Iranian J Publ Health, Vol. 37, No.4, 2008, pp.1-18

Review Article

Glucose-6-phosphate dehydrogenase (G6PD) Deficiency

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(Received 28 Apr 2008; accepted 3 Dec 2008)

Abstract

Glucose-6-phosphate dehydrogenase (G6PD) Deficiency is the most prevalent enzymopathy in mankind. It has sex-linked inheritance. This enzyme exists in all cells. G6PD deficiency increases the sensitivity of red blood cells to oxidative damage. G6PD deficiency was discovered in 1950 when some people suffered hemolytic anemia as a result of taking antimalarial drugs (primaquin). Most people with G6PD deficiency do not have any symptoms, till they are exposed to certain medications, *Fava beans* and infections; and then their red blood cells are hemolyzed. The degree of hemolysis changes according to the degree of enzyme deficiency and the oxidant agent exposure. G6PD deficiency has many different variants and Mediterranean variant is the most common mutation in the world. G6PD deficiency is considered a health problem worldwide, especially in Asia, Middle East and Mediterranean countries. In this article, we have reviewed the importance and function of G6PD enzyme, incidence rate of G6PD deficiency in the world and Iran, genetic and variants of this enzyme, clinical manifestation, diagnosis and treatment of the enzyme deficiency.

Keywords: G6PD, Oxidative damage, Sex-linked inheritance, Hemolytic anemia, Mediterranean variant

Introduction

Glucose-6-phosphatase dehydrogenase (G-6-PD) deficiency is the most common enzymopathy in humans (1). G6PD deficiency was discovered for the first time when hemolytic anemia occurred in some persons who consumed anti-malarial drug named primaquine (1, 2). It is an X-linked disorder and is a highly polymorphic enzyme. This enzymopathy affects 400 million people worldwide (3). The enzyme gene is located on the long arm of the X- chromosome (Xq28) (1).

G6PD catalyzes the first step of pentose phosphate pathway, during this reaction NADPH is produced and protects red blood cells from oxidative damage (4-6).

Most deficient people do not show any symptoms until following exposure to oxidative drugs, some infections and ingestion of *Fava bean* (1). Mediterranean mutation is the most common variant of enzyme deficiency and often associated with favism (2, 3).

Avoiding of the oxidative agents that induces hemolytic anemia is the most important treatment in the enzyme deficiency. Neonatal screening and health education can reduce the incidence rate of G6PD deficiency clinical manifestations (1).

The goal of this article is to review the importance of G6PD enzyme in antioxidant defense enzyme system, function of the enzyme, prevalence of G6PD deficiency in the worldwide, structure and different mutations of this enzyme, The major clinical manifestations like acute hemolytic anemia induced by oxidative drugs and some infections, neonatal jaundice and chronic non-spherocytic hemolytic anemia, diagnosis and treatment of the enzyme deficiency.

Importance of G6PD Enzyme

Super oxide, hydrogen peroxide, hydroxyl radical is called ROS (Reactive Oxygen Species). They cause oxidative stress and damage cell's Membranes (7, 8).

Increased production of ROS or decreased antioxidant defense enzymes play a major role in oxidative injuries in different organs, tissues and cells including brain, heart, vascular cells (8) and causes brain diseases like Alzheimer and Parkin-

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son diseases and also considered to contribute to the aging process (9-11).

Enzymes like superoxide dismutases, catalase, glutathione peroxidases, glutathione reductase and glucose-6-phosphate dehydrogenase are antioxidant defense enzymes. In body defense anti-oxidant system, G6PD is considered as an essential modulator enzyme that has a very important role in all cells especially in red blood cells (8).

To know the crucial role of G6PD, at first the role of other anti-oxidant enzymes must be understood. Superoxide dismutase converts two super oxide radicals into one hydrogen peroxide and one oxygen (8). Catalase converts hydrogen peroxide into water and oxygen (8, 12). Glutathione peroxidase is necessary for reducing hydrogen peroxide and lipid peroxides to water and lipid alcohols (8). Glutathione reductase: main role of this enzyme is regenerating reduced glutathione (GSH) from oxidized form (GSSG) (8, 12). G6PD is a key enzyme for maintenance of redox potential in cells. G6PD produces NADPH in pentose phosphate pathway. NADPH is important as a central reductant and regulates of redox potential (13). It also acts as a cofactor for other anti-oxidant enzymes like glutathione reductase (8, 12).

Reduced glutathione is required as a cofactor for the glutathione peroxidases and, thus reduced glutathione and glutathione cycles is crucial for neutralization of hydrogen peroxide and lipid peroxides and also protects protein sulfhydryl groups against oxidation (2).

Catalase is found in two forms, active and inactive, NADPH is critical for conversion of inactive form into active form (2).

Different studies point out the importance of G6PD enzyme in other cell functions like its control of cell death. G6PD is a principal enzyme in cell death and intracellular redox potential needs to be regulated to control cell death (13). As the production of ROS increases, so does cell death.

In another study, role of anti-oxidant enzyme and oxidative stress in Parkinson disease was surveyed. One hundred and fifteen patients with Parkinson and 37 healthy people were selected. In these samples, activities of superoxide dismutase, Catalase, Glutathione peroxidase and G6PD in red blood cells were measured. They showed that activities of this enzyme in patients were significantly lower than normal person. These findings demonstrated that oxidative stress is the main cause of the start and progress of neurodegenerative in the patients and can also be related with intensity of the disease (14).

Function of G6PD

G6PD catalyzes the first step in the pentose phosphate pathway, converts Glucose-6-phosphate into 6-phosphogluconolactone and during this conversion, the important reductant metabolite named NADPH is provided. The pathway is the only source for producing of NADPH in red blood cells (2), because they lack mithochondria, nucleus and ribosomes and other pathways that produce NADPH(4). NADPH is necessary for generating of GSH from its oxidized form, GSSG, and subsequent maintenance of intracellular GSH pools. GSH maintains normal structure, elasticity and integrity of red blood cells, and sustain hemoglobin in ferrous state that is essential for carrying oxygen (4). G6PD and NADPH are key factors for protection of red blood cells from oxidative damage and peroxides (2). Peroxides are usually removed from red blood cells by glutathione peroxidase that uses reduced glutathione. Reduced glutathione reacts with harmful peroxides and neutralize them. In this reaction reduced glutathione is oxidized and glutathione reductase regenerates reduced glutathione by using of NADPH. NADPH is oxidized and G6PD is required for producing reduced NADPH again (1, 2).

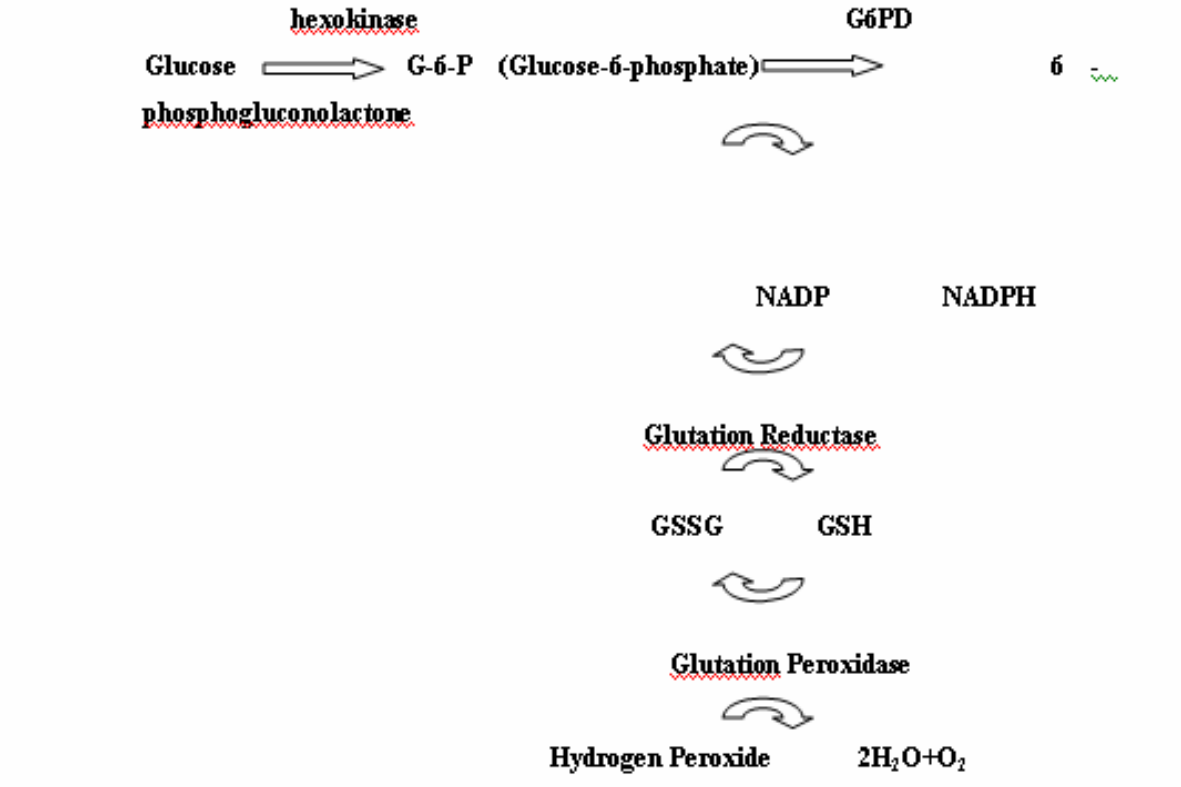

Fig. 1: Function of G6PD (5)

Catalase is another anti-oxidant enzyme that is abundant in red blood cells and helps to the removal of peroxides from red blood cells through activation by NADPH (2). Unless peroxides are neutralized, they will cause oxidative injuries. Hemoglobin and red blood cell membrane molecules that contain SH groups are destroyed (1, 2).

Hemoglobin is denatured irreversibly, precipitates and forms Heinz bodies. Heinz bodies destroy membranes of red blood cells then leads to haemolysis and acute anemia.

Regarding to the roles of NADPH in redox state of cells, G6PD is the principal enzyme in chain reaction that is necessary for protecting all cells especially red blood cells against oxidant agents (2). Then G6PD-deficient cells especially red blood cells are susceptible to damage by reactive oxygen species and oxidative stress (2).

Malaria and G6PD deficiency

The geographical distribution of malaria is similar to the world distribution of deficient G6PD variants. It is postulated that the high frequency of G6PD deficiency has arisen because G6PD deficient variants confer some resistance against severe malaria caused by *Plasmodium falciparum* (4, 15, 16). The exact mechanism of this protection is still unknown. Red blood cells are the host cells for Plasmodium falciparum. *Plasmodium* parasites oxidize NADPH and diminish the level of reduced glutathione (GSH) in red blood cells. This effect in G6PD deficiency is more severe, leading to oxidative-induced damage to the RBC (4). Also *Plasmodium* parasites break down hemoglobin, and release toxic substances like Fe, which is a source of oxidative stress and it will cause hemolysis (17). Therefore the growth of *Plasmodium* parasites is decreased. In addition, damaged red blood cells are removed by phagocytosis at an early ring-stage of parasites' maturation, and that decreases the growth of parasites even more (1, 18).

Farhud et al. performed a study in the north of Iran. They measured serum proteins and immunoglobulins in favic patients and healthy controls, both school boys. The results showed higher amounts in healthy individuals and normal range in patients. The normal range in the patients is suggested to be due to positive selection that induces a developed immune response and produces better chances not to get affected by some other endemic infectious diseases such as malaria (19).

Genetics, structure

The gene for the G6PD enzyme is one of the important genes located on the telomeric region of the long arm of X chromosome (Xq28) (1, 5, 20), are more likely to affect males than females. Males are more likely than females to suffer all X-linked genetic conditions, such as G6PD deficiency (21).

Clinical and biochemical analyses have characterized more than 400 (2, 22) variants most emerging from point mutations in the coding region of gene (2, 23), base changes that result in amino acid substitution, displaying a field of phenotypes with different abnormal enzyme activity and wide ranging degree of clinical symptoms (23). Monomer of G6PD has 515 amino acids with a molecular weight 59 kDa (2, 24).

G6PD in the active form consists of the same subunits of either dimmer or tetramer and includes tightly bound NADP (2, 24). It is supposed that Lys and Arg, amino acids 386 and 387 in enzyme, bind one of the phosphates in NADP (2). The shift between two active forms depends on PH. Aggregation of inactive monomers and conversion into an active form requires presence of NADPH (2, 24).

Variants of G6PD

According to the level of enzyme activity, World Health Organization classified variants of G6PD to five groups (15, 25).

Class 1: Severe deficiency of the enzyme with Chronic nonspherocytic hemolytic anemia.

Class 2: Severe deficiency of the enzyme, enzyme activity is less than 10% of normal.

Class 3: Moderate deficiency of the enzyme, enzyme activity is %10-60 of normal.

Class 4: Very mild to none deficiency of the enzyme, enzyme activity is %60-100 of normal.

Class 5: There is increased enzyme activity.

Mutations that are responsible for class 1 variants are confined to the NADP binding site of the enzyme or glucose-6-phosphate binding site (2, 24). They are located near the carboxy end of the enzyme (25). They form severe clinical symptoms because they are clustered at the position involved in the dimmer formation of the active form of G6PD (26, 27) and influence stability and activity of enzyme (27). But mutations that cause mild clinical symptoms are located at the amino end of the molecule (25). G6PD variants that have been discussed in this article are shown in Table 1. G6PD variants that have been characterized at the DNA level are shown in Table 2.

Table 1: G6PD variants that have been discussed in this article (2)

Biochemical variants	Nucleotide substitution		Amino acid substitution		WHO class
A^-	202G	A	68Val	Met	3
	376A	G	126Asn	Asp	
Mediterranean	563C	T	188Ser	Phe	2
Mahidol	487G	A	163Gly	Ser	3
Viangchan	871G	A	291Val	Met	2
Cosenza	1376G	C	459Arg	Pro	2
Chatham	1003G	A	335Ala	Thr	3

Table 2: G6PD variants that have been characterized at the DNA level (2)

Variant	Nucleotide Substitution	WHO Class	Amino Acid Substitution
Gaohe	95 A G	2	32 His Arg
Gaozhou			
Sunderland	105-107 del	1	35 Ile del
Aures	143 T C	2	48 Ile Thr
Metaponto	172 G A	3	58 Asp Asn
A$^-$			
Distrito Federal			
Metera			
Castilla	202 G A	3	68 Val Met
Alabama	376 A G		126 Asn Asp
Betica			
Tepic			
Ferrara			
Ube	241 C T	3	81 Arg Cys
Konan			
Lagosanto	242 G A	3	81 Arg His
Vancouver	317 C G	1	106 Ser Cys
	544 C T		182 Arg Trp
	592 C T		198 Arg Cys
Sao Borga	337 G A	4	113 Asp Asn
A	376 A G	4	126 Asn Asp
Chinese- 4	392 G T	?	131 Gly Val
Ilesha	466 G A	3	156 Glu Lys
Mahidol	487 G A	3	163 Gly Ser
Plymouth	488 G A	1	163 Gly Asp
Chinese-3	493 A G	2	165 Asn Asp
Shinshu	527 A G	1	176 Asp Gly
Santamaria	542 A T	2	181 Asp Val
	376 A G		126 Asn Asp
Mediterranean			
Dallas			
Birmingham	563 C T	2	188 Ser Phe
Sassari			
Cagliari			
Panama			
Coimbra	592 C T	2	198 Arg Cys
Santiago	593 G C	1	198 Arg Pro
Sibari	634 A G	3	212 Met Val
Minnesota			
Marion	637 G T	1	212 Val Leu
Gastonia			
Harilaou	648 T G	1	216 Phe Leu
Mexico City	680 G A	3	227 Arg Gln
A-	680 G T	3	227 Arg Leu
	376 A G		126 Asn Asp
Stonybrook	724-729	1	242-243
	GGC del		Gly & Thr
Wayne	769 G C	1	257 Arg Gly
Cleveland	820 G A	1	274 Glu Lys
Chinese-1	835 A T	2	279 Thr Ser

Table 2: Continued…

Variant	Nucleotide Substitution	WHO Class	Amino Acid Substitution
Seattle Lodi Modena	844 G C	2	282 Asp His
Lodi Modena	844 G C	2	282 Asp His
Montalbano	854 G A	3	285 Arg His
Viangchan Jammu	871 G A	2	291 Val Met
West Virginia	910 G T	1	303 Val Phe
Kalyam Kerala	949 G A	3	317 Glu Lys
A- Betica Seima	968 T C 376 A G	3	323 Leu Pro 126 Asn Asp
Nara	953-976 del	1	319-326 del
Chatham	1003 G A	3	335 Ala Thr
Fushan	1004 C A	2	335 Ala Asp
Chinese-5	1024 C T	?	342 Leu Phe
Irepetra	1057 C T	2	353 Pro Ser
Loma Linda	1089 C A	1	363 Asn Lys
Olomouc	1141 T C	1	381 Phe Leu
Tomah Iowa	1153 T C	1	385 Cys Arg
Walter Reed Iowa City Springfield	1156 A G	1	386 Lys Glu
Guadalajara	1159 C T	1	387 Arg Cys
Mt. Sinai	1159 C T 376 A G	1	387 Arg Cys 126 Asn Asp
Beverly Hills Genova Worcester	1160 G A	1	387 Arg His
Praba	1166 A G	1	389 Glu Gly
Nashvill Anaheim Calgary Portici	1178 G A	1	393 Arg His
Alhambra	1180 G C	1	394 Val Leu
Puetro Limon	1192 G A	1	398 Glu Lys
Riverside	1228 G T	1	410 Gly Cys
Japan Shinagava	1229 G A	1	410 Gly Asp
Alhambra	1180 G C	1	394 Val Leu
Puetro Limon	1192 G A	1	398 Glu Lys
Riverside	1228 G T	1	410 Gly Cys
Japan Shinagava	1229 G A	1	410 Gly Asp
Alhambra	1180 G C	1	394 Val Leu
Puetro Limon	1192 G A	1	398 Glu Lys
Riverside	1228 G T	1	410 Gly Cys

Table 2: Continued…

Variant	Nucleotide Substitution		WHO Class	Amino Acid Substitution	
Alhambra	1180 G	C	1	394 Val	Leu
Puetro Limon	1192 G	A	1	398 Glu	Lys
Riverside	1228 G	T	1	410 Gly	Cys
Japan Shinagava	1229 G	A	1	410 Gly	Asp
Tokyo	1246 G	A	1	416 Glu	Lys
Georgio	1284 C	A	1	428 Tyr	End
Varnsdorf	3′ interon 10 splice site del		1	N/A	
Pawnee	1316 G	C	2	439 Arg	Pro
Telti Kobe	1318 C	T	1	440 Leu	Phe
Santiago de Cuba	1339 G	A	1	447 Gly	Arg
Cassano	1347 G	C	2	449 Gln	His
Union Maewo	1360 C	T	2	454 Arg	Cys
Andalus	1361 G	A	1	454 Arg	His
Cosenza	1376 G	C	2	459 Arg	Pro
Taiwan-Hakka Gifu-like	1376 G	T	2	459 Arg	Leu
Kaiping Anant Dhon Petrich Sapporo	1388 G	A	2	463 Arg	His
Campinas	1463 G	T	1	488 Gly	Val

G6PD deficiency in the World

Based on the findings of WHO, 7.5% of the world populations have one or two genes for G6PD deficiency and 2.9% are G6PD deficient (28).

The best known G6PD-deficient variants that occur at a high frequency are G6PD A^- and the Mediterranean variants. Mediterranean mutations are identified by very low activity in red blood cells (29). Mediterranean variant is the most common variant in Southern Europe, Middle East, and India (2). Rate of incidence of Mediterranean mutation in Turkey is (77%), Iran (69%), India (60.4%), and also in Pakistan (30) and Saudi Arabia the Mediterranean mutation is the prevalent variant (31).

In Kuwaiti population, the most common variants are G6PD A^- and the Mediterranean variants and also a lower rate of Chatham variant and Aures are detected in Kuwaiti population. Postulating that gene flow from the Indian Sub-continent, sub-Saharan Africa and other parts of Mediterranean is responsible for molecular heterogenity of G6PD variants in the population (30, 32). The most G6PD variant in Italy, Sardinia and Greece is G6PD Mediterranean.

In Egypt and Libya, North of Africa, G6PD Mediterranean is the most common variant (30). G6PD A^- and G6PD Mediterranean have respectively the highest rate of incidence in Algeria and both of them are associated with Favism. Molecular heterogenous G6PD deficiency in Algeria suggests gene flow from Sub-Saharan Africa and other parts of Mediterranean (33).

G6PD A^- is found in Africa, Southern Europe and all areas African people were taken to (2). G6PD deficiency in Spain is heterogenous. The most

prevalent variant in Spain is G6PD A$^-$. Two other important variants are Seattle and Union. The existence of G6PD Aures and Santamaria, that are polymorphic in Algeria, suggests significant gene migration from Africa to Europe through Spain (30, 34).

G6PD deficiency in Mexico is heterogenous and G6PD A$^-$ is relatively prevalent. Prevalence of G6PD A$^-$ and Seattle mutations in Mexico were likely introduced by African slaves and Spanish immigrants (35).

Viangchan, Mediterranean and Mahidol are common G6PD mutations in the Malays (36). Viangchan, Mahidol and canton were the most prevalent G6PD variants in Thais. G6PD Viangchan in Laotians and non-Chinese Southeast Asian population is probably the most common variant (37).

G6PD deficiency in IRAN

The prevalence of G6PD deficiency in Iranian population is 10-14.9% reported by WHO (28). The most prevalent variant of G6PD deficiency in Iran is the Mediterranean (38-40), and the next most prevalent variant is Chatham, and Chatham incidence rate is 13-27% (39).

The incidence rates of G6PD mutations in different provinces in Iran are shown in Table 3.

Table 3: The Prevalence of G6PD mutations in provinces of Iran (38, 40)

	Khorasan	**Mazandaran**	**Golestan**	**Hormozgan**	**Sistan and Balochestan**	**Gilan**	**kermanshah**
Percent of Medit mutation	66	69	62.2	79.45	80.42	86.4	91.2
Percent of Chatham mutation	12	27	26.8	8.21	2.17	9.7	7.3

The incidence rate of G6PD deficiency in Tehran neonates was 2.1% (41). In a study in Kermanshah Province 5.3% of samples were severely deficient in G6PD enzyme. Polymorphic mutations in the region were Mediterranean, Chatham, Cosenza (40). There are higher prevalence of G6PD deficiency in northern and southeastern provinces of Iran (8.6- 16.4% in Northern provinces, 12% in southern part [Shiraz] and 19.3% in southeastern of Iran) (42, 43-45).

The three mutations found in the three northern provinces of Iran were Mediterranean, Chatham, Cosenza (42). Khalili et al reported the prevalence of G6PD deficiency in Gilan, a northern province of Iran 6.4% (46). In Khorasan, Northeastern province of Iran, 22% of samples did not display one of the known mutations in Iran. Different ethnic groups who are living in this province include Persian, Turkmen, Afghan, Turk, Kurd and Arab. The unknown variants of enzyme deficiency observed in the region may bear similarities to those in Khorasan neighboring such as Afghanistan and Turkmenistan (30).

Clinical Manifestations of G6PD deficiency

Acute hemolytic anemia, neonatal jaundice and chronic non spherocytic hemolytic anemia are the major clinical manifestations associated with G6PD deficiency that discussed in this article:

1. Acute hemolytic anemia
   a. induced by oxidative drugs
   b. Favism
   c. Infection-induced hemolysis
2. Chronic non spherocytic hemolytic anemia
3. Neonatal jaundice

1. Acute hemolytic anemia

Unless exposed to oxidative agents like oxidative drugs, infections and ingestion of fava beans, most patients with G6PD deficiency show no sign of acute hemolytic anemia (1, 4). Hemolytic anemia in G6PD A$^-$ is self-limited because in this

mutation the younger red blood cells contain normal G6PD enzyme activity. But in Mediterranean G6PD with severe enzyme deficiency, hemolytic anemia is not self-limited. All red blood cells have enzyme deficiency and don't resist in hemolysis (2, 15, 47).

a. Induced by oxidative drugs

Each person's response to specific drugs is affected by genetic variations in an enzyme or enzyme system (48). Adverse drug reactions (ADRs) are a significant cause of morbidity and mortality. Acute hemolytic anemia induced by anti-malarial drugs is an example of adverse drug reactions that had been recognized for long time in G6PD deficient people. In these people, due to a defect in the gene coding for G6PD, the activity of the enzyme is reduced and that caused this adverse effect (49). Pharmacogenetics was introduced by Vogel in 1959 for study the relationship between genetic variations in genes involved in drug metabolism and drug response. More recently, the term pharmacogenomics has also been introduced, that is the broader application of genomic technologies and considers the genetic variants, patterns of gene expression and the way drugs influence gene function. It is postulated that pharmacogenomics is the study of entire genome, meanwhile pharmacogenetics is the study of a single gene. The term pharmacogenomics can be used to cover both Pharmacogenetics and Pharmacogenomics. Pharmacogenomics offers major potential benefits by improving drug response, reducing ADRs and understanding disease susceptibility (50).

Some drugs cause oxidative stress and induce hemolysis in G6PD-deficient red blood cells. They form hydrogen peroxide when they come in contact with hemoglobin (47).

During this reaction reduced glutathione is oxidized rapidly, glutathione pools are exhausted, hemoglobin is denatured and Heinz bodies are formed (2, 47). Red blood cells with enzyme deficiency are not capable of reducing NADP to NADPH for regenerating reduced glutathione from oxidized form that is necessary for inactivating peroxides and protecting cells against oxidative injuries that cause hemolysis (47, 51). Drugs, substances and herbs can induce hemolytic anemia in G6PD deficient people are shown in tables 4, 5.

Primaquine

People with G6PD deficiency are about 20 to 30 times more sensitive to the hemolytic activity of primaquine than the people with normal G6PD (52).

Mechanism for induction of hemolytic anemia was studied in rats (52, 53). Toxic metabolites of primaquin cause reduction of GSH in red blood cells (53), formation of methemoglobin (51) and Heinz bodies that induce hemolytic anemia (52, 53). The primaquine metabolite, 6-methoxy-8-hydroxylaminoquinoline after N-hydroxylation from 6-methoxy-8-aminoquinoline (52), by peroxidation of lipids in red blood cells with significant GSH and oxidation of protein in GSH-depleted red blood cells can induce hemolytic response (52).

Henna

Henna is a cosmetic dye that is used for dying hair, nails (54, 55) and also for treatment dermatitis (56). Some studies identified that henna can induce hemolytic anemia (55, 57, 58). Lawsone (2-hydroxy-1,4-naphthoquinone) is a chemical substance in henna, and its structure and redox potential is similar to naphthalene metabolites that induce oxidative damage in red blood cells especially in G6PD-deficient person (55).

Tea and Polyphenols

In a study in China effects of extracts of black tea, green tea and decaffeinated green tea and their polyphenols on G6PD-deficient red blood cell in vitro were examined. The results showed that extracts of tea and their two polyphenol (epigallocatechin-3-gallate and epigallocatechin) changed oxidative condition in G6PD- deficient red blood cells in vitro. Level of GSH is lowered; methemoglobin, hemoglobin and GSSG are raised. The observed changes depend to doses of tea extracts and polyphenols that are used. These changes are not observed in normal red blood cells (59).

Table 4: Drugs and substances should be avoided by G6PD deficient individuals (1, 2, 60).

Drugs and substances (group)	Examples
Anti malarial drugs	Primaquin
Sulphonamides	Sulphacetamid, Sulphametoxazole, Sulphanilamid, Sulphapyridin
Sulphones	Thiazolesulfone, Dapsone
Other sulphur-containing drugs	Glibenclamide
Nitrofurans	Nitrofurantoin(Furadantin)
Other drugs	Toluidin blue, Trinitrotoluene(TNT), Urate oxidase, Phenylhydrazine, Furazolidone (Furoxone), Methylene Blue, Nalidixic acid, Niridazole, Phenazopyridine, Isobutyl Nitrite, Acetanilide, Aspirin
Cosmetic substance	Henna
Other substances	Naphthalene, Moth balls, High-dose of vitamin K or ascorbic acid
Food substance	Fava beans

Table 5: Drugs and Substances (with their molecular formulation) should be avoided by G6PD deficient individuals according to the G6PD Deficiency Association (61)

Name	Molecular Forumla	Risk Levels	Population at risk
Acetanilide (acetanilid)	$C_8 H_9 N O$	High	Medit., Asian
Acetylphenylhydrazine (2-Phynylacetohydrazide)	$C_8 H_{10} N_2 O$	High	All
Aldesulfone sodium (sulfoxone)	$C_{14} H_{14} N_2 Na_2 O_6 S_3$	High	All
Aminophenazone (aminopyrine)	$C_{13} H_{17} N_3 O$	Low	All
Antazoline (antistine)	$C_{17} H_{19} N_3$	Low	All
Arsine	$As-H_3$	High	All
Ascorbic Acid	$C_6 H_8 O_6$	Low	All
Beta-Naphthol (2-Naphthol)	$C_{10} H_8 O$	High	All
Chloramphenicol	$C_{11} H_{12} C_{12} N_2 O_5$	High	Medit., Asian
Chloroquine	$C_{18} H_{26} Cl N_3$	High	Medit., Asian
Ciprofloxacin	$C_{17} H_{18} F N_3 O_3$	High	Medit., Asian
Colchicine	$C_{22} H_{25} N O_6$	Low	All
Dapsone (diaphenylsulfone)	$C_{12} H_{12} N_2 O_2 S$	High	All
Dimercaprol	$C_3 H_8 O S_2$	High	All
Diphenhydramine (difenilhydramine)	$C_{17} H_{21} N O$	Low	All
Dopamine (L-dopa)	$C_8 H_{11} N O_2$	Low	All
Doxorubicin	$C_{27} H_{29} N O_{11}$	High	Medit., Asian
Furazolidone	$C_8 H_7 N_3 O_5$	High	All
Glibenclamide	$C_{32} H_{28} Cl N_3 O_5 S$	High	Medit., Asian
Glucosulfone (glucosulfone sodium)	$C_{24} H_{34} N_2 Na_2 O_{18} S_3$	High	All
Isobutyl Nitrite	$C_4 H_9 N O_2$	High	Medit., Asian
Isoniazid	$C_6 H_7 N_3 O$	Low	All
Menadiol Sodium Sulfate (Vitamin k4 sodium sulfate)	$C_{11} H_8 Na_2 O_8 S_2$	High	All
Menadione (menaphtone)	$C_{11} H_8 O_2$	High	All
Menadione sodium Bisulfite (Vitamin K3 sodium bisulfite)	$C_{11} H_8 O_2 NaHSO_3$	High	All
Mepacrine (Quinacrine)	$C_{23} H_3O Cl N_3 O$	High	Medit., Asian
Mesalazine-5-Aminosalicylic Acid(paraminosalicylic acid)	$C_7 H_7 N O_3$	High	Medit., Asian
Methyltioninium Chloride (methylene blue)	$C_{16} H_{18} Cl N_3 S$	High	All
Nalidixic Acid	$C_{12} H_{12} N_2 O_3$	High	Medit., Asian
Naphtalene, Pure (naphtalin)	$C_{10} H_8$	High	All
Niridazole	$C_6 H_6 N_4 O_3 S$	High	All
Nitrofural (nitrofurazone)	$C_6 H_6 N_4 O_4$	High	All
Nitrofurantoin	$C_8 H_6 N_4 O_5$	High	All
Norfloxacin	$C_{16} H_{18} F N_3 O_3$	Low	All
O-Acetylsalicylic Acid (acetylsalicylic acid)	$C_9 H_8 O_4$	High	Medit., Asian

Table 5: Continued…

Name	Molcular Formula	Risk Levels	Population at Risk
O-Acetylsalicylic Acid (acetylsalicylic acid)	$C_9 H_8 O_4$	High	Medit., Asian
Oxidase, Urate (urate oxidase)	_____	High	Medit., Asian
Pamaquine	$C_{42} H_{45} N_3 O_7$	High	All
Para-Aminobenzoic Acid (4-Aminobenzoic Acid)	$C_7 H_7 N O_2$	Low	All
Paracetamol (acetaminophen)	$C_8 H_9 N O_2$	Low	All
Pentaquine	$C_{18} H_{27} N_3 O$	High	All
Phenacetin (acetophenetidin)	$C_{10} H_{13} N O_2$	High	Medit., Asian
Phenazone (antipyrine)	$C_{11} H_{12} N_2 O$	Low	All
Phenazopyridine	$C_{11} H_{11} N_5$	High	Medit., Asian
Phenylbutazone	$C_{19} H_{20} N_2 O_2$	Low	All
Phenytoin	$C_{19} H_{20} N_2 O_2$	Low	All
Phynylhydrazine	$C_6 H_8 N_2$	High	All
Phytomenadione (Vitamin K1)	$C_{31} H_{46} O_2$	Low	All
Primaquine	$C_{15} H_{21} N_3 O$	High	All
Probenecid	$C_{13} H_{19} NO_4 S$	High	All
Procainamide	$C_{13} H_{21} N_3 O$	Low	All
Proguanil (chlorguanidine)	$C_{11} H_{16} Cl N_5$	Low	All
Pyrimethamine	$C_{12} H_{13} Cl N_4$	Low	All
Quinidine	$C_{20} H_{24} N_2 O_2$	Low	All
Quinine	$C_{20} H_{24} N_2 O_2$	Low	All
Stibophen (2-(2-Oxido-3,5-Disulphonatophenoxy)-1,3,2,Benzodioxastibole-4-6-Disulphonate)	$C_{12} H_4 Na_5 O_{16} S_4 Sb$	High	All
Streptomycin	$C_{21} H_{39} N_7 O_{12}$	Low	All
Sulfacetamide	$C_8 H_{10} N_2 O_3 S$	High	All
Sulfacytine	$C_{12} H_{14} N_4 O_3 S$	Low	All
Sulfadiazine	$C_{10} H_{10} N_4 O_2 S$	Low	All
Sulfadimidine	$C_{12} H_{14} N_4 O_2 S$	High	All
Sulfafurazole (sulfafurazone, sulfisoxazole)	$C_{11} H_{13} N_3 O_3 S$	High	Medit., Asian
Sulfaguanidine	$C_7 H_{10} N_4 O_2 S$	Low	All
Sulfamerazine	$C_{11} H_{12} N_4 O_2 S$	Low	All
Sulfamethoxazole	$C_{10} H_{11} N_3 O_3 S$	High	All
Sulfanilamide (Sulphanilamide)	$C_6 H_8 N_2 O_2 S$	High	All
Sulfapyridine	$C_{11} H_{11} N_3 O_2 S$	High	All
Sulfasalazine, Salazosulfapyridine (salazopyrin)	$C_{18} H_{14} N_4 O_5 S$	High	All
Thiazosulfone (thiazolesulfone)	$C_9 H_9 N_3 O_2 S_2$	High	Medit., Asian
Tiaprofenic Acid	$C_{14} H_{12} O_3 S$	Low	All
Tolonium Chloride, Tolonium Chloride (toluidine blue)	$C_{15} H_{16} Cl N_3 S$	High	All
Trihexyphynidyl (benzhexol)	$C_{20} H_{31} N O$	Low	All
Trimethoprim	$C_{14} H_{18} N_4 O_3$	Low	All
Trinitrotoluene (2,4,6-Trinitrotoluene)	$C_7 H_5 N_3 O_6$	High	Medit., Asian
Tripelennamine	$C_{16} H_{21} N_3$	Low	Medit., Asian

Food substances and herbs that should be avoided by G6PD deficient people
Fava Beans
Some prefer also to avoid red wine, all legumes, blueberries (also with yogurt), soya products, tonic water.
Chinese Herbs to Avoid: Cattle Gallstone Bezoar (Bos Taurus Domesticus), Honeysuckle (Lonicera Japonica), Chimonanthus Flower(Chimonanthus Praecox), Huang Lian (黄连), 100% Pearl Powder

b. Favism

Favism is hemolytic anemia which occurs after the ingestion of fava beans especially fresh fava beans in G6PD-deficient individual and that's why the highest incidence rate of favism is at the time of harvest (1, 2, 15, 62).

Favism is always observed in people with G6PD deficiency, but all G6PD-deficient people do not develop hemolysis. Therefore, G6PD deficiency is an essential factor for the occurrence of favism but it is not enough (2, 15). Most cases of favism are observed in Mediterranean type of G6PD-deficient because the level of enzyme activity is very low and deficiency is severe, and occasionally in individuals with G6PD A^- variant (1, 2).

Clinical symptoms of favism are pallor, jaundice, hematuri and acute hemolytic anemia occurs 24-48 h after consumption of fava beans, suddenly (1, 15, 63). Ahaptoglobinemia was found in favism patients (64, 65). There is a low haptoglobin serum in G6PD deficient individuals. Haptoglobin is a serum protein of the alpha-2 fraction, binds to free hemoglobin whenever intravascular hemolysis occurs, the complex cleared by phagocytes and then haptoglobin disappeared from plasma (65, 66).

Vicine and convicine are pyrimidine glucoside that are abundant in fava beans and make up 6.7 g/100 g of dry weight of fava beans (67). These substances are metabolized by B-glucosidase in body to divicine and isoramil that are unstable aglycons, and are oxidized rapidly and form hydrogen peroxide and superoxide anion. These metabolites oxidize reduced glutathione in normal and G6PD-deficient red blood cells (67-69). Depletion of reduced glutathione and impairment of some important enzyme induce oxidative stress in G6PD-deficient red blood cells and lead to acute hemolytic anemia called favism (2, 68, 69).

c. Infection-induced hemolysis

The most common cause of hemolysis is possibly the infection in G6PD-deficient individuals (1, 2). Viral, bacterial and rickettsial infections, especially hepatitis, pneumonia and typhoid fever induce hemolysis in G6PD- deficient people (1). During phagocytosis, leukocytes may release active oxygen species that induce oxidative stress to the erythrocytes, and will damage them and will cause hemolysis (1, 2).

2. Chronic non spherocytic hemolytic anemia

Some of the rare variants of G6PD deficiency which are designated as class 1 variants, according to the classification of WHO, are associated with Chronic non spherocytic hemolytic anemia (1, 2, 26).

Individuals in this class have very low enzyme activity (26) and suffer from hemolytic anemia even when oxidative agents are not present (2). They are variably anemic in steady state condition (1, 2). Splenomegaly is commonly present. The disorder is usually identified during infancy and childhood (15).

3. Neonatal jaundice

Serum bilirubin levels are determined by production of bilirubin, bilirubin conjugation and elimination. Hyperbilirubinemia is caused by the imbalance between the rate of production of bilirubin, the end product of heme metabolism, and restricted excretion of bilirubin in newborns (70, 71). The average total serum bilirubin level is usually 5-6 mg per dl (86-103 μmol per l) in full term newborns (71). Hyperbilirubinemia occurs due to either physiologic or pathologic causes (71). Physiologic jaundice occurs when the serum total bilirubin is in a range of 7 to 17 mg per dl (104-291 μmol per l). A total serum bilirubin level higher than 17 mg per dL is considered pathologic hyperbilirubinemia. One of the common risk factors for pathologic hyperbilirubinemia in newborn infants is deficiency of G6PD enzyme (71). Deficiency of this enzyme is the most prevalent enzymopathy in red blood cells that causes hemolysis and hyperbilirubinemia (72). Hyperbilirubinemia can be very severe in G6PD-deficiency and induces permanent damage to the brain and causes kernicterus and death (72). Overproduction of unconjugated bilirubin and lack of proper management of hyperbilirubinemia cause changes in the mitochondria of the basal ganglia and leads to impaired mitochondrial respiration, and also induce apoptosis, and cause bilirubin encephalopathy (73).

The pathogenesis of hyperbilirubinemia in G6PD-deficient newborn babies is different from that in G6PD-normal ones. Meanwhile hemolysis is considered to be a principal cause of bilirubinemia in G6PD-normal neonates; but diminished bilirubin conjugation would be the main cause of hyperbilirubinemia in G6PD-deficient newborn infants (70). Profile of serum bilirubin in newborns with G6PD-deficiency showed that the amount of total and unconjugated bilirubin is high and conjugated bilirubin is low. These levels of different forms of bilirubin that are seen in the neonates are similar in conditions of partial deficiency of the bilirubin conjugating enzyme UDP glucuronosyltransferase, such as Gilberts syndrome. High levels of unconjugated bilirubin in G6PD-deficient neonates are the result of an interaction between G-6-PD deficiency and variant promoter for the gene encoding this enzyme, UDP glucuronosyltransferase (74).

Although there is a natural immaturity of bilirubin conjugationin in neonates, the bilirubin conjugation ability of G6PD-deficient neonates who are also heperbilirubinemic is even less efficient. Bilirubin conjugation ability in G6PD-deficient neonates may become worse due to increased hemolysis and more bilirubin production (70, 74).

Diagnosis

Beutler fluorescent spot test, dichlorophenol indophenol decolourization and quantitative spectrophotometric assey are methods used for the diagnosis of G6PD deficiency (15, 75). Beutler fluorescent spot test is the most acceptable method for screening of G6PD deficiency (76). During this method, the rate of NADPH production from NADP by G6PD is measured under ultraviolet light (15, 66). G6PD non-deficient blood samples fluoresce brightly, but deficient samples show little or no fluorescence (75-77).

When individuals are actively hemolyzing, the test can show normal results wrongly, because sustaining younger erythrocytes show normal enzyme activity or near normal. Thus the individuals should be screened several weeks after a hemolytic episode (15, 75).

By using the Quantitative spectrophotometric method, activity of G6PD Enzyme was determined by measuring the rate of the reduction of NADP to NADPH in the presence of G6P and hemolysate (15, 76). Another Screening method for G6PD deficiency is dichlorophenol-indophenol (DPIP)dye decolorization. This method is used for determining of G6PD in red blood cells. By this method hetrozygotes are diagnosed easily and is used when a large number of population are screened for determination of G6PD deficiency (15).

Laboratory tests and clinical features in patients with G6PD deficiency and hemolysis are: Hemoglobinuria, Increased indirect bilirubin, Elavated serum lactate dehydrogenase,

Low serum haptoglobin (up to ahaptoglobinemia), Complete blood count (CBC), elevated reticulocyte count, Heinz bodies are presented on peripheral blood smear, Comb's test (the test in hemolysis phase is negative) (77, 78).

Treatment

The main treatment for G6PD deficiency is avoidance of oxidative agents like infection, fava beans and oxidative drugs that induce hemolysis (1, 4). Hemolysis may be so severe that it may even require blood transfusion (2). Screening of newborns for early diagnosis of G6PD deficiency and proper education can reduce the incidence of clinical symptoms (1). These methods have been successfully applied in northern Sardinia and the result was that the incidence of Favism has become less and also in Singapore kernicterus in the neonates is now very rare. Proper control and early treatment in neonatal jaundice are very important (1). Phototherapy is used to decrease bilirubin concentration and when the bilirubin levels exceeds 20 mg/dl, exchange transfusion is necessary (2). In regions that G6PD deficiency is prevalent, there is a grave danger of giving G6PD-deficient blood to such newborns and this has to be prevented (1). Using desferrioxamine could make the attacks of Favism less severe. Use of Sn-mesoporphyrin (SnMP) that inhibits heme oxygenase and decreases bilirubin production in G6PD-deficient neonates has decreased the need

for phototherapy and exchange transfusion (1, 79, 80). Because of some adverse effects of Sn-mesoporphyrin**,** SnMP should only be used for neonates who are in a clear danger of developing bilirubin-induced neurologic dysfunction or those who are taking part in clinical trials (79). In clinical experiments, use of antioxidants like vitamin E and selenium have not shown any benefit for the treatment of G6PD deficiency (1).

Conclusion

G6PD deficiency is one of the most common X-link inherited hemolytic disorders reported, affecting around 400 million people worldwide. The main function of G6PD is to protect the RBC against oxidative damage. The most important way for prevention and reduction in the incidence rate of clinical symptoms of G6PD deficiency is to avoid oxidative agents like infection, fava beans and oxidative drugs that induce hemolysis, also screening of newborns for early diagnosis of G6PD deficiency and proper education is recommended.

Acknowledgements

The authors are both thankful to Prof A Jazayery, School of Public Health, and Dr H Sadighi, Genetic Clinic, for reading the manuscript and giving some suggestions.

This study was supported partly by Iran TWAS chapter based at ISMO in Tehran.

The authors declare that they have no conflict of interests.

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