PHYSICAL MEDICINE AND REHABILITATION APPROACHES IN THROMBOSIS ASSOCIATED WITH COVID-19

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Abstract
An increasing number of publications have supported the determination of thrombosis associated with coronavirus disease 2019 (COVID-19). Despite prophylactic drug applications, post-COVID-19 thrombosis cannot be completely prevented. Thrombosis becomes a complex problem that is difficult to avoid, particularly in intensive care patients. It is also possible to see cases of thromboembolism secondary to quarantine and home isolation. In addition to the classical pathophysiological mechanisms in Virchow’s triad, more complex processes specific to COVID-19 may also trigger thrombosis. The aims of this review were to describe physical medicine and rehabilitation practices that can be applied in addition to medical recommendations for thrombosis in COVID-19 patients, and to explain the specific features and mechanism of action of these methods. This process, which starts with education sessions, should continue to reduce immobility as much as possible. Personalized exercise programs should be recommended after evaluating the individual’s condition, exercise history, risk of falling, and comorbid diseases. In parallel with technological progress, more innovative devices have been developed and thus mechanical compression methods and neuromuscular electrical stimulation have become available for this purpose. The most important features of physical medicine and rehabilitation practices are the relatively low cost and the low incidence of complications.

Keywords: COVID-19, SARS-CoV-2, Thrombosis, Prophylaxis, Rehabilitation, Physiotherapy, Exercise

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COVID-19 AND THROMBOSIS
Coronavirus disease 2019 (COVID-19) emerges as a clinical reflection of the interaction between the immune system of individuals and severe acute respiratory syndrome virus 2 (SARS-CoV-2) [1]. Although some patients have a mild or asymptomatic disease process, severe COVID-19 is clinically closely related to thromboembolic complications and respiratory failure [2]. There are several studies supporting the relationship between COVID-19 and the risk of thrombosis. Klok et al. [3] evaluated COVID-19 patients followed up in the intensive care unit under low molecular weight heparin thromboprophyaxis, and the incidence of thromboembolic events was reported to be 31%. The incidence of venous thromboembolism is higher in favor
of COVID-19 when COVID-19 patients followed up in the intensive care unit are compared with patients under treatment in the intensive care unit with different diagnoses. This suggests that the process involves much more complex mechanisms than immobilization [4]. The main mechanism for thrombosis comprises stasis, endothelial damage and hypercoagulation, defined as Virchow's triad. Various lifestyle factors, drugs used, and comorbid diseases also trigger this process. Endothelial damage caused by inflammation promotes thrombosis progression. In addition, the hypercoagulation process is sustained by a reduction in fibrinolysis, stimulation of the tissue factor pathway, and NETosis. In response to inflammation, the release of neutrophil extracellular traps (NETs) from neutrophils arises via a particular process (NETosis) [5]. NETosis is one of the cornerstone processes connecting induction of inflammatory mediators, platelet and endothelial activation, clot formation and resistance to fibrinolysis. Although NET formation has a significant role in the immune response, inflammation and coagulation steps come into contact in this process, and platelet, endothelial cell and FXII activations are supported [6]. It is considered that the complement activation process also participates in the pathophysiology of thrombosis and has an important role [7]. The dynamic relationship of the triad of inflammation, activated complement system and coagulation cascade has been suggested to play a crucial role in the physiological process of COVID-19 and to be effective in inducing disseminated intravascular coagulation.

In studies on COVID-19 patients, microthrombosis has been found in alveolar structures, unlike standard pulmonary embolism [8]. This pulmonary microthrombosis process has been associated with hypoxemia at the onset of adult respiratory distress syndrome in COVID-19 patients. Ventilation/perfusion mismatch due to microthrombosis and an increase in dead space cause hypoxemia clinical status [9]. It has been determined that pulmonary thrombosis in COVID-19 is not frequently associated with deep vein thrombosis and originates primarily from the lungs rather than the venous circulation [10]. However, it is difficult to argue that patients with COVID-19 are not prone to deep vein thrombosis. In an autopsy study, 12 COVID-19 patients were examined and although there was no clinical suspicion, deep vein thrombosis findings were found in 7 patients [11]. In another study involving 26 COVID-19 patients, microthrombosis has been found in alveolar structures, unlike standard pulmonary embolism [9]. It has been determined that pulmonary thrombosis in COVID-19 is not frequently associated with deep vein thrombosis and originates primarily from the lungs rather than the venous circulation [10]. However, it is difficult to argue that patients with COVID-19 are not prone to deep vein thrombosis. In an autopsy study, 12 COVID-19 patients were examined and although there was no clinical suspicion, deep vein thrombosis findings were found in 7 patients [11]. In another study involving 26 COVID-19 patients in the intensive care unit, the frequency of venous thromboembolism was detected as 69% by routine ultrasound examination in patients under prophylactic or therapeutic anticoagulation [12]. This review aimed to describe physical medicine and rehabilitation approaches that can be recommended for the management of COVID-19-related thrombosis. The prophylactic methods that can be applied in home isolation before COVID-19 are listed, as well as the approaches that can be recommended during and after COVID-19. This study also aimed to explain the unique features, application terms and mechanisms of action of these methods.

SEARCH STRATEGY
A literature search was performed according to the review strategies suggested by Gasparyan et al. [13]. Web of Science, Scopus, and MEDLINE/Pubmed databases were searched with the terms 'COVID-19 thrombosis physical therapy', 'COVID-19 thrombosis physiotherapy' and 'COVID-19 thrombosis physical medicine'. First, the titles and abstracts were scanned and articles related to the subject were determined. Then, a full-text review was conducted by the authors (BFK and AA). Articles involving physical medicine and rehabilitation approaches in COVID-19-related thrombosis were evaluated.

PHYSICAL MEDICINE AND REHABILITATION APPROACHES IN THROMBOEMBOLISM PROPHYLAXIS UNDER PANDEMIC CONDITIONS
This article describes the physical medicine and rehabilitation approaches for COVID-19-related thrombosis, including education, mobility, exercise, mechanical compression (compression stockings and intermittent pneumatic compression), and neuromuscular electrical stimulation (Figure 1).

Education
Education is a method accepted as a cornerstone for individuals at potential risk for the development of thromboembolism. To reduce the risk, appropriate education programs should be established not only for individuals at risk of thromboembolism, but also for family members. Educational programs should be supported with visual materials, and the level of comprehension of the subjects should be increased [14]. The main points that the education sessions should cover are as follows: factors that increase the risk of thromboembolism, possible consequences and effects of thromboembolism, practices that reduce the risk of thromboembolism, complaints and findings that raise suspicion of thromboembolism, what to do in case of suspected thromboembolism, and the necessity of complying with the recommendations [15].
Immobilization is one of the key factors inducing the development of thromboembolism and is an important problem for patients isolated at home or treated in a hospital setting. Individuals who are confined to a wheelchair or bed for more than half of their time outside the bed are accepted as having high potential for thromboembolism [16]. Therefore, the importance of avoiding immobilization should be particularly emphasized to patients. Educational programs have been shown to significantly increase compliance with recommendations for thromboembolism prophylaxis [17]. In addition, Piazze et al. [17] reported that only 3% of individuals actively participated in the question-answer part at the end of the education sessions. This result suggests that prepared high-quality visual materials can be used as an alternative education method to save human resources.

Mobility
Decreased mobility is a well-known factor for thromboembolism; however, the link between the degree and duration of reduction in mobility and thromboembolism has not been clearly established [18]. Supporting this view, a relationship between loss of mobility for 3 days or more and ultrasonographically detected thromboembolism has been demonstrated [19]. There are case reports of thromboembolism in individuals who are isolated at home due to COVID-19 and have a history of long-term immobilization [20]. The conditions that emerged as a result of the pandemic recall the concept of eThrombosis, which was first introduced in 2003 [21]. In this case report, Beasley et al. [21] described a clinical state of acute pulmonary thromboembolism in a young man due to computer use for more than 18 hours. The main mechanism in the formation of eThrombosis is the slowdown in blood flow caused by sitting for very long hours and immobility. Healy et al. [22] reported that the risk of thromboembolism increased 2.8-fold in those who spent 10 hours a day on the computer in work or home conditions and those who spent at least 2 hours in front of the computer without getting up. eThrombosis has come to the fore again with the changes in lifestyle caused by the pandemic. The trend of teleworking, particularly the isolation of the geriatric population, and individuals with comorbid diseases, have led to pandemic-induced inactivity [23]. It is necessary to raise more awareness about the role of long-term computer-based work and inactivity in the etiopathogenesis of thromboembolism. At this point, the unfavorable effects of immobilization should be added to the educational programs described in the previous section. If home isolation is unavoidable, a variety of home-based exercises and in-home mobilization should be encouraged. Keeping exercise and mobilization diaries with easy-to-use applications will both increase the motivation of individuals and be useful in tracking compliance with the recommendations.

Exercise
When the classical pathophysiology of thromboembolism is considered, the preventive effect of exercise is more clearly understood. Slowing down or stasis in blood flow, increased coagulation, injury and inflammation of the vessel walls are the three main causes of thrombosis [24]. Exercise programs increase blood flow velocity by inducing muscle and thoracic pumps, thereby preventing stasis. Previous studies have revealed that ankle exercises increase blood flow velocity regardless of the prone or supine position [25]. In addition, studies on healthy control subjects and patients with acute deep vein thrombosis have shown that exercises involving the upper half of the body increase blood flow [26]. The secondary effects of exercise programs are based on the changes they create on the coagulation system. The effects of short-term aerobic exercise have been evaluated and have revealed that aerobic exercise has the potential to reduce factors such as plasminogen activator inhibitor-1, von Willebrand factor antigen, and fibrinogen. Thus, the tendency for coagulation decreases [27]. Another mechanism is related to the effects of exercises on inflammation. Chen et al. [28] assessed the impacts of low-load resistance exercises and reported that this exercise program could prevent thrombosis by reducing the inflammation cascade. Apart from all these mechanisms, another positive feature is the psychologically beneficial influence of exercise programs. Individuals can feel a sense of being able to control or prevent health problems, having a sense of playing an important role in the recovery period. In addition to all these positive effects of exercise programs, the lack of cost is a feature that should be emphasized especially in low-income countries. Another point to be emphasized is that exercise programs should be individualized. Personalized programs should be created by experienced health personnel, taking into account age, exercise history, comorbid diseases, drug use, and COVID-19 status. The determination of exercise intensity is also important. Exhaustive exercise programs above capacity have been associated with increased thromboembolism in elderly and obese patients [29]. Some sample exercises are given below (programs should be individualized and their intensities determined) [30, 31]:
• Aerobic exercises (walking, dancing, cycling)
• Calf pump exercises
• Active ankle exercises, including dorsiflexion, plantar flexion, inversion, eversion
• Lower extremity range of motion exercises (depending on the individual's condition, passive, active-assistive or active).
• Deep breathing exercises
• Arm up-down exercises
• Arm abduction-adduction exercises

**Mechanical compression**

Studies of patients with various diseases, individuals who have taken long plane trips, post-operative patients, and those who need long-term care have shown that different mechanical compression methods have beneficial effects in terms of thromboembolism risk [32-35]. The most commonly used methods for this purpose are compression stockings and intermittent pneumatic compression. Compression stockings compress the vessels, resulting in a reduction in vessel diameter. Studies with Doppler ultrasound also support this physiological effect [36], showing increased venous blood flow. As a result, it has been concluded that compression stockings prevent venous distension by mechanical means and prevent stasis by increasing blood flow. The device, which inflates with air by means of an electric pneumatic pump, has the effect of pumping the blood towards the proximal with the compression effect. Inflating and deflating times and pressure values in these processes vary between devices. Although the preventive effect of these methods is clear, studies of patients with acute and symptomatic thromboembolism have reported conflicting results [37]. In previously published meta-analyses, it has been emphasized that intermittent pneumatic compression considerably reduces the risk of deep vein thrombosis. However, in a significant number of the studies in the meta-analysis, intermittent pneumatic compression and compression stockings were used in combination, and the variability of the devices in the studies is also a handicap [38, 39]. Considering patients at high risk, perhaps the most important advantage of these methods is that they do not increase the risk of bleeding. Therefore, mechanical compression methods continue to attract attention in the prevention of thromboembolism, particularly in patients with active bleeding or at high risk for bleeding.

Mechanical compression devices should be preferred during the immobilization period of patients and until full ambulation is achieved; however, these devices are not appropriate for use in extremities with a high risk of ischemia [37]. Prior to downsizing of intermittent pneumatic compression devices, the main handicap was the large size and the need for a static power supply. After the development of smaller and more comfortable devices with batteries, these problems began to be overcome. However, there are some patients that find mechanical compression methods uncomfortable and refuse to use them. Severe polyneuropathy, loss of sensation, decompensated heart failure, arterial occlusion-insufficiency, and dermatological diseases causing widespread lesions can be considered contraindications for the use of mechanical compression methods.

Protocols for the use of these methods are not fully established. When to start for maximum benefit? How long should a method be used? Should the method be combined with other treatment modalities? What are the most useful pressure inflation rates? These are questions that await clarification.

**Neuromuscular electrical stimulation**

Neuromuscular electrical stimulation is a physical therapy modality in which electrical impulses are applied via electrodes placed on the skin to activate muscle contraction either directly by stimulating the muscle group or indirectly via the nerve innervating the muscles. It has been demonstrated that muscle pumps, in which the activity is increased by neuromuscular electrical stimulation, cause an increase in venous time-averaged mean velocity, peak venous velocity and volume flow values [40]. The role of neuromuscular electrical stimulation in thromboembolism prophylaxis started with research about 50 years ago; however, its use only in patients under anesthesia has prevented it from being a widely-used method due to the lack of technological opportunities [41]. With the development of modern devices, the need for anesthesia has been eliminated and devices that cause less painful stimuli have been developed. Modern neuromuscular electrical stimulation devices are portable and battery-powered, and can be easily attached to the desired area with self-adhesive electrodes. An exemplary mechanism is stimulation of the common peroneal nerve with intermittent electrical stimulation followed by triggering of ankle dorsiflexion. Inducing this movement with electrical stimulation activates the muscle pump, creates a compression effect on the veins and increases venous return, similarly to the walking cycle [42]. Several studies of healthy volunteers have supported the stated effect of electrical stimulation [43-45]. In addition, neural stimulation of vascular structures may elicit a direct antithrombotic effect as a factor not included in the Virchow's triad. Activation of neurogenic pathways can suppress thrombotic
processes [46]. Previous study results have shown that neuromuscular electrical stimulation applications have sufficient patient compliance and are well tolerated [47]. Based on previous studies of intensive care unit patients, it is thought that neuromuscular electrical stimulation can be used as an alternative thromboembolism prophylaxis method in COVID-19 patients [48]. In addition to the positive effects of this method, there are some deficiencies and handicaps. Neuromuscular electrical stimulation has the potential to cause muscle fatigue. Contractions provided by electrical stimulation are asynchronous and the effect may not be equivalent to physiological contraction. Considering that superficial stimuli may not reach deep tissues and muscles, it is obvious that deep muscle groups cannot be activated sufficiently [49].

CONCLUSION
Current evidence indicates a tendency to develop thrombosis in patients with COVID-19. In addition, this clinical thrombosis cannot be completely prevented despite medical treatment or prophylaxis. At this point, the importance of non-pharmacological methods emerges. The most important features of these methods are their relatively low cost and minimal complication risk. These methods can be recommended prophylactically to both COVID-19 patients and individuals who are isolated at home due to quarantine conditions. In particular, non-device-dependent education, mobilization, and exercise can come to the fore for this purpose. Before approaching thrombosis with physical medicine and rehabilitation methods, education should be provided on the subject. Explaining the importance of the subject and the benefits to be provided by the recommendations in detail to the individuals will increase their compliance. The critical point for mobilization and exercise is planning in accordance with the individual’s condition. The condition of the individual, exercise history, lung capacity, risk of falling, age, and comorbid diseases should be evaluated by a professional experienced in exercise physiology, and personalized programs should be created. Although it seems like a drawback that mechanical compression methods and neuromuscular electrical stimulation are device-dependent, this problem has been partially overcome with the spread of easy-to-use and portable devices in parallel with technological developments. These methods can also be used safely in appropriate individuals. Education should be part of this process before, during and after COVID-19. Mobility and exercise should be performed before and after COVID-19, taking into account the condition of individuals. Considering the device requirement of mechanical compression and neuromuscular electrical stimulation, it would be beneficial to recommend these methods during and after COVID-19.

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CONFLICTS OF INTERESTS
Both authors have completed the ICMJE Disclosure Form (http://www.icmje.org/disclosure-of-interest/; available on request from the corresponding author). Both authors declare that there are no potential conflicts of interest.

DISCLAIMER
No part of this review is copied or published elsewhere in whole or in part.
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COVID-19 БАЙЛАҢЫСТЫ ТРОМБОЗДАР КЕЗІНДЕ ФИЗИОТЕРАПИЯ ЖӘНЕ БАСҚА ДА ОҢАЛТУ АМБАЛАРЫ

Түйіндеме
Тромбоз бен коронавирустар (COVID-19) корреляциясының растығы тәсілдімдірдің сәйкес келеді. Алдын-ала мақсатында дәрі-дәрежедері қоңыры қарасты, COVID-19 кейін тромбозды алдын алу мүмкін емес. Тромбоз - бұл асересе қарқынды терапия науқастары арасында орын алу мүмкіндігі әскену. Сондай-ақ, қарантин мен үй ғана қаладындағы оқшау-шығу тұтындаған тұындыған тұрмбоздылық ұақыттары болуы мүмкін. Вирхов триадасының классикалық патофизиологиялық механизмерінен бақақ, COVID-19-ға тән қурделі процетер тұмбоз тудуы мүмкін. Бұл шолудың мақсаты физиотерапия және әнді тұлғаларының сипаттау әрекетін қысқақұрып, олар COVID-19-ға қалдыққан науқастарда тұмбозды әлемдегі бойынша медициналық ұсынымдары қосымша мүмкін болуы мүмкін, сондай-ақ өсі әдістердің ерекшеліктері мен әсер ету механизмінің түсіндірісі. Оқу сабақтарынан басталатын әнді тұлғалардың процесі қимылсыздығы азайтуға ықпал етеді. Жеке жаттығу құарламаларының адаимының қалыңдығы, құлақ қауіпін және ілесе ауруларын баяуға сәу есуы құresden және алатын. Бұғынғы мақсаты - физиотерапия мен әнді құрылатын технологиялық құрылымдар арқылы ерекшеленіп, механикалық әсер етеді және жүйкелі-бұштыққа электрлік шығын айтарға әдістері қол жетімді болуы мақсатын жоқ етеді. Солсындырылған түрде теменің құны және ақпараттардың аз қытайлы жүргізілуі физиотерапия мен әнді тұлғаларының тәжірибелерінің мәнін арта құру мақсатын қолдану қажет.

Түйіндемеде
COVID-19, SARS-CoV-2, тұмбоз, алдын алу, физиотерапия, жаттығулар.

ФИЗИОТЕРАПИЯ И ДРУГИЕ РЕАБИЛИТАЦИОННЫЕ ПОДХОДЫ ПРИ ТРОМБОЗАХ, СВЯЗАННЫХ С COVID-19

Резюме
Все большее количество публикаций подтверждает корреляцию тромбоза и коронавируса (COVID-19). Несмотря на профилактическое применение лекарств, тромбоз после COVID-19 нельзя предотвратить. Тромбоз является осложнением, которое трудно избежать, особенно среди пациентов интенсивной терапии. Также возможны случаи тромбоэмболии, вызванной карантином и домашней изоляцией. Помимо классических патофизиологических механизмов триады Вирхова, более сложные процессы, специфичные для COVID-19, также могут вызывать тромбоз. Целью этого обзора было описать методы физиотерапии и реабилитации, которые могут быть дополнением медицинских рекомендаций по лечению тромбоза у пациентов с COVID-19, а также объяснить особенности и механизм действия этих методов. Процесс реабилитации, который начинается с учебных занятий, должен способствовать сокращению неподвижности. Индивидуальные программы упражнений следует предлагать после оценки состояния человека, риска падений и сопутствующих заболеваний. Сегодня разработаны инновационные устройства для физиотерапии и реабилитации, доступны методы механического сжатия и нервно-мышечной электростимуляции. Наиболее важными особенностями физиотерапии и реабилитационных практик являются относительно низкая стоимость и низкая частота осложнений.

Ключевые слова: COVID-19, SARS-CoV-2, тромбоз, профилактика, реабилитация, физиотерапия, упражнения

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