Saudi Journal of Biological Sciences 28 (2021) 3540–3547

Contents lists available at ScienceDirect

Saudi Journal of Biological Sciences

journal homepage: www.sciencedirect.com

Review

A comprehensive insight into the role of zinc deficiency in the renin-angiotensin and kinin-kallikrein system dysfunctions in COVID-19 patients

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ARTICLE INFO

Article history:
Received 4 February 2021
Revised 7 March 2021
Accepted 8 March 2021
Available online 16 March 2021

Keywords:
Zinc
COVID-19
Kinin–kallikrein system
Renin-angiotensin system
Bradykinin

ABSTRACT

Hypozincemia is prevalent in severe acute respiratory syndrome coronavirus-2 (SARS-COV-2)-infected patients and has been considered as a risk factor in severe coronavirus disease-2019 (COVID-19). Whereas zinc might affect SARS-COV-2 replication and cell entry, the link between zinc deficiency and COVID-19 severity could also be attributed to the effects of COVID-19 on the body metabolism and immune response. Zinc deficiency is more prevalent in the elderly and patients with underlying chronic diseases, with established deleterious consequences such as the increased risk of respiratory infection. We reviewed the expected effects of zinc deficiency on COVID-19-related pathophysiological mechanisms focusing on both the renin–angiotensin and kinin-kallikrein systems. Mechanisms and effects were extrapolated from the available scientific literature. Zinc deficiency alters angiotensin-converting enzyme-2 (ACE2) function, leading to the accumulation of angiotensin II, des-Arg9-bradykinin and Lys-des-Arg9-bradykinin, which results in an exaggerated pro-inflammatory response, vasoconstriction and pro-thrombotic effects. Additionally, zinc deficiency blocks the activation of the plasma contact system, a protease cascade initiated by factor VII activation. Suggested mechanisms include the inhibition of Factor XII activation and limitation of high-molecular-weight kininogen, prekallikrein and Factor XII to bind to endothelial cells. The subsequent accumulation of Factor XII and deficiency in bradykinin are responsible for increased production of inflammatory mediators and marked hypercoagulability, as typically observed in COVID-19 patients. To conclude, zinc deficiency may affect both the renin–angiotensin and kinin-kallikrein systems, leading to the exaggerated inflammatory manifestations characteristic of severe COVID-19.

Contents

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Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.sjbs.2021.03.027
1319-562X/

1. Introduction

Since December 2019, the world has been facing a pandemic caused by the highly contagious severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (Habibzadeh and Lang, 2020; Phan et al., 2020). To date, despite extensive research, no consistently effective and widely available antiviral drug to treat or prevent coronavirus disease-2019 (COVID-19) exists (Ahsan et al., 2020; Ali et al., 2020).

Studies have established that zinc deficiency (defined as serum zinc < 70 μg/dL) is prevalent in COVID-19 patients, up to 50% (Jothimani et al., 2020). Hypozincemia has been considered a risk factor for severe COVID-19, as suggested by the increased prevalence of zinc deficiency in COVID-19 patients with severe manifestations (Jothimani et al., 2020; Yasui et al., 2020). There was a clear overlap between patients usually exhibiting zinc deficiency, i.e. the elderly and chronic inflammatory and autoimmune disease patients, and patients found at risk for severe COVID-19 (Arentz et al., 2020; Wessels et al., 2020).

Zinc can affect SARS-COV-2 replication and cell entry (Kumar et al., 2020; Rahman and Idid, 2020; Wessels et al., 2020). Alternatively, the link between zinc deficiency and COVID-19 severity has been interpreted as being related to the effects of zinc deficiency on various metabolic systems involved in COVID-19 manifestations (Arentz et al., 2020; Kumar et al., 2020; Rahman and Idid, 2020; Wessels et al., 2020). Zinc deficiency is responsible for deleterious effects on the immune response due to alterations in the number and functions of immune cells, elevation of pro-inflammatory mediators, and increase in reactive oxygen species (ROS), altogether facilitating the incidence of infections (Beck et al., 1997; Wessels et al., 2013; Wessels et al., 2017). Zinc deficiency has been observed in ~ 16% of deep respiratory infections (World Health Organization, 2003) and correlated with more frequent and severe episodes (Hulisz, 2004; Khera et al., 2020; Malik et al., 2014). The pathophysiological consequences of zinc deficiency in COVID-19 patients are presented in Table 1.

Therefore, zinc has been supplemented in numerous antiviral drug protocols aiming at improving drug efficacy (Derwand and Scholz, 2020; Rahman and Idid, 2020). The possible benefits of zinc supplementation in reducing COVID-19 severity and related complications, at least in patients at risk of zinc deficiency was hypothesized (Arentz et al., 2020; Wessels et al., 2020) (Table 2); however, no definitive high-level evidence exists to support such an intervention.

Pathogenesis of COVID-19 manifestations has been continuously clarified since January 2020. The pro-inflammatory manifestations in SARS-COV-2-infected patients has been mainly attributed to the possible disturbances of two systems, the renin-angiotensin and the kinin-kallikrein systems (Gouda and Mégarbane, 2020; Zwaveling et al., 2020). Interestingly, zinc was shown to act as important cofactor in the normal functions of various physiological systems including these two systems as well as the plasma contact activation system, a protease cascade initiated by factor VII activation (Fig. 1), which also play a major role in the onset of various complications related to COVID-19.

Current data suggest that zinc may play a crucial role in COVID-19 severity. However, its exact role in COVID-19 pathophysiology is poorly understood. We aimed to review the effects of zinc on both the renin-angiotensin and kinin-kallikrein systems, since shown to be highly involved in COVID-19 pathophysiology and in most of the resulting clinical manifestations. The three main electronic databases (Pubmed, Embase and Google Scholar) were searched for the 1990/01–2020/12 period using the following keywords ("Zinc" OR "Hypozincemia") AND ("COVID-19" OR "SARS-Cov-2" OR "renin-angiotensin" OR "kinin-kallikreine"). Our research was limited to the available English reports (abstracts or full texts). We selected all reports (original and review articles) focusing on the pathophysiological mechanisms and clinical consequences of zinc deficiency in COVID-19 patients.

2. Effects of zinc on COVID-19-related alterations in the renin-angiotensin system

SARS-CoV-2 enters the cells following the interaction of its Spike protein with the cell receptor, the angiotensin-converting enzyme-2 (ACE2) (Walls et al., 2020). This interaction results in ACE2 down-regulation (Hoffmann et al., 2020; Silhol et al., 2020) leading to the reduction in angiotensin II degradation (Gouda and Mégarbane, 2020). Interestingly, angiotensin II was shown to mediate the pro-inflammatory condition, vasoconstriction, increased vascular permeability, arterial vascular thrombosis and fibrosis (Senchenkova et al., 2010; Yang et al., 2015).

ACE2 is a zinc-containing metallo-enzyme mostly expressed at the cell membrane of vascular endothelia and pneumocytes (Sodhi et al., 2018). Zinc homeostasis is essential for ACE2 enzymatic activity as zinc binds to its active center (Wessels et al., 2020). Increase in zinc was reported to alter ACE2 function by interfering with its ability to metabolize its substrates (Speth et al., 2014). In addition, ACE-2 expression is possibly influenced by zinc homeostasis (Wessels et al., 2020). Zinc affects ACE2 expression when combined with other medication that facilitates its cellular entry (Lee et al., 2021). This has been considered as beneficial to prevent SARS-CoV-2 infection and zinc supplementation was suggested to be useful in inhibiting the interaction between the viral Spike protein and ACE2, thus preventing viral entry into the cell (McPherson et al., 2020). On the other hand, zinc deficiency may increase ACE2 receptor activity and thus enhance the risk of SARS-COV-2 infection (Mayor-Ibarguren et al., 2020) (Fig. 1). Although no study has assessed the effects of zinc deficiency on ACE2 activity, zinc deprivation was reported in the rat to inhibit the activity of ACE, a homologue zinc-containing metallo-enzyme (Reeves and O'Dell,

Table 1
Pathophysiological consequences of zinc deficiency in COVID-19 patients.

Mechanisms	Molecular consequences	Final effects
Inhibition of ACE-2 (a zinc metalloproteinase enzyme) (Wessels et al., 2020)	Accumulation of angiotensin II	Increased inflammation and vasoconstriction (Griendling et al., 1994; Lee et al., 2014)
	Inhibition of degradation of des-Arg9-bradykinin and Lys-des-Arg9-bradykinin	Increased inflammation (Imai et al., 2005; Sodhi et al., 2018)
Inhibition of ACE (a zinc metalloproteinase enzyme) (Reeves and O'Dell, 1986)	No effects on angiotensin II	None
Inhibition of cathepsin L (Lockwood, 2013)	Deficiency in bradykinin and increase in LMWK at the infection site	• Inhibition of the contact system activation • Vasoconstriction (Browning et al., 1987) • Increased fibrinolysis • Increased inflammation
Inhibition of FXII interaction with surfaces or with activators (Rojkjaer and Schousboe, 1997b; Schousboe, 1993) Inhibition of FXII autoactivation to FXIIa (Bernardo et al., 1993; Vu et al., 2013)	Accumulation of FXII directly leading to • Trigger of IL-6 and IL-23 expression (Toossi et al., 1992) • Promotion of neutrophil degranulation (Wachtfogel et al., 1986) • Upregulation of IL-8, IL-1β, IL-6, and TNF-α expression (Hess et al., 2017) • Enhancement of monocyte-derived IL-1 activity (Toossi et al., 1992) • Activation of FXII-related plasminogen (Hofman et al., 2016)	
Inhibition of HMWK and FXII binding to endothelial cells (Vu et al., 2013)	Inhibition of prekallikrein activation to kallikrein leading to: • Inhibition of bradykinin formation from HMWK • Inhibition of FXII auto-activation • Inhibition Hageman factor fragment formation (Stavrou and Schmaier, 2010) • Activation of urokinase plasminogen activator on the endothelium (Hofman et al., 2016)	
Inhibition of the interactions between Hsp90 and prekallikrein-HMWK complex (Joseph et al., 2013)	Inhibition of bradykinin formation from HMWK (Joseph et al., 2009)	

ACE-2, angiotensin-converting enzyme-2; FXII, factor XII; HMWK, high-molecular-weight kininogens; Hsp90, heat shock protein 90; IL, interleukin; TNF-α, tumor necrosis factor-α

Table 2
Presumed effects of zinc supplementation on COVID-19 manifestations.

Pathophysiological roles of zinc	Presumed effects of zinc supplementation on COVID-19-related pathology
Inhibition of ACE-2 ability to metabolize its substrates (Speth et al., 2014)	Inhibition of the interaction between ACE-2 and SARS-CoV-2 viral S protein and thus prevention of viral cell entry (McPherson et al., 2020)
Facilitation of FXII activation to FXIIa (Rojkjaer and Schousboe, 1997b; Schousboe, 1993)	– Prevention of the inhibition of the contact system activation that's is required to limit SARS-CoV-2-related endothelial injury (Huertas et al., 2020)
Facilitation of HMWK and FXII to bind to the endothelial cell membrane (Vu et al., 2013)	– Vasodilatation limiting the tissue consequences of SARS-CoV-2-induced vasoconstriction (Ruocco et al., 2020)
Facilitation of the interaction between Hsp90 and prekallikrein-HMWK complex (Joseph et al., 2013)	– Decrease in SARS-CoV-2-induced fibrinolysis (Jacob et al., 2020)

ACE-2, angiotensin-converting enzyme-2; FXII, factor XII; HMWK, high-molecular-weight kininogens; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

1986). Plasma zinc plays a major role in the development of early clinical signs of zinc deficiency, possibly acting biochemically by reducing the activity of various zinc-dependent peptidases such as ACE (White, 1988). However, no changes in serum angiotensin II and bradykinin concentrations were observed following ACE inhibition in these experimental models.

3. Effects of zinc on COVID-19-related alterations in the kinin-kallikrein system

Kininogens are processed by kallikreins as follows: high-molecular-weight kininogens (HMWK) are processed by plasma kallikrein to bradykinin while low-molecular-weight kininogens (LMWK) are processed by tissue kallikrein to Lys-bradykinin. Bradykinin and Lys-bradykinin stimulate bradykinin receptor-B2 (B2R) on the endothelial cells. Both molecules are further metabolized to des-Arg9-bradykinin (from bradykinin) and Lys-des-Arg9-bradykinin (from Lys-bradykinin), which are ligands of the bradykinin receptor-B1 (B1R), also present on the endothelial cells and upregulated under inflammatory conditions (Jurado-Palomo and Caballero, 2017).

The kinin-kallikrein system is tightly connected to the innate inflammation. Bradykinins stimulate B2R with various organo-protective effects such as endothelial nitric oxide (NO) production, vasodilation, and antithrombotic effects (Fernandes et al., 2001; Gouda and Mégarbane, 2020; Heitsch, 2002; Rahman et al., 2014). Of note, bradykinin-mediated endothelial NOS activation is responsible for short burst of NO and thus results in protective organ effects. By contrast, stimulation of B1R, which is poorly expressed on endothelial cells and up-regulated in inflammatory conditions, enhances the pro-inflammatory response and vasoconstriction that contributes to organ injury including acute respiratory distress syndrome (ARDS) (Heitsch, 2002; Murugesan et al., 2016; Qadri and Bader, 2018).

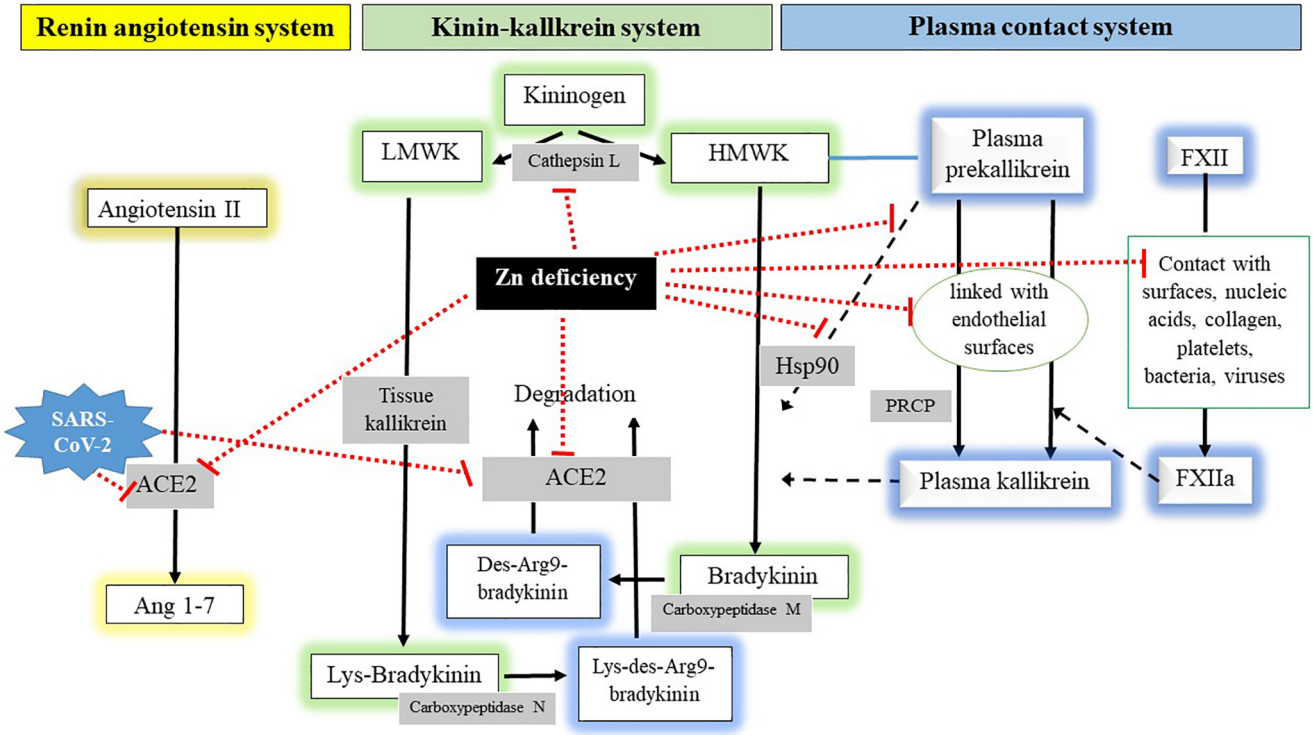

Fig. 1. Effects of zinc depletion and severe acute respiratory syndrome coronavirus-2 (Sars-CoV-2) infection on the plasma contact, renine angiotensine and kinin-kallkrein systems. Red dotted lines represent inhibitory effects. ACE-2, angiotensin-converting enzyme-2; FXII, factor XII; HMWK, high-molecular-weight kininogens; Hsp90, heat shock protein 90; PRCP, prolylcarboxypeptidase; Zn, zinc.

3.1. Zinc and COVID-19-related effects on des-Arg9-bradykinin

Studies suggested that COVID-19 dysregulates the kinin-kallikrein system (Gouda and Mégarbane, 2020; van de Veerdonk et al., 2020). ACE2 inhibition decreases degradation of des-Arg9-bradykinin and Lys-des-Arg9-bradykinin leading to an increase in their effects on B1R resulting in enhanced inflammation and vasoconstriction (Gouda and Mégarbane, 2020). Therefore, zinc deficiency-mediated ACE2 inhibition may be hypothesized as a potential enhancer of B1R-related proinflammatory effects.

3.2. Zinc and COVID-19-related effects on LMWK

Cathepsin L, a lysosomal cysteine endopeptidase, acts as kininogenase independently of tissue kininogenases at the infection site (Hoffmann et al., 2020), since tissue kininogenases are unable to process bradykinins (production of LMWK and HMWK from kininogen) at the infection site during inflammation (Desmazes et al., 2003). Moreover, SARS-COV-2 entry into the cells is mediated by cathepsin L (Hoffmann et al., 2020). Interestingly, *in vitro* experiments showed that low zinc concentrations in the buffer reaction inhibit the enzymatic activity of cathepsin L, suggesting that zinc is an overriding factor of the peptidolytic mechanism (Lockwood, 2013) (Fig. 1). Therefore, zinc deficiency in addition to the supposed cathepsin L monopolization by the virus may result in deficiency in bradykinins and increase in LMWK at the site of infection (Gouda and Mégarbane, 2020).

3.3. Zinc and COVID-19-related effects on the contact activation system

HMWK, one of the major components of the plasma contact system, is cleaved by plasma kallikreins to produce cleaved HMWK and bradykinin (Yamamoto-Imoto et al., 2018). Plasma contact system activation is initiated either by Factor XII (FXII) auto-activation upon contact with negatively charged artificial or biologic surfaces in a process called contact activation or by active plasma prekallikrein called prekallikrein-mediated heteroactivation (Maas and Renné, 2018) (Fig. 2). FXII can be directly auto-activated following its contact with nucleic acids, collagen, platelets and microbial polyphosphate (Naudin et al., 2017) or by binding to the surface of bacteria, fungi and viruses (Maas et al., 2011).

Activated FXII (FXIIa) initiates the intrinsic pathway of coagulation activation and the plasma contact activation system of bradykinin production (Renné and Stavrou, 2019). The plasma contact activation system is used to define FXII, HMWK, and plasma prekallikrein together (Renné and Stavrou, 2019). FXIIa activates plasma prekallikrein to plasma kallikrein, which in turn liberates bradykinin from HMWK, activates FXII and cleaves α-FXIIa to form β-FXIIa (FXII fragment or Hageman factor fragment) that is responsible for activation of the complement system (Stavrou and Schmaier, 2010).

Zinc potentiates FXIIa generation from FXII through multiple pathways (Vu et al., 2013). Zinc binds to FXII through four zinc-binding sites (Rojkjaer and Schousboe, 1997a). Zinc binding to FXII induces conformational changes potentiating FXII interactions with surfaces or activators (Rojkjaer and Schousboe, 1997b; Schousboe, 1993). Zinc is required for optimal FXII auto-activation from polyanionic surfaces (Schousboe, 1993). Zinc binding to FXII enhances its auto-activation by at least 10-fold (Bernardo et al., 1993). Moreover, zinc binding to FXII potentiates its binding to its activators, kallikrein and FXIIa.

In addition, zinc inhibits FXIIa, thus playing a regulatory control role in the contact system activation. Zinc inhibits prekallikrein activation by FXIIa in a dose-dependent manner. Zinc promotes HMWK binding to anionic surfaces facilitating its function as cofactor in the contact system activation that bridges prekallikrein and kallikrein onto the surfaces and endothelial cells (Vu et al., 2013).

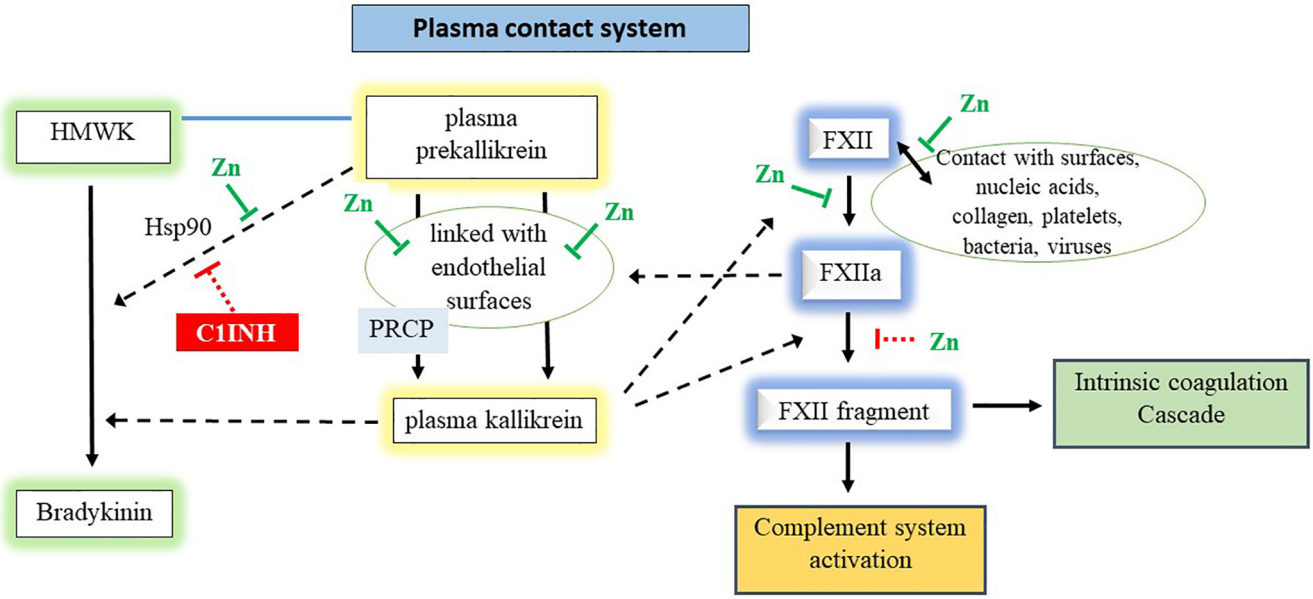

Fig. 2. Roles of zinc in the contact activation system. Zinc is required for the activation of FXII to FXIIa and inhibition of FXIIa degradation; for adhesion of high-molecular-weight kininogens (HMWK)-prekallikrein complexes to the endothelial cell membranes needed for their activation; and for the alternative pathway of bradykinin synthesis directly through the action of prekallikrein. Red dotted lines represent inhibitory effects and green plain lines stimulatory effects. ACE-2, angiotensin-converting enzyme-2; C1inh, C1-inhibiteur; FXII, factor XII; HMWK, high-molecular-weight kininogens; Hsp90, heat shock protein 90; PRCP, prolylcarboxypeptidase; Zn, zinc.

Interestingly, the amount of zinc needed to promote FXII binding to endothelial cells in the contact system activation is 33- to 50-fold higher than the amount needed for HMWK binding (Zhao et al., 2001).

Zinc deficiency and zinc supplementation may not necessarily have opposite effects. However, although not directly investigated and based on extrapolations from experiments with zinc supplementation, we can suggest that zinc deficiency leads to the inhibition of the contact system activation with inhibition of FXII activation, inhibition of prekallikrein, HMWK and FXIIa binding to endothelial cells, inhibition of the kallikrein processing from prekallikrein and inhibition of bradykinin synthesis from HMWK (Fig. 1). Moreover, zinc deficiency significantly decreases the vasodilator effects of bradykinin (Browning et al., 1987) since the contact activation system is the classical pathway of bradykinin production during inflammation (Ghebrehiwet et al., 1983).

3.3.1. Zinc and COVID-19-related effects on alternative pathways of bradykinin production

On the endothelial cells surface, the prolylcarboxypeptidase (PRCP) converts prekallikrein to kallikrein more efficiently than FXIIa (Mahdi et al., 2003) (Fig. 2). PRCP is a serine protease enzyme that cleaves angiotensin II, angiotensin III and prekallikrein (Tabrizian and Tahmineh, 2014). PRCP is an alternative peptidase to ACE2 that catalyzes the conversion of angiotensin II into angiotensin-(1–7) (Grobe et al., 2013). Interestingly, clinical and biological manifestations attributed to PRCP dysfunction and COVID-19 are paralleled well, including increased risk of pneumonia, onset of hypertension, increase in angiotensin II, increase in ROS, endothelial dysfunction and pro-thrombotic trends (Silva-Aguiar et al., 2020). As the majority of circulating prekallikrein is bound to HMWK and as zinc facilitates HMWK binding to the endothelial cells, zinc is important to localise prekallikrein on to the endothelial cells (Maas and Renné, 2018; Qadri and Bader, 2018). Zinc deficiency may thus be responsible for PRCP dysfunction by preventing prekallikrein from binding to endothelial cells to be a substrate for PRCP.

Prekallikrein can directly activate HMWK to bradykinin without being activated to kallikrein (Fig. 2). This is facilitated by endothelial cell-derived factors such as heat shock protein 90 (HSP90) and prolyl carboxypeptidase. Although most of plasma prekallikrein circulates as a complex with HMWK, this activation is inhibited *in vivo* by various molecules and mainly the C1-inhibitor (C1INH). Interestingly, C1INH inhibition was involved in COVID-19-related complications with reported improvement when patients were treated with C1INH (Thomson et al., 2020). This peptide has no effect on kallikrein-related activation of HMWK (Joseph et al., 2009) while zinc is required as a cofactor for this reaction (Kaplan et al., 2002). Additionally, interaction between Hsp90 and prekallikrein/HMWK complex specifically requires zinc (Joseph et al., 2013). Therefore, zinc deficiency may prevent activation of HMWK to bradykinin even in case of C1INH deficiency.

3.3.2. Consequences on coagulation of the inhibition of FXII activation

As for the fibrinolytic system, FXIIa can activate the plasminogen and the prekallikrein activates the urokinase plasminogen activator on the endothelial cells thus increasing fibrinolysis (Hofman et al., 2016). Inhibition of FXII activation in relation to zinc deficiency may result in clotting failure with the risk of misinterpretation of the coagulation tests. Patients most commonly present prolonged prothrombin time and activated partial thromboplastin time (aPTT) with elevated D-dimer and fibrin degradation products (Tang et al., 2020). FXII may be deficient despite the absence of bleeding tendency (Bowles et al., 2020). As reported in studies using FXII-targeting RNA Aptamer to inhibit FXII activation, inhibition of FXII activation results in increased clotting times and aPTT (Woodruff et al., 2013). Adding FXII to serum in clotting assays investigating FXII deficit tests may or not result in the correction of the clotting time and is thus able to differentiate between factor deficiency and the presence of an inhibitor of coagulation (Bowles et al., 2020). By leading to the inhibition of FXII and contact system activation thus resulting in the accumulation of FXII and prekallikrein, zinc deficiency may be the cause of increased fibrinolysis.

3.3.3. Consequences on the inflammatory response of inhibition of FXII activation

FXII can directly trigger interleukin (IL)-6 and IL-23 expression by splenic dendritic cells (Toossi et al., 1992) and promote neu-

trophil degranulation (Wachtfogel et al., 1986). FXII alone can directly upregulate the expression of IL-8, IL-1β, IL-6, and tumor necrosis factor-alpha (TNF-α), independently of plasma kallikrein (Hess et al., 2017). Consistently, exposure of FXII to blood monocytes in the presence of lipopolysaccharide (LPS) enhances IL-1 activity (Toossi et al., 1992). This was clearly evidenced by the significant increase in FXII in the bronchoalveolar fluid when comparing ARDS non-survivors to survivors (Hess et al., 2017). Interestingly upregulation of IL-8, IL-1β, IL-6, and TNF-α have been suggested as strong non-survival predictors in COVID-19 patients (Del Valle et al., 2020).

Zinc deficiency may markedly alter the inflammatory response in COVID-19 patients with inhibition of intrinsic pathway of coagulation and increased aPTT and D-dimer (Table 1). Since zinc deficiency decreases FXII activation, proinflammatory cytokine production would decrease. Therefore, in COVID-19 patients, IL-6 and TNF-α serum levels remain independent and significant predictors of disease severity and death. Supplementation of zinc may alleviate the inflammatory response due to bradykinin production, but may also increase the risk of FXII activation and initiation of the coagulation cascade (Table 2).

4. Conclusion

Both the renin-angiotensin and kinin-kallikrein systems whose dysfunction accounts for a major mechanism in COVID-19 pathophysiology, are affected by zinc deficiency, thus possibly exaggerating COVID-19 manifestations. Zinc deficiency leads to ACE2 dysfunction, enhancing its enzymatic activity, which, although not proved yet, may be responsible for increased binding to SARS-coV-2. Zinc deficiency leads to ACE2 dysfunction, possibly enhancing COVID-19-associated ACE2 downregulation. ACE2 dysfunction affects both systems leading to the accumulation of angiotensin II, des-Arg9-bradykinin and Lys-des-Arg9-bradykinin, leading to enhanced pro-inflammatory response, vasoconstriction and prothrombotic effects. In addition, zinc deficiency affects cathepsin L functions resulting in the deficiency of bradykinins at the infection site and the decrease in their vasodilation activities. Finally, zinc deficiency inhibits the contact system activation by limiting FXII activation and inhibiting HMWK, prekallikrein and FXII binding to the endothelial cells, thus enhancing FXII accumulation and bradykinin deficiency. Taken together, these effects seem to contribute to increasing the production of inflammatory mediators and to altering the coagulation parameters in COVID-19 patients. However, whether zinc supplementation in COVID-19 patients may improve the outcome remains to be established.

5. Authors' contributions

ASG, FGA and BM have participated in drafting the manuscript and approved its final version.

Funding

There is no funding source.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

The authors would like to thank Mrs. Alison Good (Scotland, UK) for her helpful review of the manuscript.

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