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Research Article

Hypocalcemia and Acute Traumatic Coagulation Disease

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ABSTRACT

Although trauma surgeons have generally improved the treatment of various types of trauma worldwide, trauma remains the second leading cause of human death, accounting for approximately 40% of pre-hospital deaths and 10% of global deaths. Deaths caused by post-traumatic bleeding account for approximately 40% of the total number of traumatic deaths. Trauma has a high mortality rate because it often combines with a serious complication, namely, Acute Traumatic Coagulation (ATC). The pathogenesis of ATC is diverse, and post-traumatic hypocalcemia is often a neglected cause. Therefore, this article primarily reviews the causes of post-traumatic hypocalcemia and the mechanism by which post-traumatic hypocalcemia leads to ATC.

Keywords: Hypocalcemia; Coagulation disorders; Trauma; ATC

INTRODUCTION

With the development of society and transportation, an increasing number of trauma patients have been reported, and the mortality and disability rates remain high. The degree of injury varies greatly, gradually becoming the main cause of human death [1]. Based on incomplete statistics, trauma is the second leading cause of human death, accounting for approximately 40% of pre-hospital deaths and 10% of global deaths; therefore, trauma is known as a "silent epidemic" [2]. Among them, post-traumatic bleeding accounts for about 40% of the total number of traumatic deaths [3]. Under normal circumstances, after active hemostasis, fluid replacement, blood transfusion, and other expansion treatments, bleeding is unlikely to cause death. However, severe bleeding caused by trauma is often accompanied with severe complications such as ATC which makes it difficult to stop bleeding, thereby leading to death.

ATC refers to the rapid activation of coagulation, fibrinolysis, and anticoagulation pathways in the body after severe trauma, leading to acute coagulation dysfunction that occurs rapidly after trauma, manifested as pathological bleeding caused by abnormal coagulation function, progressing rapidly, and ultimately leading to patient's death from massive bleeding. ATC is a common and complex disease that can worsen the prognosis of trauma patients. Its pathological and physiological processes are complex, leading to tissue perfusion, an inflammatory response, and the dynamic imbalance of various coagulation systems. Coagulation disorders are an independent risk factor for death in trauma patients, accounting for approximately 40% of deaths after trauma [3,4]. According to the definition of Brohi, et al., the diagnostic criteria for ATC are that the Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT) of trauma patients increase by one more than five times [5]. The pathological mechanisms of ATC include six aspects, namely, trauma, inflammation, shock, hemodilution, hypothermia, and acidosis [6]. After extensive theoretical and practical proof, Ca^{2+} plays an indispensable role in the coagulation process and varying degrees of role in the abovementioned six aspects [7]. Result showed that the lower the concentration of Ca^{2+}, the longer the APTT [7], which confirms that hypocalcemia has a significant impact on coagulation. Hypocalcemia is an underappreciated complication after severe trauma. In the early stages of severe trauma (within 48 hrs after injury), patients are prone to electrolyte and internal environmental disturbances. Hypocalcemia is a common clinical practice, and its onset and severity are influenced by multiple mechanisms. Moreover, the serum Ca^{2+} level of patients with multiple injuries is significantly and negatively correlated with ISS scores [8,9]. The negative consequences of hypocalcemia have direct or indirect effects on various parts of the traditional fatal triad (acidosis, coagulation dysfunction, and hypothermia). Therefore, Kronstedt S, et al., believed that hypocalcemia should be included in the fatal triad and expanded into a fatal diamond,

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which together increases the mortality rate of trauma patients [10,11]. Considerable research and analysis have demonstrated the correlation between severe post-traumatic hypocalcemia and mortality. The incidence of hypocalcemia in trauma patients is high, so elucidating the causes of traumatic hypocalcemia and its potential mechanisms in inducing ATC is important.

METHODOLOGY

Causes of hypocalcemia after trauma

Hypocalcemia, or low calcium levels in the blood, can occur after trauma due to a variety of mechanisms. Below are some common causes:

Stress and hypocalcemia: Severe trauma is a strong stressor that can lead to the rapid activation of the hypothalamic pituitary adrenal cortex system. Ca^{2+} is crucial for various physiological activities within cells, including nerve conduction and skeletal and smooth muscle contraction. When the body is severely injured, this series of physiological activities becomes more stress induced, leading to a large amount of Ca^{2+} being transferred to cells and a decrease in serum Ca^{2+} levels [12]. Simultaneously, stress can lead to a rapid increase in cortisol levels in the blood circulation, counteracting the effect of Para Thyroid Hormone (PTH), and an increase in cortisol level can inhibit the activity of PTH, which cannot correct hypocalcemia in a timely manner. In addition, an increase in cortisol level can inhibit the reabsorption of Ca^{2+} in the renal tubules, thereby exacerbating hypocalcemia [13,14].

Bleeding and hypocalcemia: Severe multiple injuries, such as visceral parenchymal organ injuries, limb crushing injuries, and pelvic and femoral fractures, often combine with massive bleeding. Most post-traumatic bleeding can be controlled through injury control strategies such as external pressure, radiation embolization, or surgical repair. However, considering severe trauma, patients often have severe coagulation dysfunction, and bleeding cannot be quickly controlled in a short period of time, resulting in excessive loss of Ca^{2+} in the blood [2,9]. In addition, after bleeding occurs in the body, the anticoagulant system will be quickly activated in a short period of time. Ca^{2+}, which is known as coagulation factor IV in the coagulation mechanism, is widely involved in the three major coagulation pathways in the body and is a necessary cofactor for the activation of various coagulation factors. Therefore, serum Ca^{2+} is consumed in large amounts in a short period of time, leading to hypocalcemia [7,15].

Shock and hypocalcemia: As mentioned earlier, trauma often leads to uncontrollable massive bleeding, rapidly developing from local trauma to diffuse bleeding in multiple parts of the body, with a large amount of bleeding and often accompanied with haemorrhagic shock. Trauma can also cause traumatic and septic shock. When the body experiences shock, multiple organs experience reperfusion injury, causing systemic tissue ischemia and hypoxia, indirectly affecting calcium pump function, leading to impaired intracellular and extracellular Ca^{2+} exchange and increased Ca^{2+} influx. Ischemia and hypoxia can cause changes in cell membrane permeability and a decrease in ATP synthesis, leading to insufficient energy supply. Moreover, ischemia and hypoxia can lead to a decrease in calcium pump activity and Ca^{2+} influx, leading to a decrease in blood calcium [1].

Blood transfusion and hypocalcemia: Trauma patients often require a large amount of blood transfusion, which refers to blood transfusions that reach or exceed the patient's own blood volume within 12 hrs (or 24 hrs) or more than half of the patient's total circulating blood volume within 3 hours [16]. However, a large amount of blood transfusion often leads to various adverse reactions, such as hypocalcemia. Hypocalcemia after massive blood transfusions is primarily due to blood products that contain anticoagulant citrate, which can accumulate in the body when too much stored blood is injected. Citrate ions that have not been metabolized by the liver will combine with free Ca^{2+} in the blood to form a "soluble complex", leading to a decrease in blood calcium, which is also known as citrate poisoning [17]. In addition, when the blood transfusion rate exceeds the metabolic rate of citrate in the liver, citrate accumulation occurs, and ischemic hypoxia caused by traumatic shock and hypothermia caused by excessive input of stored blood further reduce the clearance rate of citrate [11,12].

Inflammation and hypocalcemia: Trauma is an important factor leading to an inflammatory response, and inflammatory response and infection are common pathological and physiological processes after trauma [18]. Infection is the main cause of death after 5 days of trauma, and based on statistics, infection accounts for 78% of all late-stage deaths [18]. Based on the research conducted by Qi, et al., [19], and others, the levels of Ca^{2+} in severely infected patients significantly decrease, and a significant positive correlation is found between Ca^{2+} levels and the degree of infection. Under inflammatory conditions, the levels of endotoxins or pro-inflammatory cytokines rapidly increase. These factors are transported to the entire circulatory system during the acute phase of infection, disrupting the integrity of the cell membrane or causing dysfunction of calcium channels (such as calcium pumps or Na^{+}/Ca^{2+} exchangers), leading to the uncontrolled diffusion of Ca^{2+} on the cell membrane. Simultaneously, the process of Ca^{2+} flowing from the blood to the intercellular zone may result from the synergistic effect of endotoxins and cytokines. A number of inflammatory mediators are released into the bloodstream, and Ca^{2+} can bind to corresponding receptors on the cell membrane, producing a second messenger to participate in the regulation of inflammatory reactions, thereby jointly causing a decrease in blood calcium [20]. In addition, inflammation causes stress, leading to the inhibition or resistance of PTH secretion and the redistribution of intracellular and extracellular Ca^{2+}. As Meurer, et al., concluded, the severer the inflammation, the lower the Ca^{2+} concentration [21].

RESULTS AND DISCUSSION

Mechanism of ATC caused by post-traumatic hypocalcemia

The physiological hemostasis mechanism primarily includes three aspects: Vascular contraction, platelet hemostasis thrombus formation, and the formation and maintenance of fibrin clots [22]. In addition, Ca^{2+} plays a key role in vascular tension, platelet function, and endogenous and exogenous pathway-mediated coagulation, and it is widely involved in the three major coagulation processes [23]. Therefore, post-traumatic hypocalcemia mainly causes ATC by affecting physiological hemostasis.

Effect of low calcium level on vascular contraction: The

contraction of blood vessels relies on vascular smooth muscle cells, which are the main components of blood vessels and play an important role in maintaining the appearance and elasticity of blood vessels. The contraction of vascular smooth muscle cells is a physiological process of hemostasis, and the "trigger point" of vascular smooth muscle cell contraction is the formation of a transverse bridge between actin and myosin. The increase in intracellular Ca^{2+} concentration has a significant promoting effect. The contraction of vascular smooth muscle cells is regulated by the phosphorylation state of myosin light chain 20, which is regulated by Myosin Light-Chain Kinase (MLCK) and myosin light-chain phosphatase. Ca^{2+} and Ca^{2+} dependent MLCK activities play a crucial role in the contraction of vascular smooth muscle cells. MLCK can be activated by increasing the concentration of Ca^{2+} and Ca^{2+}/calmodulin complexes in the cells. This method leads to the connection of myosin as well as vasoconstriction (Figure 1) [24,25]. Thus, Ca^{2+} plays an important role in the contraction of vascular smooth muscle cells. When trauma causes a decrease in Ca^{2+} concentration in the blood, the influx of Ca^{2+} decreases, hindering the formation of the transverse bridge between actin and myosin.

The normal contraction function of vascular smooth muscles decreases, leading to coagulation dysfunction, unstoppable bleeding, and ATC.

Effect of low calcium level on platelet function

Low calcium levels, a condition known as hypocalcemia, can significantly impact various physiological processes, including the function of platelets. Platelets, or thrombocytes, are small blood cells essential for normal blood clotting.

Effect of low calcium level on platelet activation: When the vascular endothelium is damaged, platelets quickly adhere to the collagen active site under the endothelium through membrane adhesion receptors, leading to platelet activation. This process is regulated by the von Willebrand factor and GP Ib-IX-V complex. Ca^{2+} provides energy for activated platelets by activating ATPase, promoting platelet contraction and deformation, while releasing active substances such as ADP and TXA2, or forming thrombin during coagulation, thereby activating platelet membrane glycoprotein IIb/IIIa (GP IIb/IIIa) that binds to fibrinogen, causing increased platelet adhesion, and leading to platelet aggregation and thrombosis in Figure 2 [26].

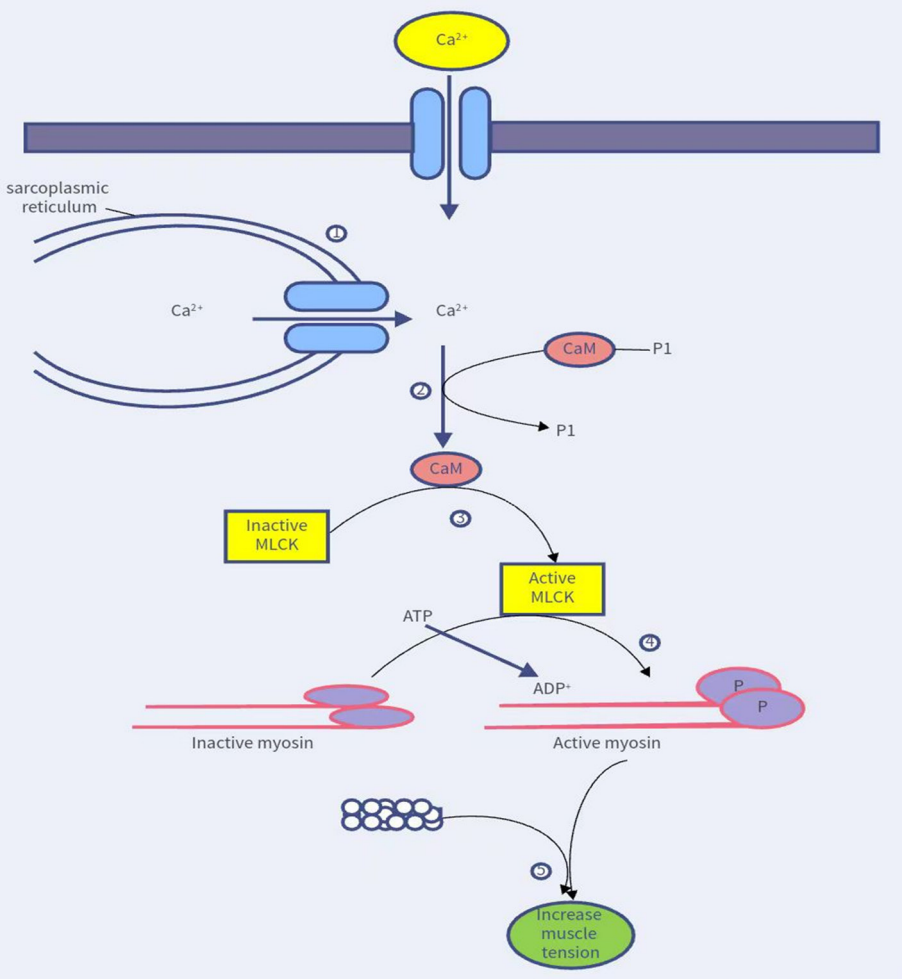

Figure 1: Process of Ca^{2+}-induced vasoconstriction. **Note:** 1) When Ca^{2+} enters cells and is released from the sarcoplasmic reticulum, the intracellular Ca^{2+} concentration increases; 2) Ca^{2+} binding to Calmodulin (CaM); 3) The Ca^{2+}-CaM complex activates Myosin Light-Chain Kinase (MLCK); 4) MLCK phosphorylates the head light chain of myosin and increases myosin ATPase activity; 5) The active myosin transverse bridge slides along the actin, producing muscle tension.

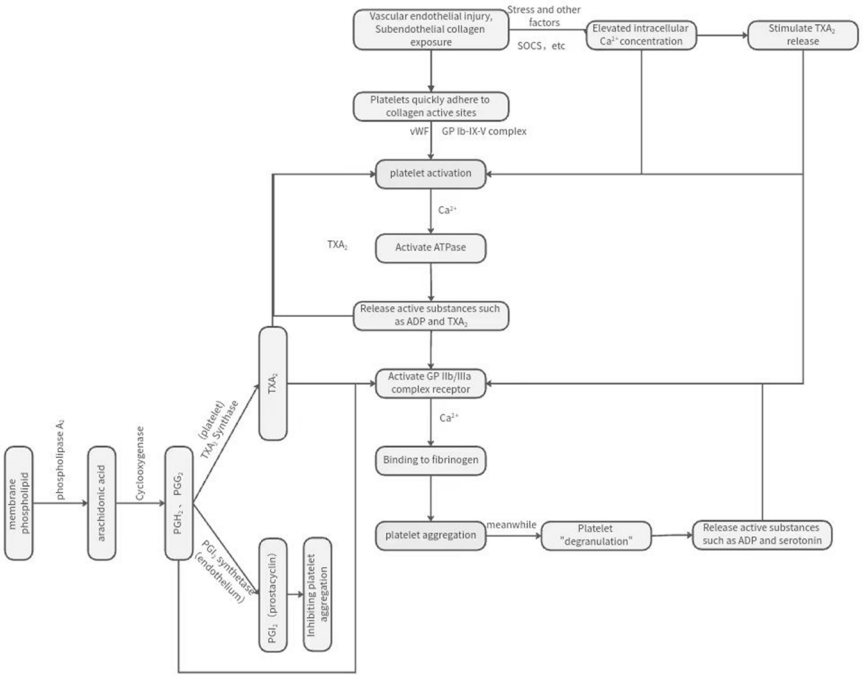

Figure 2: Activation and aggregation of platelets.

Platelet activation is the starting factor for natural hemostasis and thrombosis, and an increase in intracellular Ca^{2+} concentration is a necessary condition for platelet activation, which plays a crucial role at several levels of platelet activation. In addition, the increase in intracellular Ca^{2+} concentration not only leads to platelet activation but also stimulates the release of TXA2, which further stimulates platelet activation, resulting in an increase in intracellular Ca^{2+} concentration. This factor has become the main marker of platelet activation [27,28]. Therefore, when trauma causes hypocalcemia through a series of pathophysiological mechanisms, the amount of Ca^{2+} entering the cytoplasm of platelets decreases, leading to impaired platelet activation and the inability to form blood clots, thereby causing ATC.

Effect of low calcium level on platelet aggregation: Platelet aggregation involves Gp IIb/IIIa on the surface of platelets, Fg, and Ca^{2+} in the blood, all of which are indispensable [29].

When blood vessels are damaged, the subendothelial matrix is exposed, and platelets adhere to the endothelial tissue at the site of the damaged vessels through various adhesion molecules. Once adhesion occurs, the aggregation of platelets also occurs [30]. When platelets begin to aggregate, various active substances such as Prostaglandins G2 and H2 (PGG2 and PGH2), TXA2, and ADP can be produced through "degranulation" and the catalytic action of various enzymes on the platelet plasma membrane.

These active substances are crucial for platelet aggregation, with the most important being ADP, which can activate platelet membrane glycoprotein GP IIb/IIIa and then bind to fibrinogen in the presence of Ca^{2+}, causing platelet aggregation to form platelet emboli [31,32]. Therefore, Ca^{2+} plays a crucial role in platelet aggregation. When the level of serum Ca^{2+} decreases, the platelet membrane glycoprotein GP IIb/IIIa cannot bind to fibrinogen, and platelet aggregation cannot occur, resulting in the formation of stable hemostatic clots at the damaged site, thereby leading to coagulation disorders. Within a certain range, the platelet aggregation rate is positively correlated with Ca^{2+} concentration [29] (Figure 2).

Effect of low calcium level on coagulation pathways

Calcium is an essential ion in the body, playing a crucial role in numerous physiological processes, including blood coagulation.

Role of Ca^{2+}in the endogenous coagulation pathway: The endogenous coagulation pathway indicates that all factors involved in coagulation come from the blood and are activated by contact factors (FXII, prekallikrein, and high-molecular-weight kininogen) that come into contact with the surface of foreign bodies; hence, it is also known as the contact pathway. When the vascular wall is damaged, FXII contacts negatively charged subendothelial collagen fibers, and it is activated as FXIIa, which can activate the formation of the prekallikrein α-kallidinogenase, and α-kallidinogenase itself can activate FXII and establish a positive feedback loop. After contact activation, FXIa activates FXI to FXIa, which then activates FIX and FVIII to form FIXa and FVIIIa. In the presence of Ca^{2+} and a phospholipid surface, FIXa and FVIIIa combine to form a FIXa-FVIIIa-Ca^{2+}-phospholipid surface complex, which activates FX and enters the common coagulation pathway [33]. In addition, Ca^{2+} is an important cation in the body, which can serve as a cofactor for factors V, VII, VIII, IX, X, and XIII, thereby promoting their activation [34]. Therefore, the main role of Ca^{2+} in the endogenous coagulation pathway is to participate in the formation of endogenous coagulation complexes (FIXa-FVIIIa-Ca^{2+}-phospholipid surface complexes) and promote the activation of factors VIII, IX, and X.

Role of Ca^{2+} in the exogenous coagulation pathway: The

initiating factor of the exogenous coagulation pathway is Tissue Factor (TF); hence, the exogenous coagulation pathway is also known as the TF pathway. However, under normal physiological conditions, no TF is found in the plasma. When blood vessels are damaged or endothelial cells are stimulated by factors such as endotoxin, immune complexes, and TNF, TF appears in the plasma. At this time, TF will bind to FVII in the blood with the participation of Ca^{2+} to form the FVII-Ca^{2+}-TF complex. Once FVII binds to TF, it will be quickly activated by FXa, FIXa, thrombin, and FVIIa to form FVIIa with a strong enzymatic activity.

Subsequently, FVIIa-Ca^{2+}-TF complexes (where those activated by FVIIa are referred to as self-activated) are generated. The function of the FVIIa-TF complex is to activate FX and FIX and transform them into activated FXa and FIXa, respectively. This process also requires the participation of Ca^{2+}. The newly generated FXa and FIXa can activate FVII to convert it into FVIIa, thereby forming a positive feedback amplification effect of coagulation activation. Therefore, the main role of Ca^{2+} in the extrinsic coagulation pathway is to participate in the formation of extrinsic coagulation pathway complexes (FVIIa-Ca^{2+}-TF complexes) and promote the activation of factors VII, IX, and X. The activated IX and X can also activate VII, thereby promoting extrinsic coagulation [35,36].

Role of calcium level in the common coagulation pathway: The activation of FX during the formation of fibrin is a common pathway for internal and external coagulation, which includes two stages: Thrombin production and fibrin formation. FX is mainly activated by endogenous coagulation complexes (FIXa-FVIIIa-Ca^{2+}-phospholipid surface complexes) and exogenous coagulation pathway complexes (FVIIa-Ca^{2+}-TF complexes) to form FXa. In addition, Ca^{2+}, as a cofactor of FX, activates FX to a certain extent. The generated FXa will combine with FVa in the presence of Ca^{2+} and the phospholipid surface to form a 1:1 complex, which is known as the prothrombin complex.

This complex activates prothrombin into thrombin, and after thrombin is generated, it cleaves fibrinogen in plasma to convert it into fibrin. In addition, thrombin can activate various coagulation factors such as FV, FVII, FVIII, FXI, and FXIII in plasma [37,38]. With the assistance of FXIIIa, various fibrin monomers are interconnected through covalent bonds to form stable and firm insoluble fibrin, completing the coagulation process [39]. Therefore, the role of Ca^{2+} in the common coagulation pathway is mainly involved in the formation of the prothrombin complex (FXa-FVa-Ca^{2+}-phospholipid surface complex), promoting the activation of FX and FXIII.

As mentioned previously, Ca^{2+} is an important cation in the body, and it plays a fundamental role as a cofactor in enzymatic coagulation reactions. Ca^{2+} participates in the formation of exogenous coagulation pathway complexes (FVIIa-Ca^{2+}-TF complexes), endogenous coagulation pathway complexes (FIXa-FVIIIa-Ca^{2+}-phospholipid surface complexes), and common coagulation pathway complexes (FXa-FVa-Ca^{2+}-phospholipid surface complexes), thereby accelerating coagulation factor activation, initiating the three major coagulation pathways, and promoting the activation of coagulation factors (V, VII, VIII, IX, X and XIII), prothrombin, and fibrinogen to form fibrin, completing the entire coagulation process (Figure 3). Therefore, when various traumatic factors lead to a decrease in blood calcium level, the three major coagulation pathways are affected to varying degrees, which results in varying degrees of prolongation of PT, APTT, and thrombin time, ultimately leading to coagulation dysfunction, namely, ATC.

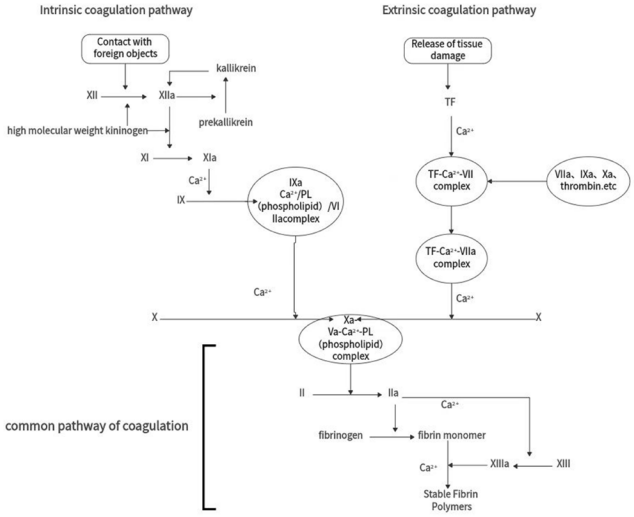

Figure 3: Role of Ca^{2+} in the coagulation pathway.

CONCLUSION

Factors such as stress, bleeding, shock, blood transfusion, and inflammation play an important role in post-traumatic hypocalcemia. Ca^{2+}, as a coagulation factor IV in the blood, is widely involved in platelet activation and aggregation; the formation of endogenous coagulation pathway complexes, exogenous coagulation pathway complexes, and common coagulation pathway complexes; and the normal contraction function of vascular smooth muscles. In addition, Ca^{2+} can serve as a cofactor to promote the activation of various coagulation factors. Therefore, when trauma leads to hypocalcemia, the aforementioned coagulation mechanisms are affected to varying degrees, leading to coagulation dysfunction in the body. In clinical practice, while actively dealing with the primary cause of trauma, actively monitoring changes in serum Ca^{2+} level, identifying and correcting hypocalcemia as soon as possible, preventing ATC caused by hypocalcemia, reducing the mortality rate of trauma patients, and improving the prognosis of trauma patients are necessary.

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AUTHOR CONTRIBUTIONS

JZ conceptualized the review, analyzed the data, and helped write the manuscript. YZ, HL, LT, QW and XW helped to write the manuscript and prepared the figures. All authors read and approved the final manuscript. All authors contributed to the article and approved the submitted version.

DATA AVAILABILITY

Not applicable.

COMPETING INTERESTS

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. All authors read and approved the final manuscript. All authors contributed to the article and approved the submitted version.

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COI STATEMENT

I, Yajun Zou, attest on behalf of all authors, that we had full access to the data of the study, conducted all data analyses independently from the funding entity, and take complete responsibility for the integrity and accuracy of the data reported in the manuscript. Besides, JTACS COI Disclosure forms for all authors have been supplied and are provided as supplemental digital content.

HUMAN AND ANIMAL RIGHTS

This article does not include any primary data from human or animal research as it is a review article.

INFORMED CONSENT

Informed consent for this study there were no participants and thus no informed consent was required.

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