REVIEW ARTICLE

Vitamin K and Glucose-6-phosphate Dehydrogenase Deficiency: A Perspective

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Abstract

The use of vitamin K in a patient with suspected or proven glucose-6-phosphate dehydrogenase (G6PD) deficiency is a controversial topic with divided opinions even among the subject experts. We thus aim to summarize the available literature and provide the personal viewpoint of the authors on this aspect.

Keywords: Glucose-6-phosphate dehydrogenase deficiency, Review, Vitamin K.

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Vitamin K

Vitamin K acts as a cofactor for enzymes that activate vitamin-K-dependent proteins involved in important physiological functions involving regulation of blood coagulation, prevention of vascular calcification, bone metabolism and modulation of cells.[1,2] It is a fat-soluble vitamin characterized by the presence of a 2-methyl-1, 4-naphthoquinone ring (Fig. 1).[3]

Vitamin K_1 (phylloquinone or phytonadione or phytomenadione) and K2 (menaquinone) are two naturally occurring forms. Vitamin K_1 contains a phytyl side chain at the C3 position. It is available in India in both injectables (1 mg/0.5 mL and 10 mg/1 mL vials) and oral formulations (10 mg tablets).

Vitamin K_2 (menaquinone-MK) containspolyprenyl side chain at the C3 position. It has several isoforms depending on the length of the side chain, which ranges from 4 to 13. It is denoted as MK-*n* (*n* is the number of unsaturated β-isoprenoid units in the chain).[4] Menaquinone-4 (MK-4) is the most active isoform and provides protection from osteoporosis to pathologic calcification. Mammals including humans can themselves synthesize some amount of MK-4 from Vitamin K_1. Vitamin K_2 is also produced in the gastrointestinal tract by the resident bacterial flora, but their bioavailability is low.[5–7]

Vitamins K_1 and K_2 have different tissue distribution and bioavailability. Vitamin K_1 and MK-4 were present in the plasma for 8–24 hours after administration. Bioavailability is also dependent on vitamin K sources.[8] The amount of absorbed Vitamin K_1 from vegetable products is lower than the equivalent dose given as a supplement.[9]

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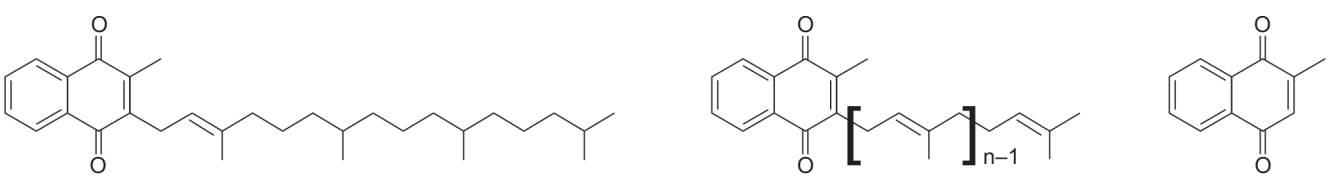
Vitamin K also includes a few synthetic forms. Vitamin K_3 (menadione) is a synthetic form of vitamin K having no substituent at the C3 position. It acts as a provitamin and is water soluble. Due to the high risk of allergic reactions and toxicity like neonatal brain damage secondary to free radical generation, it is not recommended for human use. It is also used as a feed additive for animals.[10] Despite being banned by the Food and Drug Administration in the United States, the pharmaceutical formulation of vitamin K_3 (an injection) for human use is still available in some countries including India.[11] Vitamin K_4 and K_5 are also synthetic and possess anticancer properties.



Vitamin K1 (phylloquinone) | Vitamin K2 (menaquinone) | Vitamin K3 (menadione)

Fig. 1: Chemical structure of different forms of vitamin K; from Bus K, Szterk A. Relationship between structure and biological activity of various vitamin K forms. Foods 2021;10(12):3136

Natural Sources

Plant sources such as green leafy vegetables (spinach, broccoli, and cabbage) and vegetable oils (olive, rapeseed, soybean oil, and margarine) mainly contain phylloquinone (Vitamin K_1). Dairy and poultry products are the main sources of menaquinone (vitamin K_2) in the form of MK-4. Fermented products such as cheese, curd etc. have a high content of long-chain menaquinones as longer isoprenoid chains (MK-6, MK-7, and MK-9) are produced by bacteria. Antibiotics decrease the production of vitamin K_2 by interfering with normal gut flora.[12]

G6PD Deficiency

The enzyme glucose-6-phosphate dehydrogenase (G6PD) is present in all cells of the body. It has a pivotal role in the body's antioxidative defence. G6PD is required for the generation of nicotinamide adenine dinucleotide phosphate (NADPH), which maintains glutathione in the reduced form, to counteract the oxidant stresses on the erythrocyte. It catalyzes the first step in the hexose monophosphate pathway and is responsible for the reduction of NADP to NADPH. NADPH itself acts as a hydrogen ion donor, reverting in the process to NADP. These hydrogen ions contribute to the stability of catalase (an important antioxidant) converting oxidized glutathione to its reduced form. The latter neutralizes oxidants by itself becoming oxidized. The newly formed NADP must once again be converted to NADPH in order for the process to continue.[13] The primary effects of G6PD deficiency are hematological because the erythrocytes have no alternative source of NADPH.

The G6PD deficiency is inherited as an X-linked Mendelian pattern.[14] According to a recent meta-analysis overall magnitude of the frequency of G6PD deficiency is 8.5% in the Indian population.[15]

Hemolytic anemia and methemoglobinemia are known complications in patients with G6PD deficiency. It can be triggered by various oxidative stressors like drugs, food and metabolic state. Jaundice in G6PD-deficient individuals is an interplay between the G6PD-deficient state, environmental factors and genes encoding bilirubin conjugation (Fig. 2). Environmental triggering a G6PD-deficient individual initiates hemolytic process producing sufficient amounts of bilirubin in an auto-cascade pattern to overwhelm the liver's conjugative capacity.[16] Trigger factor-induced acute hemolysis following definite triggers like fava beans and primaquine are beyond doubt.[17,18] Out of the 73 children with a G6PD deficient state who presented with severe hemolytic anemia in Mayotte, France (2013–2020), there was no case where any drugs (vitamin K or others) were found as triggers while ingestion of fava bean ingestion was found in only one child.[19]

Newborns and G6PD Deficiency

Hyperbilirubinemia resulting from G6PD deficiency is well documented in the newborn period. Concerns have been raised regarding the role of vitamin K as one of the possible drugs triggering hemolysis in G6PD deficient infants by decreasing glutathione concentrations in normal infant erythrocytes.[20] Studies based on hematological markers of hemolysis have confirmed higher rates of hemolysis secondary to trigger factors in neonates with G6PD deficiency than in G6PD normal neonates. It is usually mild to moderate in relation to the degree of hyperbilirubinemia and is not commonly associated with anemia.[21,22] Three publications provided limited evidence of harm with the use of vitamin K in G6PD deficient subjects.[23–25] Of the 30 G6PD deficient neonates, only four treated with vitamin K and two with no treatment became jaundiced in a randomized controlled trial to receive vitamin K or no treatment.[24]

However, few reports of massive acute hemolysis, severe anemia, and hyperbilirubinemia require plasma exchange as rescue therapy in the newborn period in both term and preterm newborns who received four Vitamin K_1. Causal association with Vitamin K_1 administration could be established in none, as the episodes of severe hemolysis did not occur until 5–11 days after the Vitamin K_1 dose.[23] Hyperbilirubinemia in neonates with G6PD deficiency is postulated to be secondary to the interplay of reduced hepatic

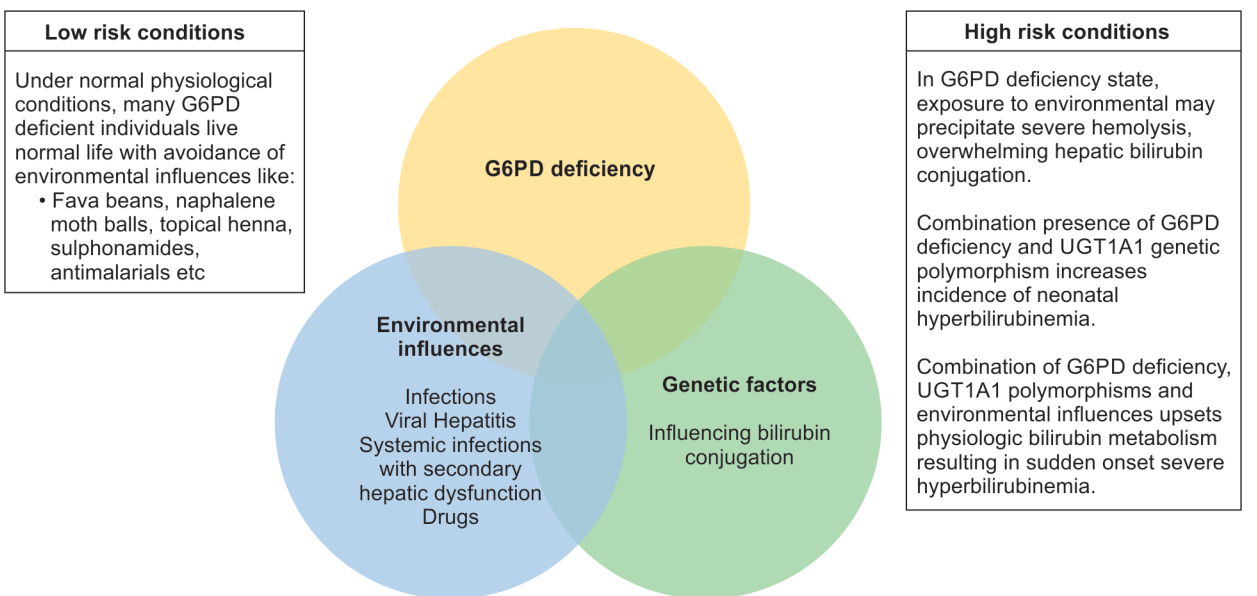


Fig. 2: Interplay of various factors in the pathogenesis of hyperbilirubinemia in G6PD deficient subjects; adapted from Kaplan (2010). G6PD deficiency and severe neonatal hyperbilirubinemia: a complexity of interactions between genes and environment. Seminars in fetal and neonatal medicine, 148–156

conjugation and excretion of bilirubin.[14,26–28] rather than only increased bilirubin production resulting from hemolysis.[28]

Many G6PD deficient newborns, following discharge as a healthy newborn or after resolution of neonatal hyperbilirubinemia requiring birth hospitalization phototherapy, develop a sudden and exponential increase in serum bilirubin to neurotoxic concentrations requiring readmission. The majority of these cases have identifiable triggers.[16] Extreme neonatal hyperbilirubinemia following discontinuation of phototherapy in G6PD-deficient newborns is often in a continuum with or an exacerbation of the earlier, more moderate process and the two entities are closely interrelated. It can be explained by the resumption of the rate of bilirubin rise similar to that before phototherapy was initiated.[29]

Infections and G6PD Deficiency

Intravascular hemolysis at presentation is encountered in 1.5–4% of children with acute viral hepatitis in children,[30,31] though the etiology of hemolysis was not well described in these studies. Underlying G6PD deficiency is often said to be unmasked during such episodes where there is the usual practice of administering vitamin K. There were initial reports of intravascular hemolysis in G6PD deficient patients precipitated by vitamin K.[32] However follow-up studies show that only one-third (36%) of those with intravascular hemolysis during acute viral hepatitis are confirmed to be G6PD deficient and another 7% show direct Coomb's test positivity.[33] Even with acute concomitant hemolysis, fat-soluble vitamin K (phytonadione) is a safe alternative in such patients with acute viral hepatitis (AVH).[20]

The degree of hyperbilirubinemia in AVH has been shown to be more pronounced with the erythrocyte defect conditions. In a study of 125 cases of viral hepatitis, 16 subjects with a G6PD deficient state, five with β-thalassemia trait and remaining 104 non-G6PD deficient were included. Hemolysis was observed in 23% (24 of 104) of the nondeficient subjects, 87% (14 of 16) of those with G6PD deficiency, and 80% (four of five) of the β-thalassemia heterozygotes. Moderate and severe hemolysis occurred only in 37% (six of 18) children with G6PD deficiency and in 60% (three of five) with thalassemia trait. Hemolysis was only mild in nondeficient patients. Literature witnessed various reports of hemolysis occurring in children with the Mediterranean variant and Negros with G6PD deficiency, during the course of both acute and chronic viral hepatitis.[34,35] G6PD deficiency or thalassemia trait potentially modifies the clinical course of viral hepatitis by favoring the induction of hemolysis and hyperbilirubinemia.[36] Recently, a case of acute hepatitis B infection precipitated severe hemolysis and renal failure in an undiagnosed G6PD deficient patient and treatment with entecavir caused marked improvement.[37] Early recognition and diagnosis of complicated hepatitis B infection leading to severe hemolysis and renal failure allowed prompt treatment with antiviral drugs along with supportive treatment for G6PD deficiency.

Both acute and chronic phases of hepatitis E infection show extrahepatic manifestations like anemia, including aplastic anemia, autoimmune/nonimmune hemolytic anemia, neurological complications, arthritis, pancreatitis, glomerulonephritis, cryoglobulinemia of hepatitis E virus (HEV)—induced anemia, including aplastic anemia and autoimmune hemolytic anemia.[36,38–40] More supportive evidence in the context of viral hepatitis-triggered G6PD deficiency comes from recent studies analyzing hepatitis E-induced hemolytic anemia where significantly reduced glutathione in the red blood cells (RBCs) in G6PD deficient state with an accumulation of oxidants due to hepatic dysfunction.[41,42] Inverse correlation (inverse) between the sudden decrease in hemoglobin and hepatitis E viral RNA load suggests that HEV-RNA levels may be associated with the occurrence of haemolytic anemia in G6PD deficient patients.[41]

Prospective studies in children suffering from chronic hepatitis B with and without G6PD deficiency have shown abnormally low levels of glutathione in the course of the disease, reverting to normal after recovery.[43,44] Partially oxidative metabolites are released in infectious hepatitis which decreases glutathione in erythrocytes. In the G6PD deficient state, there is preexisting decreased capacity of deficient erythrocytes to reduce the oxidized glutathione. Further lowering of glutathione in hepatitis results in RBC destruction due to impaired integrity of G6PD deficient RBCs.Following infection with the hepatitis virus, patients with G6PD deficiency and lower than normal glutathione and NADPH levels present with massive haemolytic anemia.[45] If this assumption is true, hemolysis should be proportional to the extent of hepatocytic injury—the severe the injury, the higher the release of oxidative metabolites, though the interplay of genetic, and etiologic environmental factors like intake of complementary and alternate drugs impacts the clinical course. By this assumption, hemolysis in a G6PD deficient state with hepatitis is attributed more to oxidative products, secondary to hepatocyte injury rather than to vitamin K administration. Some report decreased osmotic fragility during the initial phase of viral hepatitis, though its exact mechanism is yet to be elucidated. Macrocytes and target cells may contribute to the lowering of osmotic fragility.[46]

The association of the other infections with G6PD deficiency is also reported in the literature. Case report of dengue fever complicated with acute hemolysis, methemoglobinemia, hepatitis, and rhabdomyolysis in G6PD deficient state adds support to oxidative stress being the trigger rather than vitamin K.[47] Though is no direct association between G6PD deficiency and dengue severity or viral replication through altered redox state of dengue virus 2 infected monocytes from G6PD-deficient individuals appears to augment viral replication in these cells.[48] Also, dengue virus 2 infected G6PD-deficient individuals may contain higher viral titers, which may be significant in enhanced virus transmission along with granulocyte dysfunction.[49]

There have been four anecdotal case reports of the first episode of G6PD deficiency-associated hemolysis and methemoglobinemia after acquiring COVID-19 infection, with no recent exposure to oxidative drugs, vitamin K or fava beans.[50,51] There have been reports of G6PD deficiency-related hemolysis being triggered by bacterial infections (mainly pneumonia) and viral upper respiratory tract infections without administration of vitamin K.[52]

Thus, all cases of anemia in a child with viral hepatitis and other infections should always be carefully evaluated for the suspected underlying hemolytic state.

Author's Viewpoint

- Mild to moderate degree of hemolysis is a known complication of acute viral hepatitis (A, B, or E). Severe hemolysis may be encountered more frequently in patients with coexisting G6PD deficiency. We postulate that viral infection itself can provoke severe hemolysis in enzyme-deficient patients. G6PD deficient state with concomitant hepatocytic injury produces additional oxidative stress which triggers intravascular hemolysis. There is very little evidence that vitamin K is the real culprit alone.

- There is no actual scientific evidence to prove that vitamin K actually causes hemolysis in G6PD deficient patients as an independent factor. This is corroborated by the scarce reports of proven acute hemolysis after vitamin K injection in newborns despite the known overall high frequency of G6PD deficiency in the general population, along with almost universal administration of injectable vitamin K in this population. Authors do not themselves check G6PD levels before giving vitamin K injections in their own institute, even in patients with jaundice and have never actually encountered acute hemolysis secondary to vitamin K use in their clinical practice.

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