Clinical Nutrition Highlights

eNewsLetter

Nestlé HealthScience

Resources for nutritional management of patients with COVID-19

Translational research results show promise for future management of mild-to-moderate COVID-19.

- In March 2020, the molecular aspects of coronavirus disease 2019 were reviewed in the publication titled, *'The molecular story of COVID-19: NAD⁺ depletion addresses all questions in this infection'*.[1] In concluding remarks, the authors recommended to evaluate whether supplements of Nicotinamide Adenine Dinucleotide (NAD^+) precursors could improve clinical outcomes among COVID-19 patients in registered clinical trials.
- A separate group of researchers published a review that named a lack of NAD^+ inside cells as a key factor in the development of cytokine storms in COVID-19 patients.[2]
- Results of an *in vitro* study showed that boosting low cytoplasmic NAD^+ may restore antiviral PARP functions to support innate immunity.[3]
- In April 2020, results from a case study of a woman age 55y, with a BMI in the range of obesity, were reported. Use of a cocktail of supplemental nutrients including the NAD^+ precursor nicotinamide mononucleotide (NMN), tri-methyl-glycine, zinc sulfate and salt helped to reverse the cytokine storm after COVID-19 infection.[4]
- Positive results are now available from a phase 2 study that aimed to evaluate the efficacy, tolerability and safety of supplementation with a combination of metabolic cofactors including the NAD^+ precursor nicotinamide riboside (NR) among ambulatory COVID-19 patients.[5]
- Further research is warranted, and initiation of a phase 3 study would be suitable.[5]

REFERENCES

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AIM

- To offer relevant translational research results showing promise for the future management of mild-to-moderate COVID-19.
- To provide a summary of the new publication from Altay O, et al. (2020) demonstrating that the majority of patients recover* more quickly with the added supplementation of a combination of metabolic cofactors including high levels of NR, than with conventional care (6.6 days vs 9.3 days, respectively).

*Based on the time needed for 50% of the patients to recover.

Study Summary:

Combined metabolic cofactor supplementation accelerates recovery in mild-to-moderate COVID-19

Altay O, Yang H, Aydin M, Alkurt G, Altunal N, Kim W, Akyol D, Arif M, Zhang C, Dinler-Doganay G, Turkez H, Shoaie S, Nielsen J, Boren J, Doganay L, Uhlen M, Mardinoglu A

medRxiv 2020.10.02.20202614; doi: https://doi.org/10.1101/2020.10.02.20202614

Objective: This study aimed to evaluate the efficacy, tolerability and safety of supplementation with a combination of metabolic cofactors among ambulatory COVID-19 patients in a randomized, controlled, open label, placebo-controlled, phase 2 trial.

Background: The COVID-19 pandemic is characterized by a high fatality rate and numerous reports suggest that people with metabolic abnormalities -- hypertension, high blood sugar, obesity, high triglycerides and low HDL cholesterol -- have greater risk of developing severe outcomes. While clinical signs of COVID-19 essentially manifest as respiratory tract infection, it can also be accompanied by systemic inflammatory responses. COVID-19 infection induces strong interactions between components of metabolic syndrome, metabolic abnormalities, and viral pathobiology. Previous studies of **combined metabolic cofactors supplementation (CMCS)** consisting of L-serine, **N-acetyl-L-cysteine (NAC), nicotinamide riboside (NR)**, and L-carnitine tartrate demonstrated safety in humans and decreased the plasma level of proteins associated with inflammation.[1,2] Other studies have proposed that CMCS components may be effective to inhibit the production of proinflammatory molecules (e.g., IL6, CCL5, CXCL8, and CXCL10) and improve impaired mitochondrial functions by reducing enhanced oxidative damage, lipid peroxidation and disturbed glucose tolerance.[3,4]

Materials and Methods: A total of 100 patients (age 18+y) with a mild-to-moderate state of COVID infection were recruited from a University Hospital. They were enrolled in the trial if diagnosed with COVID-19 by a positive real time PCR test within the last 24 hours and if judged to have a stable clinical course that could be treated on an ambulatory basis. Chest tomography (CT) was also performed, and patients who had partial oxygen saturation below 93% and required hospitalization after diagnosis were excluded. The included patients were randomly assigned on a 3:1 basis to **hydroxychloroquine (HCQ)** plus CMCS or HCQ plus placebo. The total treatment period for the HCQ was 5 days (an initial dose of 2x400 mg [oral] followed by 400 mg/day [2x200 mg oral]), and for the CMCS/placebo was 14 days. The CMCS offered L-Carnitine tartrate (7.46 g/day), NAC (5.1 g/day), NR (2 g/day), and Serine (24.7 g/day), supplied as a water soluble powder in a disposable bottle containing the entire one dose, and was consumed orally, twice/day (one dose in the morning, one dose after dinner) for two weeks. Clinical status was evaluated daily by phone, using a binomial scale for subject reported presence or absence for multiple COVID-19 related symptoms. Plasma samples for clinical chemistry analyses were collected on day 0 and day 14.

Results: A total of 93 patients completed the trial (with a mean age of 35.0y [ranging from age 19.0 - 66.0y] for the experimental group, while the average age was 32.5y [ranging from 20.0 - 58.0y] in the control group). This study population was predominantly of normal body weight, non-smoking, and free of underlying health conditions, and the combination of HCQ and CMCS significantly reduced the average complete recovery time compared with HCQ and placebo (6.6 days vs. 9.3 days, respectively) [P = .0001]. Moreover, there was a significant reduction in ALT, AST and LDH levels on day 14 compared to day 0 in the HCQ plus CMCS group. The adverse effects were uncommon and self-limiting. Only mild adverse events occurred in 2 patients in the CMCS treated group (2.8%); both patients reported a mild rash on the upper body and decided to complete the study.

Conclusion: In patients with mild-to-moderate COVID-19, supplementation with a combination of metabolic cofactors resulted in reductions in recovery time (an improvement of just over 29%) and liver enzymes associated with hepatic function compared to placebo, and was associated with a low incidence of adverse events.

Practicalities: Results of previous studies suggest that CMCS may be beneficial for the management of patients with non-alcoholic fatty liver diseases.[1,2] Results of this phase 2 study of adults with a mean age of 35y suggest that CMCS (for 14 days) combined with HCQ (for 5 days) could be well tolerated by the majority of patients with mild-to-moderate COVID. High levels of several CMCS components were used, and the effects of longer supplementation are unknown. The design of this study with CMCS cannot discern the effect of individual nutrients on clinical outcomes. Initiation of a Phase 3 study is justified.

References:

1. Zhang C, et al. The acute effect of metabolic cofactor supplementation: a potential therapeutic strategy against non-alcoholic fatty liver disease. Mol Syst Biol. 2020;16(4):e9495-e.
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3. Sahebnasagh A, et al. The prophylaxis and treatment potential of supplements for COVID-19. Eur J Pharmacol. 2020:173530-.
4. Heer CD, et al. Coronavirus and PARP expression dysregulate the NAD Metabolome: a potentially actionable component of innate immunity. bioRxiv. 2020:2020.04.17.047480.

Study Summary prepared by Nestlé Health Science