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Factor XII deficiency in asymptomatic Saudi population: A retrospective cohort study

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ABSTRACT

Factor XII (FXII) deficiency is a rare genetic blood disorder. It can lead to a higher risk of developing deep vein thrombosis or acquired thrombotic disorders than the general population. This retrospective study evaluated patients who opted for surgery and were found to have abnormal clotting profiles and clotting factors on preoperative routine blood. Patients were included regardless of whether they were symptomatic or asymptomatic. The cohort comprised 115 patients with a mean FXII level of 128.04 ± 36.93 %. Two (1.79%) patients, both of whom were women, had FXII levels <60%. The mean FXII level was 58 ± 1.41 (range, 57–59%) in this group. The present study shows the prevalence of FXII in the asymptomatic Saudi population. The results provide the normal range for FXII. The findings of our study provide the basis for diagnosing *F XII* deficiency in the asymptomatic Saudi population.

1. Introduction

Factor XII (FXII) absence, or Hageman trait, is a rare inborn syndrome that is not related with bleeding and has wide deviations in FXII activity (FXII: C) among healthy people (Maruyama et al., 2019). Patients having FXII deficiency, both heterozygous or homozygous, have reduced dependent contact activation of their endogenous fibrinolytic system in vivo (Levi and Cohn, 2019). Factor XI (FXI) has a significant role in coagulation pathways, as well as activation of Factor X, Factor VIII and Factor V, in a Factor IX-independent pathway (Amiral and Seghatchian, 2019; Puy et al., 2016). Human coagulation (FXII) is a serine protease precursor, mainly synthesized by the liver (Zhang et al., 2019). Its deficiency is an rare autosomal recessive trait associated with the prolongation of partial thromboplastin time (PTT), without increased risk of bleeding though the thrombophilic tendency (venous thromboembolism and myocardial infarction) (Elsiesy et al., 2019).

Although FXII is important for appropriate coagulation and FXII deficiency is a risk factor for the development of thromboembolism (Halbmayer et al., 1993; Wu et al., 2018). Fibrin formation is critical for hemostasis and may lead to vascular thrombosis. Plasma prekallikrein (pKal), along with coagulation FXII and high-molecular-weight kininogen, form the kallikrein-kinin system, also known as plasma contact system (Wang et al., 2019). Concomitant FXII deficiency is remarkably occasional and may cause susceptibility of the patient to chronic thromboembolic pulmonary hypertension (Bishop et al., 2019; Govers-Riemslag et al., 2019). Recently, several studies have observed relations between recurrent pregnancy loss and FXII deficiency. The results showed that plasminogen and coagulation FXII were significantly expressed during the development of TCM syndrome from liver-gallbladder dampness-heat syndrome to liver-kidney yin-deficiency syndrome (Lu et al., 2019). The contact activation system is initiated upon binding of FXII to negatively charged surfaces such as artificial chemicals like kaolin or ellagic acid, or of natural origin, such as polyphosphates, 2 collagen, 3 and nucleic acids (Visser et al.,

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2020). Moreover, eventual identification of causal factor lacks or even "inhibitors" may (e.g., FVIII or FIX deficiencies or inhibitors) or may not (e.g., FXII deficiency) be clinically important (Favaloro, 2020). FXII is significant in originating stimulation of inherent coagulation pathway (Chaudhry et al., 2019).

FXII deficiency is commonly asymptomatic, and thus, it is detected accidentally through preoperative blood tests. In FXII deficiency, the PTT (i.e., the time for the blood to clot) is abnormally prolonged (Renne and Gailani, 2007; Girolami et al., 2004; Fernandes et al., 2018). Further, serum prothrombin time (PT) is also unusually long. The level of FXII in blood tends to vary greatly. Some studies reported that FXII deficiency may be a risk factor for thrombi formation at an early age. Particularly, individuals with former deficiency may have a greater risk for developing deep vein thrombosis or acquire thrombotic disorders than the general population. FXII deficiency is also associated with recurrent miscarriages and primary recurrent abortion. Also, women with secondary recurrent abortion tended to have FXII deficiency (Braulke et al., 1993; Yamada et al., 2000; Matsuura et al., 2001; Lee and Silver, 2000; Pauer, 2003). FXII may also, directly or indirectly, upregulate various mediators involved in inflammation response (Jansen et al., 1996; Juhn et al., 2008). However, despite the clinical impact of FXII deficiency, its exact incidence in the general population remains unknown. Although it is reported to occur in approximately 1 per 1 million population (Colman, 2003). This study is designed to assess the incidence of FXII deficiency in patients undergoing surgery.

2. Material and methods

This retrospective study enrolled patients who were undergoing surgery and were accidentally diagnosed with abnormal clotting profile and clotting factors on preoperative routine blood tests. These patients' profiles were obtained from King Saud University Medical City, Riyadh, KSA from January 2017 to January 2018. All patients were asymptomatic, and their coagulation screening test, PT, and activated PTT were estimated. Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were expressed as number (percentage). $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS for Windows 21.0 (IBM Corp., Armonk, NY).

3. Results

The cohort comprised 115 patients with a mean FXII level of 128.04 ± 36.93% (as shown in Table 1, see Fig. 1). There were 2 (1.79%) patients who had FXII levels < 60%, and both were women. Particularly, their mean FXII level was 58 ± 1.41 (range, 57–59%). The remaining 113 (98%) patients had FXII levels ≥60% (mean, 129.28 ± 36.04). In total, 87 (75.6%) patients (23 men and 59 women) had FXII within the normal range of 60–150. These patients had a mean FXII value of 112.8 ± 17.8. In particular, 10 (8.69%) patients, 46 (40%), 31 (26.9%), and 26 (22.6%) patients had a mean FXII level of 79.8 ± 8.49 (range, 60–90), 108.7 ± 9.02 (range, 91–120), 129.5 ± 9.45 (range, 121–150), and 184.38 ± 20.04, respectively (as shown in Tables 2 and 3, see Fig. 2).

Table 1
Factor XII in Asymptomatic Saudi Population.

Factor XII Range	Number (%) of Patients.
ALL	115 (100%)
<60	2 (1.79%)
60–90	10 (8.69%)
91–120	46 (40%)
121–150	31 (26.9%)
>150	26 (22.6%)

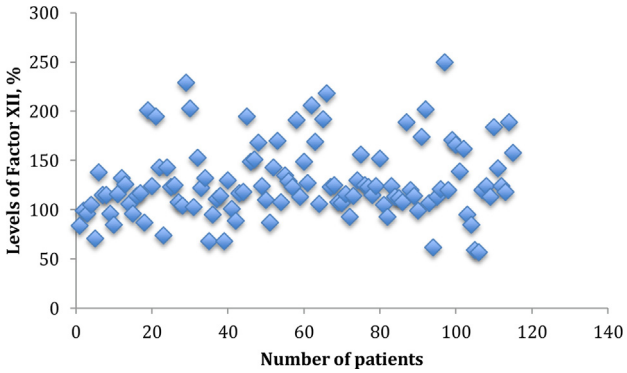

Fig. 1. Factor XII levels among Saudi population.

Table 2
Factor XII Mean Levels in Subgroups.

Factor XII Range	MEAN ± SD
ALL	128.04 ± 36.93
<60	58 ± 1.414
60–90	79.8 ± 8.49
91–120	108.7 ± 9.02
121–150	129.5 ± 9.45
>150	184.38 ± 20.04

Table 3
Normal and abnormal levels of Factor XII in Asymptomatic Saudi Population.

Factor XII Range	Number (%) of Patients	Mean ± SD
Deficient <60	2 (1.79%)	58 ± 1.414
Normal 60–150	87 (75.6%)	112.8 ± 17.8
Above normal >150	26 (22.6%)	184.38 ± 20.04

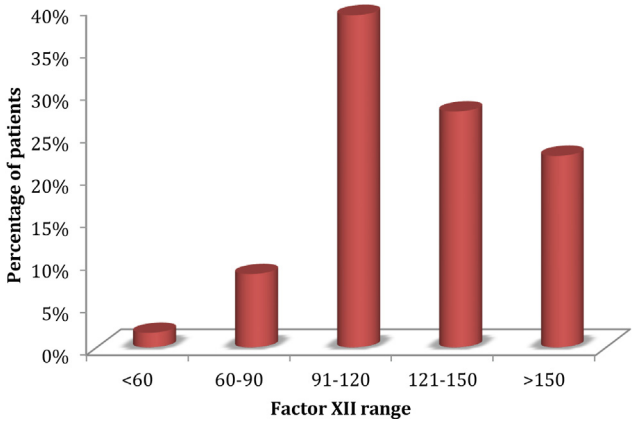

Fig. 2. Range of Factor XII levels in patients.

4. Discussion

The rate of FXII deficiency occurrence in the common asymptomatic population is still unknown. Studies have shown its prevalence to be 1 in per million population (Colman, 2003).

There are no data on the occurrence of FXII deficiency within the asymptomatic Saudi population. However, our result of the current study shows that this population has silent FXII deficiency. Meanwhile, FXII deficiency is prevalent in approximately 1.5–3.0%

of the normal population (Halbmayer et al., 1994). In a study with patients taking anticoagulants in Austria, 15% had FXII deficiency. Also, family history of thrombosis could be established in 67% of these patients (Halbmayer et al., 1992).

A study from Korea reported FXII deficiency in 9/226 patients undergoing surgery who were otherwise asymptomatic (Kang et al., 2016). Similarly, a previous report by Al-Fawaz et al. reported FXII deficiency in 1.2% of the cohort (Al-Fawaz et al., 1996). Asymptomatic prolongation of PTT is most commonly reported in FXII deficiency (Al-Harbi et al., 2017), but it may also present as other hemorrhagic manifestations (Halbmayer et al., 1992). Patients with congenital FXII deficiency do not bleed (Ji, 2016); particularly, FXII deficiency does not cause any abnormal bleeding even after trauma or surgery. Further, in vivo and in vitro studies showed the importance of FXII in inflammatory responses. The combination of proinflammatory and procoagulant reactions causes various disorders affecting the cardiovascular system.

Dysregulated hemostatic activity is believed to contribute to the development of thrombotic diseases such as pulmonary embolism, myocardial infarction, and stroke. However, only a few studies have systematically compared the incidence or severity of thromboembolic events between normal individuals and those with severe FXII deficiency. FXII and FXI have emerged as promising targets, whose inhibition has the potential to prevent thrombosis with minimal impact on hemostasis. However, despite the advantages of FXII inhibition, it should also be noted that FXII has been linked to inflammatory disorders like multiple sclerosis, rheumatoid arthritis, and colitis (Göbel et al., 2018).

5. Conclusion

The present study comprehensively determined the normal range of FXII activities in an asymptomatic Saudi population. FXII deficiency was identified in 2 (1.79%) patients. Our results suggest the normal range of FXII that can be helpful in diagnosing FXII deficiency among asymptomatic patients. FXII deficiency should be evaluated in patients undergoing surgery to avoid abnormal clotting in the postoperative period. The public awareness program converging on its initial diagnosis, treatment, and genetic counseling amongst Saudis should be initiated.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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