Review Article:

G6PD Deficiency in the Gulf Region: A Systematic Review of Prevalence, Genotypic, and Phenotypic Variants

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Abstract:

Glucose-6-phosphate dehydrogenase (G6PD) deficiency, an X-linked recessive disorder affecting approximately 400 million individuals globally, impairs red blood cells' ability to counter oxidative stress, presenting primarily as neonatal jaundice and hemolytic anemia, with significant prevalence in malaria-endemic regions. This systematic review examines the prevalence, genotypic and phenotypic diversity, and demographic characteristics of G6PD deficiency specifically within the Gulf Region. The review was conducted according to PRISMA guidelines and registered with PROSPERO (ID: CRD42024514065). A comprehensive literature search was performed in February 2024 using PubMed and Web of Science databases via Rayyan, including studies published in English discussing G6PD deficiency in the Gulf region published up to January 2024, with data independently screened and extracted by multiple authors. Eligible study designs included randomized controlled trials, cohort studies, cross-sectional studies, case-control studies, case series, and case reports, with quality assessments performed using the Newcastle-Ottawa Scale for cohort studies and the Joanna Briggs Institute checklist for cross-sectional studies. The systematic search identified 181 articles, narrowed to 36 after screening. Most studies were cross-sectional (n=32) and conducted primarily in Saudi Arabia. Sample sizes ranged from 23 to 48,889 (total=145,174), showing prevalence between 0.67%-42.7%, highest in Saudi Arabia's Eastern province. The Mediterranean mutation was most common; favism (55%-89%) was a frequent clinical manifestation, while many individuals remained asymptomatic, highlighting variable expressivity of G6PD deficiency. The review demonstrates that the prevalence of G6PD deficiency varies significantly across the Gulf region (0.67%–42.7%), influenced by geographic location, historical malaria endemicity, and consanguinity, with the Mediterranean variant being the most common genetic mutation. Limitations include variability in methodologies, underrepresentation of certain regions, and lack of longitudinal studies, highlighting the need for larger-scale studies to clarify prevalence, genetic variants, and long-term clinical outcomes.

Keywords:
G6PD, enzyme deficiency, anemia

Introduction:

G6PD is an important enzyme in the pentose phosphate pathway (PPP). It creates nicotinamide adenine dinucleotide phosphate (NADPH) and is the rate-limiting step in the PPP. It also plays a key role in maintaining cellular redox balance[1]. Affecting almost 400 million individuals worldwide, G6PD deficiency is an X-linked recessive disease and the most common human enzymatic anomaly that is essential for maintaining the structural integrity and functionality of red blood cells (RBCs) by counterbalancing oxidative stress [2], Its higher prevalence in malaria-endemic areas suggests a selective advantage against Plasmodium falciparum infection [2,3]. This deficiency comes from harmful mutations in the G6PD gene, which reduces response to oxidative stress and shows clinically as neonatal jaundice and severe hemolytic anemia, with variation in degree depending on the particular G6PD variant [2,4]. G6PD deficiency is a significant public health concern in Gulf countries, with varying prevalence rates: 4.76% in Saudi Arabia[5], 2.51% among neonates in Qatar[6], and a range of 2% to 31% in Arab countries[7]. High frequency in Oman is partially attributed to extensive consanguineous marriages, which may account for 25% of the population and raise vulnerability to diseases and higher mortality rates among G6PD-deficient people[8]. The deficiency also aggravates the severity of infections, including COVID-19, where individuals with G6PD-deficient showed notable variations in hematological and biochemical markers, therefore indicating a greater risk for severe consequences[9]. Specifically aiming to estimate the prevalence of G6PD deficiency in the Gulf Region, this systematic review aims to provide a thorough overview of the frequency and various genotypic and phenotypic variants of G6PD deficiency, and to characterize the demographic features of G6PD patients in the Gulf Region.

Methods & Materials:

Registration and reporting:

In this systematic review, we followed the International Prospective Register of Systematic Reviews (PROSPERO) statement (ID: CRD42024514065). All steps of this study were performed according to the PRISMA guidelines for reporting in systematic reviews and meta-analyses[10].

Literature Search Strategy:

A systematic review of published literature on G6PD deficiency in the Gulf region was conducted in February 2024. We conducted our search using the following electronic databases: PubMed and Web of Science for all published studies till January 2024. These databases were viewed via Rayyan (Rayyan (https://www.rayyan.ai/). Using the following keywords: G6PD, "Glucose-6-Phosphate Dehydrogenase Deficiency", "G6PD enzyme deficiency", prevalence, epidemiology, incidence, frequency, occurrence, variants, mutations, genotype, alleles, polymorphisms, Gulf region, Saudi Arabia, Qatar, Kuwait, Bahrain, Oman, and United Arab Emirates. The duplicates were removed by using Rayyan.

Screening and Selection of Studies:

We included all English studies that assessed the G6PD deficiency in the Gulf region. There are no restrictions for age, or sex were applied. Review articles, meta-analysis/systematic review, narrative review, editorials, and duplicates were excluded. Studies reported no outcome of interest were also excluded. We assessed for eligibility in two steps; screening the titles and abstracts, and then reviewing the full texts, studies that met our criteria were included in our study. The screening process was done by three independent authors and any disagreements were then resolved by a fourth author.

Study Design and Criteria:

Results from literature searches were included if they included G6PD deficiency patients and it was conducted in the Gulf region. We included randomized controlled trials, prospective and retrospective cohort studies, cross-sectional studies, case-control studies, case series, and case reports. We excluded studies that met the following criteria: non-English studies, Review articles, meta-analysis/systematic review, narrative review, and editorials, and studies that reported no outcome of interest.

Data extraction:

Three authors collected data from retrieved studies including the general information: first author's name, publication year, study design, country, sample size, inclusion /exclusion criteria, outcomes, and conclusion. Additionally, baseline data was collected including the

medical history, medications, nationality, and age at diagnosis. Data related to the target outcome was also collected and this includes the overall prevalence of G6PD deficiency, prevalence by gender, nationality, and age group, type of G6PD mutations identified, frequency of each mutation, association of specific mutations with the severity of G6PD deficiency, symptoms and signs, severity of symptoms, and triggers for hemolytic episodes.

Quality Assessment and Level of Evidence:

The quality assessment for the included studies was conducted by one author using the Newcastle Ottawa Scale (NOS) to evaluate the methodological quality of cohort studies. This scale consists of eight items divided into four categories (selection, ascertainment, causality, and reporting). Scores range from 0 to 9, with a score of 7 to 9 indicating a high-quality study with low risk of bias, a score of 4 to 6 indicating a fair-quality study with moderate risk, and a score of 0 to 3 indicating a low-quality study with the highest risk of bias [11]. In addition, The Joanna Briggs Institute (JBI) was used to assess the methodological quality of cross-sectional studies for possible bias in their design, conduct, and analysis. It consists of eight questions to determine if the studies are high or low quality (Table 1 and 2) [12].

Table 1: Quality assessment of the included analytical cross-sectional studies using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for analytical cross-sectional studies.

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Final Quality Assessment
Al-Ali (1996)	+	+	+	+	?	-	+	?	Fair
Dallol et al. (2012)	+	+	+	+	-	-	+	+	Fair
White et al. (1993)	+	+	+	+	?	?	+	+	Good
El-Hazmi & Warsy (1989)	+	+	+	+	?	-	+	+	Fair
Gari et al. (2010)	+	+	+	+	-	-	+	?	Fair
Warsy & El-Hazmi (2001)	+	+	+	+	?	-	+	?	Fair
Samilchuck et al. (2003)	+	+	+	+	-	-	+	?	Fair
Tork et al. (2021)	+	+	+	+	?	?	+	+	Good
El-Hazmi et al. (1995)	+	+	+	+	?	-	+	?	Fair
El-Hazmi et al. (1994)	+	+	+	+	?	-	+	?	Fair
El-Hazmi & Warsy (1988)	+	+	+	+	?	-	+	?	Fair
El-Hazmi & Warsy (1986)	+	+	+	+	?	-	+	?	Fair
Mohammed et al. (1992)	+	+	+	+	-	-	+	?	Fair
D'Souza et al. (1998)	+	+	+	+	?	-	+	?	Fair
Bayoumi et al. (1996)	+	+	+	+	-	-	+	+	Fair
Daar et al. (1996)	+	+	+	+	-	-	+	-	Fair
Amro et al. (2014)	+	+	+	+	?	-	+	+	Good
Al-Jaouni et al. (2011)	+	+	+	+	-	-	+	?	Fair

Al-Ali et al. (2002)	+	+	+	+	-	-	+	?	Fair
AlFadhli et al. (2005)	+	+	+	+	-	-	+	+	Good
Nasserullah et al. (1998)	+	+	+	+	?	-	+	?	Fair
Gelpi & King (1977)	+	+	+	+	?	-	+	?	Fair
El-Hazmi et al. (1991)	+	+	+	+	?	-	+	?	Fair
Samilchuck et al. (1999)	+	+	+	+	?	-	+	?	Fair
Alharbi & Khan (2014)	+	+	+	+	-	-	+	+	Good
Othman et al. (2019)	+	+	+	+	?	-	+	?	Fair
Malik et al. (2021)	+	+	+	+	?	-	+	+	Good
Al-Nuaim et al. (1997)	+	+	+	+	-	-	+	?	Fair
El-Hazmi & Warsy (1992)	+	+	+	+	?	-	+	?	Fair
El-Hazmi & Warsy (1994)	+	+	+	+	?	-	+	+	Good
Abdulrazzaq et al. (1999)	+	+	+	+	+	?	+	?	Good
Alshomar et al. (2023)	+	+	+	+	?	-	+	+	Fair
Al-Arrayed et al. (2003)	+	+	+	+	-	-	-	+	Fair

Q1, Were the criteria for inclusion in the sample clearly defined?; Q2: Were the study subjects and the setting described in detail?; Q3, Was the exposure measured in a valid and reliable way?; Q4, Were objective, standard criteria used for measurement of the condition?; Q5, Were confounding factors identified?; Q6, Were strategies to deal with confounding factors stated?; Q7, Were the outcomes measured in a valid and reliable way?; Q8, Was appropriate statistical analysis used?

+, Yes; -, No; ?, Unclear

Table 2: Quality Assessment and Risk of Bias Using the Newcastle-Ottawa Scale (NOS) for Cohort Studies.

Study	Selection	Comparability	Outcome	Total Score	Risk of Bias
Al-Sheryani et al. (2023)	+++	-	++	5/9	Moderate
Albagshi et al. (2020)	+++	+	++	6/9	Moderate

High risk of bias: 0-3 stars Moderate risk of bias: 4-6 stars Low risk of bias: 7-9 stars

Results:

The primary results of the search:

We conducted a systematic search using PubMed/MEDLINE and Web of Science online databases for all relevant literature using a standardized and comprehensive search strategy. Our initial search had no timeframe limitations and covered all articles from inception until March 2024. The search resulted in a total of 181 articles, after that we removed all duplicates and ended up with 129 articles to be included in the screening phase. Screening was divided into two phases; the first phase of screening using the titles and abstracts of the articles conducted by three independent authors. Any disagreements were resolved by a discussion among all authors including one senior author. 76 Articles were excluded during this phase. The second phase of screening involved reading the full-texts of the remaining articles to check whether they fit the inclusion criteria or not. The full-texts of 11 articles were not accessible,

so they were excluded. Five articles had an outcome not relevant to our review's question, and as such, they were excluded. Following these screening phases, 36 articles met our inclusion criteria and were included in the final review (Figure 1; PRISMA CHART)

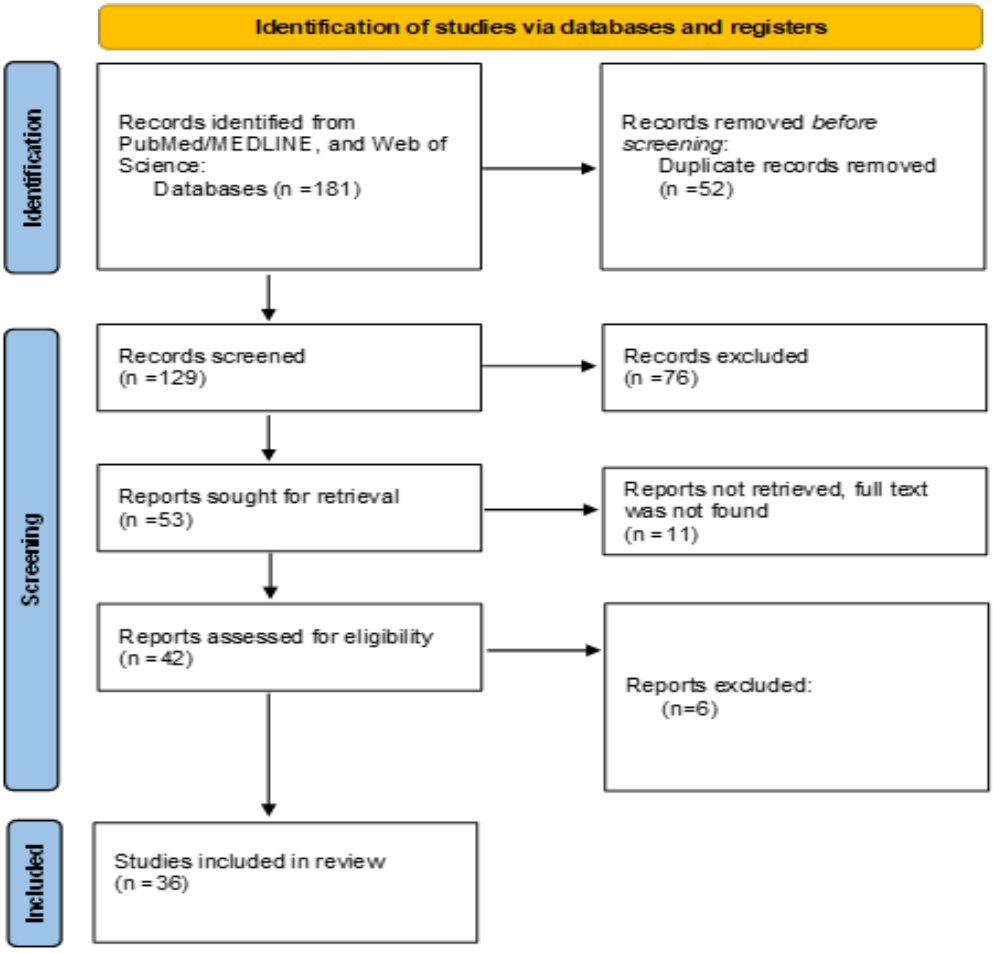


Figure 1: The PRISMA flowchart of included studies.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

An overview of the reviewed studies' characteristics:

This review included 36 studies published between 1977 and 2023[3,13–46 47]. Out of the 36 included articles, the majority were conducted in Saudi Arabia (n=23), followed by Kuwait (n=4), United Arab Emirates (n=3), Oman (n=3), Bahrain (n=2), and Qatar (n=1).

Most of the included studies were cross-sectional studies (n=32), two studies were retrospective in nature, one study had a prospective design, and in one study the design was that of a mixed design (Table 3 and 4).

Table 3: Study Characteristics and Prevalence of G6PD Deficiency in the Gulf Region.

Study & Study Design	Country	Study Design	Sample Size	Age Group	Overall Prevalence of G6PDd	Male Prevalence	Female Prevalence
Al-Ali et al. (1996)	Saudi Arabia	Cross-sectional	757	20-45 years	42.7%	42.7%	NA
Abdulrazzaq et al. (1999)	United Arab Emirates	Mixed design	8198	Infants	9.1%	15%	5%
Alshomar et al. (2023)	Saudi Arabia	Retrospective	313	0-16+ years	2.9%	5%	0%
Dallol et al. (2012)	Saudi Arabia	Cross-sectional	249	Newborn-50 years			
White et al. (1993)	Oman	Cross-sectional	952	Not specified	18.45%	27.3%	11%
El-Hazmi & Warsy (1989)	Saudi Arabia	Cross-sectional	847	Not specified	12.3%*	12.75%	11.58%
Gari et al. (2010)	Saudi Arabia	Cross-sectional	862	18-42 years	5.1%	8.1%	2.8%
Warsy & El-Hazmi (2001)	Saudi Arabia	Cross-sectional	24407	2-70 years	6.9%*	9.05%	4.1%
Samilchuck et al. (2003)	Kuwait	Cross-sectional	1080	Not specified	6.5%	6.5%	
Tork et al. (2021)	Saudi Arabia	Cross-sectional	100	Mean age 5.3 months (SD: 2.76)	17.9%		
El-Hazmi et al. (1995)	Saudi Arabia	Cross-sectional	820	Not specified	6.71%*	7.67%	5.41%
El-Hazmi et al. (1993)	Saudi Arabia	Cross-sectional	1409	Not specified	5.89%*	Makkah: 5.5%; Bisha: 7.67%	Makkah: 4.2%; Bisha: 5.41%
El-Hazmi et al. (1994)	Saudi Arabia	Cross-sectional	689	Not specified	4.92%*	5.5%	4.2%
El-Hazmi & Warsy (1988)	Saudi Arabia	Cross-sectional	402	Not specified	6.47%	9.8%	2.8%
El-Hazmi & Warsy (1986)	Saudi Arabia	Cross-sectional	2936	Not specified	60%		
Mohammed et al. (1992)	Bahrain	Cross-sectional	10327	Infants	21%	64.6%	35.4%
D'Souza et al. (1998)	Kuawit	Cross-sectional	110	Not specified			

Bayoumi et al. (1996)	United Arab Emirates	Cross-sectional	166	12-16 years old	11%	11%	
Daar et al. (1996)	Oman	Cross-sectional	23	Not specified	21%		
Bin Amro et al. (2014)	United Arab Emirates	Cross-sectional	6302	Not specified	99%	11.6%	3.6%
Al-Jaouni et al. (2011)	Saudi Arabia	Cross-sectional	1584	from Infants to adults	11%	11%	
Al-Sheryani et al. (2023)	Oman	Prospective	145	Not specified	89%	88.78%	89.36%
Al-Ali et al. (2002)	Saudi Arabia	Cross-sectional	154	Not specified	84.42%		
Alfadhli et al. (2005)	Kuwait	Cross-sectional	1291	Not specified			
Nasserullah et al. (1998)	Saudi Arabia	Cross-sectional	12220	Infants	Qatif:30.6% AlHasa:14.6%	Qatif:35% AlHasa:19.4%	Qatif:21% AlHasa:8.2%
Gelpi & King (1977)	Saudi Arabia	Cross-sectional	369	16-30 years	18%	18%	
El-Hazmi et al. (2008)	Saudi Arabia	Cross-sectional	429	Not specified			
Samilchuck et al. (1999)	Kuwait	Cross-sectional	206	Not specified	4.5%	5.73%	2.56%
Albagshi et al. (2020)	Saudi Arabia	Retrospective	48889	0-14 years	25%	33.8%	13.5%
Alharbi & Khan (2014)	Saudi Arabia	Cross-sectional	2100	17–50 years	4.76%	4.76%	
Othman et al. (2019)	Saudi Arabia	Cross-sectional	194	Not specified	30.4		
Malik et al. (2021)	Qatari	Cross-sectional	6045	Not specified	5%		
Al-Nuaim et al. (1997)	Saudi Arabia	Cross-sectional	1039	newborn	3.8%	3.605%	0.195%
Al-Arrayed et al. (2003)	Bahrain	Cross-sectional	5685	16-17 years	23.2%	11.4%	11.9%
El-Hazmi & Warsy (1992)	Saudi Arabia	Cross-sectional	1015				
El-Hazmi & Warsy (1994)	Saudi Arabia	Cross-sectional	960		Severe G6PD:61.154% Partial G6PD :9.24%	Severe G6PD : 39.806%. Partial G6PD : 2.72%.	Severe G6PD :21.348% Partial G6PD :6.97%.

Table 4: Genetic Variants and Clinical Features of G6PD Deficiency in the Gulf Region.

Study & Study Design	Country	Most Common Variants	Frequency of Variants	Clinical Features
Al-Ali et al. (1996)	Saudi Arabia	Mediterranean	Not specified	
Abdulrazzaq et al. (1999)	United Arab Emirates	Mediterranean mutation (nt563 C→T, Ser188Phe), African mutation (nt202 G→A, Val68Met)	Mediterranean: 96% African: 4%	Anemia: 14/746 Failure to thrive: 1/746 Neonatal hyperbilirubinemia: 1/746
Dallol et al. (2012)	Saudi Arabia	AURES mutation (p.Ile48Thr) .1 2. Mediterranean variant (p.Ser188Phe) 3. A- mutation variants (p.Val68Met, p.Asn126Asp) 4. SIBARI mutation (p.Met212Val) 5. VIANGCHAN mutation (p.Val291Met) 6. ANANT mutation (p.Arg463His) 7. Novel haplotypes named Jeddah A, B, C, D, and E with combinations of the other mutations.	AURES: 30% in males .1 2. Mediterranean: 17.8% in males 3. A- mutation: 15% in males 4. SIBARI mutation: rare (only 2 individuals) 5. VIANGCHAN mutation: one individual	
El-Hazmi & Warsy (1989)	Saudi Arabia	G6PD B+ (normal enzyme) .1 2. G6PD A+ (African variant with almost normal activity) 3. G6PD A- (reduced activity) 4. Mediterranean variant 5. Mediterranean-like variant	+G6PD B .1 Males: 77.69% Females: 72.2% 2. G6PD Mediterranean: Males: 12.55% Females: 11.28% 3. G6PD Mediterranean-like: Males: 8.17% Females: 13.11% 4. G6PD A+: Males: 1.19% Females: 0.3% 5. G6PD A-: Males: 0.2% Females: 0.3%	
Gari et al. (2010)	Saudi Arabia	Mediterranean mutation: Characterized .1 by a C->T substitution at nucleotide 563 .of exon 6 2. SIBARI mutation: Characterized by an A->G transition at nucleotide 634 of exon 6, resulting in a codon change from ATG to GTG at codon 212.	Mediterranean mutation: 51.1% of .1 G6PD deficient samples 2. SIBARI mutation: only in one case	

Warsy & El-Hazmi (2001)	Saudi Arabia	G6PD-B+ (normal enzyme phenotype) .1 2. G6PD-Mediterranean (associated with severe deficiency) 3. G6PD-A+ (African variant with almost normal activity) 4. G6PD-A- (African variant with reduced activity) 5. G6PD-Med-like (variant with activity between 20%-60% of normal)		
Samilchuck et al. (2003)	Kuwait	563C>T (Mediterranean): the most .1 .common variant found 202 .2G>A (A-): associated with the A-variant. 3. 1003G>A (Chatham) 4. 143T>C (AURES)	Mediterranean: 72.9% .1 202 .2G>A (A-): 14.3% 3. 1003G>A (Chatham): 7.1% 4. 143T>C (Aures): 1.4% 5. Unknown mutations were found in 4.3% of cases	
Tork et al. (2021)	Saudi Arabia	Mediterranean mutation (563 C>T) .1 2. Chatham mutation (1003 G>A) 3. Mahidol mutation (487 G>A)	Mediterranean mutation (563 C>T): 47% .1 2. Chatham mutation (1003 G>A): Reported in a very few cases 3. Mahidol mutation (487 G>A): Also reported in a very few cases	
El-Hazmi et al. (1995)	Saudi Arabia	+G6PD-B .1 2. G6PD-A+ 3. G6PD-Mediterranean 4. G6PD-Mediterranean-like	G6PD-B+: 84.4% in males, 81.77% in .1 females 2. G6PD-A+: 0.43% in males, 0.57% in females 3. G6PD-Mediterranean: 7.67% in males, 5.413% in females 4. G6PD-Mediterranean-like: 7.46% in males, 8.55% in females	

El-Hazmi et al. (1993)	Saudi Arabia	+G6PD-B .1 2. G6PD-A+ 3. G6PD-A- 4. G6PD-Mediterranean 5. G6PD-Mediterranean-like	:In Makkah 1. G6PD-B+: 71.72% in males, 64.49% in females 2. G6PD-A+: 2.88% in males, 0.33% in females 3. G6PD-Mediterranean: 5.497% in males, 2.93% in females 4. G6PD-Mediterranean-like: 19.63% in males, 26.06% in females 5. G6PD-A-: 0.26% in males, 1.30% in females In Bisha: 1. G6PD-B+: 84.43% in males, 85.47% in females 2. G6PD-A+: 0.43% in males, 0.57% in females 3. G6PD-Mediterranean: 7.67% in males, 5.41% in females 4. G6PD-Mediterranean-like: 7.46% in males, 8.55% in females 5. G6PD-A- was not encountered in Bisha.	
El-Hazmi et al. (1994)	Saudi Arabia	G6PD-B+ (normal activity) .1 2. G6PD-A+ 3. G6PD-A- 4. G6PD-Mediterranean 5. Variant with same mobility as G6PD-B+ but with reduced activity	+G6PD-B Males: 71.73% Females: 64.49% G6PD-A+: Males: 2.88% Females: 0.33% G6PD-A-: Males: 0.26% Females: 1.30% G6PD-Mediterranean: Males: 5.497% Females: 2.93% G6PD-Mediterranean-like(variant with reduced activity): Males: 19.63% Females: 26.06%	

El-Hazmi & Warsy (1988)	Saudi Arabia	Mediterranean variant	G6PD B+: 85.3% in males, 91.5% in -1 females 2- G6PD A': 4.9% in males, 0% in females 3- G6PD A+: 5.8% in males, 0.56% in females 4- G6PD Mediterranean: 2.7% in males, 1.1% in females 5- G6PD Mediterranean-like: 1.3% in males, 1.1% in females 6- Heterozygotes G6PD: Not applicable in males, 5.08% in females	
El-Hazmi & Warsy (1986)	Saudi Arabia	G-6-PD Mediterranean -1 2- G-6-PD Mediterranean-like 3- G-6-PD A-	:Al-Hafouf-1 G-6-PD Mediterranean: 26.1% in males, 12.7% in females G-6-PD Mediterranean-like: 1.3% in males, 5.9% in females G-6-PD A-: 2.1% in males, 2.0% in females 2-Khaiber: G-6-PD Mediterranean: 6.2% in males, 2.3% in females G-6-PD Mediterranean-like: 13.1% in males, 10.7% in females G-6-PD A-: 1.1% in males, 0.6% in females 3-Jaizan: G-6-PD Mediterranean: 17.6% in males, 4.1% in females G-6-PD Mediterranean-like: 13.0% in males, 12.1% in females G-6-PD A-: 2.8% in males, 0.7% in females	

D'Souza et al. (1998)	Kuwait	G6PDMed (563C→T)	:Allele Frequency .1 - Males: 6.35% - Females: 4.25% - Overall population: 5.09% 2.G6PDMed (563C→T): - Sample size: 110 individuals - Individuals with mutation: 7 (6.36% of sample) - Hemizygous males: 4 - Heterozygous females: 2 - Homozygous females: 1 - Prevalence of G6PDMed mutation: 7.2% of randomly selected Kuwaitis - Severely deficient variants (hemizygous or homozygous): 4.5% of sample.	
Bayoumi et al. (1996)	United Arab Emirates	G6PD Mediterranean mutation .-1 - Nucleotide change: 563 C→T - Amino acid change: 188 Ser → Phe 2-. G6PD A-mutation - Nucleotide change: 202 G→A - Amino acid change: 68 Val → Met 3- G6PD Aures mutation - Nucleotide change: 143 T→C - Amino acid change: 48 Ile → Thr		

Daar et al. (1996)	Oman	G6PD Mediterranean (563 C→T,-1 188Ser → Phe) 2- G6PD A- (202 G→A, 68 Val→ Met and 376 A→G, 126 Asn →Asp) 3-G6PD Chatham (1003 G→A, 335 Ala→ Thr)	G6PD Mediterranean (563 C→T, 188 .1 :Ser → Phe) Total: 17 Males: 15 (presumed) Females: 2 (homozygous) 2. G6PD A- (202 G→A, 68 Val→Met and 376 A→G, 126 Asn→Asp): Males: 1 Females: 1 (compound heterozygote with G6PD Mediterranean) 3. G6PD Chatham (1003 G→A, 335 Ala→ Thr): Total: 2 4. Unidentified mutations: Total: 2 (not Mediterranean, A-, Chatham, or Aures) 5. G6PD Mediterranean: Silent mutation at nt 1311: Present in all chromosomes NlaIII site in intron 11: Present in all chromosomes 6. G6PD Chatham: Found on 2 different haplotypes 7. Normal chromosomes (19 total): nt 1311 mutation: Present in 9 NlaIII site in intron 11: Present in 10	
Bin Amro et al. (2014)	United Arab Emirates	Mediterranean .1 2. Aures	Mediterranean (563C→T): 78% Aures (143T→C): 12% Africa A- (202G→A): 8% Chatham (1003G→A): 1% Union (1360C→T): Not present Silent (1311C-T): Observed in 98.3% of subjects with Mediterranean mutation	

Al-Jaouni et al. (2011)	Saudi Arabia	G6PD Mediterranean .1 2. G6PD Aures 3. G6PD Chatham	:G6PD Mutations .1 - G6PD Mediterranean mutation: observed in 98 (89.1%) cases - G6PD Aures: observed in 11 (10.0%) cases - G6PD Chatham: observed in 1 (0.9%) case - G6PD A⁻ mutation: None of the samples showed this mutation 2. Polymorphism Analysis: - Samples from 29 deficient subjects (25 males and 4 females) were examined - Nucleotide 1311T (p.Tyr437Tyr) polymorphism was observed in 14 (42.4%) of 33 chromosomes studied (25 males and 4 females) - This polymorphism was associated with: - G6PD Mediterranean: n = 9 (31.0%) - G6PD Aures: n = 4 (13.8%)	
Al-Sheryani et al. (2023)	Oman		:Mediterranean variant .1 94% - had this variant - Among those with partial deficiency, 33% had this variant 2. Variant A-: - 8 cases (5.5%) 3. Chatham variant (G1003A): - 3 cases (2.1%) 4. Cosenza variant: - 1 case (0.7%) 5. Exon 11 variant: - 1 case (0.7%) 6. No mutation found: - 2 female participants with partial deficiency had no mutation identified.	

Al-Ali et al. (2002)	Saudi Arabia	Mediterranean variant -1 2- G6PD A- 3- G6PD Med/A-	Variant: Mediterranean .1 Mutation: 563 C→T Number of Cases: - Males (M): 96 - Females (F): 34 Range of Residual Activity: 2-5% Total Cases: 130 2. Variant: A- Mutation: 202 G→A Number of Cases: - Males (M): 9 - Females (F): 0 Range of Residual Activity: 2-12% Total Cases: 9 3. Variant: Med/A- Mutations: - 563 C→T - 202 G→A Number of Cases: - Males (M): 0 - Females (F): 6 Range of Residual Activity: 2-10% Total Cases: 6 4. Unknown Number of Cases: - Males (M): 9 - Females (F): 0 Range of Residual Activity: 2-10%	
Alfadhli et al. (2005)	Kuwait	G6PD-Mediterranean-1 2-G6PD-A-	.G6PD-Mediterranean(563C>T):0.742%-1 2-G6PD-A-(202G-A3764>G):0.124%. 3-G6PD-Chatham(1003G>A):0.101%. 4-G6PD-Aures(143T>C):0.034%.	
Nasserullah et al. (1998)	Saudi Arabia	Mediterranean mutation		
Gelpi & King (1977)	Saudi Arabia	Mediterranean mutation	.Mediterranean mutation:13%-1 2-G6PD-A+:2%. 3-G6PD-A-: 0.8%.	
Samilchuck et al. (1999)	Kuwait	Mediterranean mutation(563C>T)-1 2-G6PD-A-(202G>A) 3-G6PD-A+(376>A)	:Mediterranean mutation(563C>T)-1 .0.0503 2-G6PD-A-(202G>A):0.0215. 3-G6PD-A+(376>A):0.0108.	Neonatal jaundice ,and hemolytic anemia

Albagshi et al. (2020)	Saudi Arabia			
Alharbi & Khan (2014)	Saudi Arabia		%G6PD-A-:G202A 6%and A376G	
Othman et al. (2019)	Saudi Arabia	G6PD-Mediterranean-1 2-G6PD-B+	G6PD-Mediterranean: 67.8%-1 2-G6PD-B+: 14%	Pallor, tiredness and dark .urine
Malik et al. (2021)	Qatari	G6PD-Mediterranean-1 2-G6PD-A+ 3-G6PD-Asahi 4-G6PD-Chatham 5-G6PD-Aures	.G6PD-Mediterranean:0.0563%-1 2-G6PD-A+:0.0194%. 3-G6PD-Asahi:0.00785%. 4-G6PD-Chatham:0.0050%. 5-G6PD-Aures:0.00380%.	
Al-Nuaim et al. (1997)	Saudi Arabia	G6PD-B+(normal enzyme-1 phenotype) 2-G6PD-Mediterranean 3-G6PD-A+ 4-G6PD-A-	G6PD-B+:0.943% in males-1 and females. 2-G6PD-Mediterranean:0.0341%in males,0.0019% in females. 3-G6PD-A+:0.0208%in males,0.0059% in females 4-G6PD-A-:0.0019% in males.	
El-Hazmi & Warsy (1992)	Saudi Arabia	G6PD-B+(normal enzyme-1 phenotype) 2-G6PD-A+ 3-G6PD-Mediterranean(associated with severe deficiency) 4-G6PD-A- 5-G6PD-Mediterranean-like	,G6PD-B+:0.944%in the males-1 0.966% in females. 2-G6PD-Mediterranean:0.0282% in the males,0.0085% in females. 3-G6PD-A+:0.0164%in the males, 0.0068% in females. 4-G6PD-Mediterranean-like:0.0094% in the males,0.0102% in females. 5-G6PD-B+/A+: 0.0085% in females. 6-G6PD-A:0.0023% In males.	
El-Hazmi & Warsy (1994)	Saudi Arabia	G6PD-B+(normal enzyme)-1 2-G6PD-A+ 3-G6PD-A- 4-G6PD-Mediterranean(associated with severe deficiency) 5-G6PD-Mediterranean-like	G6PD-B+:0.5611%in males,0.6854% in-1 .females 2-G6PD-Mediterranean:0.3922%in males, 0.2022%in females. 3-G6PD-Mediterranean-like:0.0272% in males,0.0697% in females. 4-G6PD-A+:0.0136%in males,0.0135% in females. 5-G6PD-A–:0.0058% in males, 0.0112% in females.	

Participant Characteristics:

Sample sizes ranged from 23 to 48889 participants, with a total number of participants included in this review of 145174 participants. 48.8% of participants were males and 51.2% were females. Most studies focused on newborns and infants, and 13 studies included children, adolescents, and adults. The majority of studies focused on the native population of the country it was conducted in, except one study in the UAE that included a variety of ethnic groups including Omanis, Baluchis, Yemenis, and Bedouins.

Prevalence of G6PD Deficiency:

Regarding the prevalence of G6PD deficiency in the Gulf region, it varied significantly from region to region ranging between 0.67% to 42.7%. In the UAE, the reported prevalence of G6PDd ranged from 7.4% to 11%, while in Oman it was between 18.45% to 25%, and in Bahrain it was reported to be around 21% to 23%. Kuwait and Qatar showed the lowest prevalence rates of (5.1%-6.5%) and 5%, respectively.

In Saudi Arabia, it is widely reported that the prevalence differs in different regions of the country, which was also noticed in our review. Saudi Arabia demonstrated the highest intra-country variation given that it is the largest country among the Gulf countries with a prevalence ranging from 2.9% to 42.7%. The Eastern province of Saudi Arabia has shown the highest prevalence ranging from 25% to 42.7%. On the other hand, other regions of Saudi Arabia such as Al-Qassim showed a prevalence between 2.9 to 7% and the Western Region showed prevalence rates of 4.9% to 6.9%.

When stratifying the prevalence based on gender; males consistently had a higher prevalence ranging between 3.6% to 33.8% when compared to females (0% to 13.5%). Distribution of prevalence based on age was not usually reported since some studies analyzed the prevalence on neonates; however, it was reported in three studies, and it was shown that the prevalence ranged between 1.1% to 18.8% in infants, while it was between 5.7%-24.7% in children, and in adults it was reported to be 4.5%-6.5%.

Genetic Variants and Mutations:

The Mediterranean variant (563 C→T) was the most common genetic mutation, encompassing 51.1% to 98% of all G6PD deficient cases across 15 different studies. The second most common variant was the A- variant (202 G →A and 376 A→G), with frequency rates ranging from 2% to 15% in eight studies. Other variants reported included the Chatham variant (1003 G →A), which was reported in five studies with frequencies ranging from 0.9% to 7.1%, and the Aures variant (143

T→C) which was reported in four studies with frequencies ranging from 1.4% to 12%.

Clinical Manifestations:

Five studies reported that the incidence of favism ranged between 55% to 89% of all included patients; which was the most commonly reported manifestation. Other manifestations included neonatal jaundice and hemolytic anemia; however, specific incidence rates were not mentioned. Fava bean ingestion was the main triggering factor for hemolytic episodes, other triggers included infections which was reported as a trigger in 50% of cases in one study. It is important to mention that several studies observed a high number of asymptomatic individuals among G6PD deficient patients; this highlights the variable expressivity of this genetic condition.

Discussion:

Global prevalence:

The prevalence of G6PDd varies significantly by geographic location, with the highest prevalence being reported in countries of the sub-Saharan African regions such as Nigeria and Sudan which was reported to have prevalence rates as high as 31% [48,49]. The Middle East is another region where G6PDd is considered to be exceptionally high as shown in this review. Whereas the prevalence in other regions such as Western Europe and South America are reported to be sub 1% [48].

Prevalence variation in the Gulf region

In Saudi Arabia, significant genetic diversity exists among different regions, resulting in varying disease prevalence across the country's provinces[45]. Warsy et al. conducted a study on the distribution of G6PD deficiency in the Saudi population, revealing that the Eastern Province exhibited the highest frequency of G6PD deficiency, followed by the Southwestern Province, while the Northern Province had the lowest prevalence [8]. Which was corroborated by Al-Ali et al., where they found similar results, identifying that the Eastern Province of Saudi Arabia, specifically Al-Qatif and Al-Hassa, had the highest prevalence of G6PD deficiency[1]. Similarly, another study revealed that Al-Qatif exhibits the highest gene frequencies for G-6-PD deficiency genes [46]. These frequencies are associated with the historical prevalence of malaria in Al-Qatif. Despite the eradication of malaria from the region, the high frequency of the gene continues to persist [46]. Studies conducted in other regions of Saudi Arabia, such as Al-Ula and Bisha found the prevalence of G6PDd significantly lower compared to the prevalence in the eastern province of Saudi Arabia. However, it was higher than the frequencies reported from Riyadh and Najran [38]. Despite the

low prevalence of G6PDd in the Northern regions, it remains a significant cause of hemolysis, accounting for approximately one-third of diagnosed cases [42]. In the central province, the prevalence of G6PD deficiency was observed to be the lowest compared to previous studies conducted in Saudi Arabia. In Al-Qassim region, a relatively low prevalence of 2.9% was reported. Similar findings were established in another study, indicating a resemblance to those encountered in Riyadh [13,47]. There is a very low frequency of G6PD deficiency genes in Riyadh, this is attributed to the fact that the central province has never been endemic for malaria due to its dry climate. The low prevalence of G6PD deficiency in Riyadh may be the result of population movement to the area, as it does not seem that independent mutations have occurred in this region [43]. G6PD deficiency is typically more prevalent in males due to the mode of inheritance being X-linked. However, the observed number of deficient females exceeds what would be expected based on Hardy-Weinberg equilibrium. This could be attributed to high rates of consanguinity and intermarriage among Saudis, as well as the severe manifestation of G6PD deficiency in females who are carriers, resulting from the preferential inactivation of the X-chromosome [21,42].

In a study conducted in Kuwait, it was found that 6.5% of Kuwaiti males have G6PD deficiency [15]. Furthermore, another study found the prevalence among the Kuwaiti population to be 4.5% [39]. Notably, Kuwait has no history of malaria, similar to the central province of Saudi Arabia. This prevalence of G6PD deficiency could be attributed to ancient Arabic tribes migrating to the area from neighboring regions that are endemic for malaria [29].

In the UAE, the prevalence of G6PD deficiency is lower compared to other Gulf countries. Specifically, the prevalence in Abu Dhabi is 7.4%, 11% in Al-Ain, and 9.1% in Al-Ain infants [13,23,41]. In UAE females the prevalence was high may be attributed to X-inactivation or the presence of an 'enhancer' gene [20]. In Oman, there is a high prevalence of G6PD, ranging from 18.45% to 26% [16,19,40]. Similarly in Bahrain, there is a high prevalence of G6PD deficiency, ranging from 21% to 23.2% [28,44]. Lastly in Qatar, the prevalence of G6PD is approximately 5% [3].

Clinical Manifestations:

G6PD deficiency is characterized by the destruction of red blood cells, resulting in increased hemoglobin catabolism and a subsequent reduction in blood hemoglobin levels. This is followed by increased activity in the bone marrow, as indicated by elevated reticulocyte counts, bilirubin levels, and lactate dehydrogenase levels[13]. Patients

typically present with fatigue, pallor, dark urine, and clinical jaundice [28]. Among the factors contributing to hemolysis, fava beans have been identified as a Main trigger. However, in Arar, Saudi Arabia, found that infections account for approximately fifty percent of hemolysis cases, followed by fava beans and certain medications, as fava beans are not commonly consumed in this region [42]. Typically, G6PD deficiency is not detected in heterozygous females; however, it may result in manifestations in females in some conditions. These conditions include X-inactivation of the normal allele, preferential expression of the G6PD-deficient allele, and the presence of an "enhancer" gene that increases the likelihood of expressing G6PD deficiency[20]. G6PD-Mediterranean is the most prevalent symptomatic variant of G6PD deficiency, commonly referred to as favism, characterized by a high incidence of hemolytic anemia under oxidative stress. In contrast to the African mutation, where hemolysis has been observed in a small number of individuals [18,20]. On the other hand, the G6PD Chatham variant presents a mild or asymptomatic form of the deficiency [33]. A study indicated that patients with Mediterranean mutation require exchange transfusion more compared to Chatham mutation, the need for exchange transfusion was found to be less, However, this difference was not statistically significant [43]. The variability in clinical manifestations among patients with G6PD deficiency may be because there are over 180 known mutations of the G6PD gene which affects enzymatic activity leading to a spectrum of clinical outcomes [13].

Genetic variants:

In Saudi Arabia, genetic variants of G6PD deficiency vary across different regions. The G6PD-Mediterranean variant is the most observed variant across all areas of Saudi Arabia, while G6PD-A+ and A- variants occur at a low frequency [42]. The G6PD-A - variant accounts for 2% of G6PD deficiency cases in Saudi males and is not a major cause of G6PD deficiency, and the highest frequency of this variant was reported in Al-Ula in contrast to Bisha the G6PD-A- variant has not been found[24,40]. Additionally, there are infrequent variants such as the SIBARI mutation, which was found in three cases in the Western region, indicating significant genetic heterogeneity in this region. This diversity is expected due to Jeddah's unique geographical location as a meeting point of three continents, resulting in a population with various ethnic backgrounds [38,46].

Different genetic variants of G6PD deficiency have different levels of enzymatic activity, and their severity could

differ substantially and require different management. In G6PD deficiency, each region has a different distribution of the genetic variants of G6PD deficiency and their relative frequencies could differ dramatically among regions; for example, the most common genetic variant of G6PD deficiency reported in Ethiopia was a mutation in G267+119C/T [50]. This type was not seen among our population. In Southern Croatia, one paper reported that the most common genetic variant of G6PD deficiency was the G6PD Cosenza variant, which made up approximately 38% of all G6PD deficiency cases, and the Mediterranean variant of G6PD deficiency was the second most common[51]. In the Han Chinese population, the most common G6PD variant identified was G6PD Kaiping, followed by G6PD Canton; both of which were not present in the studies reviewed in this paper [52]. Similarly, another common variant of G6PD deficiency in Thailand which was the G6PD Mahidol variant was not present in our study [53]. Our review demonstrates that the most common variant in our region is the Mediterranean variant of G6PD deficiency followed by the A- variant, both of which were not very common in other regions of the world. It is worth noting that the Mediterranean variant usually demonstrates very low levels of enzymatic activity, and therefore it is crucial to understand these differences in presentations between different variants and populations. It is also important to recognize the most common variants in our population to enhance and improve the quality of care provided for these patients.

Factors contributing to regional variations :

It is worth noting that many studies found that G6PD deficiency is more common in malaria-endemic areas, and many experts hypothesize that there is a link between the prevalence of malaria and the distribution of G6PD deficiency variants 7,[51–53]. This was also notable in our review, where the most prevalent region of Saudi Arabia for G6PD deficiency was the eastern region, which is also the region with the highest prevalence of malaria in the country.

Clinical & public health implications:

These genetic variations among different regions are very important in understanding the specific presentation and triggers of different genetic variants, as it has been demonstrated that different genetic variants could present differently. This makes understanding the regional distribution and the frequencies of each genetic variant of G6PD deficiency

crucial in providing the most specific and appropriate management individualized to each patient based on their specific genetic variant [54].

Strengths Limitations and Future Directions:

This systematic review provides an updated insight into the prevalence and variation of G6PD deficiency in the Gulf region; as it shows that the prevalence of G6PD deficiency is significantly variable between different regions of the Gulf. It also highlights the different genetic variants of G6PD deficiency that are prevalent in this region, as it showed that the Mediterranean variant was the most common. It also characterizes the most common presentations of G6PD deficiency patients. However, this review does not come without its limitations; such as the variability in sample sizes and methodologies of included studies that might result in some under-represented regions. It was also shown that most studies conducted about this topic and that were included in this review were cross-sectional studies, which limits the understanding of long-term outcomes and implications of G6PDd. This review only included English studies, which might've led to the exclusion of some studies published in the local languages of the region. We recommend conducting larger-scale prevalence studies across all Gulf countries to further understand the accurate scale of the disease. It would also be helpful to explore the relationship between G6PDd and consanguinity and other hereditary diseases in the region. During our review process; we have not found any longitudinal studies that describe the long-term outcomes and implications of the disease in this region, it would be a very important aspect to study about this condition.

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