European Journal of Internal Medicine xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

Association of glycated hemoglobin with hemoglobin levels in elderly nondiabetic subjects☆

Alon Grossman [a,b,*], Anat Gafter-Gvili [b,c], Hemda Schmilovitz-Weiss [b,d], Nira Koren-Morag [b,e], Yichayaou Beloosesky [b,f], Avraham Weiss [b,f]

[a] Department of Internal Medicine E, Rabin Medical Center — Beilinson Hospital, Petach Tikva 4941492, Israel
[b] Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv 6997801, Israel
[c] Department of Internal Medicine A, Rabin Medical Center — Beilinson Hospital, Petach Tikva 4941492, Israel
[d] Gastroenterology Unit, Rabin Medical Center — Hasharon Hospital, Petach Tikva 4941492, Israel
[e] Department of Epidemiology and Preventive Medicine, Tel Aviv University, Tel Aviv 6997801, Israel
[f] Department of Geriatrics, Rabin Medical Center — Beilinson Hospital, Petach Tikva 4941492, Israel

ARTICLE INFO

Article history:
Received 1 May 2016
Received in revised form 16 August 2016
Accepted 19 August 2016
Available online xxxx

Keywords:
HgbA1C
Anemia
Hemoglobin
Elderly

ABSTRACT

Background: Glycated hemoglobin (HgbA1C) is being increasingly used for the diagnosis of diabetes mellitus due to its high availability and reproducibility. Several studies have shown that HgbA1C levels may be affected by levels of hemoglobin and nutritional factors associated with anemia, such as vitamin B12 and iron deficiency. However, none included elderly subjects. The aim of the present study was to investigate these effects in the older nondiabetic population.

Methods: A retrospective cohort study design was used. The computerized database of a large health management organization was reviewed for all subjects without diabetes mellitus who underwent at least one measurement of HgbA1C and other hemoglobin parameters in 2002 at age ≥ 65 years. HgbA1C levels were correlated with hemoglobin, hematocrit, ferritin, iron, transferrin, vitamin B12, and folic acid levels.

Results: A total of 11,352 subjects met the study criteria. Those with HgbA1C levels in the highest quintile (6.21–6.49%, 44.4–47.7 mmol/mol) had significantly lower levels of hemoglobin, hematocrit, and iron than patients with HgbA1C levels in the lowest quintile (<5.4%, 36 mmol/mol), but no linear correlation was found. There was no correlation of HgbA1C level with levels of ferritin, vitamin B12, and folic acid.

Conclusions: In elderly nondiabetic subjects, HgbA1C levels are not correlated with hemoglobin level or nutritional factors associated with anemia and may be interpreted without consideration of these factors.

1. Introduction

Glycated hemoglobin (HgbA1C) is being increasingly used for the diagnosis and follow-up of diabetes as it is highly available and represents glucose control in the long term. However, the assay is limited by the potential interference of hemoglobin variants and factors associated with anemia which can affect HgBA1C levels and lead to false-positive or false-negative results [1–3]. Furthermore, none of the studies conducted to date focused on elderly subjects. The aim of the present study was to evaluate the association of HgbA1C with hemoglobin and nutritional factors causing anemia in the older nondiabetic population.

2. Patients and methods

2.1. Setting and patients

Clalit Health Services (CHS) is the largest health management organization in Israel, with about 4 million members. Its comprehensive computerized data warehouse aggregates and stores continuous real-time input from physicians and health service providers, including demographic parameters, medical diagnoses, findings on in-hospital and outpatient laboratory tests, and medications dispensed, for each of its members.

The cohort for the present retrospective study consisted of individuals insured by CHS-Tel Aviv District branch which covers a mainly urban and Jewish population. Inclusion criteria were performance of at least one serum HgbA1C measurement in 2002 at age > 65 years, in addition to complete blood count and tests for vitamin B12, folic acid, ferritin, and iron during the same year. The CHS database was queried for demographic parameters, co-morbidities, outpatient laboratory

☆ All authors had access to the data and a role in the writing of the manuscript.

* Corresponding author at: Department of Internal Medicine E, Rabin Medical Center — Beilinson Hospital, Petach Tikva 4941492, Israel.
E-mail addresses: alonanat75@gmail.com (A. Grossman), anatga2@clalit.org.il (A. Gafter-Gvili), hemdaw1@netvision.net.il (H. Schmilovitz-Weiss), nira.morag@gmail.com (N. Koren-Morag), beloy@clalit.org.il (Y. Beloosesky), avrahamw@clalit.org.il (A. Weiss).

http://dx.doi.org/10.1016/j.ejim.2016.08.024
0953-6205/

data, and medications dispensed. Patients were excluded if they had a history of diabetes mellitus, defined as fasting plasma glucose level > 126 mg/dL on two occasions or a single measurement of plasma glucose > 200 mg/dL or HgbA1C ≥ 6.5% (48 mmol/mol) or receipt of a prescription for oral or injectable anti-diabetes medication. Patients with a pre-2002 documented diagnosis of chronic kidney disease, which has been found to influence HgbA1C levels [4,5], or hemoglobinopathy were excluded as well. Both chronic kidney disease and hemoglobinopathy were defined by a record of such a diagnosis in the medical record prior to the first HgbA1C used for the analysis.

The study was approved by the ethics committee of CHS. In accordance with the Israel Ministry of Health regulations, the need for informed consent was waived because the data were collected anonymously from electronic medical records.

2.2. Laboratory analysis and patient stratification

All HgbA1C tests for subjects insured by CHS-Tel Aviv District are performed in a single central laboratory using a Tosoh G7 or G8 Analyzer (Tosoh Bioscience, San Francisco, CA) based on high performance liquid chromatography–cation exchange chromatography. Calibration is traceable to the National Glycohemoglobin Standardization Program (NGCP). For the present study, HgbA1C values measured for each subject in the cohort in 2002 were stratified by quintiles, as follows: <5.4%, 5.41%–5.7%, 5.71%–5.9%, 5.91%–6.1%, and 6.11%–6.49%. HgbA1C levels were then correlated with levels of hemoglobin, hematocrit, ferritin, iron, transferrin, vitamin B12, and folic acid measured in the same year.

2.3. Statistical analysis

Data were analyzed with SPSS software version 21.0. (SPSS Inc., Chicago, IL). Continuous variables (hemoglobin, and laboratory factors associated with anemia) are presented as means and standard deviations. Relationships between HgbA1C and other hematologic parameters were analyzed by nonparametric Spearman correlations. One-way analysis of variance (ANOVA) was used to evaluate differences in hematologic parameters by HgbA1C quintiles. The level of significance was set at 0.05.

3. Results

A total of 29,651 individuals underwent at least one HgbA1c test in 2002 at age > 65 years. Of these, 15,435 had diabetes mellitus and 2469 had chronic kidney disease or hemoglobinopathy. An additional 395 subjects were missing data on complete blood count and anemia for 2002. The final cohort consisted of 11,352 individuals (Fig. 1), 7170 female and 4182 male; 3993 (35%) were aged 65–75 years, 5790 (51%) 75–85 years, and 1569 (13.8%) ≥85 years.

The hematologic parameters of the study subjects by HgbA1c quintiles are presented in Table 1. Subjects with HgbA1c levels in the highest quintile (6.21%–6.49%, 44.4–47.7 mmol/mol) had significantly lower mean levels of hemoglobin, hematocrit, and iron than patients with HgbA1C levels in the lowest quintile (<5.4%, 36 mmol/mol), although the difference in mean levels of the hematologic parameters between successive quintiles was marginal. HgbA1C levels directly correlated with blood glucose levels ($r_s = 0.297$), but the correlation with hemoglobin was negligible, for the entire cohort ($r_s = -0.083$), for males and females separately ($r_s = -0.093$ and $r_s = -0.06$, respectively; Fig. 2), and by age ($r_s = -0.069$, 65–75 years; $r_s = -0.072$, 75–85 years; and $r_s = -0.017$, >85 years). There was also no correlation of HgbA1C levels with hematocrit ($r_s = -0.021$) or iron level ($r_s = -0.141$). Mean ferritin level was higher in the patients with higher levels of HgbA1C. There was no consistent correlation of HgbA1C levels with levels of ferritin ($r_s = -0.066$) or with levels of vitamin B12 ($r_s = -0.009$) or folic acid ($r_s = -0.011$).

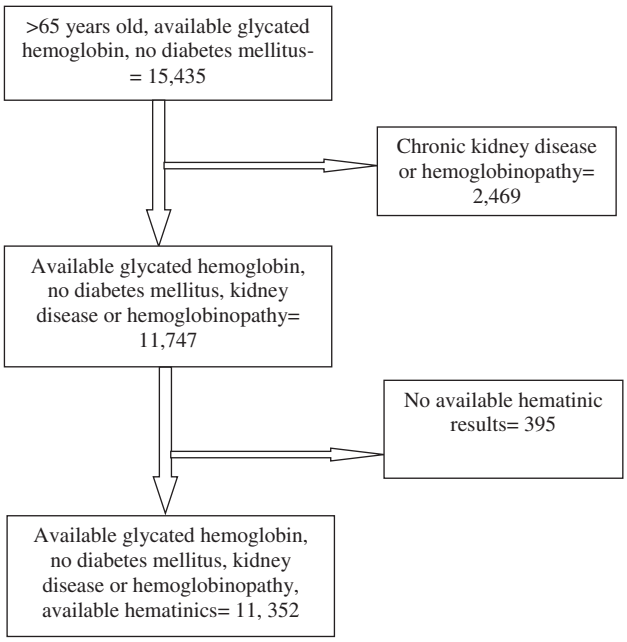

Fig. 1. Flow chart for final cohort selection.

4. Discussion

In this very large retrospective cohort study of elderly nondiabetic community subjects, hemoglobin levels were significantly lower in those with HgbA1C levels in the highest quintile compared to subjects with HgbA1C levels in the lowest quintile. However, the difference in hemoglobin levels between quintiles was marginal, and there was no linear correlation between HgbA1C concentration and either hemoglobin level or nutritional factors causing anemia. The lack of a correlation of HgbA1C and hemoglobin levels was evident in both sexes and across all age groups within the cohort.

The use of HgbA1C for the diagnosis and follow-up of diabetes mellitus is based on studies showing an association of HgbA1C with hemoglobin levels in heterogeneous populations. However, the best-characterized association is between HgbA1C and the hemoglobinopathies [6–8], which are quite rare. Furthermore, this practice has raised concerns given the reported association of high HgbA1C levels with iron-deficiency anemia [9–12] in both diabetic [13] and nondiabetic subjects [14,15]. This finding may be explained by the decreased production of erythrocytes in iron-deficiency states which leads to a relatively older population of erythrocytes that have a stronger capability of binding glucose, resulting in falsely elevated HgbA1C levels. The same may be true for all nutritional deficiencies (e.g., vitamin B12, folic acid), but the evidence in these cases is less robust [10]. There have been no studies of the association between HgbA1c levels and nutritional factors causing anemia in the elderly population, in whom prevalence rates of both anemia and diabetes mellitus are particularly high [16,17]. In addition, given that HgbA1C was found to be associated with mortality in older nondiabetic subjects [18], the recognition of factors that may interfere with HgbA1C interpretation is extremely important.

To the best of our knowledge, ours is the only study to date evaluating the effect of hemoglobin and nutritional factors on HgbA1C in the elderly. Although the association between hemoglobin and hematocrit and HgbA1C was inconsistent, hemoglobin levels were significantly, albeit marginally, lower in subjects with HgbA1C levels in the highest quintile. As patients with hemoglobinopathies and chronic kidney disease were excluded from the analysis, this finding cannot be attributed to the presence of these conditions. Given the lack of an association of HgbA1C with nutritional factors causing anemia in this study, it seems

Please cite this article as: Grossman A, et al, Association of glycated hemoglobin with hemoglobin levels in elderly nondiabetic subjects, Eur J Intern Med (2016), http://dx.doi.org/10.1016/j.ejim.2016.08.024