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ORIGINAL ARTICLE

Glucose-6-phosphate dehydrogenase deficiency and risk of diabetes: a systematic review and meta-analysis

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Abstract Emerging epidemiological evidence suggests that patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency may have a higher risk of developing diabetes. The aim of the review was to synthesise the evidence on the association between G6PD deficiency and diabetes. A systematic search on Medline, EMBASE, AMED and CENTRAL databases for studies published between January 1966 and September 2016 that assessed the association between G6PD deficiency and diabetes was conducted. This was supplemented by a review of the reference list of retrieved articles. We extracted data on study characteristics, outcomes and performed an assessment on the methodological quality of the studies. A random-effects model was used to compute the summary risk estimates. Fifteen relevant publications involving 949,260 participants were identified, from which seven studies contributed to the meta-analysis. G6PD deficiency was associated with a higher odd of diabetes (odds ratio 2.37, 95% confidence interval 1.50–3.73). The odds ratio of diabetes among men was higher (2.22, 1.31–3.75) compared to women (1.87, 1.12–3.12). This association was broadly consistent in the sensitivity analysis. Current evidence suggests that G6PD deficiency may be a risk factor for diabetes, with higher odds among men compared to women. Further research is needed to determine how G6PD deficiency moderates diabetes.

Keywords Glucose-6-phosphate dehydrogenase deficiency · Gender · Diabetes · Prevalence

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Introduction

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is one of the most common genetic disorders affecting approximately 400 million people worldwide [1]. Several recent studies have reported a relationship between G6PD deficiency and incidence of diabetes [2–4]. However, it remains unclear if G6PD deficiency itself may increase or decrease the risk of diabetes. In the current study, we systematically reviewed all available epidemiological evidence on the relationship between G6PD deficiency and prevalence of diabetes.

Methods

Data sources and searches

A literature search was performed up to September 2016 in Medline, EMBASE, CENTRAL and AMED for studies examining the association between patients with G6PD deficiency and diabetes. This was supplemented with a manual search of references cited by selected articles.

Study selection

We included cohort or cross-sectional studies that examined patients with either self-reported or diagnosed diabetes

(including type 1, type 2, gestational, insulin-dependent and insulin-requiring diabetes) and diagnosed with G6PD deficiency. Two investigators (SWHL and NML) independently screened all studies and extracted data. Any discrepancies were resolved by discussion. To assess the quality of the included studies, we used the Cochrane risk of bias assessment tool for non-randomised studies of intervention (ROBINS-I) tool [5].

Data synthesis and statistical analysis

To summarise the relationship between G6PD deficiency and diabetes prevalence, we pooled the diabetes prevalence using the aggregate study-level data using a random-effects model. To evaluate the heterogeneity across studies, we used the Cochrane Q statistic and the I^2 statistic. We also explored the potential explanations by stratification of studies as well as using random-effects meta-regression analyses. All analyses were performed using Stata statistical software version 13.0 (StataCorp, College Station, TX, US).

Results

Description of studies and participants

We identified 15 eligible studies representing a total of 949,260 participants (Supplementary Fig. S1), with sample sizes between 54 and 940,085. Participants aged 4 and 85 years were recruited over a period ranging from 1 month to 14 years. Most of the studies were cross-sectional, and seven were case-control studies with two being nested case-control studies (Table 1). Study population included six from Asia, five from Europe, three from Africa and one from South America. Six studies only included men in their study population while another one study included only women.

All studies had an unclear risk of bias for confounders, and the risk of bias from exposure measurement was unclear, given that most of the studies measured the presence of G6PD deficiency only once (Supplementary Table S1). The overall risk of bias for most studies was unclear except for one study which was judged to be at high risk as the controls were recruited at a different period [6].

Association between diabetes prevalence and G6PD deficiency

Several studies found a positive association between G6PD deficiency and diabetes [2, 3, 7–10]. For example, in the study by Heymann et al., the authors found that patients aged 45–64 years with G6PD deficiency had a 1.44 times higher prevalence of diabetes compared to those without G6PD deficiency at this age group. This was similarly noted in other studies which had found that G6PD enzyme activities were consistently reported to be lower among patients with diabetes compared to normal controls [11–14].

Two other studies examined the prevalence and severity of retinal complications in patients with G6PD deficiency and diabetes. Results of these studies were mixed, with one study reported an acceleration of microvascular complication [15] while another reported otherwise [16]. A similar trend was noted in studies examining the relationship between G6PD deficiency and glycaemic control. The study by Meloni and colleagues reported that HbA1c levels were lower in diabetes with G6PD deficiency compared to those with normal G6PD levels [17]. In contrast, Akter et al. reported that HbA1c levels were higher in G6PD-deficient individuals compared to those with normal G6PD [4].

Meta-analysis

Pooled results of the seven studies that examined the prevalence of diabetes in G6PD deficiency showed that overall, patients with G6PD deficiency were associated with an increased risk of diabetes. The summary odds ratio (OR) was 2.37 (95% CI 1.50–3.73), with higher odds among men compared to women (OR 2.22 (95% CI 1.31–3.75) vs. 1.87 (1.12–3.12); Fig. 1). However, there was evidence of heterogeneity in the estimates (I^2 = 88.2%, $p < 0.001$). We subsequently examined the potential sources of heterogeneity which could have influenced the results. We found that when stratified according to study design, these associations are consistent in cross-sectional studies but not case-control studies. Other factors such as gender, types of diabetes examined as well as diabetes definitions were not associated with overall effect size (Supplementary Table S2). In meta-regression analyses, we found that study design accounted for 24% of the total heterogeneity. The data was, however, insufficient to analyse the role of different G6PD variants or degree of G6PD enzyme activity on the prevalence of diabetes. Sensitivity analyses suggest the results were broadly consistent with some form of asymmetry noted suggesting small study effects (Supplementary Fig. S2).

Discussion

To our knowledge, this is the first systematic review and meta-analysis to-date that examines the relationship between G6PD deficiency and diabetes. Overall, the pooled results from 7 studies with 893,408 participants suggest that patients with G6PD deficiency have a 2.37

Table 1 Characteristics of studies included in the systematic review

Author, year, country	Study participants and sampling method	Race/ethnicity	Study objective and outcome ascertainment	Study design, study period	G6PD variant examined	Study findings
Studies that examine relationship between G6PD deficiency and diabetes prevalence						
Adinortey, 2011, Ghana	422 subjects from the diabetic clinic of the Central Regional Hospital and Cape Coast metropolis of Ghana	Ghanians	To determine the association between G6PD deficiency and diabetes mellitus. Diabetes: fasting plasma glucose ≥7 mmol/L, G6PD deficiency: fluorescence spot test	Cross sectional; December 2009–May 2010	Not reported	The prevalence of G6PD deficiency was higher in diabetics (50.7%) compared to normal controls (22.3%). In patients with G6PD deficiency, the relative risk of developing type 2 diabetes was 1.61 times higher
Heymann, 2012; Israel	940,085 male subjects registered with the Maccabi Healthcare Services, Israel	Israeli	To determine the prevalence of G6PD deficiency in patients with diabetes. Diabetes: NR, G6PD deficiency: quantitative method	Cross sectional, database review; 2003 to 2010.	Not reported	There was a significantly higher proportion of patients with G6PD deficiency among the diabetic population aged 45–64 years when compared to the general population
Meloni, 1992; Italy	630 diabetic males (211 with IDDM and 419 NIDDM) recruited from the University of Sassari and 1646 controls from a favism campaign	Sardinian, Italian	To determine the association between G6PD deficiency and incidence of diabetes. Diabetes: NR, G6PD deficiency: fluorescence spot test	Case-control, 1975–1977 (controls) and May–September 1989 (diabetes)	Not reported	No association was noted between G6PD deficiency and diabetes mellitus
Niazi, 1991, Saudi Arabia	258 subjects with diabetes mellitus from the King Fahad National Guard hospital and 258 healthy controls who were blood donors	Saudi	To determine the association between G6PD deficiency and diabetes mellitus. Diabetes: fasting plasma glucose >6.7 mmol/L and/or 2 h postprandial blood glucose >7.9 mmol/L, G6PD deficiency: enzyme activity measured quantitatively by spectrophotometry	Nested case-control; NR	Not reported	A significantly higher prevalence of G6PD deficiency was noted among patients with diabetes mellitus (12.4%) compared to healthy population control (2.0%)
Saeed, 1985, Iraq	318 subjects from the outpatient clinic of Yarmouk Teaching Hospital, Baghdad	Iraqi	To determine the prevalence of G6PD deficiency in diabetic patients compared with controls. Diabetes: NR, G6PD deficiency: fluorescence spot test	Case-control; NR	Not reported	A significantly higher prevalence of G6PD deficiency was found among diabetic patients (19.6%) compared to control (10.4%). The number of patients with G6PD deficiency was higher in men with longer duration of diabetes
Saha, 1979, Singapore	609 male subjects with type 2 diabetes and 747 normal subjects recruited from the Tan Tock Seng Hospital, Singapore	Chinese 69.3%, Malay 10.8%, Indian 19.9%	To determine the incidence of G6PD deficiency, ABO blood groups and haemoglobin types in diabetics compared with healthy controls. Diabetes: standard glucose tolerance test, G6PD deficiency: fluorescence spot test	Case-control; NR	Not reported	A higher prevalence of G6PD deficiency was observed in Chinese and Indian patients with diabetes
Santana, 2014, Brazil	1478 male from Manaus, Brazil	Brazilian	To estimate the frequency of impaired fasting glucose and diabetes among G6PD deficiency patients. Impaired fasting glucose 6.1–6.9 mmol/L, diabetes mellitus	Cross sectional; March 2009–March 2010	African variant (84.8%),	G6PD-deficient males were more prone to have impaired fasting plasma glucose and diabetes

Table 1 (continued)

Author, year, country	Study participants and sampling method	Race/ethnicity	Study objective and outcome ascertainment	Study design, study period	G6PD variant examined	Study findings
			≥7 mmol/L and/or history of known diabetes, G6PD deficiency: enzyme activity measured quantitatively by spectrophotometry		Mediterranean variant (15.2%)	
Studies that examine HbA1c levels in type 2 diabetes with G6PD deficiency						
Akter, 2010; Bangladesh	60 female subjects recruited from the Bangladesh Institute of Health Sciences Hospital, Bangladesh and 30 controls from personal contact	Bangladeshi	To determine the G6PD deficiency status among female type 2 diabetic patients and its relationship with HbA1c. Diabetes: NR, G6PD deficiency: enzyme activity measured quantitatively by spectrophotometry	Case-control; January 2009–December 2009	Not reported	Female patients with type 2 diabetes had lower G6PD enzyme activity compared to healthy controls
Meloni, 1994; Italy	632 male subjects with diabetes mellitus (211 with IDDM and 421 with NIDDM)	Sardinian, Italian	To evaluate the HbA1c levels of diabetics with or without G6PD deficiency. Diabetes: physician diagnosed based upon fasting plasma glucose and blood immunoreactive insulin, G6PD deficiency: fluorescence spot test	Cross sectional, NR	Not reported	Diabetic patients with G6PD deficiency had lower HbA1c levels compared to those with normal G6PD levels
Studies that examine the prevalence and severity of retinal complications in diabetes patients with G6PD deficiency						
Cappai, 2011; Italy	54 male subjects with type 1 diabetes recruited from the Diabetes Centre of Ospedale San Michele, Italy or through referral	Sardinian, Italian	To determine the prevalence and severity of retinopathy in diabetic patients and how G6PD deficiency affects disease severity. Diabetes: NR, G6PD deficiency: database report/measured prospectively	Cross sectional; NR	Not reported	A higher number of patients with G6PD deficiency had proliferative retinopathy and there was a trend for increased frequency of microalbuminuria
Pinna, 2013; Italy,	390 male diabetic with severe retinal complications and 390 age-matched controls	Sardinian, Italian	To compare the G6PD deficiency prevalence in men with severe retinal vascular complication compared to age-matched non-diabetic controls and ascertain the role of G6PD deficiency. Diabetes: treatment history for diabetes or fasting plasma glucose ≥7 mmol/L and/or 2 h postprandial blood glucose >11.1 mmol/L, G6PD deficiency: enzyme activity measured quantitatively	Nested case-control; January 1994 to December 2008	Not reported	In patients with G6PD deficiency, there was a trend for protection against diabetic proliferative diabetic retinopathy
Studies that examine the G6PD enzyme activity in type 2 diabetes patients						
Festus, 2012; Nigeria	100 subjects recruited from the Irrua Specialist Teaching Hospital	Nigerian	To determine the activity of G6PD enzyme in patients with type 2 diabetes. Diabetes: NR, G6PD deficiency: enzyme activity measured quantitatively by spectrophotometry	Cross sectional; September 2011 to January 2012	Not reported	Patients with diabetes had lower G6PD enzyme activity compared to healthy controls
Mahmoud, 2013; Egypt	60 subjects recruited from Sohag University Hospital, Egypt	Not reported	To study the G6PD enzyme activity and correlate its activity to protein oxidation marker in type 2 diabetic patients. Diabetes: NR, G6PD deficiency: enzyme	Case control; NR	Not reported	Patients with diabetes had lower G6PD enzyme activity and total thiol group content levels while protein carbonyl

Table 1 (continued)

Author, year, country	Study participants and sampling method	Race/ethnicity	Study objective and outcome ascertainment	Study design, study period	G6PD variant examined	Study findings
			activity measured quantitatively by spectrophotometry			was higher compared to healthy controls
Rashidi, 2009, Iran	200 subjects aged 30–60 years old from the Zahedan University of Medical Sciences	Iranian	To evaluate the difference in G6PD activity among diabetics and non-diabetics and the impact of hyperglycaemia on the G6PD enzyme activity. Diabetes mellitus: fasting plasma glucose >7 mmol/L or 2 h postprandial >11.1 mmol/L, G6PD deficiency: fluorescence spot test	Cross sectional; October 2006	Not reported	Patients with diabetes mellitus had lower G6PD enzyme activity compared to healthy controls. Subgroup analysis showed that diabetics with higher BMI or with dyslipidaemia had even lower G6PD enzyme activity compared to diabetics without dyslipidaemia
Wan, 2002; Taiwan	893 subjects from the Chang Gung Memorial Hospital, Taiwan	Taiwanese 76.7%, Chinese 4.5%, Hakka 17.3%, Aborigimies 1.5%	To evaluate the relationship between G6PD activity and diabetes. Diabetes mellitus: physician diagnosis, G6PD deficiency: enzyme activity measured quantitatively by spectrophotometry	Cross sectional; September 1999 to May 2000	Canton variant (50%), Kaiping variant (50%)	There was no difference in the prevalence of G6PD deficiency among diabetics and control. However, patients with diabetes had lower G6PD enzyme activity compared to controls.

times increased odds of developing diabetes compared to unaffected individuals, with men appearing more likely to be affected compared to women.

This finding raises several potential ramifications from a public health perspective which merits some discussion. As G6PD deficiency is an x-linked hereditary disease, the defect commonly affects males as opposed to females [18]. Furthermore, findings from several studies [19, 20] have also suggested that males and Asians also have a higher risk of developing diabetes. Taken together, this suggests that there may be a further increase in the prevalence of diabetes among future generations since these are genetically transmitted. In addition, because diabetes compounds cardiovascular risk factors, we are likely to expect an increase in prevalence of cardiovascular disease in the future. As such, we recommend that all G6PD-deficient individuals should be screened for diabetes regularly and at a younger age compared to the unaffected population. These findings also suggest that it may be beneficial to include this information on association especially in patient information leaflets given to all parents with G6PD-deficient children.

Strengths and limitations

This analysis offers several strengths. Firstly, as a systematic review and meta-analysis, the study has greater power to detect any differences than any of the individual studies identified. Secondly, the study used a broad range of keywords as well as inclusion of a citation tract to identify for recently published studies, without any language restrictions. Thirdly, this study was done in accordance with the PRISMA [21] and MOOSE [22] guidelines. Finally, this is the largest confirmatory work to date examining the association between G6PD deficiency and diabetes.

This study has several limitations. Firstly, many of the studies reported in the review did not systematically examine the class of G6PD enzyme variant of their patients. This information would have provided researchers useful insights into the possible implications of this deficiency, as different variants have been shown to correspond with various levels of enzyme activities [18]. Another limitation of the review is the wide variation in the methodologies of the included studies, with fewer than half of the eligible studies having contributed suitable data for our meta-analysis. Furthermore, in our meta-analyses, substantial heterogeneity existed despite grouping studies according to patient and study characteristics as well as outcome definition. This suggests that much of the heterogeneity was unexplained and precluded the presentation of summary estimates.

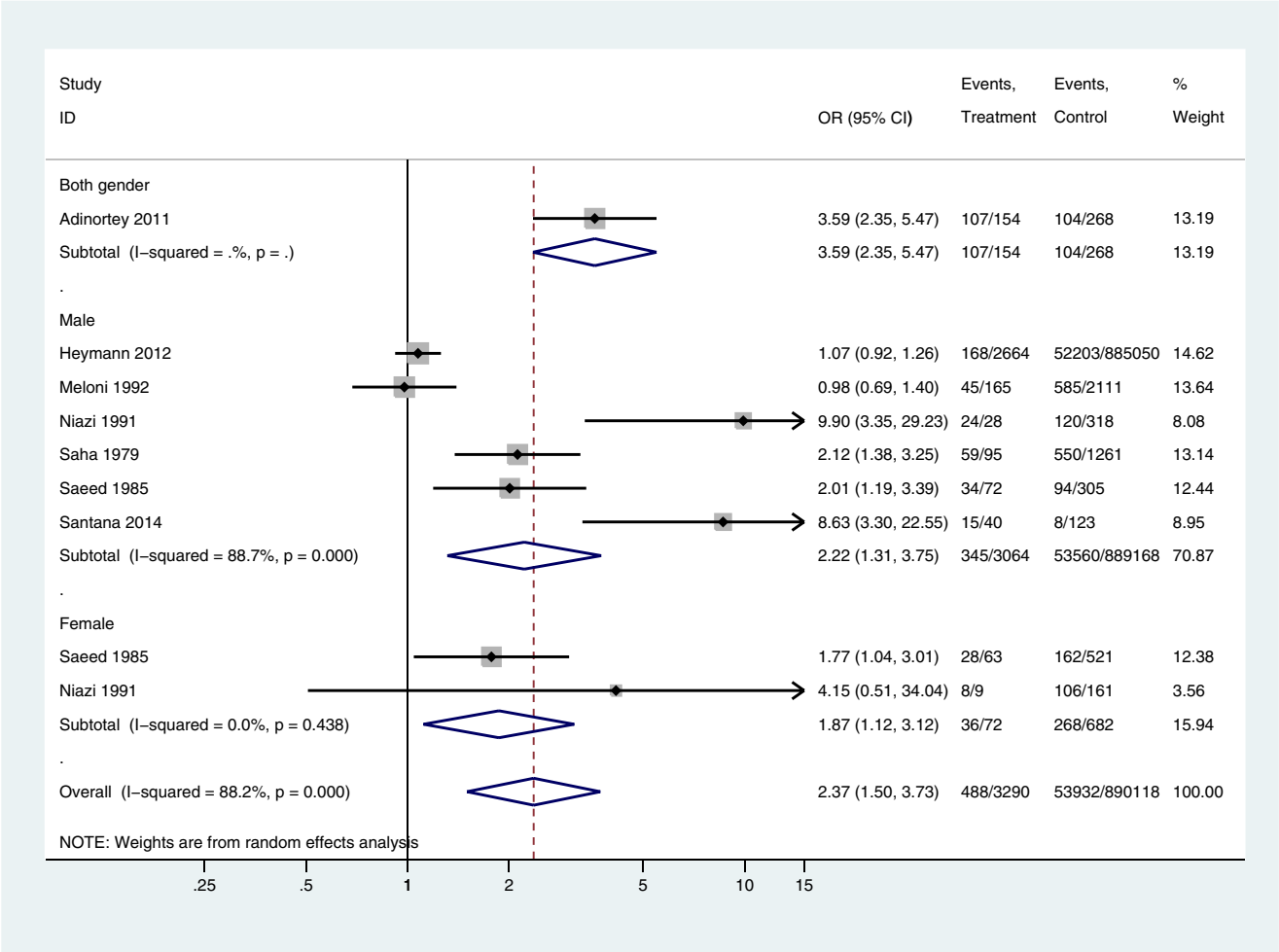

Fig. 1 Forest plot of prevalence of diabetes for G6PD-deficient individuals by sex. The area of each square is proportional to inverse variance of estimates. *Horizontal lines* indicate the 95% confidence interval

Finally, studies were included from over three decades, in which the definition and criteria for diabetes have been revised regularly. For example, in 1997, the threshold of diabetes diagnosis using fasting plasma glucose was lowered [23]. As such, inclusion of older studies may have led to an underestimation of diabetes prevalence.

In summary, patients with G6PD deficiency appear to have an increased odd of developing diabetes compared to unaffected controls. As the current unprecedented growth of diabetes is becoming a national and worldwide public health problem, further studies into how G6PD deficiency increases risk of diabetes is required. A large longitudinal study that measures glycosylated haemoglobin, fasting plasma glucose at baseline and over time should be established to fill in the gaps in our understanding of mechanisms by which G6PD deficiency moderates diabetes especially by sex. In addition, clinicians also need to consider having more routine screening of diabetes especially among G6PD-deficient individuals, in view of the increased risk especially among men.

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Author contributions SWHL, NML and YKL undertook the literature search and reviewed the abstracts and full articles. SWHL conceived the idea, drafted the initial manuscript and performed the statistical analysis. All authors designed the study, contributed to the discussion and critically reviewed the final manuscript.

Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

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