

# Can erythrocytes behavior in microcirculation help the understanding the physiopathology and improve prevention and treatment for covid-19?

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**Abstract.** Low plasma estrogens, vitamin D deficiency, obesity, diabetes, cardiovascular diseases, thromboembolism, and impaired microcirculation are linked to the severity of covid-19. Studies have suggested that these comorbidities also are related to erythrocyte factors linked to increased blood viscosity in microcirculation such as erythrocyte aggregation and erythrocyte deformability. Increased blood viscosity in microcirculation can lead to a decrease in oxygenation and nutrition of tissues. Therefore erythrocyte aggregation and erythrocyte deformability may be involved in covid-19 severity, leading to tissue hypoxia and a decrease of drug concentration in affected organs. If this relationship is demonstrated, erythrocytes factors can be used to monitor treatments for improve microcirculatory fluidity that may decrease covid-19 severity. Lifestyle improvement and treatments such as vitamin D and estrogens supplementation are some possible approaches to improve microcirculation and covid-19 prevention and treatment.

Keywords: Covid-19, hemorheology, microcirculation, estrogen, diabetes, vitamin D, obesity, cardiovascular diseases

## 1. Introduction

Covid-19 has caused a brutal toll of death and morbidity worldwide. By the beginning of December 2020, more than 70 million people were infected and more than 1.5 million deaths were documented worldwide [1]. This communication was done from a need to provide a possible alternative approach to the pathophysiology, prevention, and treatment of the disease, to try to improve morbidity and mortality by covid-19 and similar diseases.

Studies have suggested that low plasma estrogens [2, 3], vitamin D deficiency [4], obesity [5], diabetes [6], and cardiovascular diseases [7] are factors linked to the severity of covid-19. The most severe forms of covid-19 are often cursed with thromboembolic events [8–12] and impaired microcirculation [13–16]. Therefore factors related to all these conditions (low estrogens, vitamin D deficiency, obesity, diabetes, cardiovascular diseases, thromboembolic events, and impaired microcirculation) might be implicated in the pathophysiology of covid-19 complications.

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## 2. Blood viscosity in microcirculation

Firstly, is necessary the understanding blood viscosity in microcirculation. Blood is a non-Newtonian fluid, and the behavior of erythrocytes interferes with blood viscosity. The blood viscosity in microcirculation approaches plasma viscosity in vessels bigger than erythrocytes [17]. The importance of erythrocytes in blood viscosity increases as blood vessel diameter decrease and their influence is greater in vessels smaller than 300  $\mu\text{m}$ . Two erythrocyte factors can increase blood viscosity in microcirculation: The increased erythrocyte aggregation and the decreased erythrocyte deformability [18, 19]. There are also some compensatory factors, as the diameters of the vessels become smaller than 300  $\mu\text{m}$ . In these very small vessels, hematocrit decreases (Fåhræus effect) and there is a decrease of blood viscosity as the vessel diameter decrease (Fåhræus and Lindqvist effect), reducing the microvascular resistance associated with an accumulation of RBC in microcirculation, mainly in the bifurcations [20]. Therefore, low erythrocyte aggregation and high erythrocyte deformability are critical for blood flow in microcirculation. Impaired viscosity in microcirculation can impair the delivery of oxygen and nutrients to the tissues [21–24]. Therefore erythrocyte aggregation and erythrocyte deformability can interfere with oxygenation and nutrition of organs and tissues. If these erythrocytes behavior are altered in covid-19, it may be an explanation for the lesions caused by disease.

## 3. Covid-19 comorbidities and erythrocyte behavior

Secondly, several comorbidities related to the severity of infection by the new coronavirus have been related to the behavior of erythrocytes in the microcirculation, namely erythrocyte aggregation and erythrocyte deformability, as listed below.

### 3.1. *Low estrogen*

Studies have suggested that men are more susceptible and have a higher mortality rate by covid-19 than females, and the hormonal influence has been suggested as the reason for this difference [2, 25]. A study also suggests that postmenopausal women are more susceptible to covid-19 than premenopausal women [3]. Low estrogen also has been linked to erythrocytes behavior. When natural estrogen beta-estradiol or synthetic ethinyl estradiol are added to men's blood, erythrocyte deformability increase accordingly with hormone's concentration [26]. Transdermal beta-estradiol in hysterectomized women increases erythrocyte deformability and decreases erythrocyte aggregation [27]. Therefore, low estrogen is associated with hemorheological parameters linked to impairment in microcirculation which can explain why this factor is associated with severity and death for covid-19.

### 3.2. *Vitamin D deficiency*

Low vitamin D is a risk factor for infection and hospitalization due to covid-19 [4, 28]. Low plasma levels of vitamin D have been associated with the worst prognosis of covid-19 [29]. Low vitamin D also has been linked to impaired hemorheology. In postmenopausal women, lower levels of 25-OH vitamin D in the blood are related to higher RBC aggregation and lower RBC deformability [30]. Therefore impaired hemorheology can explain why low vitamin D is associated with the worst prognosis of covid-19.

### 3.3. *Obesity*

Most patients requiring mechanical ventilation for covid-19 are obese, and obese patients are more likely to die from covid-19 [5, 31]. Obesity also has been associated with hemorheological impairment.

Patients with abdominal obesity show decreased erythrocyte deformability [32] while super obese patients show increased erythrocyte aggregation compared with morbid obese patients [33]. Patients with obesity and higher erythrocyte aggregation also have a higher risk of deep vein thrombosis [34]. Therefore, obesity is associated with both impairment of hemorheological parameters and severity of covid-19.

### 3.4. *Diabetes*

Type 2 diabetes (T2D) has been associated with severity and mortality for covid-19 [6, 35]. T2D also has been associated with impaired hemorheology in microcirculation. The erythrocyte deformability is reduced in T2D patients compared with healthy controls and is even worse in T2D patients with complications as nephropathy or retinopathy [36]. Patients with T2D and non-alcoholic fatty liver diseases have higher whole blood viscosity and increased RBC aggregation [37]. Erythrocyte aggregation also is increased in poorly controlled T2D patients compared with non-diabetic controls [38]. Therefore, T2D is associated with a severity of covid-19 and impairment of hemorheological parameters in microcirculation.

### 3.5. *Cardiovascular diseases*

Pre-existing cardiovascular diseases also have been linked with severity and mortality in patients with covid-19 [7]. Studies have also reported impairment of hemorheological parameters in cardiovascular diseases. Erythrocyte aggregation has been related to Lewis negative phenotype (individuals with increased atherosclerosis risk) along with inflammatory markers [39]. Patients with arterial hypertension have a decrease in erythrocyte deformability and an increase in erythrocyte aggregation [40, 41]. The severity of arterial hypertension is associated with increased erythrocyte aggregation and decreased erythrocyte deformability [42–44]. Erythrocyte deformability along with plasma viscosity and whole blood viscosity is associated with Framingham cardiovascular risk score [45]. Erythrocyte aggregation and erythrocyte deformability also are linked to long term fatal and non-fatal events in transmural myocardial infarction survivors [46].

## 4. **Erythrocyte behavior and tissue hypoxia**

As stated above, several comorbidities related to severity and death by covid-19 also are related to hemorheological parameters linked to microcirculatory impairment such as erythrocyte aggregation and erythrocyte deformability. Tissue hypoxia has been reported in death by covid-19 [47]. Hemorheological impairment can lead to a decrease to nutrition and oxygenation of the tissues, leading to hypoxia and a decrease of available nutrients [21–24]. Hypoxia and lack of nutrients in various tissues and organs can be a plausible explanation of the deleterious effect of the infection of the new coronavirus. Some drugs can act *in vitro* against the new coronavirus but fail to treat the patient already infected [48]. A possible explanation can be that the drug cannot reach the place of the infection in the minimal inhibitory concentration due to microcirculatory impairment.

## 5. **New possible approaches for covid-19 prevention and treatment**

Therefore, erythrocyte aggregation and deformability may be biomarkers for prevention and treatment approaches for covid-19, but this relationship should be confirmed. If a treatment improved these hemorheological parameters than microcirculation, tissue nutrition and tissue oxygenation should also be improved.

If covid-19 is related to hemorheological impairment, prevention of infection severity by the new coronavirus may be possible by improving hemorheological parameters while improving the comorbidities related to covid-19. Changes in lifestyle such as diet and physical activity have been reported to improve both red blood aggregation and deformability in diabetic subjects [49]. Erythrocyte aggregation also can be improved in obese subjects after diet, dependent on weight loss [50, 51]. Therefore, lifestyle improvement may enhance hemorheological parameters and its role in the prevention of severity of covid-19 should be investigated.

Although low vitamin D is related to the severity of covid-19 [4, 29] and impaired hemorheology [30], it has not yet been possible to verify whether vitamin D supplementation can prevent severe cases [52]. An approach that can be investigated is to determine which dose of vitamin D3 is necessary for improves hemorheology. If it is possible to determine the ideal dose or ideal blood concentration of vitamin D to improve blood rheology, this approach can become simple and inexpensive management for the prevention and treatment of covid-19.

This same approach can be used to test the ideal dose of female hormones to improve hemorheology in postmenopausal women since hormones such as estradiol have been shown to improve both erythrocyte aggregation and deformability [26, 27]. In the same way, currently approved treatments for covid-19 can be evaluated if they can improve these erythrocytes parameters.

## 6. Conclusion

In conclusion, many studies are suggesting that comorbidities linked to severe covid-19 are also related to erythrocyte factors that increase blood viscosity in microcirculation, such as erythrocyte aggregation and erythrocyte deformability. The impaired microcirculation can be an explanation for the tissue lesion as seen in covid-19 severe cases. Changes in lifestyle, supplementation of hormones and vitamins, and drug treatments are some of the possible actions to improve hemorheology and the severity of the disease.

## Conflict of interest

The authors have no conflict of interest to report.

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