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RESEARCH ARTICLE

«Long COVID» Molecular Genetic Markers in Patients with Type 2 Diabetes Mellitus

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ABSTRACT.
Coronavirus infection influences on multiple organs and contributes to the progression of concurrent diseases. The most notable and outstanding changes and COVID complications appear in patients with pre – existing cardiovascular and metabolic disturbances especially in elderly. There is evidence that acute viral as well as chronical diseases promote rapid cell senescence and prolong the process of recovery from disease. This review reflects the main common points and axis joining the pre-existing diseases and coronavirus infections complications and resolution. Diabetes mellitus type 2 and cardiovascular diseases (hypertension) predispose to severe outcome of the disease and the COVID-19 mortality risk. The Klotho protein level may be promising predictor of COVID severity and complications in many patients. In order to control properly the rehabilitation process and estimate the level of treatment efficacy we tried to reflect the property of milestone clue biomarker of senescence and cell damage – Klotho protein.

Key words. Diabetes mellitus, COVID, «Long COVID», senescence, Klotho protein, biomarkers.

Introduction.

The recent findings have shown COVID-19 to cause dramatically multiple and postpone consequences revealing months afterwards. This syndrome gained the name "Long COVID". This is a complex term describing the post - SARS-CoV-2 infection resolution. The most frequently marked complaints are «brain fog», depression, shortness of breath, fatigue, cough, muscle soreness, headache. Recent reports have demonstrated hormonal impairments, lower libido and hair loss. These symptoms may appear just after the resolution of infection or develop after weeks, the intensity varies from mild to severe, the outcome is not yet clear. Comorbid adults over 65 years old are at the higher risk of death and problematical resolution of COVID-19. Also male gender and aging are the prognostic markers of deeper lesions [1-4]. Pre-existing cognitive impairment also increases mortality risk. Concurrent diseases increasing mortality (hypertension and metabolic disorders) invest seriously to the «Long COVID» syndrome [5]. The predicting biomarker could be rather helpful in clinical practice for proper prophylaxis of complications and lowering mortality risks. Such biomarker has to reflect the cumulative changes and lesions and be rather specific for COVID, senescence and hypertension and metabolic disorders at the same time. One of the most promising biomarker may be level of Klotho protein associated with mentioned conditions.

Senescence associated secretory phenotypes and Klotho proteins.

Diabetes mellitus type 2 (T2DM) predisposes to severe outcome of the disease and the COVID-19 mortality risk [6]. T2DM has a bidirectional relationship with COVID-19. Chronic systemic inflammation, high coagulation activity, immune response impairment, probable direct pancreatic viral damage might be among the underlying binding mechanisms in-between diabetes and COVID-19 [7]. COVID-19 promotes exacerbation of tachycardia, muscle degradation (sarcopenia), endothelial dysfunction in patients with diabetes. In many patients glucose control is not sufficient so decompensation appears [8].

As COVID-19 tends to be more severe in older patients so there is an obvious relationship between aging and the infection. The viral invasion and replication provoke cellular senescence and irreversible cell-cycle arrest that can be induced. Senescent cell develop a phenomenon called SASP (senescence associated secretory phenotypes). These cells secrete a variety of pro-inflammatory factors cytokines and chemokines such as CXCL-10, IL-6, IL-8, IL-12, IL-1, CCL-2, Interferon-gamma, and TNF-alpha. Developed under COVID infection senescent cells are resistant to apoptosis and can result in metabolic, hypoxic, mechanical stress, intracellular tissue damage [9-11]. Some senescent cells can acquire SASP properties. These SASP factors can induce local and systemic inflammation, fibrosis, tissue damage, progenitor cell dysfunction, depletion of nicotinamide adenine dinucleotide (NAD+) and increased production of reactive oxygen species by healthy cells, induction of senescence in non-senescent cells, induce platelet activation and blood clotting and immune system dysfunction [12-14].

Accordingly, accumulation and sustained presence of viral induced senescent cells with a SASP can cause dysfunction and contribute to cognitive, metabolic, physical, and vascular dysfunction, tissue fibrosis, prolong recovery from the disease, increase severity of consequences and mortality rate [15-17].

However, timely cleavage of those already formed senescent cells with a tissue-destructive SASP can alleviate dysfunction related to systemic diseases and aging. There is evidence of beneficial use of exogenous Klotho transplantation to the patients. Klotho Therapeutics™ (KTI) is using biotechnology to mimic the human protein. [18].

Accumulation of senescent cells appears to confer risk for developing a more severe case or complications from COVID-19 [19-22]. The SASP profile cells due to Klotho insufficiency impair immune system functioning and involves explosion of cytokines, including IL-6, IL-RA, TNF-a, and IL-1, so called and notorious «cytokine storm», especially in coronavirus [23]. This evidence is responsible for high risk of mortality and cell damage.

Increased inflammatory state of in ageing and comorbid individuals (with metabolic and cardiovascular disorder), who have increased pre-existing senescent cell burden, can become more prone to SARS-CoV-2 infection [24]. This probability explains why the elderly and patients with pre-existing senescence-associated conditions are more susceptible to either more severe cases of acute COVID-19 and/or prolonged time of recovery afterwards [25].

Moreover high-protein, low-calorie and low-calorie high-protein could increase Klotho-α level in aging organism [26]. So the metabolic dysfunctions in aging, cell senescence and severity of coronavirus may have more common in pathogenesis than it's expected to consider.

Fibroblast growth factor and Klotho proteins.

The family of Klotho proteins, αKlotho and βKlotho, are essential components of endocrine

fibroblast growth factor (FGF) receptor complexes, as they are required for the high-affinity binding of FGF19, FGF21 and FGF23 to their cognate FGF receptors (FGFRs). Klotho can be promising regulating molecule. This protein causes activation of N-methyl-D-aspartate receptor (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) on the post-synaptic membrane. This activation leads to long term potentiation which is the process of strengthening the synapse based on recent pattern of activity, stable and strong synaptic activity that effects positively on cognitive function in aging patients. FGF19 is a «satiety molecule» secreted in the intestine along with food consumption. And then it binds to the βKlotho-FGFR4 complex in hepatocytes to enable metabolic responses to feeding. During starvation and intermittent fasting conditions, the liver secretes the «starvation molecule» FGF21. It induces metabolic responses to fasting stress through the activation of the hypothalamus-pituitary-adrenal axis and the sympathetic nervous system following binding to the βKlotho-FGFR1c complex in adipocytes. Osteocytes release FGF23 in response to phosphate intake and FGF23 binds to αKlotho-FGFR complexes. These complexes are expressed most abundantly in renal tubules to regulate bone metabolism. The FGF-Klotho axis has a crucial role in the pathophysiology of ageing-related disorders, e.g. metabolic disorders, tumors, hyperlipidemia and chronic kidney disease. Therefore, targeting and monitoring FGF-Klotho endocrine axis might have therapeutic benefit in variety of conditions [27-30].

Conclusion.

The level of Klotho protein might be not only the predictor of marker of lesions degree especially in «Long COVID» patients but the marker of treatment efficacy for optimization of individual pharmacotherapy [31]. This approach could be effective to prevent dangerous diseases outcomes as well as lower risk of mortality [32].

Author Contributions

AU and YuS designed and performed the research study, LL and YuS were in charge of the correction of the language and writing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicate.

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Conflict of Interest

The authors declare no conflict of interest.

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