

Does the use of cysteine-rich whey protein supplements (Immunocal®) improve the health well-being of COVID-19 patients? A qualitative study

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ABSTRACT

Introduction: In the context of SARS-CoV-2 infection, it has been proposed that oxidative stress may contribute to the management of COVID-19 severity. The impact on the well-being of patients with COVID-19 using cysteine-providing supplements has not yet been evaluated and there is a need to understand the benefits and limitations they may offer.

Aim: The aim of this study is to understand the experiences of improved well-being with cysteine-rich whey protein supplementation (Immunocal®) in patients with COVID-19.

Methods: A qualitative study was conducted by conducting semi-structured interviews with four participants taking Immunocal® while they had COVID-19. Participants were randomly recruited through internet networking. Ethical approval was obtained from the University ethics committee. Participants were informed of the study objectives two days in advance and consent was obtained before interviews began. We used the 16-item "Use of Immunocal supplement for COVID-19" (USIC-19) questionnaire to inquire about COVID-19 behavior (time of illness, symptoms, and severity of illness) and the experience of using the supplement during illness. Confidentiality was maintained throughout this study.

Results: All participants presented mild discomfort such as headache, weakness, and tiredness when they had COVID-19 impacting most of them emotionally. The use of Immunocal® produced a partial improvement in all patients as only two continued to experience fatigue. Immunocal® improved the mood (50%) and physical health of the participants. In addition, participants reported that the supplement was recommended and dosed primarily by a consultant and that they did not feel hesitant to use it because of previous experiences of friends and family. The daily dosage of half of the participants was two sachets and all felt the need to consume the supplement which resulted in daily use.

Conclusion: Following the daily dosage indications of the consultants, the participants who have consumed Immunocal® have presented a partial improvement of the symptoms related to COVID-19, however, they feel the need to consume the supplement daily to improve their quality of life.

Keywords: COVID-19, cysteine, SARS-CoV-2, glutathione, whey protein, therapeutic-option, oxidative stress

INTRODUCTION

Undoubtedly, 2020/2021 represent challenging years for all governments worldwide due to the coronavirus disease pandemic (COVID-19), as nearly three years after the onset of this respiratory disease it has caused ~535 million infections and ~6.4 million deaths globally [1]. To prevent the development of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections and reduce severe complications such as respiratory failure and high mortality, clinical practices recommend the use of antivirals (such as hydroxychloroquine, chloroquine, remdesivir, and lopinavir) accompanied by macrolides (azithromycin) with oxygen

supplementation and nutritional therapies, as ~15% progress to critical stages resulting in a mortality rate of 10×10,000 people [2-5]. An effective therapy has not yet been found and therapeutic protocols have been changed causing different efficacy and adverse events during its application, which are also important causes of COVID-19-related mortality [2, 6, 7]. This has generated chaos in the populations leading them to seek other therapeutic options, many of an empirical nature and others based on traditional medicine [8].

It has been suggested that SARS-CoV-2 acts on the pulmonary epithelium, causing inflammatory conditions leading to reduced gas exchange capacity [9]. In the last two years pharmacological therapies [2, 3, 6, 9] have focused on stopping this viral progress with various strategies, while

Table 1. 16 items of the questionnaire “Use of Immunocal supplement for COVID-19” (USIC-19)

No.	Item
1	How did you take the news when you were informed that you had COVID-19?
2	What symptoms did you experience during the first days of the disease?
3	What symptoms do you have now?
4	By taking the Immunocal supplement, have any symptoms improved, i.e., have the discomforts decreased or do you feel the same?
5	What was your condition when you were not taking Immunotec?
6	How has Immunotec improved your health these days?
7	And how did it influence your health so much after taking it?
8	Do you feel the need to take it to improve your quality of life?
9	What is your daily dose of Immunocal?
10	Did you know about the product before, hear about it or have any information about it?
11	Did you have any doubts, fears, fears when you started taking it?
12	Did you feel any discomfort after taking it?
13	How do you remind yourself to take it, does a family member remind you or do you do it by yourself?
14	Do you consider that you are dependent on Immunocal?
15	Have you had a COVID-19 check-up?
16	In how many weeks did you recover from COVID-19?

empirical therapies seek to alkalinize the body, prevent nasal congestion, strengthen the immune system with vitamin and protein supplements, among others [10]. However, the proposed therapies have not fully addressed oxidative stress as a contributor to inflammation and as an axis of disease aggravation and progression.

Because of the possibility that patients with COVID-19 may have reduced antioxidant defenses (that is, affecting glutathione oxidase pathways) may explain the lung damage associated with cumulative co-factors such as hypertension, aging, and malnutrition, this possible event [11, 12] has been highlighted as key to the COVID-19 roadmap, focusing analyses more on understanding why the pathophysiology is related to oxidative stress than on the experiences and increased well-being in SARS-CoV-2 infected subjects. It is also necessary to understand the phenomenon of using protein (such as cysteine-rich whey protein) and vitamin supplements to combat COVID-19, as the widespread use of these has been very prevalent during the spread of the disease, and many “supplements” may not have actually provided improvement to patients.

Therefore, the aim of this study was to understand the experiences of improved well-being with cysteine-rich whey protein supplementation (Immunocal®) in patients with COVID-19 through semi-structured interviews.

MATERIALS AND METHODS

Study Design and Participants

A qualitative study was designed with semi-structured online interviews with four individuals (two from Peru and two from the United States) who had COVID-19 and were consuming the cysteine-rich whey protein supplement Immunocal® (Immunotec Inc., Quebec, Canada). Participants were randomly selected through internet networking and were voluntarily invited to participate following purposive sampling [13]. All patients were over 18 years old and of both genders. Two days before the interview they were given the necessary information about the study and signed the informed consent form.

Interviews

The interviews were conducted between June 23 and 30, 2021. In accordance with the regulations of each country, the

COVID-19 prevention protocols were respected, and the interviews were conducted virtually. The meeting links were sent by WhatsApp and the video calls were made on the free access platform Google Meet for Windows. The interviews were conducted in Spanish, were recorded and the average interview time was 28 minutes.

The 16-item questionnaire “Use of Immunocal supplement for COVID-19” (USIC-19) (**Table 1**) was elaborated based on two main dimensions: the first was to inquire about the behavior of COVID-19 (time of illness, symptoms, and severity of illness) in each participant, and the second was to know experience of using the cysteine-rich whey protein supplement (Immunocal) during the illness (**Figure 1**). This instrument was reviewed and validated by three experts following the consolidated criteria for reporting qualitative research for qualitative studies [14].

Data Manipulation

The interviews were recorded and transcribed by two authors (**JM-S** and **BC**). All data were coded and entered into NVivoO 12 (QSR International, Melbourne, Australia) for pooled analysis. Each of the interviews was analyzed following the techniques for qualitative studies [15].

RESULTS

In the present study, there were four participants (two in the United States and two in Peru), three female (one elderly), all with completed high school education and living with family members. To avoid identifiable data, these students were given the pseudonyms Britney, Alice, Austin, and Fenix.

The selection criteria for choosing interviewees were persons who had contracted the COVID-19 virus treated with the whey cysteine protein supplement (Immunocal®). All interviewees indicated having been a symptomatic patient, with symptoms similar to those of a common cold, such as muscle pain, headache, and general malaise. By the day of the interview all the interviewees were recovered, 50% of them no longer had any symptoms and the other 50% reported feeling only fatigue (progressive and inconstant), although as Fenix relates the previous symptoms were subtle:

“I had not felt the symptom, as I had a sore throat, I went to the doctor and he told me, do you have coronavirus? No, I always suffer from a sore throat, I tell



Figure 1. Word cloud about the experience of cysteine-rich whey protein supplementation (Immunocal) for COVID-19 (Source: Authors' own elaboration)

him, and he tells me that I have COVID-19, but by that time I was walking normally, I had no symptoms, I only had a sore throat, I had phlegm, he gives me my prescription, I go, I buy my prescription, I start taking the medicines, that's when I get sick, by midday I could no longer get up" (P4).

It is not known if any of the interviewees contracted the virus again, as none of them had been tested recently. As for the emotional factor, 75% expressed having been negatively affected by the news of having contracted the virus (mainly with feelings of guilt, fear, and worry).

The approach that the interviewees had towards Immunocal showed that 75% stated that they had learned about the product by word of mouth, through family or friends, while only 25% indicated that they had learned about the product through the recommendation of a physician. On the other hand, all the interviewees stated that they did not feel fear or had doubts about consuming the product, while 75% argued that this was because they had good references from their close circle regarding the effects of the product.

Regarding the application of Immunocal, the daily consumption dose for half of the interviewees was two sachets and for the other 50%, four sachets. These doses were recommended by the consultants (saleswoman) of the product, and none received medical guidance on the exact dose of consumption, as Austin points out

"you take two sachets if you are a healthy person, and four or more if you have a chronic problem such as

diabetes or cancer (...) sometimes I used to take four sachets, but now because of the economy I only take two, as the consultant Lucia told me" (P1).

Almost all of them consumed these products because of the testimonies of their friends, which is why they opted to try it and above all because the severity of COVID-19 was mild:

"My husband took it for health reasons, together with my daughter who had a cough, asthma and pulmonary fibrosis, they did not take COVID-19 aggressively, so we used it with more tranquility" (P2).

Despite the scarce information on this supplement, all interviewees reported not being afraid of its consumption:

"I am not afraid, because everyone mentioned that when you have COVID-19 you should eat a lot of eggs. And the immunocal has more than 40 eggs in an envelope" (P2).

In addition, they base their lack of fear on the testimonies of friends who trust this product:

"I was not afraid because I had a friend whose husband was undergoing dialysis, and well, the boy was skinny. Then she also began to know about this product and to consume it, after a short time, I think two months, the boy began to improve, his face began to gain weight, his blood pressure was low, now the boy is fine, so seeing all that, I trusted in Immunocal" (P4).

After taking it in the first few days, all participants indicated that they felt better and that they reduced the discomfort associated with COVID-19; however, 50% felt tired despite taking the Immunocal supplement. The participants' accounts may indicate how they felt the improvement: "*discomfort decreased*" (P2) and "*all symptoms improved a lot*" (P3). After a few days, all the participants felt physically even better, they no longer felt discomfort, and even half of the interviewees added that their mood was positively affected. Let's see how Immunocal has helped Alice:

"Immunocal has helped me a lot, both for my bones (...) it helped me a lot, I used to take it because I got tired, I used to walk a block and I got tired, and I had to sit anywhere because I could not. Until now I keep taking the immunocal and I feel good, I do not get tired anymore, I do not know if that's what has helped me" (P1).

The time it took each patient to recover from COVID-19 was an average of two weeks, specifically, 50% recovered in two weeks, 25% in one month, and the remaining 25% in less than a week. Despite the positive effects of Immunocal on the patients and the fact that they still continue to consume it daily, all of them assured that they are not dependent on the product, 50% argued that this is because they consider that it is only a supplement. Regarding its use as a supplement, Britney said:

"I feel more active and eager to do my work" (P1),

while Alice said:

"It has improved my mood and I feel more active in my daily work, because Immunocal is a nutritional supplement."

It is evident how efficient the consumption of this supplement has been for her life despite having been infected by SARS-CoV-2:

"It has influenced a lot, it has influenced everything, ah, because before I had a headache, now I do not ..." (P3).

Finally, all participants feel the need to consume Immunocal to improve their quality of life. However, this product may present gastrointestinal distention if there is no moderate rehydration, transient rash¹⁶, but all participants report no discomfort after ingestion of Immunocal sachets:

"I have no discomfort, I felt better than I was" (P3).

Regarding the reminder to take it, she said:

"My family is still looking after me and they are the ones who take turns giving me Immunocal. I still cannot do it on my own" (P2).

Only one of the participants mentioned having problems remembering what time to take it, the others have no problems with it. However, the time of consumption seems to be unclear among the participants, i.e., some take it as a nutritional supplement after intake and others during prolonged fasting:

"No, I only take it on an empty stomach, I think that way I can absorb all the nutrients correctly" (P4).

DISCUSSION

The study has shown that all participants consider it necessary to consume cysteine-rich whey protein supplementation (Immunocal[®]) because they have partially decreased their COVID-19 related symptoms improving their physical health and mood. None of the participants were afraid of its use because they had good references from their close circle, but the daily dosage of consumption, as well as the recommendation of the product, were mostly given by a consultant/salesperson of this supplement.

During the first days of illness, the patient with COVID-19 felt general malaise related to symptoms of a common cold. In addition, he indicated that he was emotionally affected by the news and had pre-existing medical conditions. Most of the patients approached Immunocal[®] because they had good references from their close circle; they found out about the product by word-of-mouth recommendation, through family or friends; and none of them expressed fear regarding its consumption. In view of this, the patients opted to use Immunocal[®] and administered a daily dose of two to four sachets. The results were positive: the patients' discomfort decreased, and they reported an improvement in their physical and emotional state. All patients agreed that the consumption of the serum was necessary to improve their quality of life and that they have not generated any dependence towards Immunocal[®], since it is only a supplement. The patients took an average of two weeks to recover and currently do not present any symptoms.

The main strength of the present study is that it is the first qualitative research that has been conducted in Peru and the world on the improvement of the health well-being of patients with COVID-19 with the use of cysteine-rich whey protein supplements, making it an excellent starting point for future research. On the other hand, the use of the semi-structured interview for data collection provided greater flexibility to the interviewer, opening up the possibility of obtaining more valuable and relevant information [15]. Likewise, the very nature of the qualitative study allowed the researcher to delve deeper into the results, and even use his or her own criteria and experience in the field of health to draw valuable conclusions, unlike when using a quantitative method.

The importance of N-acetylcysteine as a suppressor of human immunodeficiency virus replication has been known for decades [17]. N-acetylcysteine has been shown to be effective in the management of acute lung injury, systemic lupus erythematosus patients, and ventilator-associated pneumonia, improving their outcomes [18-20]. In the face of SARS-CoV-2, glutathione has been proposed as a determinant of the severity of COVID-19 [11, 12]. In fact, initial in silico studies have described that N-acetylcysteine could be a direct inhibitor of SARS-CoV-2, since it requires the Mpro protease for viral replication, thus N-acetylcysteine could bind to Cys 145 a site of Mpro activation, which could inhibit its protease activity to subsequently inhibit viral replication [21, 22]. Another in vitro study has shown that 54.3% of SARS-CoV-2 were inhibited by N-acetylcysteine in VeroE6 cells [23].

A recent review has posited that N-acetylcysteine supplementation is a potential tool against SARS-CoV-2 and may suppress viral replication [24]. However, clinical trials demonstrating its potential benefits have yet to be evidenced, but several studies have posited that its use alone, in various

doses or in combination with other antiviral agents or vitamins (i.e., vitamin D) can dramatically reduce the rate of hospitalization, mechanical ventilation, and mortality [23-25]. In view of this growing interest, interestingly our results have shown that there is an improvement in symptoms and physical well-being following its adjunctive use in the management of COVID-19. This first phenomenological approach allows not only to understand the physiological and pharmacological processes of using cysteine-rich whey protein supplementation, but also to approach the patient and the processes of improvement during the course of the disease.

We report for the first time that the use of cysteine-rich whey protein supplementation (Inmunocal®) in patients with COVID-19 has led to physical and emotional benefits, however, the lack of clarity in the regulation of its dosage, as well as the free trade and counseling by consultants are two worrying phenomena. The first of these has to do with the dosage of the supplement used during the course of the disease. Previously, the study in [18] has shown that consumption of 2,400 mg per day of cysteine can rapidly increase glutathione levels in patients with SLE, which was not achieved with a low dose (600 mg, twice daily). In contrast, the study in [19] has shown that patients treated with 600 mg cysteine twice daily developed significantly less clinically confirmed pneumonia compared with placebo (26.6% vs. 46.6%), while the study in [20] has shown that the use of intravenous cysteine (40 mg/kg/day) reduced the need for ventilatory support and mortality in patients with acute lung injury.

Our study has shown that half of the participants with COVID-19 have reported using more than four sachets of Inmunocal® per day without a prescription or nutritional or medical monitoring. One review has described a progressive therapeutic strategy for COVID-19 cases based on clinical manifestations such as fever (1,200 mg bid. P.O.), pneumonia (100 mg/kg/day IV), and multiple organ failure (150 mg/kg/day IV) [24].

Currently, there are no studies from reliable sources that reveal the exact dosage of the supplement Inmunocal®, neither for patients with COVID-19 nor for the general population; however, there are images and information from consultants of this product recommending the use of two sachets in healthy patients and four or more in patients with a chronic disease (i.e., patients with mild pain can consume 20 grams of Inmunocal® and in severe cases, the dosage could be increased to 30 grams)[26]. Although Inmunocal® is not a drug and does not present an exact dosage of administration, it is not strange to see that the posology of the consultants recommends the use of the sachets according to some diseases and disorders. Some consultants recommend in their “basic dosage” table the use of one to two sachets per day to prevent diseases, three to four sachets per day if there is an intermediate level disease, and if there is a delicate or severe condition, it is advised to take four to six sachets per day. In addition, it is recommended to start consumption on an empty stomach progressively until reaching the appropriate dosage level and it is suggested to start with Inmunocal® Mx and then combine it with Inmunocal® Platinum depending on the ailment [27]. In our study, 50% of the participants stated consuming two sachets daily and half of them consumed four sachets daily, in agreement with the instructions of the consultants based on freely available indications that circulate on the Internet [28].

In order not to fall into the set of supplements, solutions and potions that have claimed to be effective against COVID-19

as shown by some previous studies [29, 30], it is necessary to clarify the effective dosage using scientific evidence for the general population as well as for those suffering from diseases, since adverse events associated with their use have been reported [16]. These risks associated with glutathione supplementation have included gastric cramps, nausea, abdominal distension, and allergic reactions, as well as chronic supplementation has been associated with low serum zinc concentration [31]. Future studies are needed to evidence the effects of supplementation in COVID-19 patients as no reports of adverse reactions linked to its use are available.

This study has presented the following limitations:

1. This exploratory study has been conducted with participants from two countries, however, it is necessary to apply the questionnaire to consumers from other regions.
2. The interviews were conducted in 2021, it is possible that previous and constant consumption of cysteine-rich whey protein supplements, as well as previous infections and administered vaccines play a role in protection against SAR-CoV-2.
3. In this qualitative study, we evaluated the improvement of well-being by Inmunocal® showing that half of the participants have not presented other symptoms after infection, however, there are other brands of supplements that should be evaluated to compare their effects on the health of patients with COVID-19.

In conclusion, participants who have consumed cysteine-rich whey protein supplementation (Inmunocal®) have presented a partial improvement of COVID-19 related symptoms. Following the daily dosage indications of the consultants, the participants were able to improve their physical health and mood, however, they revealed the need to consume the supplement daily to improve their quality of life. A regulation of the supplement and clarification of the recommended dosage with the use of evidence-based nutrition is important, since the partial improvement in the well-being of patients with COVID-19 is inconclusive, but opens avenues to explore the potential pharmacopreventive, therapeutic, and in vivo toxic effects with chronic use of this supplement alone or in combination with other agents.

Author contributions: **BC:** provided the study concept and design, data management and curation, and wrote the manuscript; **JM-S:** provided the design and concept, data acquisition, formal analysis, and wrote the paper; **DB:** data management and curation, formal analysis, and wrote the manuscript; & **HC-P:** provided the design, project management, and wrote the manuscript. All authors have agreed with the results and conclusions.

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Declaration of interest: No conflict of interest is declared by authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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