



# Kinin–kallikrein system; a possible pathway responsible for COVID-19

Keivan Mohammadi<sup>1\*</sup>, Aliye Tabatabaee<sup>2</sup>, Mojtaba Akbari<sup>2</sup>

<sup>1</sup>Department of Cardiology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

<sup>2</sup>Isfahan Endocrine and Metabolism Research Centre, Isfahan University of Medical Sciences, Isfahan, Iran

## \*Correspondence to

Keivan Mohammadi, Email:  
k1mohamadi@yahoo.com,  
keivan@edu.mui.ac.ir

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## Key point

Kinin–kallikrein system might be a responsible component in the clinical observations of patients with COVID-19. If we shift our focus to breaking the inflammation cascade of kinin–kallikrein system or blocking the kinin–kallikrein system activation, we probably would achieve more success in lowering COVID-19 symptoms.

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COVID-19, with more than 3.5 million confirmed positive cases and 250000 deaths worldwide, is a universal problem. COVID-19 pandemic is the third outbreak of the *Coronaviridae* family (1) and by far is the most widespread and devastating one. We speculate that the kinin–kallikrein system is involved in clinical manifestation of COVID-19, such as inflammation, pain, dry cough, and organ failure (Figure 1). Some studies have suggested that kinin–kallikrein system plays a role in the pathogenesis of acute respiratory distress syndrome (ARDS) (2).

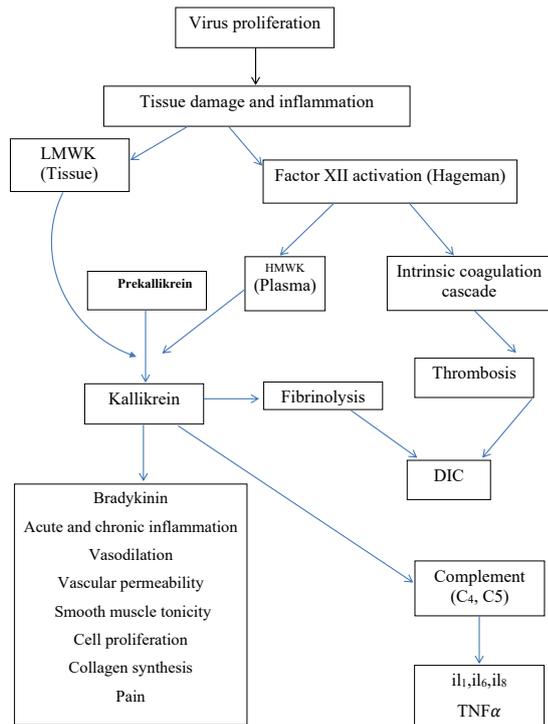
Kinin–kallikrein system includes proteins factor XII (FXII), prekallikrein (PK), and high molecular weight kininogen (HMWK). The final production of this system is kinins (bradykinin-related peptides), namely bradykinin (BK) and kallidin (KD). We hypothesize that lung tissue damage resulted from SARS-Cov-2 proliferation leads to the activation of kinin–kallikrein system with two different pathways. The first pathway, the plasma kinin–kallikrein system, involves the intrinsic coagulation system, where activated FXII (FXIIa) activates pre-kallikrein to kallikrein. Then, kallikrein cleaves plasma HMWK, then BK is released (2,3). The second pathway engages tissue kallikrein and low-molecular weight kininogen (LMWK), where tissue kallikrein liberates KD from LMWK in an FXII-independent manner (3).

Kinins stimulate endothelial cells and are involved in different physiological and pathological processes. Kinins can lead to inflammation, vasodilation, elevated vascular permeability, contraction of vascular smooth muscle cells (VSMC), releasing tissue-type plasminogen activator (t-PA), nitric oxide release and consequently pain and dry cough. Therefore, dysregulation of kinin–kallikrein system might result in hypotension, angioedema, and cardiovascular and kidney disorders (2,3).

The activation of FXII and subsequently, activation of plasma kinin–kallikrein system are not only involved in kinins production but also results in activation of complement system and fibrinolysis pathway (2). Both the fibrinolysis pathway and the intrinsic coagulation system can eventually lead to disseminated intravascular coagulation. Interestingly, the risk of developing disseminated intravascular coagulation is high in patients with COVID-19 (4) which could show the link between kinin–kallikrein system and COVID-19.

Kinin–kallikrein system might be a responsible component in the clinical observations of patients with COVID-19. However, some of the existing proposed treatment approaches for COVID-19 focus on alleviating the inflammation and/or removing pro-inflammatory mediators, while the whole process of kinin–kallikrein system is still





**Figure 1.** The proposed pathway for COVID-19. LMWK, low molecular weight kininogen; HMWK, High molecular weight kininogen; DIC, disseminated intravascular coagulation.

happening and damaging lungs. If we shift our focus to breaking the inflammation cascade of kinin–kallikrein system or blocking the kinin–kallikrein system activation, we probably would achieve more success in lowering COVID-19 symptoms.

**Authors’ contribution**

KM and MA contributed to conception and design, literature search, and providing the figure. AT contributed in the literature search and wrote the manuscript. KM and MA edited the manuscript critically.

**Conflicts of interest**

The authors declare no conflict of interest regarding the publication of this article.

**Ethical considerations**

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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