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# Photobiomodulation therapy for chronic knee pain in obese patients in pre-rehabilitation for bariatric surgery: randomised, placebo-controlled, double-blinded, clinical trial protocol

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## ABSTRACT

**Introduction** Obesity has become a worldwide public health problem and is directly linked to loss of quality of life, complications and comorbidities. One of them is chronic pain, especially in the knees, which increases significantly and proportionally with weight gain. In patients with severe obesity, with indication for bariatric surgery, the presence of chronic pain disables and often prevents their participation in a pre-surgical rehabilitation programme. As an analgesic therapy, photobiomodulation (PBM) has been studied with safety, efficacy, well-tolerated used and low costs. Thus, this study aims to evaluate the use of PBM for the treatment of chronic knee pain in obese patients undergoing a pre-surgical rehabilitation programme for bariatric surgery.

**Methods and analyses** This is a double-blinded, randomised, placebo-controlled clinical, superiority, trial protocol. The PBM will be applied in bilateral knees and lumbar paraspinal points levels referring to the roots of innervation of the knee. The outcomes evaluated will be pain intensity, functionality, quality of life and clinical signs of neurological sensitization of chronic knee pain pathways.

**Ethics and dissemination** This protocol has already been approved by the Comitê de Ética em Pesquisa do Hospital das Clínicas da Universidade Federal de Goiás/EBSERH—Ethics Committee and it is following SPIRIT guidelines. The results will be statistically analysed and subsequently published in peer-reviewed journals.

**Trial registration number** Clinical Trials Platform (https://clinicaltrials.gov/) with the number NCT05816798.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This protocol is a randomised, placebo, double-blinded controlled trial on photobiomodulation (PBM) treatment for obesity patients suffering from chronic pain.
⇒ The PBM protocol will be applied directly in the topography of pain associated with paraspinal stimulation targeting the origin of neural sensitization mechanisms of chronic pain.
⇒ Protocols aimed to apply to patients with chronic knee pain who have other comorbidities should be adapted to the particularities of these patients.
⇒ Since our sample will be composed of patients with pain with a minimum visual analogue scale of 40, we will include patients with pain ranging from moderate to high grade, which may impact the results, as patients with mild pain may not respond sufficiently to generate a statistical difference between the pre- and post-treatment moments.

## INTRODUCTION

The world health panorama has shown a growing concern and allocation of resources to chronic diseases since these are the main reasons for increased disabilities and loss of quality of life worldwide.[1 2] Among these chronic conditions, obesity stands out. The WHO has recognised that obesity has become a public health concern. The Global Burden of Disease Study results showed that high body mass index (BMI) has become a major challenge, as it is directly linked to many health problems, such as cardiovascular, diabetes, kidney and neoplasm diseases.[2 3] In addition, chronic pain affects 33% of obese people and is also more prevalent in obese than non-obese patients.[4]

Chronic musculoskeletal pain compromises the performance of daily and practical activities of obese individuals. Furthermore, longitudinal evidence shows that high BMI not only precedes but is also a predictor of knee pain.[5] Underweight individuals (BMI <18.5) had a prevalence of knee pain of 12.1%, those with desirable weight (BMI 18.5 and 24.9) had a prevalence of knee pain of

15.2%, and those with BMI ≧40 had a prevalence of knee pain of 55.7%.[6]

In populations with severe obesity, bariatric surgery is indicated to reduce the risk of complications and comorbidities that arise due to excess weight.[7] Nonetheless, for a satisfactory result of bariatric surgery, it is necessary to carry out a pre-surgical rehabilitation programme consisting of therapeutic exercises aimed to improve cardiorespiratory fitness and mobility.[7] However, despite advances in therapeutic techniques aimed for analgesia, due to the chronicity and severity of pain, few advances are made functionally in these pre-surgical programmes, which impact negatively on clinical and functional post-surgical results.[8] The persistence of chronic knee pain in this population becomes a limitation for the individual's daily activities, in addition to hindering their participation and adherence to the pre-rehabilitation programme for bariatric surgery.[5]

Chronic pain does not only refer to pain that persists lasting longer than 3 months but is already well established to be related to central and peripheral neurological sensitization mechanisms with chronic pain, low response to conventional treatments, functional impact and poor prognosis.[9] In chronic pain therapy, the multimodal approach is more effective to control the symptoms. Medications that act on different anatomical sites of the pain pathway are needed.[9]

In addition, non-pharmacological measures are also applied in a broad way. The use of cognitive-behavioural measures, exercises, proper nutrition, ergonomic modifications and physical therapies such as electric stimulation or photobiomodulation (PBM) is now considered a fundamental key point in the treatment of chronic pain.[10]

PBM is an effective analgesic non-pharmacological therapy, which can be safely and easily applied by a qualified professional. The association of PBM with kinesiotherapy sessions may be a good option to alleviate pain and promote a faster return to functional status.[11–14] PBM refers to a series of therapies, in which non-ionising, non-thermal light beams, including LEDs and lasers in the visible and infrared spectra, are used for the interaction with biological tissues from different objectives.[15] Several possible mechanisms of action have been attributed to PBM such as an increase in endogenous opioids, thermal pain threshold, and local blood circulation, ATP or neurotransmitter production at the cellular level, and oxygen consumption and anti-inflammatory cytokine changes.[15]

In this sense, numerous PBM techniques have been used in the treatment of musculoskeletal pain, and clinical studies have investigated its effectiveness with excellent results.[16] Thus, this study aimed to evaluate the effects of PBM on the pain and functionality of obese patients with chronic knee pain undergoing a pre-surgical rehabilitation programme for bariatric surgery, discussing its role as an analgesic therapy and modifier of neurological sensitization mechanisms to the pain pathway.

## METHODS AND ANALYSES

### Study design, protocol registration and recruitment

This will be a single-centre, superiority, phase II, double-blinded, randomised, two-arm, placebo-controlled clinical trial that will involve obese patients with a referral to bariatric surgery under medical follow-up in the Gastric Surgery Service of the Hospital das Clínicas da Universidade Federal de Goiás (HC-UFG) Brazil). It was registered in the Clinical Trials Platform (https://clinicaltrials.gov/) with the number NCT05816798 and follows SPIRIT reporting guidelines.[17] To achieve adequate participant enrolment to reach the target sample size, participation in the study will be offered to all obese patients in the registry database of the medical group of the hospital with referral to bariatric surgery (BMI of over 40 or over 35 plus systemic disable conditions: sleep apnea, diabetes mellitus, coronary artery disease, arterial hypertension, dyslipidemia). Once identified in the database, the potentially eligible patients for the study will be contacted by the physiotherapists, who will explain the study and verify the interest in participating. If there is interest, evaluations will be made by the principal investigator (PI) to verify the eligibility criteria. Patient enrolment for this pilot study commenced in July 2023. To date, eight patients have been enrolled, with the anticipated pilot study enrolment completed by December 2024.

### Eligibility criteria

An initial assessment will be conducted by the PI to assess the eligibility criteria and the signature of the consent form by the included patients.

- Inclusion Criteria: Obese patients with chronic knee pain undergoing medical follow-up in the Gastric Surgery Service with an indication for bariatric surgery already performed by the responsible medical team and also submitted to the programme of pre-surgical rehabilitation standard treatment for bariatric surgery at the Physiotherapy Outpatient Clinic of the Hospital. These patients have already received the medical indication of the need to undergo surgery. However, even if the indication for the procedure is already established, as usual in the hospital routine, surgery is not performed immediately. They are submitted to a standard multidisciplinary pre-surgical rehabilitation programme preoperatively.
- Patients with chronic pain (>3 months) in the knees bilaterally.
- Based on studies by Üstün *et al*[18] and Matsuse *et al*[19], we include obese patients with baseline knee pain assessed by the pain visual analogue scale (VAS) at least 40 at the moment of evaluation, using a 100 mm VAS with 0 representing no pain and 100 representing the worst pain imaginable.
- Age: 18 to 70 years.
- Agree to sign the Informed Consent Form approved by the local Ethics Committee.

### Exclusion Criteria

- Patients with a diagnosis of rheumatological, systemic inflammatory, knees previous musculoskeletal diseases, neuropathies, infections or tumours at the application site of therapy, severe psychiatric disorders requiring psychiatric care.
- Previous use of phototherapy for the same or another indication.
- Use of corticosteroids at an immunosuppressive dose (20 mg daily of prednisone or equivalent for at least 14 days) in the last 90 days.
- Systemic injections and/or joint infiltrations of corticoids or hyaluronic acid in the last 3 months.
- Withdrawal of the Informed Consent form by the participant.
- Patients excluded from the queue for bariatric surgery or the pre-surgical rehabilitation programme.
- Changes in the analgesic medication used. Changes in the dosages may be tolerated as long as there are no changes in the class of medication. The dosage modifications throughout the study, if they occur, will be described.

## Randomisation and allocation

Eligible patients will be assigned to groups with a 1:1 allocation rate into two groups. The two groups are the PBM intervention group (use of PBM therapy+pre-surgical rehabilitation standard programme of the hospital) or control group (placebo PBM therapy+pre-surgical rehabilitation standard programme of the hospital). At the time of allocation, opaque envelopes will be identified with sequential numbers with the information on the corresponding group according to the order obtained in the randomisation list by Research Randomiser online software, which generates a sequential randomisation list using random block sizes (eight patients per block). The envelopes will be sealed in numerical order until the moment of study intervention and just immediately before the PBM moment, the researcher responsible for the treatment will open one envelope (without changing the numerical sequence) and perform the indicated procedure (PBM or placebo PBM).

## Blinding

Baseline and final assessments will be conducted by the PI, who will be blinded about the randomisation and allocation of patients. Patients will also be blinded to the randomisation and allocation until the end of the study. The pre-surgical rehabilitation standard treatment will be held by a physiotherapist who is blinded to evaluation data or the treatment group. Another physiotherapist will be responsible for the application of PBM, placebo PBM and by the allocation and randomisation, but is also blinded to evaluation data. Concerning placebo treatment, our participants do not use PBM therapy routinely, and they are not familiar with the procedures or particularities of this therapy, which contributes to their inability to distinguish between regular therapy and placebo therapy. Furthermore, all participants will wear dark protective glasses, which completely block vision (used for eye safety) and contribute to the blinding of using a placebo. The recorded sound that will be used to simulate the use of the equipment (placebo PBM group) is the sound generated by the device itself in use, during its regular operation in the study.

## Sample size

The sample size was calculated based on Matsuse *et al*[19] in which VAS values were obtained for the control group (61.5±22.8) and the treated group (44.2±19.4), with a reliability of 95%, error of 5% and test detection power of 80%. Considering a VAS change of at least 20% comparing the pre and post-moments in the treatment group, the minimum sample size will be 26 patients per group. Assuming a percentage of 20% of drop-outs, the minimum sample size will be 31 patients per group.[19]

## Interventions

1. Pre-surgical rehabilitation standard programme of the hospital

All patients undergoing follow-up at the Gastric Outpatient Clinic of HC-UFG due to severe obesity and who have an indication for bariatric surgery are submitted to a standard multidisciplinary pre-surgical rehabilitation programme for 3 to 6 months preoperatively.

This programme will be maintained for all study patients, for both groups, throughout the study period and includes 2X per week activities of:

1. Cardiopulmonary physiotherapy: depending on the clinical condition may include deep breathing exercises; hands-on techniques; breathing facilitation exercises; percussions and vibrations; coughing and breathing strategies; circulation exercises; mobility assistance to move safely in bed; and sit up, stand, walk, bed and chair standing exercises to prevent deep vein thrombosis (clots) using the fitness programme.
2. Kinesiotherapy with global muscle strengthening exercises: depending on the clinical condition, these may include lifting weights, working with resistance bands, climbing stairs, hill walking, cycling, dance, push-ups, sit-ups and squats.
3. Follow-up with the nutrition team to personalised, one-on-one dietary guidance and counselling.
4. Follow-up with the psychology team to personalised one-on-one identify barriers, come up with strategies, solve problems and assist the patients in figuring out how they are going to implement some of the needed changes given their individual life circumstance.

2. PBM intervention Group

In addition to the standard treatment described above, the PBM therapy sessions will be carried out in the Physiotherapy Outpatient Clinic of the Hospital, two times per week, for 12 consecutive weeks, just after the pre-surgical rehabilitation standard programme, to improve adherence to intervention protocols. The PBM application points are as follows:

Table 1 Photobiomodulation parameters

| Parameter | Paraspinous | Knee |
|---|---|---|
| Device | Therapy EC (DMC ™) | Therapy EC (DMC ™) |
| Type of laser | Diodo | Diodo |
| Wavelength (nm) | 808 | 808 |
| Emission mode | Continuous | Continuous |
| Application technique | Perpendicular contact point | Perpendicular contact point |
| Power (mW) | 100 | 100 |
| Opening diameter (cm) | 0.031 | 0.031 |
| Beam area on target ($cm^2$) | 0.0984 | 0,0984 |
| Energy (J)/point | 3 | 4 |
| Fluence ($J/cm^2$) | 30,48 | 40,64 |
| Time (s)/point | 30 | 40 |
| Total Energy/ session (J) | 30 | 32 |

1. Transcutaneous paravertebral region bilaterally at levels of L3, L4 (iliac crest), L5, S1 and, S2 roots topography, 1 cm lateral to the spinous process, corresponding to the roots levels that innervate the knee joint (totaling 10 paraspinal points).
2. Knees transcutaneous bilaterally (four points on each knee):

- Anteromedial point.
- Anterolateral point.
- Patellofemoral joint—the apex of the patella.
- Patellofemoral-base patellar joint.

The responsible for the application will be present throughout the intervention.

The PBM parameters are described in table 1 and are based on studies by Fernandes *et al*, Zein *et al*, and Leal-Junior *et al*.[11 20 21] They also follow the recommendations of the World Association of Laser Therapy WALT.[20–22]

3. Placebo PBM therapy

Placebo group patients will receive the pre-surgical rehabilitation standard programme described above as well as a placebo PBM treatment to mask the treatment. The placebo PBM therapy has the same procedures, number of points and place of application described in the item PBM intervention group; however, the PBM equipment will be turned off. The device activation noise will be recorded and used to mimic the irradiation.

Furthermore, the PBM therapy and placebo PBM therapy will be performed on the same day that the patient is already scheduled to undergo the pre-surgical rehabilitation standard programme of the hospital, therefore not adding extra-hospital visits for the patients.

## Outcomes and measures

The primary outcomes evaluated will be pain and functionality through the following outcome measures:

- Change from baseline to 12 weeks (after PBM treatment) in the VAS.[23 24] Pain knee was evaluated using a 100 mm VAS with 0 representing no pain and 100 representing the worst pain imaginable.
- Change from baseline to 12 weeks (after PBM treatment) in the Brazilian version of Knee Injury and Osteoarthritis Outcome Score Questionnaire[25].

Secondary outcomes related to the clinical assessment of neurological sensitization of the pain pathway will be evaluated through:

- Changes from baseline to 12 weeks (after PBM treatment) in the pressure pain threshold measured bilaterally in the muscles: popliteus, sartorius, quadratus lumborum, rectus femoris, vastus medialis, vastus lateralis, adductor longus, tibialis anterior, peroneus longus, gracilis and supraspinatus ligaments between L1-L2, L2-L3, L3-L4, L4-L5, L5-S1 and S1-S2.[26 27] Pressure is applied perpendicularly to the skin at a speed of 1 kg/s by a digital pressure algometer (Instrutherm™) to patients indicate when they start to feel pain.
- Changes from baseline to 12 weeks (after PBM treatment) in the the *Pinch and Roll Maneauver*[26 28 29] at L1, L2, L3, L4, L5, S1 and S2 will be performed bilaterally to assess signs of subcutaneous hyperalgesia.

Other exploratory outcomes are related to knee function and quality of life through the following outcome measures:

- Changes from baseline to 12 weeks (after PBM treatment) in the 6 min walk test.[30]
- Changes from baseline to 12 weeks (after PBM treatment) in the Brazilian version of the SF 36 Quality of Life Scale.[31]
- Changes from baseline to 12 weeks (after PBM treatment) in the range of motion of the knee joint measured with a goniometer.

The following data will be collected from medical official records for the sample epidemiological clinical data: age, gender, BMI, life habits (alcoholism, smoking, drug use), comorbidities, use of analgesic drugs and doses and knee pain duration.

The schedule of enrolment, interventions, assessments and visits for participants is presented in figure 1. Figure 2 presents the planned flow chart showing inclusion, randomisation and participation throughout the study.

## Data collection and monitoring

An electronic spreadsheet database will be created to preserve the confidentiality of patient data and allow the exchange of information between the researchers of the group. This information will be stored for 5 years after the completion of the study in a digital file by the PI. All research data collected will be saved directly in these electronic files and stored on the research team's institutional drive server. The system has authentication password tools, access control and activity recording, ensuring security and traceability of data.

| | STUDY PERIOD | | | |
|---|---|---|---|---|
| | **Enrolment** | **Allocation** | **Post-allocation (Day Session)** | **Close-out** |
| **Timepoint (days of study)** | ***Day 01*** | ***Day 01*** | ***01-24 day session*** | ***Day 39*** |
| | | | | |
| *Eligibility screen* | X | | | |
| *Informed consent* | X | | | |
| *Allocation* | | X | | |
| *Intervention:* | | | | |
| *PBM + standard treatment* | | | X | |
| *Placebo PBM + standard treatment* | | | X | |
| *ASSESSMENTS:* | | | | |
| *Visual Analogue Scale* | | X | | X |
| *Articular Range of Motion* | | X | . | X |
| *6" min Walk Test* | | X | | X |
| *SF-36* | | X | | X |
| *KOOS* | | X | | X |
| *Central and Peripheral Sensitization clinical signs* | | X | | X |

**Figure 1** Participant timeline schedule of enrolment, interventions and assessments.

### Statistical analyses

The data will be analysed to assess the distribution of demographic data and outcome criteria by the Kolmgorov–Smirnov (KS) and Shapiro–Wilk tests. Variables are reported as means and SD. Comparison of before/after PBM 'within group' will be made using paired t-test. Comparison of changes from baseline to the endpoint (treatment vs sham) 'between groups', will be made with two-sample t-test. In case of non-normal distribution, comparisons will be made using the Wilcoxon Sign Rank test and Mann–Whitney test for paired and unpaired data, respectively. To analyse the correlation of primary and secondary outcomes the $\chi 2$ test or Pearson's exact test will be used. For all tests, a significance level of $\alpha$=5% will be established. All analyses will be performed using SPSS statistical software version 28.0 for MAC (IBM Corporation, USA).

### Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

## ETHICS AND DISSEMINATION PLAN

### Ethics

This study complies with the ethical research guidelines already approved by the ethics committee of the Comitê de Ética em Pesquisa do Hospital das Clínicas da Universidade Federal de Goiás/EBSERH-Ethics Committee with the number 5.951.619/approval number: 66250922200005078. The participants will only be included after properly obtaining consent and signing the Free and Informed Consent term. All data published or made available will not contain sensitive data that identify the patients. The study will not interfere with the

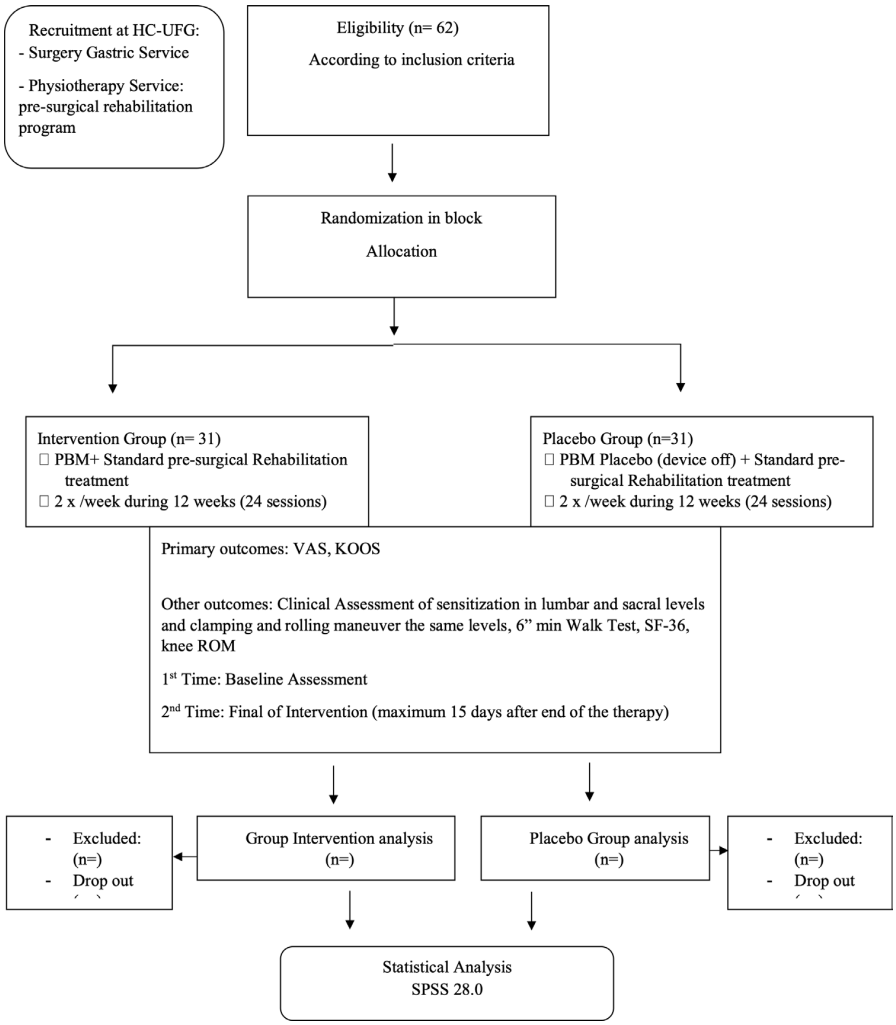


**Figure 2** The planned flow chart showing inclusion, randomisation and participation throughout the study.

clinical follow-up and medical decisions of the healthcare team or medical routine of patients.

### Safety/harms

Although the use of PBM devices is safe, the main care should be directed towards avoiding ocular injury (damage to the retina, lens such as cataracts, burns to the cornea and crystalline lens) and skin damage, such as burns, erythema and increased sensitivity.[32] To prevent these side effects, during the interventions, both examiners and patients will be wearing protective eyewear. Moreover, applications will occur after locally cleaning the device and skin. In addition, our clinical team of study has experiences and qualifications in the application of PBM therapies. After each therapeutic session, the patient will be questioned and clinically evaluated for any undesirable or adverse effect of the PBM (Adverse Effects Monitoring Sheet) by the health professional team. If there is any Suspected Unexpected Serious Adverse Reaction, the patient will be removed from the study, and the Ethical Committee will be notified to assess the need to interrupt the intervention/study and/or unblinding patients. If any other medical treatment is necessary, it will be carried out by the hospital medical team. If any adverse event occurs, participants will be withdrawn from the study, and these data will be reported. Any withdrawal or loss of patients due to adverse events will be reported.

### Dissemination Plan

The data management plan is available in the Data Management Plan https://dmphub.uc3prd.cdlib.net/dmps/10.48321/D1MW8J

Upon completion of the study, the original clinical non-identifiable collected data stored in the spreadsheets of institutional drive referring to pain, quality of life and functionality assessments will be made available in an open science repository, to collaborate with the scientific community and auditing. The results of this work after the statistical analysis (whether they are favorable or not) will be published in a peer-reviewed scientific journals.

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**Contributors** Author Contributions: conceptualisation, ACFGA, RBC, TCFB, TNSD and FARJ; study design/methodology, ACFGA and RBC; writing original draft preparation, ACFGA and RBC; writing—review and editing, RLM, ALSF, MFSDR, ACFGA, TCFB, TNSD, FARJ, RLM, ALSF, MFSDR and RBC; supervision, RBC; and project administration, ACFGA and RBC.

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**Competing interests** The authors declare no competing interests

**Patient and public involvement** Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** This study complies with the ethical research guidelines, already approved by the ethics committee by the Comitê de Ética em Pesquisa do Hospital das Clínicas da Universidade Federal de Goiás/EBSERH-Ethics Committee with the number 5.951.619 / Approval Number: 66250922200005078.

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