

Review

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COVID-19 Sequelae and Formation of Kidney Stone by Decrease in Mitochondrial Sulfur Metabolism Transsulfuration and Hyperuricemia during CKD

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Review

COVID-19 Sequelae and Formation of Kidney Stone by Decrease in Mitochondrial Sulfur Metabolism Transsulfuration and Hyperuricemia during CKD

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Abstract: Post severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2, Covid-19) sequelae's, immune and RNA based treatments are associated with the chronic kidney disease (CKD, possibly through the development of micro-stones. In addition, the circulating cytokines cocktail and viral envelope spike protein (SP) may instigate the CKD. During epigenetic regulation, Covid-19 methyltransferase (MT) methylates the DNA/RNA/Proteins/Histones and generates homocysteine (Hcy). Although cysteine promotes the growth and aggregation of calcium oxalate crystals in normal undiluted human urine. However, during elevated levels of Hcy (i.e., hyperhomocysteinemia, HHcy) due in part to the impaired transsulfuration (i.e., mitochondrial sulfur metabolism) pathways, homocysteine may be the only sulfur-denoting non-protein amino acid that may promote crystals. HHcy is associated with severity of Covid-19 infection and pneumonia post Covid-19. It is unclear however whether the HHcy facilitates homocysteine crystals. Although an E. coli strain degrades tricarboxylic acid (TCA, citric acid), and disrupts mitochondrial TCA cycle, to dicarboxylic acid (DCA, oxalic acid), DCA also promotes calcium oxalate crystals and may contribute to kidney stones, it is unclear whether gut-dysbiosis by Covid-19 infection contributes to kidney stones. Interestingly, There is robust succinylation of enzymes in TCA cycle which causes dysfunctional mitochondrial bioenergetics during Covid-19 infection. In this regards interaction between SIRT5 and mitochondrial transsulfuration during Covid-19 infection attenuates TCA cycle. Interestingly, the mitochondrial bioenergetics though sulfur metabolism participate in TCA cycle and epigenetic acetylation/succinylation, therefore, Covid-19 infection transition from acute kidney injury (AKI) to CKD by defective mitochondria sulfur metabolism (transsulfuration) pathways, forming uricemia micro stones.

Keywords: Renal complications post Covid-19 sequelae's

Key Contributions: The acute kidney injury post Covid-19 can lead to CKD by depletion of renal microvascular nitric oxide, leading to kidney stones

Running Title: Covid-19 AKI to CKD

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Introduction

Although the acute respiratory syndrome coronavirus-2 (SARS-CoV-2, Covid-19, lethal or non-lethal/asymptomatic) causes infection. However, only the immune and RNA based therapies are the current options. Post Covid-19 sequelae's are associated with chronic kidney disease (CKD) [1–5]. However, the mechanisms are far from understanding. The objective of this review is to postulate a mechanism by which acute kidney injury (AKI) leads to chronic kidney disease CKD. Interestingly, beside the viral envelope proteins, the antibody treatments for Covid-19 infection can also increase

the possibility of the development of CKD by increasing micro-stones [6–8]. Mechanistically, the entry of the various Covid-19 variants to the host is caused by viral envelope spike protein (Figure 1), therefore, it is important to determine the mechanism-based therapy for Covid-19 infection.

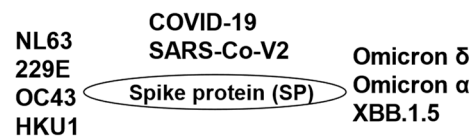


Figure 1. The primary entry of the Covid-19 and its variants, into the cell, though viral envelope spike protein (SP). Therefore, it is important to understand the mechanism by which virus enters the cell and transforms the cell metabolism causing infection.

Discussion

The epigenetic contribution to uricemia is regulated primarily by methylation (Figure 2). In this regard the levels of methionine adenosyl transferase (MAT) is important and regulates the functional regenerative capacity [9]. Interestingly, the SARS-Co-V2 methyltransferase (MT) methylates the DNA/RNA/Protein/histone and generates homocysteine (Hcy) [10]. It is known that cysteine promotes the growth and aggregation of calcium oxalate crystals in normal undiluted human urine [11,12]. The mechanism(s) are largely unknown. Interestingly, during elevated levels of Hcy (i.e., hyperhomocysteinemia, HHcy) due in part to the impaired epigenetic rhythmic methylation/de-methylation and transsulfuration (i.e., mitochondrial sulfur metabolism) pathways (Figure 2), homocysteine is the only sulfur-denoting non-protein amino acid. Although HHcy is associated with severity of Covid-19 infection and pneumonia post Covid-19 [13], the mechanisms are unclear. Also, it is unclear whether the HHcy facilitates homocysteine crystals and kidney stones post Covid-19.

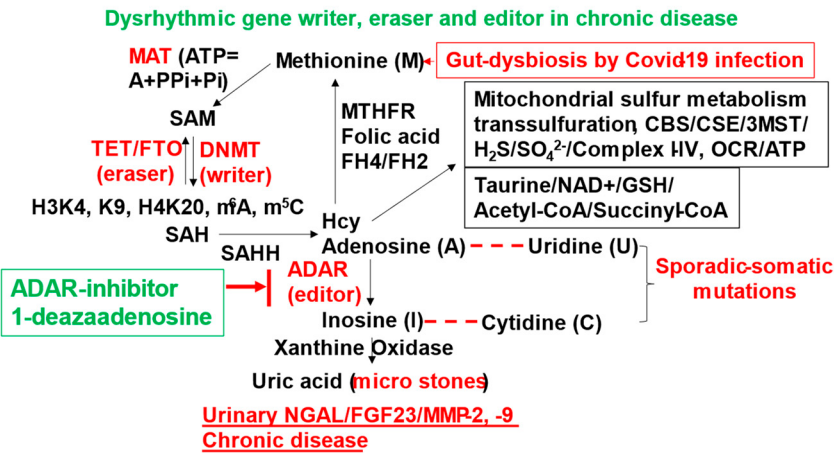


Figure 2. The viral causes gut dysbiosis (i.e., loss of taste) and therefore alters the epigenetic regulation of metabolic genes. The schematics of epigenetic 1-carbon metabolism regulation by gene writer, eraser and the RNA editor in renal remodeling and the development of chronic kidney disease and uricemia micro stones formation, during Covid-19 infection induced gut-dysbiosis.

SARS-CoV-2 enters the cell by spike protein (SP) and causes renal injury and mask ACE2 and increases availability of Ang II, 1-8 amino acid peptide and decreases Ang-II, 1-7 amino acid peptide, suggesting a role in hypertension [3,14–16]. However, there are post Covid-19 sequelae those are associated with acute kidney injury (AKI) [17–20], leading to chronic kidney disease (CKD) [21–25] and vascular coagulopathy/thromboembolism [26]. Although vascular coagulopathy and venous thromboembolism are the hallmark of Covid-19 associated morbidity and mortality, however, the rate and coagulation time, and the platelet counts are unchanged. This suggests the role of other

coagulation pathways, than thrombosis during Covid-19. Interestingly, a disintegrin and metalloproteinase thrombospondin domain 13 (ADAMTS13), a metalloproteinase instigates thrombolysis, is decreased in Covid-19 patients [27,28]. Also, there is endothelial dysfunction [29,30], vascular stiffness, perivascular fibrosis [31], and extracellular matrix (ECM) fragmentation [32–37] post Covid-19, the underlying mechanisms are unclear.

Previously, we showed activation of inflammatory M1 macrophages with renal infiltrates in the humanized angiotensin converting enzyme 2 (hACE2) mice transfected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or Covid-19-spike protein (SP)), intranasally [17]. We suggested that occurrence of Covid-19 associated coagulopathy (CAC) is influenced by TMPRSS2, ADAMTS13, NGAL and MMP- 2, and -9 factors, and an intervention with iNOS blocker may mitigate the CAC [26].

Others have shown elevation in the levels of neopterin (NPT) post Covid-19 infection [38,39]. Because NPT is generated by activated pro-inflammatory M1 macrophages in response to Covid-19 infection via inducible nitric oxide synthase (iNOS) and tetrahydrobiopterin (BH4) via peroxynitrite (ONOO-) [ROS and RNS] consequentially, this activates the proteinases. This causes to generate neopterin (NPT) by exhausting the levels of BH4 and reduces availability of BH4 to eNOS. The generating ONOO- (ROS and RNS) activates latent resident metalloproteinase including the disintegrin and metalloproteinase thrombospondin-13 domain (ADAMTS13, anti-thrombosis/anti-coagulant [40] and urinary neutrophil gelatinase associated lipocalin (NGAL, pro-thrombosis/pro-coagulant), and transmembrane serine proteinase S2 (TMPRSS2, proteolytic factor facilitates Covid-19) entry [26,41,42] and the matrix metalloproteinases (MMP), leading to shedding of the glycocalyx, endothelial dysfunction [43,44], glomerular leakage and fibrosis.

NGAL and FGF23 (hypertrophic factor) are increased during post Covid-19 sequelae [45-49]. Interestingly, Covid-19 is associated with coagulopathy in glomerular capillaries-microvascular wall, the interaction between macrophages, neutrophil and immune cells, causes build-up of damage endothelial via NETs, NGAL, iNOS, and ADAMTS, and sets the stage for pro-thrombotic and pro-coagulant [24] states. Single cell analysis also revealed activation of ADAM17 post Covid-19 invasion [50]. This also contributes to focal glomerulosclerosis lesions [51,52].

Because there was greater COVID-19 severity and mortality in males compared with females [53]. The blocking of ADAM17 and TMPRSS2 offered potential disease-modifying approaches to ameliorate enhanced severity in males [53,54]. Therefore, it is novel to measure ADAMTS and TMPRSS2 in both the males versus and females.

In addition to cellular 1-carbon metabolism, the ions and solute cellular co-transporter [55,56] SLC22A17 contributes to osmotic stress adaptation, protection against urinary tract infection, and renal carcinogenesis in part by transporting transition metals (TMs), Fe, Cd, Zn, and others [55,56]. This transporter complexing with metalloproteins cause nephrotoxicity [57–59]. In this regard, its interaction with NGAL- a metalloprotein is crucial in the sense that metalloproteinase activity of NGAL may cause tubular leakage, endocytosis, glycocalyx shedding and increase in neutrophil extracellular traps (NETs). Therefore, a treatment with DNase I may be beneficial [60,61]. The epigenetic DNA methylation, activation of transmembrane serine protease 2 (TMPRSS2) and a disintegrin and metalloproteinase thrombospondin domain 13 (ADAMTS13) have been associated of SARS-CoV-2 entry into the cells [62–65]. The mechanism(s) are unclear. TMPRSS2 processes the Covid-19 viral protein secretion. The ADAMTS13 facilitates coagulation. Because the levels of transmembrane (TMPRSS2), EMMPRIN (CD147) and ECM proteinases are elevated post Covid-19 [26,41,42]. These proteinases are associated with collagen/elastin breakdown during renal glomerular remodeling [66]. However, because the turnover of collagen is rapid than elastin [67], the degraded elastin is replaced by collagen, causing fibrosis, stiffness, and thickening of the basement membrane in the glomeruli, instigating impaired glomerular filtration rate (GFR).

We conclude that it is important to test the hypothesis if the increase in M1 macrophages iNOS decreases BH4 bioavailability to eNOS, causing glomerular capillary microvascular endothelial dysfunction. The peroxynitrite (ONOO-) activates NGAL and FGF23 (released by the kidney) and ADAMTS. This causes podocyte glycocalyx shedding, leading to glomerular leakage [68,69]. These are novel aspects of Covid-19 induced CKD.

In addition, recently mitochondrial miR-2392 was shown to drive downstream suppression of mitochondrial gene expression, increasing inflammation, glycolysis, and hypoxia, as well as promoting symptoms associated with corona virus disease (COVID-19) infection, such as respiratory congestion [70]. Interestingly, an iNOS inhibitor (aminoguanidine, AG) attenuated inflammatory miRNA-21 levels [71].

Because post Covid-19, circulating cytokine cocktail inflammatory response and viral envelope proteins, such as spike protein (SP) mimics post Covid-19 sequelae [72–76], we injected SP protein in hACE2 mice [26]. Also, co-morbidity associated with Covid-19 infection increases microparticles and further the inflammatory response [80]. The Covid-19 infection causes disruption in blood vascular endothelial layer [77] by activation of MMP8 (a neutrophil-derived MMP) and creates enlarged perivascular space (EPVS) and fibrosis [78]. We have suggested increase in inflammatory infiltrate and neutrophil gelatinase associated lipocalin (NGAL) in renal vascular coagulopathy, leading to CKD, post Covid-19 sequelae [26]. In this regard it is novel to measure NGAL activation by spike protein and its mitigation by iNOS blocker (Figure 3).

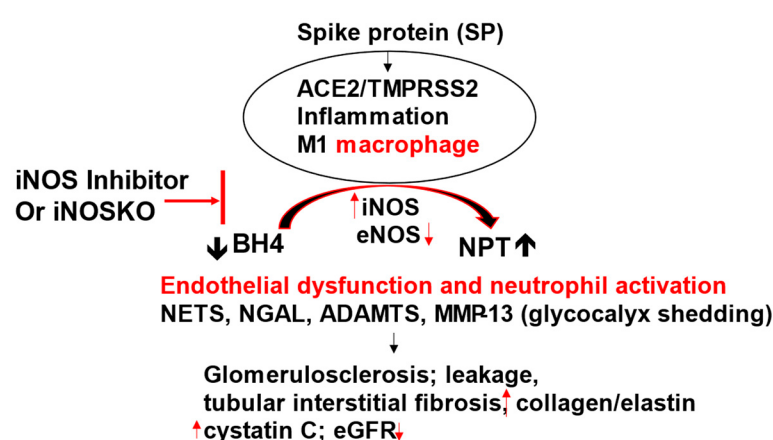


Figure 3. SARS-CoV-2 spike protein primes ACE2/TMPRSS2, causes M1 macrophage activation, increases iNOS and generates neopterin (NPT) by depleting tetrahydrobiopterin (BH₄), leading to endothelial dysfunction. The activation of NETS, NGAL, ADAMTS and MMPs/TIMPs cause proximal tubular epithelial cell and vascular injury, leakage, and CKD. The iNOS blockade or iNOSKO attenuates SARS-CoV-2 induced CKD. “Neopterin: marker to mechanism to medicine”.

Kidney Stones

Although an *E. coli* strain degrades tricarboxylic acid (TCA, citric acid), and disrupts mitochondrial TCA cycle, to dicarboxylic acid (DCA, oxalic acid) [79,80], DCA also promotes calcium oxalate crystals and may contribute to kidney stones, it is unclear whether gut-dysbiosis contributes to kidney stones post-Covid-19.

Although the severity of Covid-19 infection and pneumonia are associated with the increase levels of homocysteine (Hcy, i.e., hyperhomocysteinemia (HHcy) [81,82], the mechanisms are unclear. The focus of this article is to review the role of Hcy metabolic transsulfuration (mitochondrial sulfur metabolism and bioenergetics) pathways in the severity of long Covid-19. The 3-mercaptopyruvate sulfur transferase (3MST) converts homocysteine into hydrogen sulfide and improves endothelial function. The pyruvate supplement suppresses viral replication via induction of TCA cycle [83] and this may improve endothelial dysfunction post Covid-19 infection.

Interestingly, there is robust succinylation of enzymes in TCA cycle which causes dysfunctional mitochondrial bioenergetics pathways during Covid-19 infection [84]. In this regards interaction between SIRT5 and mitochondrial bioenergetics during Covid-19 infection [84] is suggested with the focus target for the treatment post Covid-19.

What are the underlying mechanisms for COVID-19 infection to kidney stone formation:

Interestingly, the mitochondrial bioenergetics through sulfur metabolism by 3-mercaptopyruvate sulfur transferase (3MST) participate in TCA cycle and epigenetic acetylation/succinylation (Figure 2). The dysfunctional sulfur metabolism enzymes and renal transsulfuration may increase homocysteine. This may lead to accumulate homocysteine crystal. Thus the mitochondrial bioenergetics through sulfur metabolism participate in TCA cycle and epigenetic acetylation/succinylation, therefore, Covid-19 transition acute kidney injury (AKI) to chronic kidney disease (CKD) by defective mitochondria sulfur metabolism (transsulfuration) pathways, forming kidney uricemia micro stones. Defective sulfur transferase activity i.e., mitochondrial transsulfuration pathways, in the kidney causes kidney stones in chronic kidney disease [75,86].

Conclusions and Future Direction:

Although current knowledge in Covid-19 research focus only on the infection, very little is known about the spike-protein induced viral entry and alteration in gut-dysbiosis and renal-axis-remodeling leading to CKD. Therefore, it is important to test the hypothesis that the spike protein induces iNOS, exhausts 169 BH4, increases NPT, NETs, NGAL, oxidative/peroxynitrite, activates ADAMTS, MMPs and transmembrane serine proteinase S2 (TMPRSS2) causing glycocalyx shedding, tubular epithelial leakage, and leading CKD. To address this hypothesis, it is novel to determine whether the blockade of inflammatory M1 macrophage iNOS attenuates SARS CoV-2 spike protein-induced activation NETs, NGAL, TMPRSS2, ADAMTS, glycocalyx shedding, endothelial dysfunction, collagen deposits, glomerulosclerosis, tubular interstitial fibrosis, and leakage. Interestingly, because there was greater COVID-19 severity and mortality in males compared with females. The blocking of ADAM17 and TMPRSS2 offered potential disease-modifying approaches to ameliorate enhanced severity in males.

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