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Review

Mapping of Favism and G6PD Disease in Iran: A Mini Review

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Abstract

Hemolytic illness an interaction with Vicia fava, also referred to as fava beans, results in favism. This contact can happen in a few different ways: eating raw, cooked, or dried beans; walking through fields where V. fava is grown and possibly breathing in pollen; and introducing fava beans to a breastfed baby through their mother's milk. In populations, the illness is common. For example, it's typical to walk through fields that have been planted with fava in the northern Iranian provinces of Mazandaran and Guilan. This is a problem in areas where thalassemia is common since patients there frequently need blood transfusions. Although favism has a considerable economic impact, there is a limited number of particular statistics on this matter. This paper explores the implications of recent findings on favism and G6PD for the future.

1. INTRODUCTION

An illness called favism peaks every year in the northern areas of Iran with the arrival of local broad beans in stores and shops as spring approaches. When fava or broad beans are consumed a hemolytic reaction known as favism occurs, it's interesting to note that simply walking past broad bean fields may cause illness in some individuals. The link between genetics and favism is well-established. Favism is an inherited disorder that affects individuals who lack the enzyme G6PD (glucose-6-phosphate dehydrogenase). Because this deficit is X-linked, men are more likely to have it. However, inadequate lionization or unbalanced X inactivation may also harm females with G6PD deficiency. In such cases, a woman with an X chromosomal mutation may see a reduction of almost half of her red blood cells. Because of the variability of this assumption, people are nearly as vulnerable as males (1-3). Consuming fava beans or fava bean products can cause a severe hemolytic reaction known as favism, which is characterized by the disintegration of red blood cells. Symptoms such as weariness, paleness, jaundice, and dark urine may appear six to twenty-four hours after consuming a meal containing fava beans.

It is important to remember that while favism is common in infants and children with G6PD deficiency, not everyone with G6PD deficiency develops it. Although the exact chemical relationship between G6PD deficiency and favism is unclear, G6PD genetic variants have been shown to influence drug sensitivity. Besides showing how G6PD deficiency commonly, a mapping study of favism in Iran aims to understand dietary habits and genetic factors , which contribute to such of favism in different parts of the country This mapping can help health policy makers develop

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strategies to reduce the burden of favism in society, especially on vulnerable children, by providing genetic counseling, increasing awareness, and prevention strategies a will be implemented.

2. PATHOPHYSIOLOGY OF FAVISM

The pathophysiology of favism involves a series of events following the consumption of fava beans or products containing fava beans by individuals deficient in glucose-6-phosphate dehydrogenase (G6PD). Although the incidence of hemolytic crises in G6PD-deficient individuals after ingestion of fava beans has decreased, favism is still a unique natural model for researching oxidative damage to red blood cells (RBCs) in vivo.

During a favism-induced hemolytic crisis, several changes occur in erythrocytes, including biochemical, rheological, and morphological alterations. We can observe these changes in erythrocytes isolated at different stages of the crisis. Divicine, a redox compound included in fava beans, can cause alterations in G6PD-deficient erythrocytes that are comparable to those seen during favism. This implies that the pathophysiology of favism is influenced by the poisonous compounds found in fava beans (4). It is hypothesized that extravascular (phagocytic) hemolysis—that is, the removal of injured erythrocytes from the bloodstream by macrophages—is the mechanism of action of the poisonous compounds found in fava beans. It's still unclear exactly what signal should be used in favism to identify and remove damaged RBCs. Nonetheless, complement C3 fragments and anti-band 3 antibodies placed on the injured RBCs might act as a non-self-recognition signal for monocytes and macrophages, leading to their elimination (4). Although the precise mechanisms of favism are not entirely known, ingestion of fava beans—which include potentially dangerous chemicals including vicine and convicine—and a deficit in glucose-6-phosphate dehydrogenase (G6PD) are important initiators of a hemolytic crisis. Vicine and convincing, two β-glucosides present in fava beans, can exacerbate favism in individuals with G6PD deficiency, leading to anemia due to red blood cell breakdown (5). First and foremost, the release of isouramil and divicine when the beans are eaten raw is mostly caused by the glucosidases in the beans. On the other hand, when the beans are cooked, the glucosidases are largely inactivated (6). The main reason why eating raw beans instead of cooked ones usually induces favism is probably due to the breakdown of glucosides caused by cooking and roasting, as well as the thermolability of the aglycones (7,8). We have provided a graphical abstract summarizing the pathophysiology of G6PD deficiency in **Figure 1.**

3. EPIDEMIOLOGY G6PD

G6PD deficiency is the most common human enzyme deficiency, affecting approximately 400 million people worldwide. This deficiency is particularly common in individuals of African, Asian and Mediterranean descent. Prevalence in Africa varies from region to region, ranging from 15 to 26%. Notably, the overall prevalence in Ethiopia was 3.6% based on biosensor testing, which is lower than the 7.3% reported in Gambella. The prevalence in Nigeria is 15.3% and is higher in males (24.1%) compared to females (6.6%), (9,10). The World Health Organization (WHO) estimates that 7.5% of the world population carry G6PD deficiency and 2.9% are diagnosed with G6PD deficiency.

The severity of this deficiency varies widely among racial groups. It's interesting to note that G6PD deficiency reflects the historical distribution of malaria and offers some protection against the disease. For example, it was shown that 3.2% of blood donors in Cameroon lacked G6PD (11). The polymorphic gene's mutations produce enzymatic variants with varying levels of activity leading to a range of clinical presentations of the abnormality. G6PD variations have been divided into four classes by the WHO according to their biochemical and clinical traits (**Table 1**) (12-14).

Table 1. Classification of G6PD variants

Class	G6PD Activity	Hemolysis
A	<20%	Chronic
B	<45%	Acute, triggered
C	60–150%	No hemolysis
D	Any	Uncertain clinical significance

There has been a lot of literature reporting on the association between the eating of dry or frozen fava beans (Vicia faba) and the pathological consequence of favism that follows (15). Because of their high protein content, fava beans are a great source of minerals, vitamins, and a variety of other bioactive substances, making them extremely nutritious (16).

4. RELATIONSHIP BETWEEN MALARIA, G6PD AND FAVISM

The association between malaria, favism, and G6PD deficiency is complex and multifaceted. G6PD deficiency, the most common enzyme deficiency, affects more than 400 million people worldwide. Increased protection against severe and potentially fatal malaria, especially the highly

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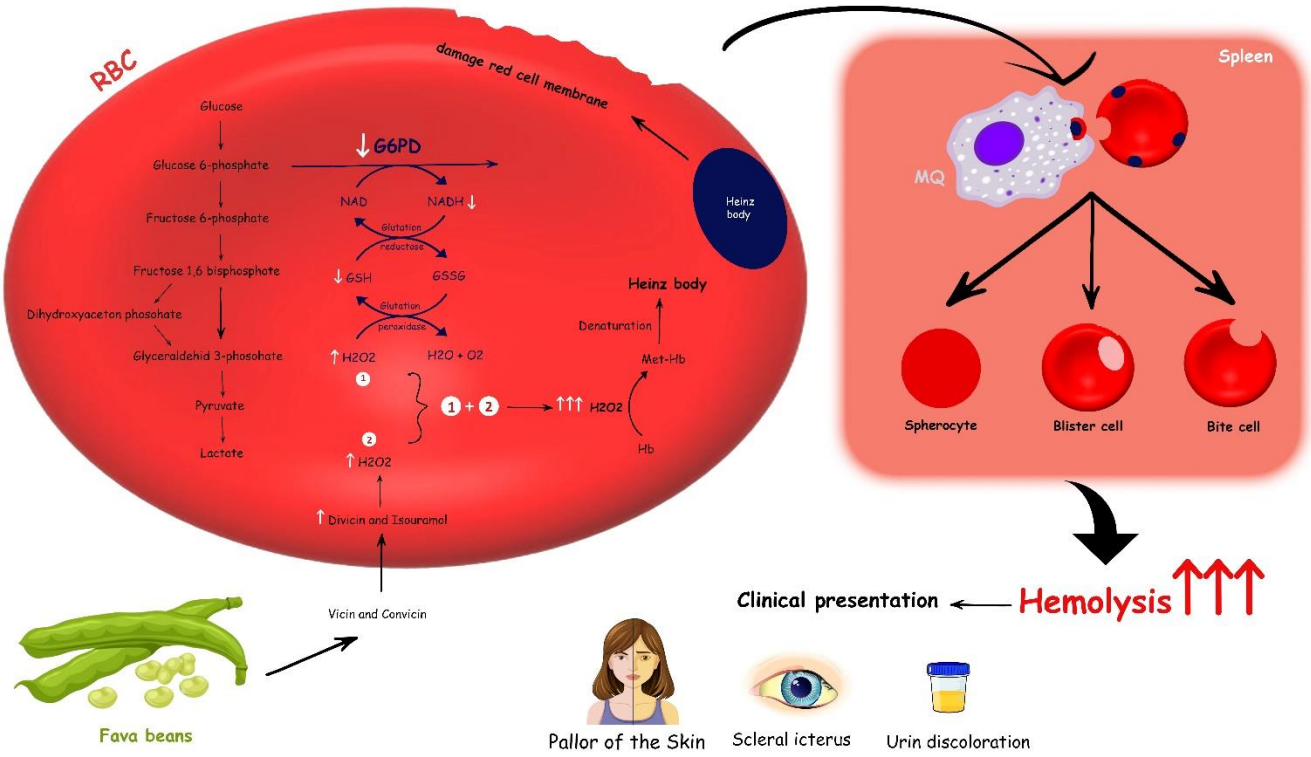

Figure 1. Pathophysiology of favism.

lethal infection caused by Plasmodium falciparum, is associated with this inadequacy. A possible explanation for this protective effect is that the spleen eliminates G6PD-deficient cells more quickly, giving an evolutionary advantage in malaria-endemic locations (17). According to a different explanation, a G6PD deficit causes resistance because the host has larger concentrations of oxidants that are harmful to the Plasmodium parasite. It is possible to think of the association between favism and G6PD deficiency as a synergy between the two disorders, providing more protection against malaria than G6PD deficiency alone (17-21).

5. INCIDENCE OF FAVISM IN IRAN

Iran has acknowledged favism over the previous seven decades. Fava beans are frequently used in a variety of Iranian cuisines, including the well-known stew from the north known as Baghali Ghatogh. Fava beans are combined with garlic, eggs, and aromatic dill in this recipe. It is usually eaten on bread or over rice together with pickled garlic and smoked fish. Additionally, faba beans are frequently used in various Iranian recipes, such as the well-liked snack Baghali Pokhte. This recipe calls for cooked fava beans that have been seasoned with angelica powder, vinegar, and salt (22). In Iran, fava beans, especially when dried, are widely consumed. Nonetheless, the Caspian Sea region has a higher prevalence of favism. Favism is a potentially deadly condition that primarily affects young people (23). Favism is an allergic response to pollen inhaled from the blooms of the fava plant or consumption of the plant's beans, pods, and sometimes leaves. Eating fava beans or simply breathing in pollen from its blooms might cause hemolytic anemia in those with favism (24-26).

The prevalence of G6PD deficiency varies across different regions, with significant sex and age differences observed. Undersnding the regional distribution and demographics of G6PD deficiency is crucial for developing effective strategies to prevent and manage favism in Iran. Iran has a high frequency of G6PD deficiency; estimates place the global number of individuals affected by this disorder at 400 million. The World Health Organization (WHO) estimates that 2.9% of the population worldwide has been diagnosed with G6PD deficiency compared to 7.5% of the population worldwide carry the deficiency (27, 28). Increased protection against severe and potentially fatal malaria, especially the

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highly lethal infection caused by Plasmodium falciparum is associated with this deficiency (29) The most common abnormal form in the Mediterranean is Among Middle Eastern peoples, including Iran, is the G6PD Mediterranean form (class II type with significant enzyme deficiency <10 of percent of normal) (30). These changes are associated with severe anemia; Anemia and reticulocytosis are usually absent, and hemolysis usually does not occur in the absence of oxidant stress.

In the northern Iranian provinces of Mazandaran and Guilan, the peak incidence of favism usually happens in May and three weeks later, respectively. According to data from 1965, there were 234 cases of favism in Mazandaran, translating to a particular incidence rate of 3.1 cases per 10,000 people. By contrast, Guilan recorded 75 cases in the same year. Comparably, in 1968, Guilan had 40 cases, or 1.5 cases per 10,000 people, compared to 105 cases in Mazandaran, or 2.6 cases per 10,000 people. The seasonal distribution of favism in Guilan indicates a clear correlation between cases and fresh fava bean availability. The majority of instances happen three to four weeks after the local broad bean harvest in May (31). The ratio of male to female patients was 2:1, most of whom were villagers. Seventy percent of the patients were younger than five years old. In comparison to Babolsar, favism was found to manifest one week earlier in Gorgan (32). Another study found that patients exhibiting favism symptoms frequently had G6PD deficiency. This study was carried out in Jiroft city, which is situated in southern Iran. 6.7% of patients had G6PD insufficiency, with 84.7% exhibiting severe deficiency and 15.3% displaying partial deficiency, according to the study. Remarkably, the study discovered a significant gender disparity in Jiroft City, with 3.4% of females and 9.3% of males displaying G6PD deficiency (33). Compared to other regions of Iran, Tehran was shown to have a comparatively lower prevalence of G6PD deficiency in infants. 3.6% of men and 1.8% of women were found to have G6PD deficiency in a study. Compared to Tehran, the provinces in the north and southeast of Iran have greater rates of G6PD deficiency, ranging from 8.6% to 16.4%. For example, the incidence was 19.3% in the country's southeast and 12% in Shiraz, in southern Iran (34). Nonetheless, it is important to note that G6PD insufficiency is common in several Eastern Mediterranean nations, including Iraq, which borders eastern Iran. It has been found that the G6PD deficit prevalence among the Kurdish people in Iraq is approximately 10.9%. The G6PD Mediterranean and Chatham variants are responsible for the bulk of cases. Similarly, the G6PD Mediterranean and Chatham variants are the most prevalent forms of G6PD deficiency in eastern Iran, especially among the region's predominately Kurdish population. According to a study carried out in Northern Iraq, which borders eastern Iran, the G6PD Mediterranean and Chatham variations were responsible for the bulk of G6PD defective variants among Kurdish Iraqis. According to the study, 8.7% of G6PD deficient males had the G6PD Chatham variant and 87.8% of G6PD deficient males had the G6PD Mediterranean variant. These are the cases from neighboring countries such as Iran and Turkey, as well as other Mediterranean nations, suggesting that these major variants are common in the region (30). A different study in Bam, Iran, reported a prevalence of G6PD deficiency of 9.09% in infants, and more frequently in males (65.4%), most of the affected patients belonged to the O+ blood group (35).

6. MANAGEMENT OF FAVISM

The primary goal of favism management is prevention. Those who lack G6PD should stay away from certain medications, foods, and substances that can result in hemolysis. Depending on the person's G6PD variation and the severity of their enzyme impairment, these substances may represent different risks (9). The following factors must be considered in dealing with favism:

1. Dietary Guidelines: Individuals with G6PD deficiency should avoid foods such as fava beans that can cause bleeding. By checking food labels for potential triggers and eating a balanced diet as recommended by a dietitian or experienced health care provider, a healthy diet can be maintained while avoiding substances if it motivates him.
2. There are some medications that should be avoided, including aspirin, quinolones, sulfones, primaquine, and chloroquine.
3. Chemical products, such as colorants, detergents, and industrial chemicals, should be avoided by those who are G6PD deficiency.

Wearing gloves and protective clothes are two appropriate preventative measures that can help reduce the risk of exposure. If hemolysis happens, it needs to be treated properly. Hemolysis-related anemia typically recovers on its own in eight to fourteen days. Seldom are transfusions required, and splenectomy is typically unsuccessful. However, phototherapy or exchange transfusions may be necessary for neonates with severe hemolytic anemia brought on either favism or neonatal jaundice. Short-term treatment with folic acid and vitamin E, either separately or combined, has been shown to significantly improve the rise in hemoglobin and hematocrit in cases of acute hemolysis caused by G6PD deficiency.

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Furthermore, it has been demonstrated that using these supplements together will improve blood indices even more. To assess how early usage of these supplements affects the requirement for blood transfusions, more research is necessary (36). It has been demonstrated that in patients with G6PD deficiency, normal saline prevents heme-induced nephropathy just as well as alkalinizing fluids. Thus, it makes sense to give this easily accessible and underutilized kind of fluid therapy more thought than alternative approaches to treatment for these patients (37). Usually, these individuals need blood transfusions, which might be difficult in a community where thalassemia is already common. The problem gets more difficult as the demand for blood and blood products rises. The blood transfusion organization has a major issue due to the co-occurrence of favism and thalassemia. The company finds it difficult to deliver enough blood and related products to meet demand (38, 39). Treating rare diseases such as favism can indeed be highly costly. Direct medical costs include the price of prescription medications, hospital stays, surgeries, and doctor visits. These costs could be associated with favism since acute hemolytic crises require immediate medical attention and may necessitate hospital stays, blood transfusions, and other forms of supportive care. Indirect costs include things like the cost of transportation to and from medical facilities, lost productivity due to illness or disability, and the need for special diets or other lifestyle modifications. These expenses can add up for those who have favism, particularly if the disorder causes severe anemia that necessitates time away from job or education. The cost of changing the family's diet or way of life to prevent a crisis from happening, or the need for caregivers to take time off work to care for a loved one during one, may also fall on the family. It is obvious that these costs could be high even though precise data regarding the financial impact of favism is unavailable. Government officials, researchers, and medical professionals must not stop analysing the financial effects of favism and devising plans to lower expenses and enhance the lives of those affected, according to recent scholarly research in the field. There are various approaches to address this, such as raising the percentage of early identification, offering therapy that is both efficient and economical, and facilitating better patient and family access to care and support (40–42).

7. CONCLUSION

Avoiding stimulants such as fava bean, some drugs, and chemical are part of managing favism. Consulting with experts and healthcare professionals is important for assessment and personal care. Because not everyone with G6PD deficiency has Favism, but everyone with favism lacks G6PD, Favism and G6PD deficiency are intricately related. It is yet unknown how precisely favism and G6PD deficiency interact chemically. Favism has traditionally been associated with many cultural practices and beliefs and has been socially and culturally accepted. Resistance to malaria, especially Plasmodium falciparum, is associated with favism and G6PD deficiency. This protection is believed to occur from either the elimination or killing of parasite-infected cells or from an increased tolerance to oxidative stress brought on by elevated levels of host oxidants. However, in those with G6PD deficiency, consuming fava beans raises the risk of hemolytic anemia. This highlights how crucial it is to diagnose G6PD deficiency before to administering antimalarial medication.

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Conflict of interest

The authors declare that they have no competing interests.

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