CORRESPONDENCE

Type 2 Diabetes in Patients with G6PD Deficiency

TO THE EDITOR: Diabetes mellitus has a substantial effect on global health, with marginalized groups often having worse outcomes.[1-3] We examined how glucose-6-phosphate dehydrogenase (G6PD) deficiency, an X-linked enzymatic deficiency common among persons of African or Mediterranean ancestry,[4] affects glycated hemoglobin levels, the purchase of diabetes medication, and the incidence of diabetes complications.

We performed a cohort study within Leumit Health Services, a national health provider, comparing 3913 patients with G6PD deficiency and 19,565 matched controls from 2003 through 2023. Male patients made up 60.5% of the study cohort (14,202 of 23,478 patients), and the mean (±SD) age was 47±20 years in each group at the end of the study period. Additional information about the study methods and the characteristics and representativeness of the study participants are provided in the text and Tables S1, S2, and S4 in the Supplementary Appendix, available with the full text of this letter at NEJM.org.

Although fasting glucose levels were similar in the two groups, glycated hemoglobin levels were significantly lower among the patients with G6PD deficiency than among the controls (4.79±0.85% vs. 5.50±0.88%, P<0.001). Regression plots of glucose and glycated hemoglobin levels in male and female patients are shown in Figure 1; at all fasting glucose levels, glycated hemoglobin levels were markedly lower among patients with G6PD deficiency than among those without G6PD deficiency. For patients with G6PD deficiency, a glycated hemoglobin level of 6.5% corresponded to a fasting glucose level of 168 mg per deciliter among male patients and 155 mg per deciliter among female patients, as compared with 126 mg per deciliter in the general population. These differences were more pronounced at higher glucose levels.

We compared patients with diabetes in the two groups, with the onset of diabetes defined as two consecutive fasting glucose levels above 126 mg per deciliter; these analyses included 418 patients with diabetes and G6PD deficiency and 2085 patients with diabetes and no G6PD deficiency (Fig. S1). For prescriptions of many of the diabetes medications sampled, the cumulative probability of receiving the medication during the study period was lower among patients with G6PD deficiency than among those without G6PD deficiency (Table S3). During the study period, the cumulative probability of receiving glucagon-like peptide 1 (GLP-1) receptor agonists was lower among the patients with diabetes and G6PD deficiency than among those with diabetes and no G6PD deficiency (adjusted hazard ratio, 0.77; 95% confidence interval [CI], 0.62 to 0.95); a similar pattern was seen for sodium–glucose cotransporter 2 (SGLT2) inhibitors (adjusted hazard ratio, 0.78; 95% CI, 0.65 to 0.94). In addition, the cumulative incidence of diabetes complications was higher among the patients with G6PD deficiency, particularly the incidence of severe kidney disease

THIS WEEK'S LETTERS

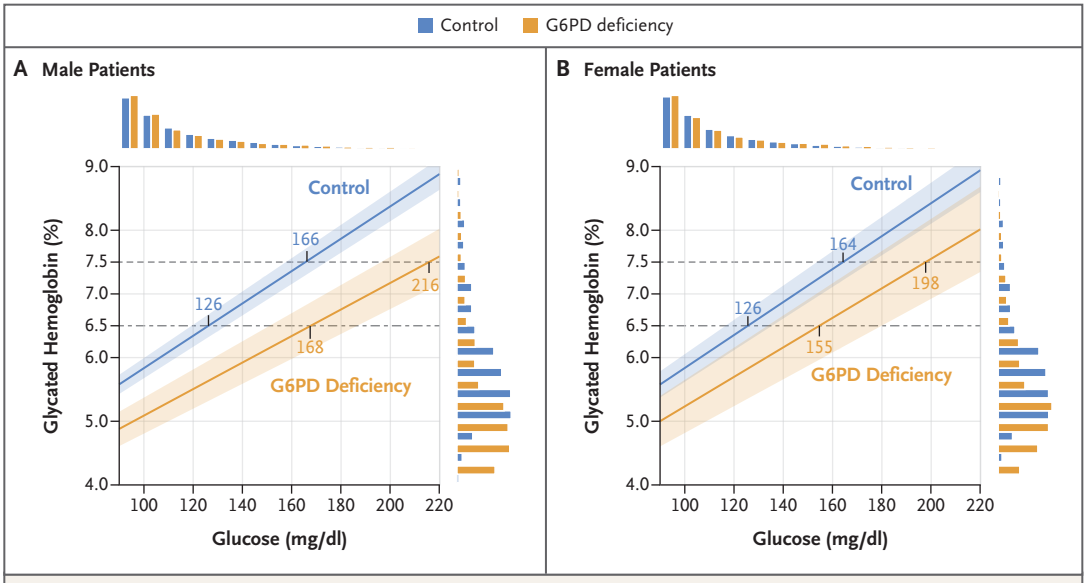

Figure 1. Regression of Glycated Hemoglobin Levels against Glucose Levels.

Shaded areas indicate 95% confidence interval, and the histograms along each axis indicate the relative frequency of the values within each group. For patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, a glycated hemoglobin level of 6.5% corresponded to a fasting glucose level of 168 mg per deciliter among male patients and 155 mg per deciliter among female patients, as compared with 126 mg per deciliter in the general population. Differences were more pronounced at higher glucose levels.

(adjusted hazard ratio, 1.51; 95% CI, 1.22 to 1.86), ischemic heart disease (adjusted hazard ratio, 1.33; 95% CI, 1.03 to 1.71), and neuropathy (adjusted hazard ratio, 1.33; 95% CI, 1.08 to 1.63).

In this study, patients with diabetes and G6PD deficiency had treatment delays (as indicated by their lower probability of receiving diabetes medications) and a higher cumulative incidence of diabetes complications than patients without G6PD deficiency. GLP-1 receptor agonists and SGLT2 inhibitors — medications that can mitigate the chronic oxidative stress associated with G6PD deficiency[5] — were less often prescribed to patients with this disorder. Treatment guidelines should account for the challenges posed by G6PD deficiency in achieving equitable and effective health care for this vulnerable population.

Glycated hemoglobin levels markedly underestimated glucose levels in patients with G6PD deficiency in this study. Thus, glycated hemoglobins may be unreliable for the diagnosis or management of diabetes in such patients.

Ariel Israel, M.D., Ph.D.

Tel Aviv University
Tel Aviv, Israel
aisrael@leumit.co.il

Itamar Raz, M.D.

Hadassah Medical Center
Jerusalem, Israel

Shlomo Vinker, M.D., M.H.A.

Leumit Health Services
Tel Aviv, Israel

Eli Magen, M.D.

Assuta Ashdod University Medical Center
Ashdod, Israel

Ilan Green, M.D., M.H.A.
Avivit Golan-Cohen, M.D., M.H.A.
Matitiahu Berkovitch, M.D.

Tel Aviv University
Tel Aviv, Israel

Eugene Merzon, M.D.

Ariel University
Ariel, Israel

A complete list of authors is available with the full text of this letter at NEJM.org.

Supported by the Leumit Research Institute.

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

1. Cowie CC, Port FK, Wolfe RA, Savage PJ, Moll PP, Hawthorne VM. Disparities in incidence of diabetic end-stage renal disease according to race and type of diabetes. N Engl J Med 1989;321:1074-9.

2. Harris MI, Eastman RC, Cowie CC, Flegal KM, Eberhardt

MS. Racial and ethnic differences in glycemic control of adults with type 2 diabetes. Diabetes Care 1999;22:403-8.
3. Smalls BL, Ritchwood TD, Bishu KG, Egede LE. Racial/ethnic differences in glycemic control in older adults with type 2 diabetes: United States 2003-2014. Int J Environ Res Public Health 2020;17:950.
4. Cappellini MD, Fiorelli G. Glucose-6-phosphate dehydrogenase deficiency. Lancet 2008;371:64-74.
5. Yang H-C, Wu Y-H, Yen W-C, et al. The redox role of G6PD in cell growth, cell death, and cancer. Cells 2019;8:1055.

DOI: 10.1056/NEJMc2406156

Myeloma Therapy for Monoclonal Gammopathy of Thrombotic Significance

TO THE EDITOR: Monoclonal gammopathy of thrombotic significance (MGTS) is a recently described highly prothrombotic neoplastic condition characterized by monoclonal anti–platelet factor 4 (PF4) antibodies.[1] Here, we describe the use of plasma-cell–directed therapy to eradicate an MGTS antibody.

A 67-year-old man who was receiving aspirin for coronary artery disease presented with thrombocytopenia (platelet count, 38,000 per cubic millimeter) and mesenteric ischemia associated with extensive splanchnic-vein thrombosis (Fig. 1A).[2] An emergency resection of the small bowel was performed. Heparin treatment worsened the splanchnic-vein thrombosis, which led to additional resection. Testing for heparin-induced thrombocytopenia (HIT) by means of both serotonin-release and enzyme-linked immunosorbent assays was positive (Fig. 1A and 1B), and the patient's treatment was switched to argatroban. Bilateral deep-vein thrombosis and pulmonary embolism developed, which led to cardiac arrest and required resuscitation. Testing also showed a monoclonal gammopathy of undetermined significance (MGUS, an IgG lambda of 0.2 g per deciliter). The patient's treatment was then switched to daily fondaparinux before discharge. Positive HIT testing, MGUS, and thrombocytopenia were persistent, and bone marrow biopsy showed 5% lambda-restricted plasma cells. Despite adherence to treatment with aspirin and fondaparinux, the patient presented with a cerebrovascular accident caused by acute occlusion of the right middle cerebral and internal carotid artery, which resulted in thrombectomy and stent placement. Clopidogrel was added to his treatment regimen.

Studies of antibody light chains[1,3] from the MGUS (Fig. 1C) and isolated anti–PF4 antibody (Fig. 1D) showed monoclonality in both cases, and the identical molecular masses of the MGUS and anti–PF4 antibody suggested they were synonymous. This finding was further supported by the ability of the immune-enriched anti–PF4 antibody to bind PF4-polyanion complexes and activate PF4-treated platelets (Fig. S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org).

In light of recurrent breakthrough life-threatening thrombosis, plasma-cell–directed therapy with daratumumab–bortezomib–dexamethasone (DVd) was initiated. The results of both MGUS and HIT serologic analysis improved concordantly, with negative results on HIT testing and undetectable MGUS protein after three treatment cycles (Fig. 1A and 1B). After completion of the third therapy cycle, the patient had a fall that led to substantial intracranial hemorrhage that was probably associated with concomitant anticoagulation and antiplatelet therapy. He underwent treatment with platelet transfusions and andexanet alfa, which did not result in recurrent thrombosis; his treatment was subsequently de-escalated to aspirin and prophylactic fondaparinux. Complete platelet recovery was attained as a result of DVd therapy, with the most recent platelet count of 214,000 per cubic millimeter, as evaluated 46 days after platelet transfusion.

In this study, we found that myeloma therapy provided substantial benefit in a patient with MGTS, a highly prothrombotic disorder in which anticoagulation and antiplatelet therapy may be inadequate.

Giselle Salmasi, M.D.
Stanford University Medical Center
Palo Alto, CA

David L. Murray, M.D., Ph.D.
Anand Padmanabhan, M.B., B.S., Ph.D.
Mayo Clinic College of Medicine and Science
Rochester, MN
padmanabhan.anand@mayo.edu

Supported by a grant (HL158932, to Dr. Padmanabhan) from the National Institutes of Health.