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Serum metabolic profiles changes observed post COVID-19 – Case report

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Abstract

COVID-19 and its consequences are still not well known. The recovery from the infection is slow and many symptoms persist for a long time. We present the influence of the SARS-CoV-2 infection on serum metabolic profiles. The profiles were obtained using NMR spectroscopy from sera collected two years prior to the infection and twice during the recovery time from otherwise healthy subject. We performed comparisons of data collected pre- with post-infection. We present the metabolites which levels were decreased after COVID-19. These metabolites are involved in metabolic pathways like the TCA cycle, purine, glycine, arginine, proline, pyruvate, taurine, alanine, glutamate, glycerophospholipids, and cholesterol metabolism, as well as fatty acid and steroid hormone biosynthesis. Studies show changes in metabolic profiles during the recovery after COVID-19 that have not been observed by standard blood tests.

Keywords: COVID-19; NMR spectroscopy; serum metabolite profiles.

Introduction

COVID-19 and its consequences are still not well known. Changes in the metabolic profile were observed in patients during the course of COVID-19 as compared to healthy controls [1,2]. However, in none of those studies the COVID-19 patients were tested prior to the infection. The recovery from the infection is slow and many patients complain of chronic fatigue even though the results of their usual blood tests are within the normal ranges. We decided to investigate the influence of the disease on metabolic profiles using data collected from a healthy woman prior and post SARS-CoV-2 infection. We used a new method for metabolic profile analysis based on NMR spectroscopy. We studied the patient affected by COVID-19 during the recovery period. Two years earlier, the patient participated as a healthy volunteer in other metabolic profile studies [3]. We used serum metabolic profiles collected one and two months after the COVID-19 diagnosis and compared them with the metabolic data obtained two years earlier.

Case report

In October 2020, 61-year-old physically active, otherwise healthy female patient was diagnosed with COVID-19. SARS-CoV-2 infection was confirmed by PCR test. The patient has no chronic diseases and was not administrated any medications during the past two years. The symptoms of COVID-19 were: fever up to 39°C, cough, weakness, appetite loss, and smell disorder. The patient was treated with non-steroidal anti-inflammatory drugs for a few days. After two weeks of diagnosing the disease only weakness and cough remained, after a month only fatigue, which persists up to today. Blood tests (total cholesterol, HDL, LDL, triglycerides, glucose) performed two months after diagnosis showed no differences as compared with past tests (two years ago) and were within normal range levels. The chest X-ray test showed no changes. Two months after the diagnosis, the serological test did not detect IgG/IgM antibodies. The local Hospital Ethics Committee approved our research protocol and the participant gave written informed consent for

participation in the study. We examined metabolic profiles of serum samples. Two sets of blood samples were collected on the clot following overnight fasting one and two months after the diagnosis. The procedure we used is described in detail in publication [3]. Metabolic profiles were obtained from NMR spectra, which were measured using Avance III HD 500 MHz (Bruker, Germany) spectrometer. We have analyzed 29 hydrophilic and 17 hydrophobic compounds or groups of compounds (Table 1). We compared the recently measured results of serum compounds metabolic profiles with ones from 2 years ago data. Table 1 present the percent changes of the metabolite levels between the present samples (1M – one moth, 2M – 2 moths) and levels from 2 years ago.

Table 1: Serum hydrophilic and hydrophobic compounds percent changes between 2 years ago studies and 1 month (1M) and 2 months (2M) after SARS-COV-2 infection.

Compound/Functional group	1M (%)	2M (%)	Probably pathomechanism
Formate	93	99	Neurotransmission disturbances, oxidative stress and energy production disturbances
Pyruvate	103	77	
Acetate	153	94	
Succinate	120	107	
Alanine	88	79	
Lysine	75*	72*	Energy production disturbances and neurotransmission disturbances
Glucose/Taurine	88	81	
Malonate/citrulline	80	74	Neurotransmission disturbances, oxidative stress
Creatine/Creatinine	77*	67*	
Glutamine	93	89	
Valine	89	88	
Isoleucine	80	78	
Phenylalanine	77	113	Neurotransmission disturbances
Tyrosine	73*	76*	
Histidine	74*	67*	
Glycine	80	72	
Phosphorylcholine/ glycerophosphorylcholine	100	81*	
Glutamate	55*	47 *	
N-Acetyl aspartate	84*	68*	
Urea	88	177	Oxidative stress
Methionine	77	65	
α–D-Glucose	114	113	Energy production disturbances
β–D-Glucose	107	81	
Lactate	156	68	
Citrate	94	92	
Acetone	133	168	
Lipids (VLDL)	53	34*	
Lipids CH_2 (LDL and VLDL)	66*	52*	
Lipids CH_3 (LDL,VLDL,HDL)	85*	69*	
Estriol	68	26	Energy and neurotransmission disturbances
Phospholipids	69	61	Energy production disturbances, the cell membrane function disturbances and T cell signaling disturbances
Phosphatidylcholine	114	100	The cell membrane function disturbances
Triglycerides	60	46	Energy production disturbances
1,3-DG, 1-MG, FA	79	66	
Saturated FA, PUFA and MUFA	66	61	Energy production disturbances, the cell membrane function disturbances and neurotransmission disturbances
Saturated FA	78	69	
Arachidonic acid (ω-6)	62	58	
Palmitic acid	41	53	
Linoleic acid (ω-6)	85	75	
Palmitic acid/ palmitoleic acid (ω-7)	86	45	
Cholesterol esters	83	78	Energy production disturbances, the cell membrane function disturbances and T cell signaling disturbances, neurotransmission disturbances
Cholestenol	75	61	
Free cholesterol	79	75	
24S–Hydroxycholesterol	47	35	
Free cholesterol and cholesterol esters	80	72	
7-Lathosterol	94	79	

* metabolite level lower than minimum for the control group calculated in our past study [3].

Obtained results indicate general lower metabolite levels measured one as well as two months after diagnosis. Changes in the metabolic levels are noticeable and although many compound levels are still in the range for the control group of subjects age 50-75, calculated in our past study [3], some of them have values below the minima. An asterisk in Table indicates metabolite levels that were lower than their minima for the control group. None of the metabolites had a level higher than their maxima. We observed that HDL, LDL and VLDL signal intensities of the patient serum were lower than their minima for the control group; however, levels of the lipid compounds extracted from these lipoproteins were not lower than minima of

the control. These changes were not observed in the usual blood tests for these lipoproteins. We have not observed changes in metabolite levels between the samples collected recently and two years earlier [3] from a healthy person of the same age and gender as the studied subject, but not affected by COVID-19.

Discussion

In our studies, we compared compound levels of serum collected from a person prior and post SARS-CoV-2 infection. Our results indicate changes in many biochemical pathways (Table 1). We have also observed changes in the acetate level during the recovery time. Several research groups [4-6] studied changes in acetate level during systemic bacterial and viral infection. Serum compounds of which levels had undergone changes are involved in pathways that participate in pathomechanisms presented in Table 1. We have observed that the disturbances in these pathways persisted two months after COVID-19. This could be the explanation of the prolonged fatigue after the negative test for the disease and slow fatigue decrease during recovery. In order for the most of these pathways to function properly, appropriate level of acetyl-CoA is necessary (data from KEGG - Kyoto Encyclopedia of Genes and Genomes). Using NMR spectroscopy, we cannot directly measure the level of acetyl-CoA because its concentration is below the detection limit. However, a decrease in the level of compounds such as tyrosine (dopamine precursor), histidine, lysine, glutamate, N-Acetyl aspartate, as well as a decrease in lipid levels indicates that one of the causes of this decreases could be also a low level of acetyl-CoA (KEGG databases). Deficiencies of these metabolites can lead to energy production and neurotransmission disturbances. Changes in amino acid levels that we have observed in the patient during the recovery time are similar to the differences of levels in patients with active COVID-19 disease compared to healthy subjects as reported by other research groups. However, contrary to their results, we have observed a decrease in the lipid compound levels [2,7,8].

The researchers [8] suggested administration of statins for patients with active COVID-19. These drugs block the synthesis of endogen cholesterol and thus influence its level not only in serum but also in the brain. Cholesterol and its derivatives in the brain affect many processes in particular those related to neurotransmission [9]. Lathosterol indicates the endogenous cholesterol synthesis rate. Low serum lathosterol level could indicate likely a bad prognosis in many diseases [10]. Lipid compounds are important for proper function of the brain [11]. They participate in numerous functions of cell membrane regulation, among others, its permeability and fluidity [12]. We have observed changes in serum cholesterol, its derivatives and other lipid compound levels in the patient during the recovery time from COVID-19.

Based on our current observation and previous metabolomics studies [3,13,14], we present a suggestion for considering the administration of an acetyl-CoA precursor (e.g. vitamin B5). However, the therapeutic dose of vitamin B5 should be established. It is likely that the amount available in dietary supplements can improve metabolism in the disrupted pathways and thus the patient's condition.

Conclusion

The NMR-based metabolic profile analysis provides a comprehensive insight into the body's functions, allows for obtaining information about a wide range of compounds, which subsequently allows for identifying disturbances in metabolic pathways. Presently used simple blood tests do not capture small changes in metabolite levels caused by the disease in individual subjects since these tests show results that are within the normal ranges.

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Ethical approval: Written consent has been obtained from the patient to allow publication of this article.

Author Contribution: BT, EZ and AS were involved in the study design, data analysis and drafting of the original version of the manuscript. All authors read, revised and approved the final manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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