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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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RATIONALE AND ANALYSIS OF THE EFFECT OF HYPERBARIC OXYGEN THERAPY IN THE RECOVERY OF LONG COVID PATIENTS.

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Abstract.

Long COVID is a common occurrence after an infection with COVID-19. Most frequent symptoms are fatigue, shortness of breath, and cognitive dysfunction. Options for treatment are limited, mainly symptomatic. There is a solid theoretical background for the successful treatment with Hyperbaric Oxygen Therapy (HBOT) of the pathophysiological changes caused by the COVID-19 infection and their reversal.

Case presentation: The data presented was collected from the test results of total of 63 male and female patients, treated from 15th January 2021 to 19th April 2022, aged 22 to 74 years old, all of them presenting with symptoms of Long COVID. A standard 2.4 ATA HBOT treatment table for approved elective HBOT indications was used for the treatment of Long COVID patients, with a course duration of 10 or 15 sessions. The key concept is that HBOT works on a cellular level, specifically affecting the oxidative phosphorylation and energy metabolism in the mitochondria.

Results: Hyperbaric Oxygen Therapy delivered positive results in all observed Long COVID related symptoms, particularly those associated with the nervous system, cognitive function, psychological well-being, and physical fatigue. Approximately 90% of all patients improved compared to their initial state, in most cases significantly. No adverse effects were reported. Feedback received three months after treatment demonstrated that the benefits were persistent.

Key words. Long COVID, HBOT, HBO2, Post COVID Fatigue, cognitive dysfunction, hyperbaric oxygen therapy.

Introduction.

Severe acute respiratory syndrome corona virus two (SARS-CoV-2) is a virus member of the Coronavirus family. It is known to be responsible for the development of a variety of symptoms, ranging from mild respiratory disease to pneumonia, respiratory failure, and death. Some of the damage persists for a prolonged period - weeks and months after testing positive for COVID-19. This is described as Long COVID [1-16]. The long-term effects can be present in all body systems, with the cardiovascular, respiratory, and neurological systems affected the most. There are prominent psychological effects as well [8].

The World Health Organisation defines Long COVID as the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation. While common symptoms of Long COVID can include fatigue, shortness of breath, and cognitive dysfunction, over 200 different symptoms have been reported that have an impact on everyday functioning [16]. These symptoms may be with a new onset, following initial recovery from an acute COVID-19 episode, or they can persist since the beginning of the initial infection. They may also fluctuate or relapse with time.

Long COVID has a tremendous impact on the life of the patients who suffer from it. There are no officially approved effective treatments for this condition at present. Most treatments are at best only symptomatic. There has been significant interest in using HBOT for the treatment of Long Covid and several randomised clinical trials have taken place. HBOT has gained popularity, and it has been successfully used in Europe and across the world as an alternative treatment for Long COVID.

What is Hyperbaric Oxygen Therapy?

Hyperbaric Oxygen Therapy (HBOT) is defined as an intervention in which an individual breathes medical grade oxygen (>99% purity) intermittently, while inside a hard sided hyperbaric chamber that is pressurised. The pressure used must be not less than 2.0 ATA for the treatment to be considered Hyperbaric Oxygen Therapy. This treatment can be administered in either mono or multi-place chambers. The mono chamber can accommodate usually only a single patient. The whole chamber is filled with 100% Oxygen, which the patient breathes directly from the surrounding atmosphere. Depending on its size, the multi-place chamber can accommodate more 3 than one patient and a supervisor. 100% medical grade oxygen is administered either via a mask or a hood, typically for a duration of 90-120 min [14].

HBOT is approved for treatment of fourteen indications for both elective (e.g., soft tissue radiation injury complications, non-healing wounds) and emergency indications (e.g., decompression illness, arterial gas embolism, carbon monoxide poisoning). There are other conditions that are under investigation as well. HBOT is considered extremely safe, with minimal potential side effects, most of them mild and transitional, commonly involving ear equalisation (i.e., middle ear barotrauma), reversible myopia, claustrophobia, and self-limiting oxygen toxicity (<1:10.000). HBOT is inexpensive, non-invasive, low risk for the patient, and provides excellent results.

Case presentation and treatment.

A total of 63 male and female patients, aged 22 to 74 years old, presenting with various symptoms of Long COVID were offered a HBOT treatment with the aim of reversing the damage caused by the COVID-19 infection.

The treatment was provided in a multi-place (10-seater) hyperbaric chamber. The usual number of patients for each compression was eight or less. The whole process of screening, control, and treatment was overseen by a hyperbaric physician. Inside the chamber, patients were accompanied and monitored by a trained hyperbaric supervisor. All Long COVID patients

were treated with a standard 2·4 ATA Hyperbaric Oxygen Therapy (HBOT) treatment protocol, normally used for treatment of elective patients with one of the approved HBO2 therapy indications. (Figure 1: HBOT Treatment table for Long COVID).

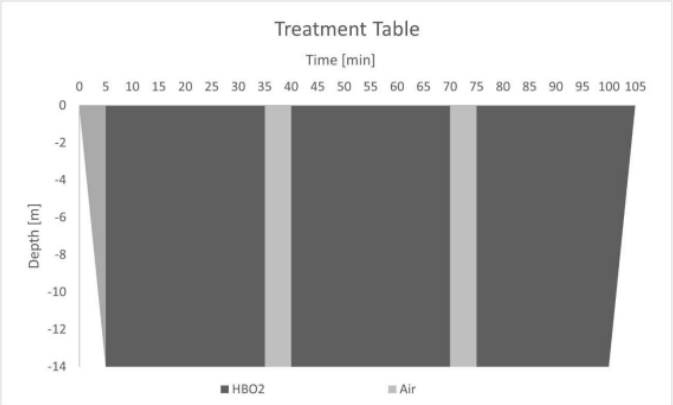

Figure 1. *HBOT Treatment table for Long COVID.*

The treatment was administered in a short, ten and fifteen sessions course. 21 patients received 10 HBOT sessions and 42 patients received 15 HBOT sessions. The sessions were administered daily, five times a week, Monday to Friday, over a two or three-week period. The number of sessions was chosen with an obvious correlation with the severity and duration of Long COVID symptoms, presence of co-morbidities, etc. In each session patients were breathing 100% medical grade oxygen, administered via masks for 90 minutes with two 5 minutes air breaks. The treatment progress was monitored with standardised tests, aiming to cover a vast array of symptoms, from the purely physical to the psychological. Below are presented the results from "NeuroTrax", a computerised cognitive test, "Chalder Fatigue scale", measuring physical and psychological fatigue, and RAND SF-36, measuring quality of life, both based on self-rating assessment.

Assessment method and Results.

NeuroTrax-Computerised cognitive test:

The test assesses brain wellness across an array of cognitive domains, including memory, executive function, visual spatial perception, verbal function, attention, information processing speed, and motor skills [3].

This test is particularly useful when it comes down to measuring cognitive dysfunction in Long COVID, where attention, information processing speed, memory and executive function seem to be the parameters affected the most.

The test is user friendly and requires little orientation and computer proficiency.

Patients perform different tasks. The test takes 45 to 60 minutes to complete, depending on the patient's age and cognitive ability. A battery of tests maps out patient's capabilities across seven categories – Memory, Executive Function, Attention, Information Processing Speed, Visual Spatial, Verbal Function, and Motor Skills. The test is performed at the beginning and at the end of treatment course. The number of patients whose results indicate improvement after HBOT is 86% in the 10 sessions group. It is even higher in the 15 sessions group, 95%

Figure 2 gives a further look into the results of those whose treatment was successful. The dotted line represents the score in the initial (pre-treatment) assessment, and the solid line - the scores from the final assessment. The score range is min 70 to max 130 points. Increasing score indicates improvement. The results demonstrate improvement across all categories. (Figure 2: NeuroTrax test average scores – First and last day of treatment).

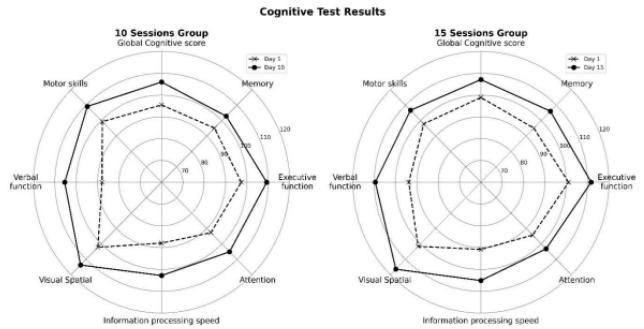

Figure 2. *NeuroTrax test average scores - first and last day of treatment.*

The Chalder Fatigue Scale questionnaire.

This test, as suggested by its name, assesses fatigue, a prominent problem in Long COVID patients. Chalder Fatigue Scale (CFQ) is widely used and trusted method of assessing fatigue, both physical and psychological.

The test comprises of eleven questions with an overall score ranging from 0 to 33 points, when using "Likert" style. The higher the number, the worse the health status of the individual. Decreasing scores indicate improvement. A difference of less than four points, while using "Likert" style scoring, is not considered important, and only patients who scored greater than that are considered to have achieved improvement.

The percentage of patients who have felt benefit from the treatment ("the success rate") is significant: 95% for the ten sessions group, and 78% for the fifteen sessions group. There is also a well pronounced difference between the first and last day of treatment, with an average score of 26 - 27 on the first day, decreasing to 7 to 10 points on the last day. As a comparison, in a study involving 361 Fatigue sufferers and 1615 individuals from the community, the mean Likert score among Fatigue sufferers was 24.4; for the community sample, the score was 14.2 [1]. The two Long Covid patients' groups results indicate significant improvement. (Figure 3: Chalder Fatigue Scale. Results).

RAND SF-36 questionnaire.

This questionnaire is a self-reported assessment of health, often used to measure a

person's Quality of Life (QOL). It comprises of 36 questions that cover eight health domains:

1) Physical functioning
2) Limitations in physical activities because of health problems
3) Limitations in usual role activities because of physical health problems

4) Vitality (energy and fatigue)
5) General mental health (psychological distress and well-being)
6) Limitations in social activities because of physical or emotional problems
7) Bodily pain
8) General health perceptions

All questions are evaluated on a scale from 0 to 100, with 100 representing the highest level of functioning possible. Aggregate scores are compiled as a percentage of the total points. The scores from those questions that address each specific area of functional health status are then averaged together, for a final score within each of the eight measured parameters [7].

The average scores presented on Figure 4 and Figure 5, first day against the last day of treatment, show significant improvement (across all categories for both groups. The percentage of patients who demonstrated improvement across all categories was 96% for the 10 procedures group and 90% for the 15 procedures group.

Patient's feedback

We have sent feedback form - EQ-5D-3L to all treated patients. They have been asked to provide feedback using a numerical scale (1 to 100) at three points in time: before the treatment, at the end of treatment, and at present time (three months and more after completion of treatment). To help people report the state of their health, a scale (rather like a thermometer) has been drawn, on which the best state of health was marked with 100 and the worst state of health was marked with 0. Patients were asked to indicate on the scale how good or bad their health was before the treatment began (Pre), when they finished treatment (Post), and right now (Now). We have received correctly completed feedback forms from 20 patients. The general trend shows retaining higher scores months after they have completed the treatment, compared to their pre-treatment score.

Out of these 20, 18 have reported that they are experiencing positive results from the treatment. Only one did not see any benefit from the treatment; one had seen good results immediately after HBOT, but months later relapsed to their

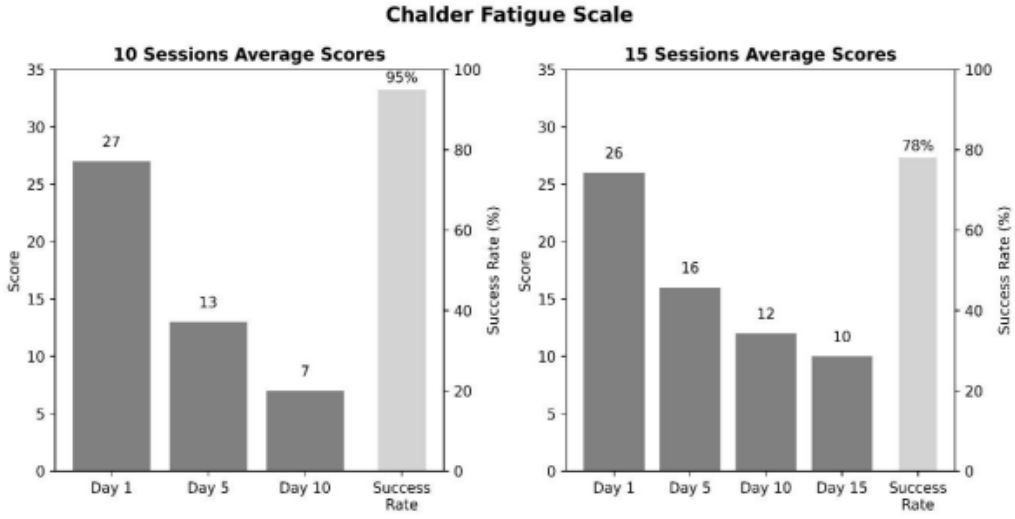

Figure 3. *Chalder Fatigue Scale results.*

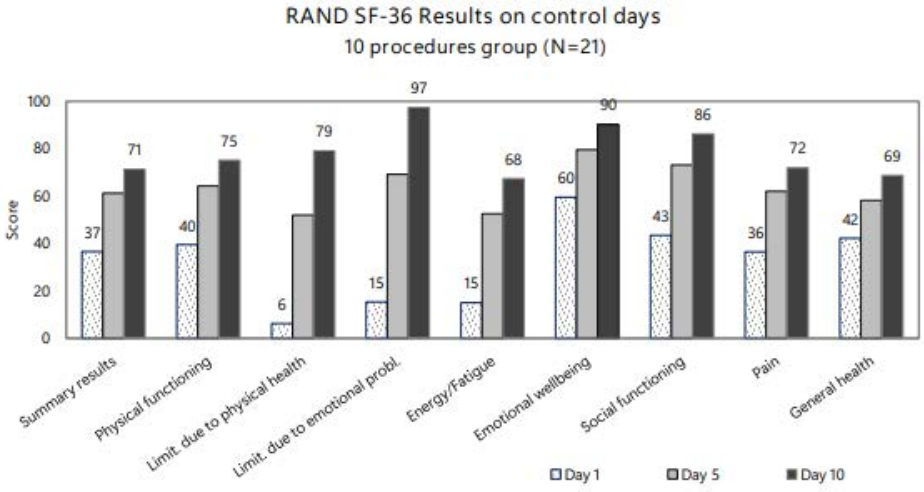

Figure 4. *RAND SF-36 Test results on 1st, 5th, and 10th day of treatment, 10 procedures group.*

initial state. From the 18 patients who had improved, 13 experienced slight regression three months after HBOT therapy, but reported that they still feel significantly better compared to their pre-treatment state. Two reported that they have kept the same high level of wellness, achieved after the treatment; another three reported that they have continued to improve even after the treatment course was completed. In most cases, the improvement was significant. (Figure 6: Patient feedback. Average score of all feedback received).

Discussion.

Why HBOT works for Long COVID. Pathophysiology of Long COVID and the place of the Hyperbaric Oxygen Therapy.

The pathophysiology of Long COVID is likely multifactorial but there are several potential mechanisms through which HBOT works in these patients. The primary one is reduction of hypoxemia, subsequent tissue hypoxia, and resulting inflammation and neuro inflammation. The argument is that HBOT works on a cellular level, specifically affecting the oxidative phosphorylation and energy metabolism in the mitochondria. A strong supporting point for this is that there has been no success in identifying abnormal laboratory test results or a particular body structure that can be responsible for the symptoms of Long COVID. Generally, most investigations, blood work, and various imaging modalities come back within the range of normal, which is in stark contrast with the severe and obvious impairment that these patients report.

The potential mechanisms by which HBOT works for Long COVID patients are discussed below.

Restoration of adequate blood and tissue oxygen levels and reversal of hypoxemia and tissue hypoxia.

One of the most important signs of a very serious and life-threatening COVID infection is hypoxemia, followed by secondary tissue hypoxia.

We now know that Corona virus gains access to body cells via the ACE receptors. Through transcription and translation, the host cells are modified to produce structural and non-structural proteins, ORF3 and ORF10. These secreted viral non-structural proteins attack the beta chain of haemoglobin and release the porphyrin molecule. This makes haemoglobin inefficient in oxygen binding, thereby reducing its oxygen carrying capacity, leading to hypoxemia and subsequently to tissue hypoxia [10]. Some patients struggle to get adequate levels of oxygen saturation in their blood, despite the administration of additional oxygen. It is believed that due to vasodilation of the pulmonary vasculature, blood is shunted away from the pulmonary circulation and as a result, a ventilation perfusion (V/Q) mismatch is created. The result is severe hypoxia that does not respond to oxygen administration [4]. From an energy generating perspective, hypoxia can be described as a state in which aerobic metabolism is reduced by a fall in PO_2 (oxygen pressure) within the mitochondria. This interferes with the process of oxidative phosphorylation and the synthesis of ATP. Hypoxia results in a complete stop of oxidative phosphorylation and the energy generation and synthesis of ATP. Of particular interest is Complex IV (Cytochrome Oxidase), which has O_2 as an electron acceptor. This Complex IV is the same target for carbon monoxide (CO) and cyanide (CN^-), which also results in complete block of electron transport and energy generation. (Figure 7: Oxidative Phosphorylation Electron transport).

HBOT is a known treatment modality that is used successfully in carbon monoxide (CO) and cyanide (CN^-) poisoning [6]. Cellular hypoxia may develop multiple organ failure because of the increased oxygen demand at tissue level. HBOT allows the delivery of oxygen at a high partial pressure, reaching tissues rapidly at elevated concentrations, which could reverse the hypoxic condition and preserve cellular metabolism [2]. HBOT has been shown to preserve mitochondrial activity [12].

Effects of Hypoxia on the Central Nervous System (CNS).

A leading symptom in Long COVID is cognitive dysfunction, otherwise known as “brain fog”. The effect of hypoxia on the CNS therefore is of particular significance. Cerebral metabolism also changes during hypoxia. The following changes in neurotransmitter metabolism are particularly significant:

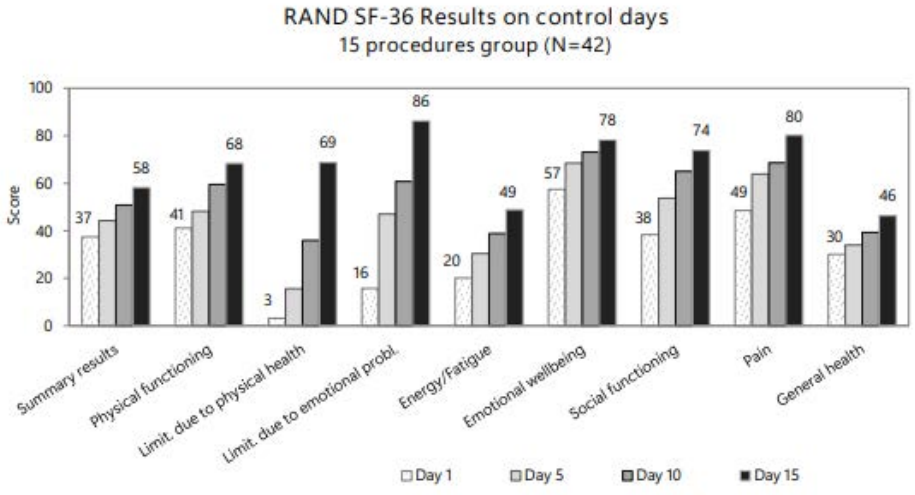

Figure 5. *RAND SF-36 Test results on 1st, 5th, 10th, and 15th day of treatment, 15 procedures group.*

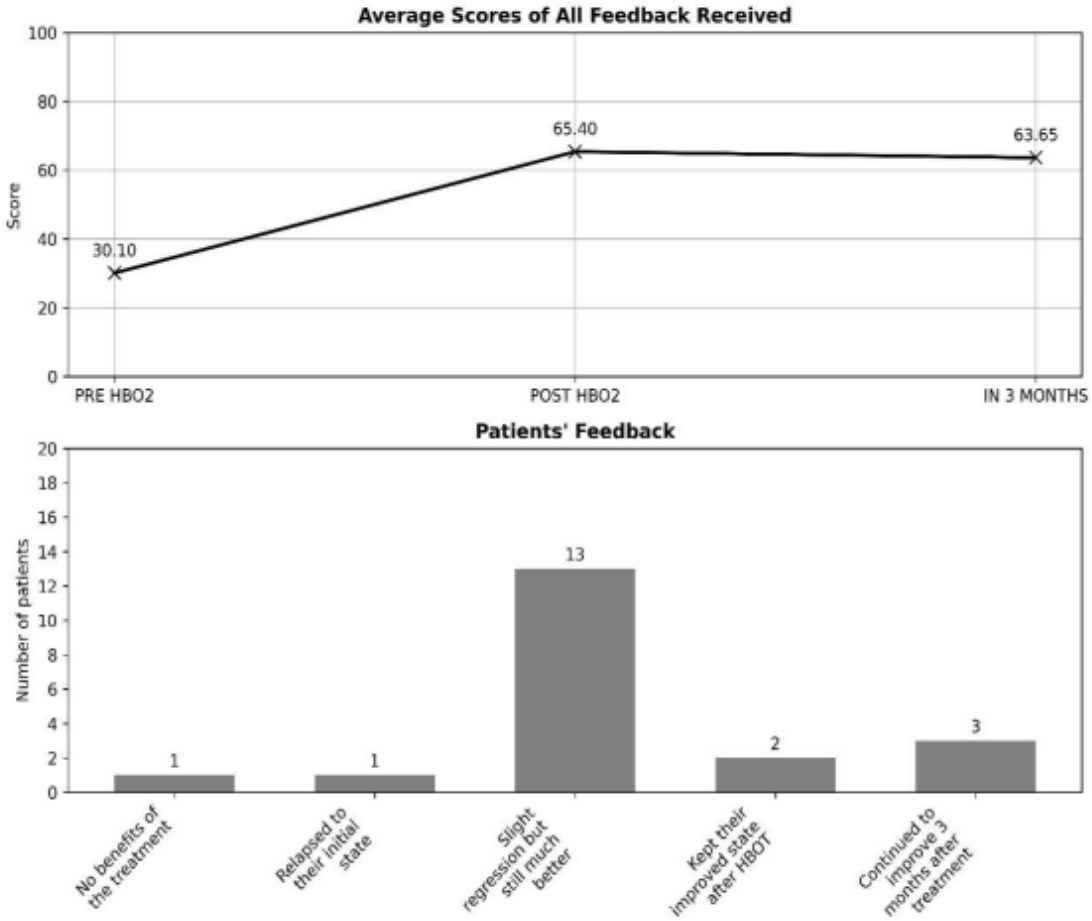

Figure 6. *Patient feedback (N=20). Average score of all feedback received.*

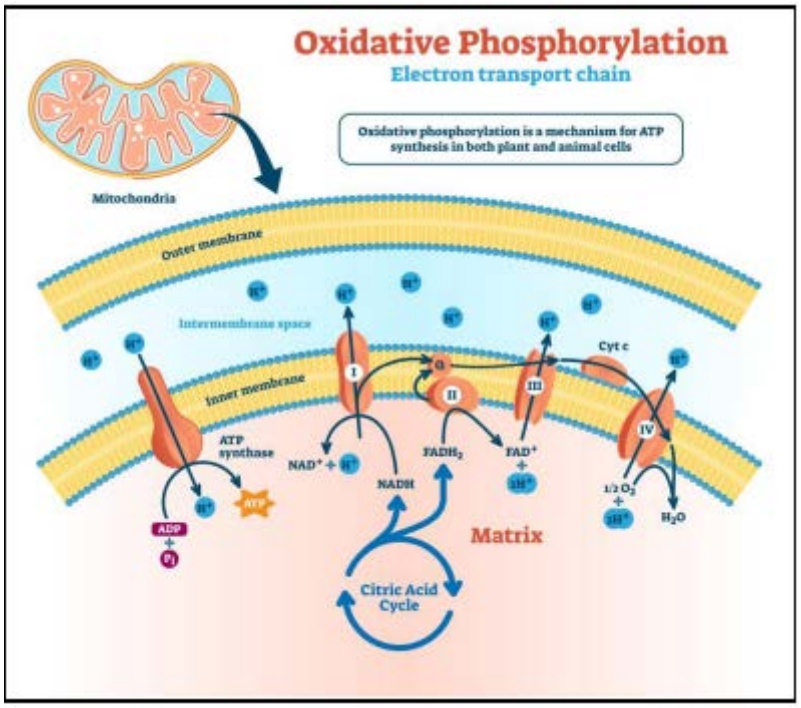

Figure 7. *Oxidative Phosphorylation Electron transport.*

– Hypoxia impairs the synthesis of acetylcholine. Decrease of acetylcholine following cerebral hypoxia correlates with impairment of memory and learning.

– Reduction of brain catecholamines. Norepinephrine, epinephrine, and dopamine are synthesized by a combination of tyrosine and oxygen. Hypoxia limits this biosynthesis. Similar reduction has been observed in the synthesis of glucose-derived amino acids as well [6].

– The electrical activity of the neurons in the brain is also remarkably sensitive to hypoxia. Disappearance of EEG activity with hypoxia and reappearance with oxygenation is related to the creatine phosphate/creatine quotient, pointing to a close relationship between brain energy potentials and EEG activity. Hypoxia is considered a causal factor in the decline in intellectual function in the elderly [6].

HBOT has a major role in the treatment of hypoxic states. HBO2 can facilitate the recovery process of neurons to synthesize protein, produce ATP, and generate action potentials.

Oxygen Debt.

Oxygen debt can be described as the minimum requirement of oxygen necessary for the tissues to maintain aerobic metabolism, minus the oxygen supply available. When there is not enough supply of oxygen, progressive oxygen debt develops leading to hypoxemia.

A characteristic feature of an infection with COVID-19 is severe arterial hypoxemia with no signs or symptoms of respiratory distress or dyspnoea. There is a discrepancy between the objective abnormal CT imaging findings and the clinical signs of dyspnoea. Guan has reported dyspnoea in only 18·7% of 1099 hospitalized COVID-19 patients despite low PaO2/FiO2. Eighty six percent of these patients had abnormal CT scans and 41% of these patients required supplemental oxygen [5]. This phenomenon has been termed silent hypoxia. The understanding of the physiology of silent hypoxia gives us a clue of how oxygen debt can be created due to prolonged periods of hypoxemia. The ability of HBOT to reverse oxygen debt is an important effect that has a prominent place in the treatment of Long COVID.

Reduction of the inflammation induced by the exaggerated immune response to COVID.

HBO2 is likely to attenuate production of pro inflammatory and inflammatory cytokines and chemokines, which are generated in response to the COVID infection [4]. There is existing evidence that HBOT can significantly reduce the generation of inflammatory stimuli of different kinds, and it has been clearly demonstrated after exercise, radiation, and surgery [15].

Reduction of inflammation via mobilisation of hematopoietic and mesenchymal stem cells.

This is another important mechanism by which HBOT has a potential long-term effect in Long COVID patients, weeks, and months after the treatment with HBOT is completed.

HBOT is known to increase the mobilisation of haematopoietic stem cells and there is existing data that they can reduce inflammation [13]. The mesenchymal stem cells have strong anti-inflammatory and immune regulatory functions [11].

Conclusion.

The rationale for treatment of Long COVID with Hyperbaric Oxygen Therapy is based on the premises that the problems of Long COVID develop on a cellular level, specifically affecting the oxidative phosphorylation in the mitochondria. The treatment with HBOT shows very encouraging results, in both the short and long term. The results presented here are observational, which does not diminish their importance. This justifies further investigation with a properly designed, randomised, double-blind, placebo controlled clinical trial, which will give more credibility to this promising treatment.

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