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ORIGINAL PAPER

Recovery of sperm quality after COVID-19 disease in male adults under the influence of a micronutrient combination: A prospective study

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Summary

***Objective:** This study aims to evaluate the safety and efficacy of a standard micronutrient preparation to improve semen parameters and seminal oxidative stress in adult male subjects after Coronavirus Disease 2019 (COVID-19) disease.*

***Methods:** For this prospective pilot study, 30 males aged 20-50 years who had recently recovered from a symptomatic SARS-CoV-2 infection were recruited from June to October 2021 through a public call for participation. Participants of the study group (n = 30) received two semen analyses according to WHO criteria at an interval of 12 weeks, during which they daily received a micronutrient preparation (L-carnitine, L-arginine, coenzyme Q10, vitamin E, zinc, folic acid, glutathione and selenium). Changes in major semen variables and seminal oxidative stress levels before and after therapy were analyzed and compared to a control group (n = 10) adhering to the same inclusion criteria, including subjects who recently recovered from symptomatic COVID-19 disease without micronutrient supplementation within the 12 weeks between the two semen analyses.*

***Results:** After 3 months of micronutrient supplementation the rate of normal semen analysis results in the study group increased significantly (p = 0.009) by 66.7%: from 50.0% before to 83.3% after therapy. There was a significant increase in progressive (p = 0.014) and overall motility (p = 0.05) as well as in the vitality (p = 0.0004) of semen cells after 12 weeks of micronutrient intake. In the control group there were no significant changes in any semen parameter or in the rate of normal semen analysis results over the 3-month observation period. In both groups, sperm density, morphology and oxidative stress did not improve significantly.*

***Conclusions:** Our data suggests that supplementation of certain micronutrients may be a safe way to support recovery of impaired semen parameters in male adults recovered from COVID-19 disease.*

KEY WORDS: *Micronutrients; Semen analysis; COVID-19; Male fertility; Antioxidants.*

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INTRODUCTION

Since the outbreak of the global coronavirus pandemic in early 2020, the *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2) is estimated to have infected more than 650 million people worldwide by the end of 2022 (1). During the last decades a remarkable depletion of sperm quality is observed even without a SARS-CoV-2 mediated acute respiratory distress syndrome (2), but therapeutic options to improve semen parameters remain very limited (3, 4).

Multiple studies demonstrated impaired semen quality parameters in men after clinically present *coronavirus disease 2019* (COVID-19) COVID-19 disease, strongly indicating potential effects of this novel RNA-virus on male fertility (5-7). Less is known about the recovery time of sperm quality deterioration after patients' convalescence. Considering current evidence it seems likely that multiple mechanisms are involved in the pathogenesis of male fertility disruptions after COVID-19 disease, including oxidative stress triggered by SARS-CoV-2 induced inflammation, testicular immune response and direct viral replication in male reproductive tissues (8-10). As underlying cellular processes remain an under-researched issue, targeted interventions to counteract semen parameter decline in male COVID-19 patients or support sperm quality recovery are lacking.

However, excess oxidative stress in the testicular environment has been shown to drastically impair spermatogenesis (11, 12). Although the ability of certain micronutrient supplements to improve semen parameters is well documented (13, 14), no previous study has investigated the effects of dietary supplements on sperm quality following viral infection such as COVID-19 disease. A better understanding of how male fertility can be supported in men infected by SARS-CoV-2 is relevant for future disease management in men seeking reproductive care following COVID-19 illness. It will also present an incentive for further research regarding potential interactions of SARS-CoV-2 with the male reproductive system.

Therefore, this study is designed to evaluate the effect, safety and efficacy of a standard micronutrient composition on all major semen variables and seminal oxidative stress markers in men after symptomatic COVID-19 disease in comparison to a control group without dietary supplement intake.

MATERIALS AND METHODS

Participants and study design

This prospective, comparative study included 40 male subjects between 20-50 years of age with symptomatic COVID-19 infection confirmed by a positive SARS-CoV-

2 PCR test of nasal or pharyngeal swabs not more than 12 weeks prior to first semen sample collection. Symptoms had to include one or more of the following: fever, cough, sore throat, headache, nasal congestion, malaise, diarrhea, loss of smell or loss of taste. Participants were excluded if reporting on a history of subfertility before COVID-19-infection, varicocele, urogenital infections, known or suspected hypersensitivity to ingredients of the study compound, history of severe disease other than COVID-19 expected to prevent compliance with the present protocol, and intake of other micronutrient or vitamin supplements within the last 4 weeks.

The recruitment of the study group of 30 men was conducted from May 2021 to December 2021. To participate, men registered voluntarily in response to calls for participation published on social media channels, in local newspapers and on the official study website. After online registration, potential participants were contacted via a short phone call from one of the study nurses to check eligibility and schedule an appointment for official inclusion and first semen sample collection at a fertility clinic in Vienna - Austria, if all study criteria were met. All subjects were informed to adhere to 2-5 days of sexual abstinence prior to semen sample collection. On the first appointment, written informed consent to participate in the study was obtained and a short questionnaire filled out by each patient, including information on previous biological children, weight and height, current medication, current or past urological conditions, smoking status and alcohol consumption habits. We chose to obtain these additional parameters considering elevated *body mass index* (BMI), tobacco and alcohol consumption as well as age are individual risk factors for male factor infertility and possible confounders influencing sperm quality parameters (15). Severity of COVID-19 disease was assessed and categorized as "*mild*" with mere symptoms like headache, sore throat and/or flu like symptoms without fever; "*moderate*" if fever over 37.5°C persisted over 3 days and "*severe*" if hospitalization was required for disease management.

Subsequent semen analysis was performed on the day of enrolment, including measurement of major semen parameters and seminal oxidative stress levels. Another appointment to repeat these tests was scheduled at an interval of 12 weeks and subjects were instructed to adhere to daily intake of a standard micronutrient preparation provided to them in the clinic until follow-up visit. At the second visit, participants were questioned about any side effects or changes observed during the 12-week micronutrient supplementation before proceeding to repeat identical semen quality work-up. Semen parameters and seminal oxidative stress before and after the 12 weeks of micronutrient supplementation were analyzed and compared to a control group of 10 men from our data base. All men included in this control group were subject to the same inclusion and exclusion criteria as the study group but did not receive micronutrient supplementation or other fertility-related treatments within the 12 weeks between their two semen analyses after recovering from symptomatic COVID-19 disease.

Micronutrient preparation

The micronutrient supplement used for this study is a clinically tested, standardized nutraceutical for male fertility enhancement (*PROfertil® - Lenus Pharma GmbH, Vienna, Austria*). Subjects from the study group were instructed to take two oral capsules of this preparation per day for 12 weeks. Two capsules contain: L-carnitine (440 mg), L-arginine (250 mg), zinc (40 mg), vitamin E (120 mg), glutathione (80 mg), selenium (60 µg), coenzyme Q10 (15 mg) and folic acid (800 µg).

Semen analysis

Semen samples were obtained by masturbation in a sterile container in a separate room next to the fertility clinics' laboratory, which is certified for semen analysis according to *World Health Organisation* (WHO) criteria. After liquefaction in a heat chamber with 37°C, semen analysis according to WHO laboratory manual (16) was performed. Evaluation included a classical semen analysis assessing volume, semen cell concentration, total semen count, progressive and total motility, normal morphology and vitality, as well as measurement of oxidative stress levels in seminal fluid. Semen parameters were considered abnormal when being lower than the fifth percentile, as suggested by WHO criteria. Therefore, normal semen analysis results required a concentration of more than 15 million sperms per milliliter, progressive motility of more than 30%, total motility in total of more than 42%, vitality of at least 54% and normal morphology of at least 4% (16, 17).

Seminal oxidative stress levels were assessed using the electrochemical *Mioxsys®*, "*the Male Infertility Oxidative System*" (*MiOXSYS, Englewood, Co, USA*). This rapid in vitro diagnostic device has shown a good sensitivity for detecting both oxidants (*Reactive Oxygen Species, ROS*) and antioxidants in a liquid sample based on measurement of the *static oxidant reductant potential* (sORP). sORP can be interpreted as direct marker for the level of oxidative stress (18).

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 29.0 (*IBM SPSS, Armonk, NY, USA*). Numerical parameters are presented as the mean plus/minus *standard deviation* (SD) and dichotomous categorical parameters as absolute and relative frequencies. Student's t-test was used to determine significance of changes of individual parameters before and after micronutrient supplementation for the study group, and before and after observational period for the control group. For the comparison of categorical data such as amount of normal semen analysis results the chi square test was applied. For all calculations, a p value < 0.05 was considered statistically significant.

Results

In total, 46 men met all study inclusion criteria and received a first semen analysis in the fertility clinic. Only 30 participants adhered to their follow-up appointment and daily intake of 2 capsules of the standard micronutrient preparation and could be included in the analysis. No serious adverse events or other adverse events were reported by any of the participants taking micronutrient supplements during the investigational period.

Table 1.
Basal patients characteristics and disease severity.

	Study group	Control group
Age [1] [years]	29.3 (± 6.1)	30.2 (± 3.7)
BMI [1] [kg/m^2]	24.4 (± 3.5)	24.8 (± 3.5)
Smoking [2] regular	4 (13.3%)	2 (20.0%)
Alcoho [2] ≥ 1/week	17 (56.7%)	2 (20.0%)
Biological child(ren) [2]	5 (16.7%)	2 (20.0%)
COVID-19 disease severity [3]		
mild [2]	20 (66.7%)	6 (60.0%)
moderate [2]	9 (30.0%)	3 (30.0%)
severe [2]	1 (10%)	1 (3.3%)

[1] Mean (± standard deviation); [2] Absolute frequency (± percentage); [3] Mild: headache, sore throat, flu like symptoms without fever; Moderate: fever over 37.5°C ≥ 3 days; Severe: hospitalization required; BMI = body weight in kg (body height in cm)^2.

The mean age was 29.3 (± SD 6.1) years in the study group and 30.2 (± SD 3.7) years in the control group. Body Mass Index (BMI) was also similar with 24.4 (± SD 3.5) kg/m^2 in the group receiving micronutrient supplementation and 24.8 (± SD 3.5) kg/m^2 in the group without dietary support. In the study group, 13% of men reported on regular smoking and 17% of them reported on already having biological children, with comparable results in the control group reporting a 20% rate for both parameters. The relative number of participants with alcohol consumption at least 1 time per week was almost 3 times higher in the group of men taking micronutrient, amounting to 57% in the study group and only 20% within the control group not receiving any fertility-related interventions. The distribution of severity of COVID-19 disease was similar in the two groups: mild, moderate and severe symptoms were reported in 67%, 9% and 1% within the study group, and 67%, 30% an 3.3% in the control group, respectively (Table 1).

After 3 months of micronutrient supplementation the number of subjects with normal semen analysis results in the study group increased significantly (p = 0.009) by 66.7%, from 50.0% before to 83.3% after supplement therapy. Results were considered normal if all semen parameters were within WHO reference limits as described in the "*methods*" section. There was a significant increase in progressive (p = 0.014) and overall motility (p = 0.05) as well as in the vitality (p = 0.0004) of semen cells after 12 weeks of micronutrient in men recovered from COVID-19 disease.

In the control group there were no significant changes in any semen parameter or in the rate of normal semen analysis results over the interval of 12 weeks. The mean sperm density and total sperm count increased in both groups during the observational period, though not significantly. Mean percentage of normal sperm morphology remained at similar levels with only minimal changes recorded in both groups. Interestingly, sORP levels showed a decrease both in the study group of COVID-19 recovered men receiving micronutrient supplementation and in the control group without treatment. Though not being significant, this decrease was more evident in the study group with a mean decrease of 13.16 mV during the period of micronutrient treatment, while in the control group the mean decrease of oxidative stress levels assessed by sORP was only 0.02 mV (Table 2).

Discussion

The results of this study revealed significantly more normal semen analysis results and a significant increase in overall sperm motility, progressive motility and vitality after 3 months of micronutrient supplementation in men recently recovered from COVID-19 disease. Sperm density and oxidative stress levels also improved during the observation period, though not significantly. There were no significant changes in semen analysis results in the control group of participants after SARS-CoV-2 infection not receiving dietary supplements. Despite trends of recovery of semen parameters after COVID-19 disease in both groups, sperm quality improvement was more evident in the study group receiving dietary support.

SARS-CoV-2 and the male reproductive system

While global COVID-19 herd immunity against certain strains of SARS-CoV-2 is rising, the possibility of new variants cannot be ruled out and infections will continue to occur (19, 20). At the same time the public is becom-

Table 2.
Semen analysis results.

	Mean before		Mean after		$\delta Mean_{bef\to aft}$		p-value	
	Study	Control	Study	Control	Study	Control	Study	Control
Volume (ml)	3.43	3.42	3.61	3.60	0.18	0.18	0.251	0.321
Density (mio/ml)	88.94	63.39	89.25	68.55	0.31	5.16	0.493	0.341
Sperm count (mio)	264.06	225.61	277.04	234.20	12.98	8.59	0.397	0.452
Progressive (%)	35.87	47.50	43.13	49.70	7.27	2.20	0.014*	0.359
Motility (%)	47.98	52.80	53.63	55.60	5.65	2.80	0.050*	0.291
Vitality (%)	65.57	77.10	81.60	79.80	16.03	2.70	0.000*	0.336
Morphology (%)	10.37	7.10	13.15	6.50	2.78	-0.60	0.087	0.254
sORP (mV)	43.46	24.47	30.30	24.31	-13.16	-0.16	0.132	0.423
N. sORP (mV*mio/ml)	1.31	0.63	0.76	0.55	-0.55	-0.07	0.183	0.261
Normal semen analysis results	15 (50%)	7 (70%)	25 (83%)	7 (70%)	10	0	0.0003*	

*sORP = Static oxidation reduction potential; N. sORP = sORP normed to sperm concentration = ORP (mV) sperm density (mioml); ($\delta MEAN_{bef\to aft}$) = Difference of means of semen parameters between number of patients with normal semen analysis results between first and second semen cell analysis; p-values of paired students-t-test for sperm parameters or χ2-Test for semen analysis results; significant changes marked by *.*

ing more aware about potential effects of a coronavirus infection on male reproductive system. The impact of SARS-CoV-2 on male fertility parameters after infection continues to be intensely researched and has been confirmed by various studies (5). A systematic review and meta-analysis conducted in 2021 revealed that compared to non-infected individuals, men recently recovered from COVID-19 had lesser semen volume, sperm concentration and motility, though not all parameters were significantly lower (6). Another more recent meta-analysis confirmed these results, demonstrating a decline in certain parameters of sperm quality in men after coronavirus infection compared to healthy controls and to individual baseline parameters before viral infection (7).

In line with these outcomes, a large percentage of participants of this study presented with at least one abnormal sperm quality parameter within 3 months since COVID-19 recovery. Most men included in this analysis experienced merely mild symptoms during coronavirus illness. Approximately one third reported moderate symptoms with fever, while only one person of each group required hospitalization due to severe symptoms. Considering the high percentage of abnormal semen analysis results at time of enrolment, SARS-CoV-2 infection seems to affect sperm quality even if symptoms are mild. Interestingly, a recent prospective cohort study found no correlation between the presence of fever or symptom severity with semen characteristics in men after COVID-19 infection (21). This is worth mentioning as the majority of COVID-19 infections disease severity will be mild, particularly in previously healthy men under the age of 65 (22).

While several publications have observed short-term effects of SARS-CoV-2 on male fertility, the infection-induced longitudinal and long-term changes in the male reproductive function are less clear. Data on semen quality over time in COVID-19 patients provides somewhat conflicting results. For example, one analysis of men infected with SARS-CoV-2 suggested a recovery time of sperm parameters to baseline values prior to infection of about 3 months (21), while another investigation indicated it may take up to up to 6 months (23). More research will be necessary to confirm if and how fast semen quality recovers after COVID-19, and to what extent recovery time may vary between patients. To explore therapeutic options that may support male fertility after coronavirus infection, it is important to understand why the male reproductive system might be especially vulnerable to SARS-CoV-2.

Various mechanisms for impaired semen quality after COVID-19 are discussed. Firstly, direct cytopathic effects of SARS-CoV-2 replication and dissemination in certain testicular cells may impair spermatogenesis during active viral disease (24). Two cell structures of particular interest in this regard are the *angiotensin converting enzyme 2* (ACE2) receptor and activating *transmembrane protease serine 2* (TMPRSS2), as only binding to ACE2 and activating TMPRSS2 enables the coronavirus to enter host cells (25). It has yet to be determined which genital tissues can indeed act as viral reservoirs for SARS-CoV-2, even though expression of ACE2 and TMPRSS2 was already discovered on several cells of the male reproductive organs, that are crucial for spermatogenesis (10, 24).

The role of oxidative stress

General immune response triggered by SARS-CoV-2 and subsequent inflammatory reactions marked by increased cytokine release leads to major *oxidative stress* (OS) as discussed in COVID-19 focused publications (8,26). OS is described as a metabolic state with an imbalance between antioxidants and oxidants, namely free radicals or *reactive oxygen species* (ROS). Cytokine storms in other viral infections have been shown to impact male fertility due to increased leucocyte infiltration and subsequent production of ROS in the male gonads (10, 27). While certain levels of ROS are crucial for physiological cell processes, an excessive production within seminal fluid can quickly exceed the neutralizing capacities of intrinsic antioxidants and cause significant cell damage. Elevated OS in the testicular microenvironment can thus drastically impair spermatogenesis and semen parameters (11, 12). Based on the limited evidence available, infection with SARS-CoV-2 may be associated with elevated OS in the ejaculate (28). Two recent investigations analyzing oxidative stress in semen samples of COVID-19 patients found higher ROS levels shortly after illness, compared to a later time point following viral infection (29, 30). Similar results were obtained in this present study, as mean OS levels in both groups were lower at the second semen analysis 3 month after first measurement directly following COVID-19 disease. However, this decrease was more evident in the study group receiving micronutrient supplementation, suggesting that intake of certain micronutrients may support reduction of ROS in the seminal fluid.

OS levels in the ejaculate of all participants were assessed by measuring the static oxidation-reduction potential (sORP), which allows for simultaneous evaluation of the balance between oxidative and reductive stress within a sample (11). Most previous research focusing on OS in the ejaculate of men after COVID-19 infection determined oxidative and antioxidative markers separately (30, 31), not considering potential reductive stress within the ejaculate (32). However, information on the true redox state of seminal fluid might of particular interest to guide reproductive management.

Micronutrients for semen quality improvement

There are currently no general recommendations on fertility management for men after testing positive for SARS-CoV-2, to reduce potential sperm quality deterioration or support recovery. Options to counteract impairment of semen parameters after recovery from COVID-19 are lacking, though especially needed for infected men with a current desire to have children, who want to optimize their reproductive health. In general, therapies to improve sperm quality are scarce (33). Research suggests that men who stick to healthy diets tend to have better semen parameters (34) and dietary supplements are frequently recommended to men struggling with infertility. Two recent systematic reviews and meta-analyses of randomized controlled trials investigating the effect of nutritional supplementation on sperm quality parameters showed similar results. *Salas-Huetos et al.* found that additional dietary selenium, zinc, and Co-Enzyme Q10 seem to significantly improve sperm concentration and motility, while carnitines supplements showed beneficial effects only on motility (14). Similarly, *Buhling et al.* demonstrated that semen parameters of infertile men may be improved with supplementation of Co-Enzyme Q10, zinc, folic acid, L-carnitine and acetyl-L-carnitine (13). However, both analyses showed notable heterogeneity regarding supplement composition, dosages and patient population. One internventional study by Rafiee et al. revealed that oral supplementation with the antioxidant *N-acetylcysteine* (NAC) may support recovery of impaired sperm quality in men following COVID-19 disease. Their findings showed that NAC intake significantly improved semen motility, concentration and morphology to levels similar to before SARS-CoV-2 infection, while sperm quality parameters of a control group not receiving NAC remained at lower levels (35).

The micronutrient regimen used in this is study a prescription free nutraceutical, which has been available on the international market for many years and contains vitamin E, coenzyme Q10, L-arginine, folic acid, selenium, L-carnitine, zinc and glutathione. Previous clinical studies with this defined composition of micronutrients suggested that daily intake may improve semen parameters and reduce sperm DNA-fragmentation index in different subfertile male patient populations (36-38). Vitamin E, L-carnitine, Glutathione and L-arginine are all known to exhibit antioxidant properties and can scavenger free radicals, which may protect spermatozoa against membrane and DNA damage caused by excess ROS in the seminal fluid. Selenium also plays a role in shielding tissues or cells from excess OS, as it acts an important co-factor for various antioxidant enzymes (39). Likewise, coenzyme-Q10 is part of the nonenzymatic antioxidant defence system of the body and also crucial for mitochondrial energy production and maturation of semen cells (40). Lastly, zinc and folate are both key molecules involved in DNA and protein synthesis in germ cells such as spermatozoa. They are essential for various stages of sperm cell development, functionality and fertilizing capability (41). Considering the mechanisms of action of these micronutrients it seems likely that their antioxidant properties play an important role to support sperm quality recovery when supplemented in patients after COVID-19 infection.

Limitations

An apparent limitation of this study is the lack of information regarding sperm quality of participants prior to SARS-CoV-2 infection. Therefore, it was not possible to determine if complete recovery of semen parameters occurred within the investigational period. Moreover, intervals between viral illness and first semen sample collection varied between participants. Regarding the study group receiving dietary support, it is not possible to confirm the extent to which improvement of semen parameters was due to micronutrient supplementation, or to potential physiological recovery of testicular function following convalescence from COVID-19. To partly compensate for this lack of information a control group of men recovered from SARS-CoV-2 infection without micronutrient supplementation was additionally analysed, though sperm quality baseline values of first semen analysis varied between study and control group. Another limitation to the power of this pilot study is the relatively low number of study group participants, and an even lower sample size for the control group. Moreover, there is no information on which SARS-CoV-2 virus strains caused the respective infections, though only two strains, alpha and delta, were primarily coexisting in Austria during the recruitment period (42). Despite these limitations, strict inclusion criteria were applied to ensure more homogeneity within both groups.

Conclusions

The results of this study suggest that supplementation of certain micronutrients in male adults after COVID-19 disease may improve recovery of sperm quality parameters and seminal oxidative stress, compared to a control group without dietary support. Despite tendencies towards sperm quality recovery in both groups, significant positive effects on certain semen parameters were only evident in the study group.

Even though dietary supplements are not intended to cure or completely prevent impairment of male reproductive function, micronutrients with antioxidative potential can be a risk-free and simple, yet effective measure to support physiological semen quality recovery after SARS-CoV-2 infection. The present findings might be especially relevant for infected men currently trying for children, and clinicians eager to optimise reproductive care for COVID-19 patients. Since this was a pilot study, future research with a larger sample size and longer post-infectious investigation of longitudinal changes in seminal parameters and oxidative stress values are warranted to confirm these effects.

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