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Prevalence of glucose-6-phosphate dehydrogenase (G6PD) deficiency in malaria endemic region of Iran (Sistan and Baluchestan Province): Epidemiological profile and trends over time

Alireza Ansari-Moghaddam¹, Hossein Ali Adineh^{1,2*}, Mehdi Mohammadi¹, Seyed Mehdi Tabatabaei¹, Iraj Zareban¹, Mansoor Ranjbar¹, Alireza Salimi¹, Ahmad Raeesi¹¹Health Promotion Research Center, Zahedan University of Medical Sciences, Zahedan, Iran.²Department of Epidemiology and Biostatistics, Iranshahr University of Medical Sciences, Iranshahr, Iran.

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ABSTRACT

Objective: To estimate the prevalence of glucose-6-phosphate dehydrogenase (G6PD) deficiency in a malarious region of Sistan and Baluchestan Province in south-east of Iran.**Methods:** A total of 2997 subjects were selected through a multistage random sampling method from 14 districts of the province. Data were collected by trained interviewers and blood samples taken on filter papers by lab technicians. Filter papers were examined for deficiency of G6PD using the fluorescent spot test.**Results:** The combined prevalence rate of partial or severe G6PD deficiency was 12% (95% CI: 10.9–13.3) among participants. Prevalence of G6PD deficiency differed by sex, age and residency of participants. Ratio of male to female with G6PD deficiency was 1.4. Age-groups of 40–49 years [13.4% (95% CI: 10.3–17.1)] and 50–59 years [13.8% (95% CI: 10.7–17.5)] had the highest prevalence of G6PD deficiency in comparison to newborns with prevalence lower than 10% [8.40% (95% CI: 4.4–14.3)]. The prevalence rates of G6PD deficiency varied from 3.30% (95% CI: 1.4–6.7) in Zahedan to 17.9% (95% CI: 13.8–22.4) in Chabahar.**Conclusions:** The present study provided valuable data for health policy makers and those who are involved in malaria elimination program.

1. Introduction

Glucose-6-phosphate dehydrogenase (G6PD) is a cytoplasmic enzyme that catalyses the conversion of glucose-6-phosphate into 6-phosphogluconolactone in the erythrocytes. This pathway is important for the production of NADPH which helps the haemoglobin and other cellular proteins to withstand oxidant stress by reducing glutathione and stabilizing catalase[1-3].

The G6PD locus is probably one of the most polymorphic loci in humans, with over 300 allelic variants reported[2], and has

different frequencies in different regions[4,5]. The variants of G6PD, depending on the degree of enzyme deficiency, have been classified into five classes, from severe deficiency to excess enzymatic activities[6].

Deficiency of the enzyme G6PD, affecting over 400 million people in the world, is a hereditary X-chromosome-linked defect[3,6,7]. This genetic defect had prevalence of 8.5% in Africa, 7.2% in Middle East, over 10% in America, and 6.7% in Iran, where malaria is a major public health concern[1,8-11]. Clinical manifestations of G6PD deficiency include acute haemolytic anemia, neonatal jaundice, and favism which are prone to affect hemizygous males and homozygous females[6,7,12,13]. Some of the triggers of haemolysis are infections, henna, fava bean (*Vicia faba*), and oxidizing agents such as primaquine, nitrofurantoin and other anti-inflammatory drugs[14-16].

The distribution of G6PD deficiency is substantially similar to that of malaria; this considerable association represents natural selection, which means parasites of *Plasmodium falciparum* and *Plasmodium vivax* invade young red blood cells, and patients with G6PD are resistant to these parasites since G6PD protects erythrocytes and creates resistance against parasites[6,17].

Malaria is an important parasitic disease in tropical regions such

*Corresponding author: Hossein Ali Adineh, Department of Epidemiology and Biostatistics, Iranshahr University of Medical Sciences, Iranshahr, Iran; Health Promotion Research Center, Zahedan University of Medical Sciences, Zahedan, Iran.

Tels: +98 9156388799, +98 5437222230

E-mail: Payam.health@yahoo.com

This study protocol was performed according to the Helsinki Declaration and was assessed for ethic issues and approved by Ethical Committee of Zahedan University of Medical Sciences, Iran. Written informed consent was obtained from the heads of households.

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as south of Iran. In Iran, in recent years, the incidence of malaria follows a downward trend and is nearly eliminated[18]. To achieve the radical treatment and elimination of *Plasmodium* parasites, especially *Plasmodium falciparum*, antimalarial drugs such as primaquine are required. These drugs act as oxidant and may lead to haemolysis in people with G6PD deficiency[6,19]. Therefore, knowledge about the prevalence of G6PD deficiency and other triggers of haemolysis for eradication of malaria is important. It is noticeable that problems such as malaria, infectious disease, illegal migrations and movement of Afghan and Pakistani refugees, special beliefs and cultures have led to no improvement in health condition in south of Iran. During the last several years, the Center for Disease Control and Prevention of Iran has initiated widespread malaria control programs. Consequently, the country has witnessed a significant reduction in the burden of malaria and it has been advancing towards malaria elimination. On the other hand, primaquine could play a vital role in malaria elimination via destroying silent hypnozoites responsible for relapse as well as attacking gametocytes responsible for local transmission. Nevertheless, primaquine as an oxidant may trigger haemolysis amongst cases with deficiency in G6PD. Therefore, understanding the frequency and geographical distribution of this genetic risk factor in malarious region of Iran would be of major public health importance in practicing primaquine treatment for malaria elimination. Hence, the present study aimed to estimate the prevalence of G6PD deficiency in a malarious region of Sistan and Baluchestan Province in southeast of Iran.

2. Method and materials

A population-based cross-sectional study was conducted to investigate the prevalence of G6PD deficiency in southeast of Iran. Population studied were individuals who live in Sistan and Baluchestan Province. In order to estimate the plausible sample size, prevalence of outcome variable was assumed to be 10%, and design effect, precision and confidence interval (CI) was considered to be 2.7%, 2% and 95%, respectively. Based on above assumption, at least 2340 subjects were required but in study process 2997 subjects were recruited.

Multistage cluster random sampling method was used to select subjects of study. Population of all health provider centers/units in the target districts were calculated cumulatively. Then clusters and head-clusters were determined using systematic random sampling method. Finally, 2997 subjects were randomly selected from 78 clusters. Each cluster comprised 8 age-groups of newborns, < 5 years, 5–9 years, 10–19 years, 20–29 years, 30–39 years, 40–49 years, and 50 years and above. The blood sample from umbilical cord of newborns was obtained from hospitals of study population as well. Indeed, each cluster contained two samples for newborn babies which produced a total of 156 participants (78 × 2) of newborns. Well-trained interviewers and laboratory technicians collected data through face-to-face interview with individuals using a pre-tested interviewer-administered structured questionnaire and blood samples were taken on filter papers. Sorted and marked filter papers with the subjects' code were examined in laboratory by Kimia Pajouhan test kit (Iran Medical Equipments and Medical Engineering Company, Tehran, Iran) which uses Beutler fluorescent spot method to identify nicotinamide adenine dinucleotide phosphate for detection of G6PD deficiency[20]. The fluorescent spot test is reliable for the detection of hemizygous males and homozygous females with a sensitivity and specificity of 100% and

99%, respectively[21].

Information collected through questionnaires as well as results of laboratory examinations were entered into SPSS software by a team of trained data entry operators under supervision of main investigators. Accordingly, data were analyzed and described using descriptive statistics (*i.e.* frequencies, percentages) and 95% CI. This study protocol was performed according to the Helsinki Declaration and was assessed for ethic issues and approved by Ethical Committee of Zahedan University of Medical Sciences, Iran. Furthermore, the health authorities of all districts were informed about the aims of the project and their consents for cooperation in this case were obtained. Additionally, written informed consent was obtained from the heads of households.

3. Results

A total of 2997 randomly selected participants from 14 districts of Sistan and Baluchestan Province were surveyed in the present study. The distribution of population according to sex and age is shown in Table 1. There is an equal gender distribution for all age groups. Overall, 2997 participants were screened for G6PD deficiency and the levels of G6PD enzyme activity among studied cases are displayed in Table 2. In the study areas, the overall prevalence rate of G6PD deficiency was 12% (95% CI: 10.9–13.3). Partial and severe deficiency of G6PD was observed in 5.3% (95% CI: 4.6–6.2) and 6.7% (95% CI: 5.8–7.7) of individuals, respectively.

Table 1

Distribution of study population by sex and age-group [n (%)].

Age-groups	Gender		Total
	Male	Female	
Newborns	68 (2.3)	72 (2.4)	140 (4.7)
< 5 years	170 (5.7)	174 (5.9)	344 (11.6)
5–9 years	164 (5.5)	163 (5.5)	327 (11.1)
10–19 years	200 (6.8)	195 (6.6)	395 (13.4)
20–29 years	253 (8.6)	242 (8.2)	495 (16.7)
30–39 years	213 (7.2)	232 (7.8)	445 (15.0)
40–49 years	204 (6.9)	197 (6.7)	401 (13.9)
50 years and above	210 (7.1)	200 (6.8)	410 (13.9)
Total	1482 (50.1)	1475 (49.9)	2957 (100.0) [*]

*: The total number of subjects is 2997, but 40 subjects were missed for gender or age variable.

Table 2

Prevalence of G6PD deficiency [% (95% CI)].

Variables		Partially deficient	Severely deficient	Total
Age-groups	Newborns	2.8 (0.8–7.1)	5.6 (2.5–10.8)	8.4 (4.4–14.3)
	< 5 years	4.9 (2.9–7.8)	5.5 (3.3–8.4)	10.4 (7.4–14.1)
	5–9 years	4.8 (2.8–7.8)	7.0 (4.5–10.3)	11.8 (8.5–15.8)
	10–19 years	3.5 (1.9–5.8)	7.0 (4.7–10.0)	10.5 (7.7–14.0)
	20–29 years	6.6 (4.6–9.2)	6.2 (4.2–8.7)	12.8 (10.0–16.1)
	30–39 years	4.9 (3.1–7.3)	7.3 (5.1–10.1)	12.2 (9.3–15.5)
	40–49 years	5.6 (3.6–8.3)	7.8 (5.4–10.9)	13.4 (10.3–17.1)
	≥ 50 years	7.4 (5.1–10.3)	6.4 (4.3–9.2)	13.8 (10.7–17.5)
Gender	Male	5.3 (4.2–6.6)	8.8 (7.4–10.3)	14.1 (12.4–16.0)
	Female	5.4 (4.3–6.7)	4.7 (3.7–6.0)	10.1 (8.7–11.8)
Nationality	Iranian	5.3 (4.5–6.2)	6.8 (5.9–7.8)	12.1 (10.4–14.0)
	Foreign immigrants	6.0 (3.2–10.1)	6.0 (3.2–10.1)	12.0 (6.4–20.2)
Total		5.3 (4.6–6.2)	6.7 (5.8–7.7)	12.0 (10.9–13.3)

When comparing G6PD deficiency by age, it was found that the highest proportion of G6PD deficiency was found in age group of 40–49 years [13.4% (95% CI: 10.3–17.1)] and 50–59 years [13.8%

(95% CI: 10.7–17.5)] in contrast to the lowest prevalence of lower than 10% in newborns [8.40% (95% CI: 4.40 - 14.3)]. Also, the prevalence rate of G6PD deficiency differed by sex (Table 2) with 14.1% (95% CI: 12.4–16.0) male participants having partial or severe G6PD deficiency compared to 10.1% (95% CI: 8.7–11.8) of female subjects.

Table 2 shows the distribution of G6PD deficiency by nationality. Among the Iranian and foreigner immigrants (Afghan and Pakistani) participants, the overall prevalence rates of G6PD deficiency were almost the same. The distribution of G6PD deficiency by gender and age is shown in Table 3. According to the findings, the prevalence of partial and severe G6PD deficiency was higher in male than female in all age groups. Ratio of male to female with G6PD deficiency ranged from 1.05 in age group of 30–39 years to 2.11 in newborns. In males, the age group of 40–49 years had the highest prevalence rate (17.2%), and newborns and the age group of < 5 years had the lowest rate (11.8%). In females, the age group of 20–29 years had the highest prevalence rate of G6PD deficiency (12%), while the

lowest prevalence rate was seen in newborns (5.6%).

Geographical distribution of G6PD deficiency is given in Table 4 and Figure 1. The prevalence rates of G6PD deficiency varied from 3.30% (95% CI: 1.4–6.7) in Zahedan to 17.9% (95% CI: 13.8–22.4) in Chabahar. The proportion of subjects with G6PD deficiency ranged from 3% to 10% in Zahedan, Dalgab, Konarak, Mehrestan and Mirjaveh, while it varied from 12% to about 18% in the remaining districts.

Table 3

Prevalence of G6PD deficiency by sex and age [% (95% CI)].

Age-groups	Male	Female	Total
Newborns	11.8 (5.2–21.9)	5.6 (1.5–13.6)	8.4 (4.4–14.3)
< 5 years	11.8 (7.3–17.6)	9.2 (5.3–14.5)	10.4 (7.4–14.1)
5–9 years	13.4 (8.6–19.6)	10.4 (6.2–16.2)	11.8 (8.5–15.8)
10–19 years	14.0 (9.5–19.6)	7.2 (4.0–11.8)	10.5 (7.7–14.0)
20–29 years	13.8 (9.8–18.7)	12.0 (8.2–16.8)	12.8 (10.0–16.1)
30–39 years	12.2 (8.1–17.3)	11.6 (7.8–16.4)	12.2 (9.3–15.5)
40–49 years	17.2 (12.2–23.0)	10.2 (6.3–15.2)	13.4 (10.3–17.1)
50 years and above	16.7 (11.9–22.4)	11.5 (7.4–16.8)	13.8 (10.7–17.5)
Total	14.1 (12.4–16.0)	10.1 (8.7–11.8)	12.0 (10.9–13.3)

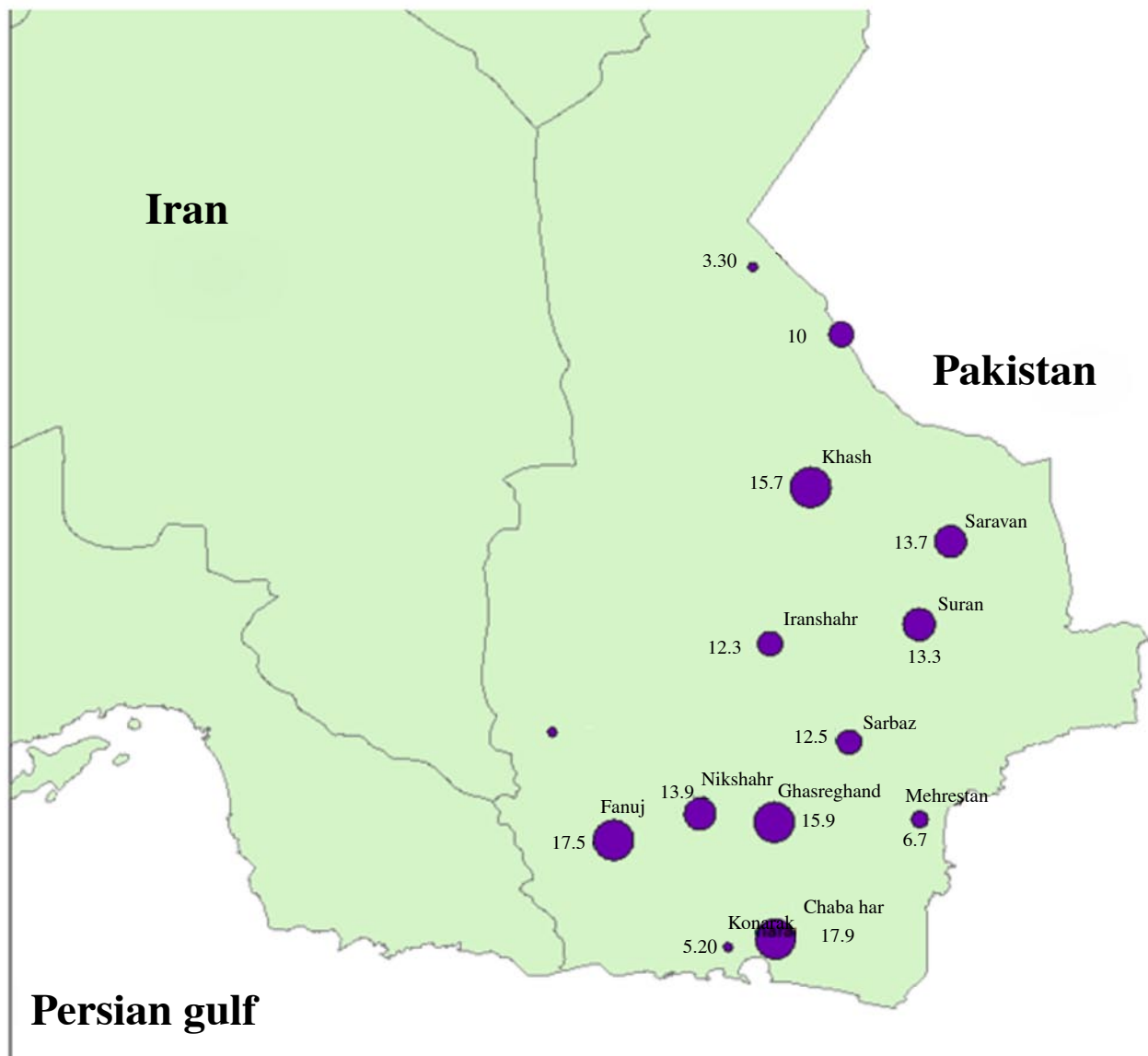


Figure 1. Geographical distribution of G6PD deficiency.

Table 4

Frequency of G6PD by region [% (95% CI)].

District	Partially deficient	Severely deficient	Total
Nikshahr	9.3 (5.2–15.1)	4.6 (1.9–9.3)	13.9 (8.8–20.5)
Ghasrghand	9.2 (4.7–15.8)	6.7 (2.9–12.7)	15.9 (9.8–23.6)
Dalغان	0.8 (0.02–4.60)	3.3 (0.9–8.3)	4.1 (1.4–9.4)
Fanoj	7.5 (3.5–13.8)	10.0 (5.3–16.8)	17.5 (11.2–25.5)
Iranshahr	3.0 (1.4–5.6)	9.3 (6.3–13.2)	12.3 (8.8–16.6)
Soran	7.3 (3.7–12.7)	6.0 (2.8–11.1)	13.3 (8.3–19.8)
Zahedan	1.9 (0.5–4.8)	1.4 (0.3–4.1)	3.3 (1.4–6.7)
Sarbaz	7.0 (4.5–10.3)	5.5 (3.2–8.5)	12.5 (9.1–16.5)
Mehrestan	2.2 (0.6–5.6)	4.5 (1.9–8.6)	6.7 (3.5–11.4)
Mirjaveh	4.2 (1.4–9.4)	5.8 (2.4–11.6)	10.0 (5.3–16.8)
Chahbahar	10.8 (7.6–14.7)	7.1 (4.5–10.4)	17.9 (13.8–22.4)
Konarak	3.3 (1.4–6.7)	1.9 (0.5–4.8)	5.2 (2.6–9.2)
Saravan	1.9 (0.8–3.9)	11.8 (8.7–15.6)	13.7 (10.4–17.8)
Khhash	6.7 (4.1–10.1)	9.0 (6.0–12.9)	15.7 (11.8–20.3)
Total	5.3 (4.6–6.2)	6.7 (5.8–7.7)	12.0 (10.9–13.3)

4. Discussion

The present study revealed a combined prevalence of 12% for both severe and partial form of G6PD deficiency in southeast of Iran. The prevalence was higher in male participants, especially in the adult age groups. Furthermore, a greater proportion of the subjects from malaria endemic districts of the study areas such as Chahbahar were also found to be G6PD-deficient. There were not noticeable differences in the prevalence of G6PD deficiency between Iranian and the foreign nationals that were investigated in this study.

In general, prevalence of G6PD deficiency varies worldwide and among different cities of a country; it ranged for neighboring countries from 1.8% in Pakistan, 3.1% in Afghanistan, 6.7% in Iran to 10.9% in Iraq[9,22–24]. Also, in malarious regions of the world, the prevalence rate of G6PD deficiency was reported to be 8% on average[25] which is lower than that (12%) in the present study. Nevertheless, the prevalence rate of the current report is lower than that of some parts of the world including Zuniga in Honduras (16.8%)[26] and is higher than that of some other areas such as Venezuela (3.6%)[26,27]. Interestingly, rate of G6PD deficiency among study participants in southeast and north of Iran is considerably higher than that in south and central part of Iran[28,29]. Furthermore the average prevalence of G6PD deficiency has been reported to be 6.7% across the country[9]. The finding can be explained by the fact that there is a protective correlation between G6PD and malaria, and other unknown factors may be involved in fluctuation of the number of people with this deficiency.

According to the previous epidemiologic studies, the prevalence rate of G6PD deficiency is higher among males than females[11,27,30–35]. In line with these studies, the current study also revealed a higher prevalence rate of G6PD deficiency among males compared to the females. The higher prevalence of G6PD deficiency in males than females could be possibly due to X-linked recessives.

Several epidemiological studies demonstrated that G6PD deficiency is mainly distributed in areas of the world where malaria was previously or is currently endemic[11,21,25,26,32,35]. Similarly, there is various geographic distribution of G6PD deficiency in the study regions with the highest prevalence rate observed in Chahbahar District as one of the previously malaria endemic areas in contrast to the lowest prevalence rate seen in Zahedan District as non-malaria

endemic region, although low/high prevalence of G6PD deficiency in endemic/non-endemic part can be due to some factors such as immigration of healthy or malarious individuals and method of sampling. Additionally, the findings showed a higher prevalence rate of G6PD deficiency in population of 50 years and older compared to the lowest prevalence rate seen in newborns. Low exposure rates of newborns to malaria might explain this variation as the country is in the malaria elimination phase.

There are some evidences that the frequency of G6PD deficiency differed across the world depending on the ethnic groups and regions[11,21,25]. On the contrary, in the present study, the distribution of G6PD deficiency was the same among the Iranian and foreign immigrants (Afghan and Pakistani participants). Similar results have been reported by previous study conducted in Brazil as well[30]. The comparable frequency of G6PD deficiency among both Iranian participants and Afghan/Pakistani participants could be possibly due to the fact that they are coming from the similar malaria endemic regions of Afghanistan and Pakistan.

In conclusion, Sistan and Baluchestan Province is amongst regions with high frequency of G6PD deficiency. In order to decrease hemolysis and other complications, screening tests are recommended to identify the G6PD deficiency, especially those born to families with a history of the disease.

Conflict of interest statement

We declare that we have no conflict of interest.

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