part of the inflammatory process [16,17].

## Conclusions

The use of biomarkers has provided an additional safety tool for clinical practice. In humans, studies have shown that the procedure preserves liver function [2]. According with [1] and ZELICKSON et al. (2009) [4], inflammatory activity is evident after 3 days as demonstrated by the increase in inflammation biomarkers and migration of immune cells to the injury site, lasting up to 30 days before start declining. Despite LMR ratio shows no statistical significance, a peak in patients submitted to either -5 or -10°C has been observed after 30 and 14 days respectively. Nevertheless, the levels returned close to baseline after 60 days.

Scientifically, cryolipolysis still can be on debate as an effective method for localized fat reduction, nevertheless, these findings support the technique as a safe by employing biochemical biomarkers to predict the potential systemic effects on patients' health.

## Declarations

**Ethics approval and aonsent to participate:** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All individuals agreed to participate in the study.

**Human rights:** This work was conducted in accordance with human study rights and approved by the Research Ethics Committee of Universidade Tuiuti do Paraná (CAAE: 17004919.3.0000.8040).

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