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The Influence of Vitamin K Levels on Blood Coagulation Factors After Tooth Extraction in Hemophilia Patients

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Abstract: *Hemophilia is a genetic disorder resulting from impaired blood clotting. This disorder can be caused by coagulation factor abnormalities due to a deficiency of clotting factors, including vitamin K. A lack of vitamin K disrupts the coagulation process, increasing the tendency for bleeding. This article aims to determine whether there is an influence of vitamin K levels on the blood clotting factors in hemophilia patients. Searching any information needed by analyzing kinds of papers of recent research from the year of 2014 until 2024. Online databases like PubMed, ScienceDirect, Google Scholar, Scopus, and ResearchGate are utilized by inserting relevant keywords, such as hemophilia, blood clotting factors, vitamin K deficiency and extraction. From 10 articles reviewed, a relationship was identified between vitamin K levels and blood clotting factors in hemophilia patients. Individuals with severe hemophilia experience bleeding episodes characterized by delayed onset, as well as bleeding into muscles, joints, and other internal structures, including the brain. Hemophilia is typically diagnosed through the identification of low or absent levels of FVIII:C or FIX:C. The genes encoding FVIII and FIX are located on the long arm of the X chromosome. Hemophilia A and B are the only hereditary clotting disorders inherited in a sex-linked recessive pattern. Vitamin K levels can influence the blood clotting factors in hemophilia patients, particularly those factors synthesized artificially.*

Key Word: *Vitamin, Blood, Tooth.*

1. BACKGROUND

Vitamin K is an essential vitamin in the coagulation process, also known as a blood clotting factor. Its primary function is to prevent excessive bleeding in the body. Vitamin K comprises a group of compounds that collectively synthesize a protein responsible for blood clotting. The most important components of this group are vitamin K1 and vitamin K2. Vitamin K1 can be obtained from green vegetables and certain other vegetables, while vitamin K2 is a group of compounds derived from meat, cheese, eggs, and synthesized bacteria. Foods rich in vitamin K offer several benefits, such as supporting bone and heart health. Additionally, vitamin K is vital for preventing excessive bleeding during injury. A deficiency in vitamin K can increase the risk of osteoporosis and heart disease and may cause conditions such as easy bruising and delayed wound healing (Menegatti, M., & Peyvandi, F., 2019).

Excessive bleeding is the primary symptom of vitamin K deficiency. Individuals with vitamin K avitaminosis may experience bleeding from minor bruises, small blood clots under the nails, bleeding in the mucous membranes lining the internal body, and the passage of dark, tar-like stools due to blood. Signs of vitamin K deficiency in infants include: (1) bleeding at the site of the cut umbilical cord, (2) bleeding from the skin, gastrointestinal tract, and nose, (3) bleeding in other areas of the body, (4) bleeding from the penis if the infant is circumcised

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at birth, and (5) sudden, life-threatening brain hemorrhages. Additionally, some adults are at risk of vitamin K deficiency if they take anticoagulants to thin the blood, consume antibiotics, suffer from conditions that inhibit fat absorption, or follow a diet completely lacking in vitamin K1 and K2 (Darman, A. A. A., & Bahraen, R., 2023).

Certain antibiotics interfere with the body's ability to synthesize vitamin K and reduce the effectiveness of vitamin K1 and K2 within the body. Furthermore, individuals with celiac disease, intestinal and bile duct disorders, or cystic fibrosis may experience fat malabsorption. This condition can disrupt the body's vitamin synthesis process and lead to vitamin K deficiency (Darman, A. A. A., & Bahraen, R., 2023).

Hemophilia is an inherited disease characterized by a blood clotting disorder. The term "hemophilia" derives from the words "hemo," meaning blood, and "philia," meaning affinity, thus referring to a condition prone to bleeding. Fundamentally, hemophilia patients face challenges related to diagnostics, high treatment costs, and psychological issues. These patients not only encounter medical problems but also psychological challenges. Hemophilia is commonly associated with bleeding disorders beneath the skin, such as easy bruising from minor impacts or spontaneous bruises after strenuous activities. Swelling in the joints, such as the knees, ankles, or elbows, is also common. Hemophilia can become life-threatening if bleeding occurs in vital organs, such as the brain (Simanjuntak, P. A. L., 2016).

Hemophilia is not only a medical or biological issue but also has psychosocial impacts. Individuals with hemophilia often face significant challenges in performing daily activities that are typically manageable. Moreover, every individual undergoes developmental stages from infancy, childhood, adolescence, to adulthood. Each stage involves specific developmental processes, and any disruption during these stages can lead to psychological consequences (Simanjuntak, P. A. L., 2016).

Hemophilia occurs due to mutations in the X chromosome gene responsible for producing clotting factors involved in the blood coagulation process. The X chromosome contains several genes that are absent on the Y chromosome. Males have one X chromosome, while females have two. Therefore, if a problem arises in the X chromosome of a male, particularly in the genes regulating factors VIII and IX, hemophilia can develop. Both Hemophilia A and Hemophilia B are X-linked recessive disorders. These two genes, which regulate factors VIII and IX, are located on the X chromosome. The gene for factor VIII is situated near the end of the long arm of the X chromosome and consists of 26 exons, increasing the risk of Hemophilia A. Factor VIII protein is synthesized in endothelial cells and the liver. Genetic disturbances, such as insertions, deletions, or inversions, can lead to low plasma levels

of factor VIII. Factor IX is encoded by the same gene that regulates factor VIII. The synthesis of prothrombin, factor VII, factor X, and protein C relies on vitamin K. In females, a defect in one X chromosome does not result in hemophilia unless both X chromosomes are affected. Females with a defect in only one X chromosome are referred to as hemophilia carriers. These carriers can pass the defective X chromosome to their offspring (Darman, A. A. A., & Raehanul Bahraen, 2023).

There are several known types of hemophilia, first is hemophilia A type of hemophilia is also referred to as classical hemophilia or hemophilia not caused by genetic factors. This condition can occur when the body lacks clotting factor VIII. It is associated with pregnancy, cancer, the use of certain medications, and autoimmune diseases such as lupus. This type of Hemophilia A is rare and can be life-threatening if it occurs. Hemophilia Type B occurs due to a deficiency of clotting factor IX. This disorder is genetically inherited from the mother but can also result from genetic changes or mutations before birth. Female infants are at a higher risk of developing Hemophilia B compared to male infants. Hemophilia C is less common compared to hemophilia A and hemophilia B. This disorder occurs due to a deficiency in the blood clotting factor, namely factor XI. Individuals with hemophilia C are difficult to diagnose due to the very mild and prolonged bleeding (Verona H, Verury. 2020).

The symptoms of hemophilia can be diagnosed based on the results of anamnesis, physical examination, and supporting tests. The anamnesis may reveal symptoms such as easy bruising and unexplained discoloration, swelling and pain in certain joints, a history of hemophilia, and a family history of similar cases, particularly among male relatives. Physical examination may show characteristic findings such as hematoma and/or hemarthrosis, recurrent joint bleeding, atrophy, muscle wasting, joint deformities, and contractures. Severe bleeding cases may present with symptoms such as pallor, hemorrhagic shock, decreased consciousness, and signs of increased intracranial pressure. Hemophilia diagnosis can be confirmed through several supporting tests, including laboratory examinations such as platelet count, bleeding time, prothrombin time, activated partial thromboplastin time, clotting time, assays for factor VIII and IX, and blood clotting factors. Radiological examinations such as X-rays, ultrasound, CT scans, MRI, and musculoskeletal external examinations may also be conducted (Darman, A. A. A., & Raehanul Bahraen, 2023).

2. METHOD

Data was obtained from previous research by searching through databases such as PubMed, ScienceDirect, Google Scholar, Scopus, and ResearchGate, along with other relevant sources. In our journal search, we used several keywords, namely "Hemophilia," "Hemostasis," and "The relationship between vitamin K and hemophilia." Inclusion criteria: (1) Studies published in Indonesian and English; (2) Studies focusing on the impact of vitamin K levels on blood clotting factors in hemophilia patients. Exclusion criteria: (1) Studies with irrelevant titles; (2) Studies not related to the impact of vitamin K levels on blood clotting factors in hemophilia patients.

The articles obtained were then reviewed, including removing duplicates from the two databases used, ensuring consistency in publication years, research topic relevance, and the alignment of research results with this literature review. The final result of this review was 10 articles, which will be used as secondary data in this article.

3. RESULT AND DISCUSSION

Table 1 presents data derived from 10 articles included in the narrative review. These articles demonstrate a correlation between vitamin K levels and blood coagulation factors in patients with hemophilia. The results will be discussed in more detail in the discussion section.

Table 1. The influence of vitamin K levels on blood coagulation factors in hemophilia patients

No.	Author	Method	Parameter	Result
1.	Kumar, M., Kumar, S., Bajpayi, S., & Kumari, R.	Case Report	Patient with vitamin K deficiency	There are numerous factors responsible for their susceptibility to vitamin K deficiency, including limited placental transfer, reduced liver stores, poor intestinal colonization, and breast milk deficiency. This report challenges the absolute efficacy of vitamin K prophylaxis in preventing classical vitamin K deficiency bleeding (VKDB) and highlights massive pulmonary hemorrhage as one of the presentations of classical VKDB. Further

				research is needed before the role of vitamin K during pregnancy can be validated for its effectiveness in VKDB prevention. This case further emphasizes the importance of a detailed evaluation of the coagulation profile, including PIVKA-II levels, before considering blood product transfusion or additional vitamin K administration to establish a definitive diagnosis, especially in cases with overlapping clinical presentations.
2.	de Koning, M. L. Y., Fischer, K., de Laat, B., Huisman, A., Ninivaggi,M., & Schutgens, R. E. G. (2017)	Comparative study	Compare trombin formation on patient with hemophilia A and patient with vitamin K antagonist	Patients with severe hemophilia have a hemostatic potential comparable to those with therapeutic INR levels. Meanwhile, one-third of patients with non-severe hemophilia exhibit significantly better hemostatic potential than patients on vitamin K antagonists (VKA) with therapeutic INR levels. These findings may indicate that anticoagulant therapy should be considered for the majority of patients with non-severe hemophilia and atrial fibrillation, where endogenous thrombin potential (ETP) could serve as a guide in the future.
3.	Shen, G., Gao, M., Cao, Q., & Li, W. (2022)	Literature review	Molecular basis of FIX deficiency in hemophilia B.	Vitamin K levels may contribute to the heterogeneity of bleeding tendencies in patients carrying mutations in the

				signal peptide and propeptide regions. Based on this, it can be proposed that oral administration of vitamin K may reduce the severity of bleeding tendencies. Although current studies primarily focus on the clinical applications of prophylaxis and gene therapy [3,99,100], greater efforts should be directed toward uncovering the molecular mechanisms of FIX deficiency, which could lead to str
4.	Menegatti, M., & Peyvandi, F. (2019)	Literature review	Management of Rare Factor Deficiencies Beyond Hemophilia	Deficiencies of fibrinogen, prothrombin, factor V (FV), FVII, FVIII, FIX, FX, FXI, and FXIII, collectively referred to as rare coagulation disorders (RCDs), can result in coagulopathies leading to spontaneous bleeding or bleeding following trauma or surgery. Unlike hemophilia A and B and von Willebrand disease, RCDs are significantly rarer, with an incidence ranging from 1 in 500,000 to 1 in 2 million in the general population. Recent advancements in novel hemostatic approaches for hemophilia, such as the use of non-replacement therapies like RNA interference, anti-tissue factor pathway inhibitors, and gene therapy aimed at improving patients' quality of life, may also

				play a pivotal role in the future treatment of patients with RCDs.
5.	Motlagh, H., Pezeshkpoor, B., & Dorgalaleh, A. (2018)	Systemic review		FIX is a single-chain, vitamin K-dependent glycoprotein containing 17% carbohydrate and is produced by hepatocytes in the liver. The plasma half-life of FIX is approximately 18 hours, with an average plasma concentration of 2.5–5 μg/mL. The most common genetic abnormality in patients with hemophilia B, occurring with a frequency of 64%, is point mutations. Overall, mutations are categorized into two main groups: type I mutations, which cause quantitative deficiencies of FIX, and type II mutations, which manifest as functional defects [1,10]. In rare cases, hemophilia B can be an acquired condition resulting from the development of antibodies against FIX [16].
6.	Darman, A. A., & Bahraen, R. (2023)	Simple randomized sampling type	Blood sample test	Hemophilia is a genetic disorder caused by abnormalities in blood clotting. This hereditary coagulation disorder is X-linked and results from a deficiency of clotting factor VIII or IX. There are two known forms of hemophilia: hemophilia A and hemophilia B. Hemophilia A is caused by a deficiency of factor VIII, while hemophilia B

				is caused by a deficiency of factor IX.
7.	Connie H Miller (2021)	Literature review	Clinical Genetics of Hemophilia B (Factor IX Deficiency)	Hemophilia B (HB) is a bleeding disorder caused by a deficiency or defect in coagulation factor IX (FIX), inherited in an X-linked manner. It results from one of over 1,000 known pathogenic variants in the FIX gene, with missense mutations and frameshift changes being predominant. Although HB primarily affects males, heterozygous females may experience excessive bleeding due to random or skewed X-chromosome inactivation. The development of antibodies against FIX replacement products (inhibitors) is rare and is associated with the type of causative variant present. Treatment involves products generated through recombinant DNA technology, with gene therapy currently being explored in clinical trials.
8.	Camire R. M. (2021)	Literature review	Factor X deficiency in blood clotting	Coagulation factor X/Xa occupies a critical position in the coagulation cascade and plays a role in each of the three main pathways (intrinsic, extrinsic, and common). Due to its central role, it serves as an attractive therapeutic target for enhancing or modulating thrombin generation. In hemophilia, strategies to increase FXa production

				(e.g., recombinant FVIIa or activated prothrombin complex concentrates, aPCC) have proven highly effective in patients with neutralizing antibodies against FVIII or FIX [41].
9.	Carcao, M. D. (2012)	Simple randomized samping type	Patients with bleeding disorders	Hemophilia is caused by a deficiency of factor VIII (FVIII) (hemophilia A) or factor IX (FIX) (hemophilia B). As both are X-linked disorders, the most affected individuals are males. Those with the most severe form of hemophilia (classified as severe) have less than 1% of the normal levels of FVIII or FIX. Such individuals experience spontaneous and recurrent bleeding without apparent trauma. Individuals with moderate or mild hemophilia have FVIII:C or FIX:C levels of 1–5% and 6–40%, respectively. These individuals are less likely to experience spontaneous bleeding but will bleed in response to trauma, surgery, or dental procedures.
10.	Zimmerman, B.; Valentino, L. A. (2013)	Literature review	Patients diagnosed with hemophilia A and B	Hemophilia A (factor VIII [FVIII] deficiency) and hemophilia B (factor IX [FIX] deficiency) are the most common severe congenital coagulation factor deficiencies. Hemophilia is an X-linked genetic disorder. Both conditions result in a similar bleeding diathesis, characterized by hemarthrosis. (Based on strong evidence). The

				optimal treatment involves recombinant factor replacement to prevent bleeding; however, this therapy faces several challenges. (Based on evidence). The most serious complication of treatment is the development of inhibitors to factor products. (Based on strong evidence). The management of patients with hemophilia is best conducted in a comprehensive care setting.

4. DISCUSSION

Hemophilia is currently the most common hereditary blood clotting disorder worldwide, primarily resulting from an X-linked recessive genetic transmission. There are two types of hemophilia: hemophilia A and hemophilia B (A Darman, A. A. A., & Bahraen, R., 2023). Hemophilia is caused by a deficiency of factor VIII (FVIII) (hemophilia A) or factor IX (FIX) (hemophilia B). Since both are X-linked disorders, the most affected individuals are males (Carcao, M. D., 2012).

Individuals with severe hemophilia experience “hemophilia-like” bleeding, primarily characterized by delayed bleeding following challenges and bleeding into muscles, joints, and other internal structures such as the brain. This bleeding pattern differs from the mucosal bleeding typically seen in von Willebrand disease (VWD) and platelet function disorders but resembles the bleeding seen in other severe coagulation factor deficiencies. Hemophilia is typically diagnosed by identifying significantly reduced or absent levels of FVIII:C or FIX:C. For all individuals with hemophilia, it is essential to determine the baseline factor levels to classify the condition as severe, moderate, or mild (Carcao, M. D., 2012).

The genes encoding FVIII and FIX are located on the long arm of the X chromosome. Hemophilia A and B are the only hereditary bleeding disorders inherited in an X-linked recessive pattern. All daughters of a father with hemophilia will be carriers, while none of his sons will be affected. Additionally, sons of a carrier mother have a 50% chance of inheriting the disorder, while daughters have a 50% chance of being carriers. Although all types of bleeding can occur in hemophilia, three critical areas of life require special attention. The first

is intracranial bleeding, which is the leading cause of death in hemophilia patients. While intracranial bleeding can occur spontaneously, it typically follows minor trauma (Zimmerman, B. & Valentino, L. A., 2013).

In cases where the coagulation profile does not strongly indicate hemophilia B, it may still be suspected if a healthy infant without known risk factors for sepsis presents with severe bleeding manifestations. Although hemophilia is predominantly inherited, approximately 30% of cases result from spontaneous mutations. Since factor VIII levels reach normal adult levels by 20 weeks of gestation, hemophilia A can only be diagnosed at birth. However, factor IX levels are only 15% of adult levels at birth, and therefore, only severe hemophilia B can be diagnosed at birth. It is thus recommended that factor IX levels be reassessed at 6 and 9 months of age in all newborns suspected of having hemophilia B (Kumar, M., Kumar, S., Bajpayi, S., & Kumari, R., 2020).

FIX belongs to the group of vitamin K-dependent glycoproteins, synthesized in the liver. Before being secreted into the bloodstream, it undergoes several intracellular processes, including cleavage and removal of the signal peptide and propeptide sequences, γ-carboxylation of several glutamic acid residues in the Gla domain, partial β-hydroxylation, N-linked glycosylation, O-linked glycosylation, sulfation, and phosphorylation. The post-translational modifications (PTMs) of FIX are diverse and heterogeneous, and the precise functions of most PTMs remain unclear. Given the various ways F9 mutations lead to hemophilia B, understanding the functional structure of FIX subdomains provides significant insights into this hereditary disorder (Shen, G., Gao, M., Cao, Q., & Li, W., 2022).

Prophylactic measures can be implemented to prevent excessive bleeding.. Prophylaxis refers to the regular administration of treatment to patients with bleeding disorders to prevent bleeding episodes and ensure both short-term and long-term health. Prophylaxis has become the standard of care for children with severe hemophilia and is gradually becoming the standard for adults with severe hemophilia. Unfortunately, due to cost constraints, prophylaxis is only accessible in the most affluent countries (Carcao, M. D., 2012). Other treatments, such as adjunctive therapies, including antifibrinolytic drugs and hormonal treatments, are typically considered for less severe mucosal bleeding or heavy menstrual bleeding. These treatments can be crucial, as they reduce the amount of clotting factor concentrates required, especially in situations where such concentrates are limited or unavailable (Menegatti, M., & Peyvandi, F., 2019).

5. CONCLUSION

Hemophilia patients have a genetic disorder that results in a deficiency of specific blood clotting factors. The most commonly affected clotting factors in hemophilia are factor VIII (hemophilia A) and factor IX (hemophilia B). Vitamin K plays a critical role in the synthesis of several clotting factors, including factors II, VII, IX, and X. In this context, vitamin K levels can influence the clotting factors of hemophilia patients, particularly synthetic clotting factors. Replacement therapy with clotting factors is the standard treatment for hemophilia. However, it is essential to note that hemophilia patients require carefully regulated and coordinated replacement therapy under the supervision of a hematologist or hemophilia specialist

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