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Glucose-6-phosphate dehydrogenase deficiency and long-term risk of immune-related disorders

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Introduction: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an X-linked enzymatic disorder that is particularly prevalent in Africa, Asia, and the Middle East. This study aimed to assess the long-term health risks associated with G6PD deficiency.

Methods: A retrospective cohort study was conducted using data from a national healthcare provider in Israel (Leumit Health Services). A total of 7,473 G6PD-deficient individuals were matched with 29,892 control subjects in a 1:4 ratio, based on age, gender, socioeconomic status, and ethnic groups. The exposure of interest was recorded G6PD diagnosis or positive G6PD diagnostic test. The main outcomes and measures included rates of infectious diseases, allergic conditions, and autoimmune disorders between 2002 and 2022.

Results: Significantly increased rates were observed for autoimmune disorders, infectious diseases, and allergic conditions in G6PD-deficient individuals compared to the control group. Specifically, notable increases were observed for rheumatoid arthritis (odds ratio [OR] 2.41, $p < 0.001$), systemic lupus erythematosus (OR 4.56, $p < 0.001$), scleroderma (OR 6.87, $p < 0.001$), pernicious anemia (OR 18.70, $p < 0.001$), fibromyalgia (OR 1.98, $p < 0.001$), Graves' disease (OR 1.46, $p = 0.001$), and Hashimoto's thyroiditis (OR 1.26, $p = 0.001$). These findings were supported by elevated rates of positive autoimmune serology and higher utilization of medications commonly used to treat autoimmune conditions in the G6PD-deficient group.

Discussion: In conclusion, individuals with G6PD deficiency are at a higher risk of developing autoimmune disorders, infectious diseases, and allergic conditions. This large-scale observational study provides valuable insights into the comprehensive association between G6PD deficiency and infectious and

immune-related diseases. The findings emphasize the importance of considering G6PD deficiency as a potential risk factor in clinical practice and further research is warranted to better understand the underlying mechanisms of these associations.

KEYWORDS

G6PD deficiency, autoimmunity, allergy, infectious diseases, fibromyalgia, hidradenitis suppurativa, rheumatoid arthritis, lupus (SLE)

Introduction

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common enzymatic X-linked human disorder and it primarily affects red blood cells (1). An estimated 400 million people worldwide carry a mutation in the G6PD gene associated with enzyme deficiency, with marked ethnic and geographic differences (2, 3). G6PD deficiency is prevalent in Africa, Asia and the Middle East. In the United States, about 14% of African-American men are affected (4, 5). There are numerous alleles of different severities and geographic propensities (6). Most individuals with G6PD deficiency remain asymptomatic or experience mild symptoms throughout their lives but may develop hemolysis under certain circumstances such as neonatal jaundice, consumption of specific medications, or following an infection.

Several studies have suggested that G6PD-deficient individuals may be more predisposed to specific autoimmune diseases (7, 8), infections (9–11) and diabetes mellitus (12, 13). Associations were found between G6PD deficiency and cardiovascular risk (14–17) in conflicting directions. Regarding malignancy, key studies have reported lower rates of cancer in G6PD-deficient patients, in particular for cancers of endodermal origin (colorectal, gastric and liver malignancies) (18, 19), but a protective effect of G6PD against cancer was not found for other types of cancer and notably hematologic malignancies (20, 21). We recently reported that individuals with G6PD deficiency had an increased risk of COVID-19 infection and severity, with higher rates of hospitalization and diagnosed long COVID (22).

To date, there is no large-scale study showing the association of G6PD deficiency with infectious and immune-related diseases

altogether. This large-scale observational study addresses this knowledge gap.

Methods

Cohort data source

We performed a retrospective cohort study using data from Leumit Health Services (LHS), one of the four nationwide healthcare providers in Israel (23). LHS has been using centrally managed electronic health records (EHR) for the last 20 years. The EHRs includes demographic data, physical measures, laboratory test results, medication prescription and purchases, and diagnosed conditions, documented by physicians according to International Classification of Diseases 9th Revision (ICD-9).

Data were collected from the LHS data warehouse as of December 31, 2022. The study cohort was drawn from a pool of over a million individuals who had been insured at least two years by LHS between 2002 and 2022.

Cohort design

The study involves the comparison of two matched groups of individuals. The G6PD deficiency group consists of patients with a documented diagnosis of G6PD deficiency or a recorded laboratory test of G6PD activity performed in LHS, resulting in a measurement below 4 U/g Hg.

The control group included individuals without G6PD deficiency who exactly matched individuals in the G6PD deficiency group on the following variables: gender, age, geographic area based socio-economic status (SES) category, ethnic group, and year of first documented visit in LHS EHR system, with a ratio of 4 controls for each included G6PD deficient patient. Individuals with G6PD deficiency for which the matching algorithm was not able to find four control individuals with identical matching features were left out from the analysis.

Demographic records were extracted from LHS data warehouse, along with ICD-9 diagnosis records matching a list of pre-defined conditions, the last recorded body mass index (BMI), blood pressure (BP) measures, and smoking habits. The last laboratory

Abbreviations: BMI, Body Mass Index; BP, blood pressure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; EHR, electronic health records; ESR, Erythrocyte sedimentation rate; G6PD, Glucose-6-phosphate dehydrogenase; ICD-9, International Classification of Diseases 9th Revision; Ig, Immunoglobulins; IQR, Interquartile range; LHS, Leumit Health Services; NET, neutrophil extracellular trap; NOX2, NADPH oxidase 2; OR, Odds Ratio; ROS, reactive oxygen species; SES, socio-economic status; SLE, systemic lupus erythematosus; SMD, standardized mean difference.

test results for a set of predefined laboratory measures performed by LHS laboratory facilities were also extracted.

Statistical methods

Statistical association was assessed using Fisher's Exact Test for binary variables, with odds-ratio and 95% confidence interval (CI). Numerical variables were tested using the Mann-Whitney U test, which does not assume a normal distribution. Cohort data extraction was performed using programs developed by Leumit Research Institute in Python. Statistics were computed in R statistical software, version 4.0.4.

Results

Demographic and laboratory characteristics

Among the pool of 1,031,354 LHS members with at least two years of medical history in the EHR, we identified 7,827 individuals with either a G6PD deficiency diagnosis or laboratory evidence of G6PD deficiency. The matching procedure selected 7,473 G6PD deficient subjects with 29,892 control subjects (4:1 control ratio) of the same gender, age, socioeconomic category, ethnic group, and year of first recorded visit in LHS (354 G6PD deficient individuals were left out for lack of proper matching controls). The demographic characteristics of the two groups are shown in [Table 1](#). The mean patient age was 29.2 ± 22.3 years, 68.7% were men, and the mean follow-up time was 14.3 ± 6.2 years in both groups. There were no statistically significant differences in gender, age, ethnic and socioeconomic groups and follow-up time between the two study groups.

Comorbidities of G6PD subjects and controls

The proportions of individuals in the two groups who had at least one diagnosis record for the studied conditions are presented in [Table 2](#), together with the odds ratio (OR) and 95% confidence intervals (CI).

General comorbidities

The proportions of patients with hypertension, ischemic heart disease, chronic obstructive pulmonary disease (COPD) and chronic kidney disease were not statistically different in the two groups, but there were comparably fewer individuals with diabetes mellitus in the G6PD deficient group (OR 0.85, 95% CI, 0.76 to 0.95, $P=0.003$).

Infectious diseases

Most infectious diseases tested were significantly more frequent among G6PD deficient subjects than in controls ([Table 2](#)), with odds

ratios typically around 1.15, with the notable exception of acute bronchitis/bronchiolitis which had a similar cumulative occurrence of ~28% in the two groups. Strong associations were observed for urinary tract infections (OR 1.19, 95% CI 1.14 to 1.27, $P<0.001$) and unspecified viral infections (OR 1.19, 95% CI 1.12 to 1.25, $P<0.001$). Staphylococcal infections were particularly more frequent among G6PD deficient patients (OR 1.62, 95% CI 1.14 to 2.27, $P<0.001$).

Allergic/atopic conditions

For most of the atopic or allergic conditions assessed, we observed a higher prevalence among G6PD deficient individuals than in the control group ([Table 2](#)), notably for allergic conjunctivitis (OR 1.25, 95% CI 1.15 to 1.36, $P<0.001$), allergy to food/unspecified (OR 1.23, 95% CI 1.15 to 1.32, $P<0.001$), contact dermatitis (OR 1.19, 95% CI 1.15 to 1.32, $P<0.001$) and allergic urticaria (OR 1.14, 95% CI 1.04 to 1.24, $P<0.001$). Asthma was slightly more frequent among G6PD deficient individuals (OR 1.08, 95% CI 1.00 to 1.16, $P=0.043$). In contrast, atopic dermatitis rate was similar among G6PD deficient patients and the control group.

Systemic autoimmune diseases

Systemic autoimmune diseases were strikingly more frequent in the G6PD group ([Table 2](#)). The association was particularly notable for scleroderma (OR 6.87, 95% CI 2.49 to 20.59, $P<0.001$), systemic lupus erythematosus (SLE) (OR 4.56, 95% CI 2.46 to 8.48, $P<0.001$), dermatomyositis (OR 3.56, 95% CI 1.70 to 7.40, $P<0.001$). Major risk associations were also observed for rheumatoid arthritis (OR 2.41, 95% CI 1.85 to 3.12, $P<0.001$), Sjögren's syndrome (OR 2.80, 95% CI 1.53 to 5.07, $P=0.001$) and ankylosing spondylitis (OR 2.52, 95% CI 1.41 to 4.42, $P=0.001$).

We confirmed these findings by querying the proportion of individuals in each group who had purchased at least once, medications commonly used for autoimmune diseases, such as methotrexate (OR 2.30, 95% CI 1.74 to 3.02, $P<0.001$), hydroxychloroquine (OR 2.78, 95% CI 2.08 to 3.71, $P<0.001$), etanercept (OR 3.51, 95% CI 2.03 to 6.02, $P<0.001$) and leflunomide (OR 3.55, 95% CI 1.93 to 6.47, $P<0.001$). We also queried serological tests commonly used to diagnose autoimmune conditions ([Table 3A](#)). The G6PD deficient group had significantly higher rates of positive serological tests for antinuclear (OR 1.81), anti-histones (OR 2.96), RNP-68 (OR 4.00), and anti-Smith (OR 5.00) antibodies.

Other inflammatory conditions

We further compared the two groups for a few organ-specific inflammatory conditions. We observed significantly higher rate of Hashimoto's thyroiditis (OR 1.26, 95% CI 1.09 to 1.44, $P=0.001$) and Graves' disease (OR 1.46, 95% CI 1.16 to 1.81, $P=0.03$). Significantly higher rates were also observed for pernicious anemia (OR 18.70, 95% CI 5.22 to 101.6, $P<0.001$), idiopathic

TABLE 1 Demographic characteristics of G6PD deficient subjects and matched controls.

N		G6PD Deficiency	Control	p
N		7,473	29,892	
Gender, No. (%)	Female	2,327 (31.1%)	9,308 (31.1%)	>.99
	Male	5,146 (68.9%)	20,584 (68.9%)	>.99
Age (years)	mean ± SD	29.2 ± 22.3	29.2 ± 22.3	>.99
follow-up (years)	mean ± SD	14.3 ± 6.2	14.3 ± 6.2	0.29
age category, No. (%)	0- 2	378 (5.06%)	1,512 (5.06%)	>.99
	3- 9	1,331 (17.81%)	5,324 (17.81%)	>.99
	10-18	1,268 (16.97%)	5,072 (16.97%)	>.99
	19-29	1,355 (18.13%)	5,420 (18.13%)	>.99
	30-39	1,053 (14.09%)	4,212 (14.09%)	>.99
	40-49	623 (8.34%)	2,488 (8.32%)	0.96
	50-59	531 (7.11%)	2,128 (7.12%)	0.98
	60-69	460 (6.16%)	1,841 (6.16%)	>.99
	70-79	260 (3.48%)	1,039 (3.48%)	>.99
	80-89	152 (2.03%)	608 (2.03%)	>.99
	>= 90	62 (0.83%)	248 (0.83%)	>.99
Socio-economic status (1–20)	mean ± SD	9.19 ± 3.56	9.14 ± 3.64	0.32
	missing	708 (9.47%)	2,832 (9.47%)	
Ethnic group, No. (%)	Arab	729 (9.76%)	2,916 (9.76%)	>.99
	General	5,096 (68.19%)	20,384 (68.19%)	>.99
	Jewish Ultra-orthodox	1,648 (22.05%)	6,592 (22.05%)	>.99
Smoking status, n (%)	Non-smoker	3,505 (76.93%)	13,073 (74.77%)	0.002
	Past smoker	83 (1.82%)	316 (1.81%)	0.95
	Smoker	968 (21.25%)	4,096 (23.43%)	0.002
	missing	2,917 (39.03%)	12,407 (41.51%)	
BP systolic (mmHg)	mean ± SD	119.8 ± 16.0	120.2 ± 16.3	0.23
	missing	2,298 (30.8%)	9,568 (32.0%)	
BP diastolic (mmHg)	mean ± SD	71.8 ± 10.2	72.4 ± 10.4	0.001
	missing	2,299 (30.8%)	9,568 (32.0%)	
BMI (kg/m ²)	mean ± SD	23.3 ± 6.2	23.4 ± 6.4	0.10
	missing	740 (9.90%)	3,626 (12.13%)	
BMI category	<18.5: Underweight	1,673 (24.8%)	6,590 (25.1%)	0.69
	18.5-24.9: Normal	2,570 (38.2%)	9,837 (37.5%)	0.28
	25-29.9: Overweight	1,575 (23.4%)	5,905 (22.5%)	0.11
	>=30: Obese	915 (13.6%)	3,934 (15.0%)	0.004
	missing	740 (9.9%)	3,626 (12.1%)	

TABLE 2 Clinical characteristics of G6PD deficient subjects and matched controls.

	G6PD Deficiency	Control	p	Odds Ratio [95% CI]
N	7,473	29,892		
General comorbidities, No. (%)				
Arterial hypertension	804 (10.8%)	3,365 (11.3%)	0.23	0.95 [0.87 to 1.03]
Diabetes mellitus	418 (5.59%)	1,952 (6.53%)	0.003	0.85 [0.76 to 0.95]
Ischemic heart disease	252 (3.37%)	909 (3.04%)	0.15	1.11 [0.96 to 1.28]
Chronic Obstructive Pulmonary Disease	212 (2.84%)	738 (2.47%)	0.08	1.15 [0.98 to 1.35]
Chronic kidney disease	109 (1.46%)	364 (1.22%)	0.11	1.20 [0.96 to 1.49]
Infectious diseases, No. (%)				
Acute sinusitis	1,424 (19.1%)	5,091 (17.0%)	<0.001	1.15 [1.07 to 1.22]
Acute bronchitis/bronchiolitis	2,083 (27.9%)	8,442 (28.2%)	0.54	0.98 [0.93 to 1.04]
Pneumonia, bacterial	275 (3.68%)	962 (3.22%)	0.047	1.15 [1.00 to 1.32]
Acute tonsillitis	4,112 (55.0%)	15,411 (51.6%)	<0.001	1.15 [1.09 to 1.21]
Cellulitis	1,688 (22.6%)	6,038 (20.2%)	<0.001	1.15 [1.08 to 1.23]
Acute gastroenteritis	3,690 (49.4%)	13,865 (46.4%)	<0.001	1.13 [1.07 to 1.19]
Urinary tract infection	1,490 (19.9%)	5,182 (17.3%)	<0.001	1.19 [1.11 to 1.27]
Viral infections (unspecified)	5,032 (67.3%)	18,968 (63.5%)	<0.001	1.19 [1.12 to 1.25]
Staphylococcal infections	50 (0.67%)	124 (0.41%)	0.006	1.62 [1.14 to 2.27]
Atopic diseases, No. (%)				
Allergic rhinitis	1,062 (14.2%)	3,732 (12.5%)	<0.001	1.16 [1.08 to 1.25]
Allergic conjunctivitis	859 (11.49%)	2,806 (9.39%)	<0.001	1.25 [1.15 to 1.36]
Allergic urticaria	722 (9.66%)	2,562 (8.57%)	0.003	1.14 [1.04 to 1.24]
Allergy to food/unspecified	1,202 (16.1%)	4,031 (13.5%)	<0.001	1.23 [1.15 to 1.32]
Asthma	1,110 (14.9%)	4,166 (13.9%)	0.04	1.08 [1.00 to 1.16]
Atopic dermatitis	1,110 (14.9%)	4,361 (14.6%)	0.57	1.02 [0.95 to 1.10]
Contact dermatitis	1,632 (21.8%)	5,700 (19.1%)	<0.001	1.19 [1.11 to 1.26]
Systemic autoimmune diseases, No. (%)				
Rheumatoid arthritis	98 (1.31%)	164 (0.55%)	<0.001	2.41 [1.85 to 3.12]
Systemic lupus erythematosus	25 (0.335%)	22 (0.074%)	<0.001	4.56 [2.46 to 8.48]
Sjogren's disease	21 (0.28%)	30 (0.10%)	0.001	2.80 [1.53 to 5.07]
Scleroderma	12 (0.161%)	7 (0.023%)	<0.001	6.87 [2.49 to 20.59]
Dermatomyositis	16 (0.214%)	18 (0.060%)	<0.001	3.56 [1.70 to 7.40]
Ankylosing spondylitis	22 (0.29%)	35 (0.12%)	0.001	2.52 [1.41 to 4.42]
Other inflammatory conditions, No. (%)				
Hashimoto's thyroiditis	277 (3.71%)	889 (2.97%)	0.001	1.26 [1.09 to 1.44]
Graves' disease	113 (1.51%)	312 (1.04%)	0.001	1.46 [1.16 to 1.81]
Pernicious anemia	14 (0.187%)	3 (0.010%)	<0.001	18.70 [5.22 to 101.6]
Idiopathic pulmonary fibrosis	15 (0.201%)	25 (0.084%)	0.009	2.40 [1.18 to 4.74]
Hidradenitis suppurativa	25 (0.33%)	39 (0.13%)	<0.001	2.57 [1.49 to 4.36]

(Continued)

TABLE 2 Continued

	G6PD Deficiency	Control	p	Odds Ratio [95% CI]
N	7,473	29,892		
Fibromyalgia	167 (2.23%)	342 (1.14%)	<0.001	1.98 [1.63 to 2.39]
Psoriasis	247 (3.31%)	836 (2.80%)	0.02	1.19 [1.02 to 1.37]
Inflammatory Bowel Disease	60 (0.80%)	179 (0.60%)	0.05	1.34 [0.98 to 1.81]
Celiac disease	33 (0.44%)	95 (0.32%)	0.12	1.39 [0.91 to 2.09]
Malignancies, No. (%)				
Hematologic malignancies	42 (0.56%)	171 (0.57%)	>.99	0.98 [0.68 to 1.39]
Solid tumors	224 (3.00%)	859 (2.87%)	0.56	1.04 [0.90 to 1.21]

pulmonary fibrosis (OR 2.40, 95% CI 1.18 to 4.74, $P=0.009$) and hidradenitis suppurativa (OR 2.57, 95% CI 1.49 to 4.36, $P<0.001$). Psoriasis rate was also elevated to a lesser extent (OR 1.19, 95% CI 1.02 to 1.37, $P=.02$). Interestingly fibromyalgia rate was significantly higher in the G6PD deficient group (OR 1.98, 95% CI 1.63 to 2.39, $P<0.001$). Inflammatory bowel disease (IBD) was more frequent with borderline statistical significance (OR=1.34, 95% CI 0.98 to 1.81, $P=.05$). We confirmed the elevated rates of pernicious anemia and thyroiditis by comparing the rate of positive tests for anti-gastric parietal cells and anti-TPO in the two groups. Both were significantly elevated (Table 3B).

Malignancy conditions

There were no statistically significant differences in the rates of hematologic malignancies and solid tumors.

Laboratory tests in G6PD subjects and controls

To better understand the biological basis of these associations, we compared laboratory test results of individuals from the two

groups. Table 4 displays the median and interquartile ranges (IQR) of the last test performed per patient together with the p-value for comparison and standardized mean difference (SMD).

As expected for a condition associated with hemolysis, we observed significantly lower levels of red blood cells ($P<0.001$, SMD=-0.419), hemoglobin ($P<0.001$, SMD=-0.225) and hematocrit ($P<0.001$, SMD=-0.165) in the G6PD deficient group. Interestingly, we also observed lower levels of white blood cells (WBC) ($P<0.001$, SMD=-0.068) in general, and more specifically, diminished monocytes ($P<0.001$, SMD=-0.141) and neutrophils ($P<0.001$, SMD=-0.058). The breakdown of cell types among WBC was not significantly different in G6PD deficiency, except for monocytes, which have a decreased percentage among WBC ($P<0.001$, SMD=-0.096), whereas the percentage of basophils was increased in G6PD deficient individuals ($P<0.001$, SMD=0.053). Platelets are also present in higher numbers in G6PD deficient patients ($P<0.001$, SMD=0.059) with increased mean platelet volume ($P<0.001$, SMD=0.052).

In biochemistry tests, we observed lower fasting glucose, creatinine and creatine kinase levels among G6PD deficient patients. Conspicuous differences were observed for iron, ferritin and transferrin saturation, which are elevated with respective SMDs of 0.369, 0.282 and 0.401 ($P<0.001$ for all), while transferrin is markedly decreased (SMD=-0.149). Interestingly both blood total protein and globulin were markedly elevated in G6PD deficiency,

TABLE 3 Autoimmune serology in G6PD deficient subjects and matched controls.

	G6PD Deficiency	Control	p	Odds Ratio [95% Confidence Interval]
N	7,122	28,488		
A. Antinuclear Antibodies (Ab), No. (%)				
Antinuclear Ab (EIA) positive	246 (3.29%)	551 (1.84%)	<0.001	1.81 [1.55 to 2.12]
Histones Auto-Ab positive	17 (0.227%)	23 (0.077%)	0.001	2.96 [1.48 to 5.79]
RNP 68 Ab positive	8 (0.107%)	8 (0.027%)	0.007	4.00 [1.31 to 12.24]
Smith (Sm) Ab positive	5 (0.067%)	4 (0.013%)	0.02	5.00 [1.08 to 25.21]
B. Cell-specific Antibodies (Ab), No. (%)				
Anti Gastric Parietal Cell Ab positive	16 (0.214%)	22 (0.074%)	0.002	2.91 [1.43 to 5.81]
Anti-Thyroid Peroxidase (TPO) positive	82 (1.10%)	227 (0.76%)	0.005	1.45 [1.11 to 1.88]

TABLE 4 Laboratory characteristics of G6PD deficient subjects and matched controls.

	G6PD Deficiency (median [IQR])	Control (median [IQR])	p	SMD
Blood Count				
Red Blood Cells (M/uL)	4.59 [4.26-4.92]	4.83 [4.50-5.16]	<0.001	-0.419
Hemoglobin (g/dL)	13.00 [11.90-14.30]	13.40 [12.20-14.70]	<0.001	-0.225
Hematocrit (%)	38.80 [35.70-42.50]	39.60 [36.40-43.30]	<0.001	-0.165
White Blood Cells (K/uL)	7.01 [5.75-8.85]	7.25 [5.94-9.07]	<0.001	-0.068
Neutrophils (K/uL)	3.41 [2.61-4.47]	3.51 [2.68-4.60]	<0.001	-0.058
Neutrophils (%)	51.70 [42.20-59.40]	51.20 [42.00-59.00]	0.15	0.011
Lymphocytes (K/uL)	2.40 [1.87-3.23]	2.47 [1.92-3.32]	<0.001	-0.047
Lymphocytes (%)	36.0 [29.0-44.5]	36.2 [29.0-44.5]	0.82	0.006
Eosinophils (K/uL)	0.19 [0.11-0.32]	0.19 [0.12-0.33]	0.002	-0.035
Eosinophils (%)	2.70 [1.70-4.40]	2.70 [1.70-4.50]	0.560	-0.008
Basophils (K/uL)	0.04 [0.03-0.06]	0.04 [0.03-0.06]	0.742	-0.007
Basophils (%)	0.60 [0.40-0.80]	0.60 [0.40-0.80]	<0.001	0.053
Monocytes (K/uL)	0.54 [0.43-0.69]	0.58 [0.46-0.73]	<0.001	-0.141
Monocytes (%)	7.80 [6.60-9.20]	8.00 [6.80-9.50]	<0.001	-0.096
Platelets (K/uL)	265 [219-321]	260 [214-318]	<0.001	0.059
Mean Platelet Volume (fL)	10.80 [10.20-11.60]	10.80 [10.10-11.50]	<0.001	0.052
Biochemistry				
Fasting glucose (mg/dL)	89.00 [83.4-96.0]	89.6 [83.8-97.1]	<0.001	-0.041
Creatinine (mg/dL)	0.70 [0.52-0.85]	0.71 [0.54-0.87]	<0.001	-0.050
Creatine Kinase (U/L)	87.0 [60.0-127.0]	95.0 [66.0-138.0]	<0.001	-0.036
Urea (mg/dL)	27.2 [22.3-33.0]	27.2 [22.2-33.2]	0.52	0.005
Uric Acid (mg/dL)	4.93 [3.95-5.98]	5.06 [4.04-6.11]	<0.001	-0.082
Iron (ug/dL)	94.0 [66.4-125.7]	80.4 [58.5-105.8]	<0.001	0.369
Ferritin (ng/mL)	69.0 [33.8-144.3]	48.0 [23.5-100.7]	<0.001	0.282
Tranferrin (mg/dL)	258 [233-288]	266 [240-295]	<0.001	-0.149
Tranferrin Saturation (%)	26.2 [18.0-35.7]	21.9 [15.6-29.0]	<0.001	0.401
Bilirubin, Total (mg/dL)	0.76 [0.55-1.09]	0.56 [0.42-0.78]	<0.001	0.225
Total Protein (g/dL)	7.18 [6.89-7.47]	7.11 [6.81-7.41]	<0.001	0.148
Globulin (g/dL)	2.86 [2.60-3.12]	2.80 [2.56-3.06]	<0.001	0.129
Immunoglobulins				
Immunoglobulin A (mg/dL)	186 [112-267.5]	159 [97-229]	<0.001	0.256
Immunoglobulin G (mg/dL)	1135 [945.5-1323]	1049 [883-1230]	<0.001	0.252
Immunoglobulin M (mg/dL)	99 [70-141]	96 [68-135]	0.07	0.049
Inflammatory Markers				
	(mean ± sth. dev.)	(mean ± sth. dev.)		
Erythrocyte sedimentation rate (mm/hr)	20.69 ± 19.82	18.98 ± 18.14	<0.001	0.093
C-reactive protein (mg/L)	7.72 ± 19.69	7.86 ± 20.58	0.15	-0.007
C3 Complement (mg/dL)	128.38 ± 24.55	130.44 ± 23.71	0.04	-0.086
C4 Complement (mg/dL)	31.71 ± 10.46	33.52 ± 10.63	<0.001	-0.170

IQR, Interquartile range; SMD, Standardized Mean Difference.

with respective SMDs of 0.148 and 0.129 ($P < .001$ for both). Among immunoglobulins (Ig), we observe markedly elevated levels for IgA and IgG with respective SMDs of 0.256 and 0.252 ($P < .001$ for both). In contrast, IgM levels were not significantly different in the two groups.

We also evaluated inflammation-associated markers. Erythrocyte sedimentation rate (ESR) is slightly higher in G6PD patients ($P < .001$, SMD=0.093), but not C-reactive protein. Levels of C4 complement were significantly decreased in G6PD deficient patients ($P < .001$, SMD=-0.170), but C3 complement were only slightly decreased ($P = .038$, SMD=-0.086).

Discussion

To our knowledge, this is the first large-scale epidemiologic analysis to assess the association between G6PD deficiency and the long-term risk of immune system associated diseases. We show G6PD deficient patients have globally higher rates of acute infectious diseases, and in particular staphylococcal infections, suggesting a predisposition to infections. The link between G6PD deficiency and infections has been previously recognized in infancy, with lack of G6PD activity identified as a risk factor for neonatal sepsis in males (10). This study is the first to show this association on a large scale and for a wide range of infectious diseases.

Another finding from our study is a higher rate of allergic diseases in G6PD-deficient subjects. No systematic review of allergic comorbidity in G6PD deficiency was found in the literature. However, a retrospective case-control study showed that G6PD deficiency is an independent risk factor for asthma (24) and G6PD was noticeably downregulated in asthmatic children (25). In asthma, the level of reduced glutathione is significantly increased, and G6PD-deficient subjects' insufficient production of NADPH may contribute to asthma pathogenesis (26). Moreover, the chronic depletion of nitric oxide in G6PD deficient subjects may affect the basal bronchodilator tone (27). In our cohort, we also found an association between asthma and G6PD deficiency (OR=1.08, $P = .043$), but much more stronger associations were present for other conditions such as allergic conjunctivitis (OR=1.25, $P < .001$), food allergy (OR=1.23, $P < .001$), and contact dermatitis (OR=1.19, $P < .001$).

The most striking finding of our study are the much-elevated rates of autoimmune diseases and chronic inflammatory conditions in G6PD deficient individuals. We notably observed markedly elevated rates of scleroderma (OR=6.87, $P < .001$), SLE (OR=4.56, $P < .001$), dermatomyositis (OR=3.56, $P < .001$), Sjögren's syndrome (OR=2.80), rheumatoid arthritis (OR=2.41, $P < .001$) and ankylosing spondylitis (OR=2.52, $P = .001$) in individuals affected with G6PD deficiency. These findings were corroborated with elevated rates of positive autoimmune serology in G6PD deficiency and higher rates of treatment with medications commonly used to treat autoimmune conditions. This is consistent with a previous study reporting lower levels of G6PD enzymatic activity in patients with rheumatoid arthritis and Sjögren's syndrome, which in many cases was subclinical and of acquired origin (28).

We also observed significantly higher rates of organ-specific inflammatory diseases such as Hashimoto's thyroiditis (OR=1.26, $P = .001$) and Graves' disease (OR=1.46, $P = .001$), and particularly elevated rates of pernicious anemia (OR=18.7, $P < .001$). We corroborated these findings with higher rates of individuals with positive anti-gastric parietal cells and anti-TPO antibodies in the G6PD group. Findings of increased rate of autoimmune thyroid disorders in G6PD patients are consistent with a recently published case-control study from North Sardinia, which identified an odds ratio of 1.36 (95% CI 1.11 to 1.60) for these disorders for G6PD patients (8).

We also observed higher rates of inflammatory bowel disease (OR=1.34, $P = .05$) and psoriasis (OR=1.19, $P = .02$) among G6PD deficient patients. Interestingly, we observed markedly higher rates for diseases for which the pathological basis is poorly understood, notably hidradenitis suppurativa (OR=2.57, $P < .001$) and fibromyalgia (OR=1.98, $P < .001$). These strong associations with G6PD deficiency suggest that metabolic pathway alterations, as those present in G6PD deficiency, may play a major role in these pathologies.

G6PD deficient individuals differed markedly from the rest of the population for commonly prescribed laboratory tests. They display diminished white blood cells counts, particularly monocytes and neutrophils. Interestingly, activated monocytes and neutrophils produce reactive oxygen species (ROS), which could be particularly harmful to G6PD-deficient cells and could lead to increased cell death. We also observed markedly increased levels of iron, ferritin, and transferrin saturation, with diminished transferrin levels. Immunoglobulins A and G levels were increased in G6PD patients and C4 complement decreased, suggesting a possible activation of the complement system in G6PD deficiency, presumably through the classical pathway and with the production of circulating immune complexes (29). Indeed, immune dysregulation may play a role in the pathogenesis of autoimmune and infectious diseases in G6PD deficiency, presumably through dysregulated NADPH homeostasis and ROS imbalances (30).

G6PD deficiency has been associated with a proinflammatory state with over-expression of IL-8, IL-4, IL-5, and IL-9 cytokines, and increased chemotaxis of eosinophils and Th2 immune polarization (31, 32). Oxidative stress had been suggested in the pathogenesis of human SLE and Sjögren syndrome (33, 34). Oxidative stress in G6PD deficient subjects contributes to developing novel epitopes by oxidizing proteins and lipids and producing anti-DNA antibodies (35, 36). Oxidative stress may also play a role in the sustained activation of lymphocytes and cause autoimmune responses by modulation of T and B cell homeostasis, leading to a loss in immunological tolerance (37, 38). These may be some of the reasons for the observed higher rates of autoimmune diseases. Their roles in food allergy, atopic and allergic contact dermatitis should be elucidated in further research. Autoimmune diseases in G6PD deficient patients may be triggered by activation of TGF- β /NADPH oxidases/ROS signaling, the expression of ICAM-1 and VCAM-1, and the adhesion of leukocytes to the endothelial cells with endothelial to mesenchymal transition (31, 39).

Several mechanisms could explain higher susceptibility to infections in individuals with G6PD deficiency. NADPH is critical for the regeneration of glutathione, reactive oxygen species (ROS) and plays an essential role in the production of reactive nitrogen species and nitric oxide (40). Immune inflammation in airway epithelial cells induces G6PD activity with the concomitant increase of glutathione, ROS, nitrotyrosine, and NADPH oxidase 2 (NOX2) (41). Experimental models have shown that G6PD inhibition suppresses airway inflammation induced by lipopolysaccharides and the ROS derived from NOX2 (42). Dysregulated redox systems and NF- κ B signaling in G6PD-deficient cells have been associated with increased susceptibility to coronavirus and enterovirus infection (43, 44). G6PD-deficient individuals also produce lower levels of pro-inflammatory cytokines, IL-6, and IL-1 β in peripheral mononuclear cells (45), and their granulocytes display diminished bactericidal activity and increased susceptibility to infection (46). Reduced expression of prostaglandin E2 and cyclooxygenase-2 (47), defective neutrophil extracellular trap (NET) formation (48), and impaired inflammasome activation have also been observed in the neutrophils of G6PD-deficient individuals (49).

In our study, we did not find a significant association between G6PD deficiency and malignancy. Earlier studies have observed decreased cancer risk in G6PD deficient patients, in particular for cancers of endodermal origin (colorectal, gastric and liver), but these findings were not replicated in other studies, notably for hematologic malignancies. In this large cohort of G6PD deficient individuals, carefully matched by multiple factors, we did not find evidence for an association between G6PD deficiency and the overall rate of both solid and hematologic cancers during a mean follow-up of 14.3 years, but the lack of statistical association could be due to the relatively low rate of malignancy (~4%) diagnosed in this relatively young cohort. It is remarkable that even though G6PD deficiency is associated with several chronic inflammatory diseases, this does not translate into cancer risk. This may be explained by the fact that G6PD deficiency is associated with multiple changes in metabolic and cellular states (6) with some changes being pro-tumorigenic and other changes being anti-tumorigenic.

Limitations

This study has the usual limitations of observational studies: potential confounders could be distributed differently between the two groups, clinical records may be inaccurate, and data may be missing. Nonetheless, the large number of participants and the scrupulous matching methodology adopted should minimize the extent of such biases. Another limitation is that the study reflects the link with the G6PD mutations prevalent in the Israeli population, in which the most prevalent mutation is the “Mediterranean” allele, which is associated with severe G6PD enzymatic deficiency (50). Unfortunately, a molecular diagnosis was not available in this large-

scale study, and risks may differ with variants present in other populations. Since we lack G6PD enzymatic measures for the whole cohort, we considered G6PD deficiency as a dichotomous trait rather than a continuous spectrum.

Another limitation is that the studied cohort was relatively young, the mean patient age was 29.2, and only 12.5% of the study subjects were above age 60. Cancer and cardiovascular disease, as well as type II diabetes and its complications occur mostly in the elderly, and this study may be insufficiently powered to detect associations for such diseases, which are diagnosed predominantly in patients older than 60.

Conclusions

In conclusion, G6PD deficiency is a condition which appears to be associated with increased susceptibility to autoimmune, infectious and allergic diseases. Additional studies are warranted to confirm these observations and investigate the mechanisms underlying the higher prevalence of these conditions in G6PD deficiency. Some of the novel associations we report with G6PD deficiency are for poorly understood conditions such as fibromyalgia or hidradenitis suppurativa, and this may suggest new directions for investigating the pathological basis of these diseases.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: Access to raw patient data is restricted to researchers approved by the institutional ethics committee. Requests to access these datasets should be directed to aisrael@leumit.co.il.

Ethics statement

This study was approved by the ethics committee of Leumit Health Services (LEU 02-23) with a waiver of informed consent. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

AI and EMa: designed research, performed research, collected, analyzed and interpreted the data, performed statistical analysis, and wrote the initial draft of the manuscript; AAS, DO, EMe, IG, AG-C, MB, ER, and SV: analyzed and interpreted data and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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