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Original article

Differential Effect of Glycosylated Hemoglobin Value and Antidiabetic Treatment on the Risk of 30-day Readmission Following a Hospitalization for Acute Heart Failure

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ABSTRACT

Introduction and objectives: In patients with heart failure and type 2 diabetes, low glycosylated hemoglobin has been related with higher risk of mortality but information regarding morbidity is scarce. We sought to evaluate the association between glycosylated hemoglobin and 30-day readmission in patients with type 2 diabetes and acute heart failure.
Methods: Glycosylated hemoglobin was measured before discharge in 835 consecutive patients with acute heart failure and type 2 diabetes. Cox regression analysis adapted for competing events was used.
Results: Mean (standard deviation) age was 72.9 (9.6) years and median glycosylated hemoglobin was 7.2% (6.5%-8.0%). Patients treated with insulin or insulin/sulfonylurea/meglitinides were 41.1% and 63.2% of the cohort, respectively. At 30 days post-discharge, 109 (13.1%) patients were readmitted. A multivariate analysis revealed that the effect of glycosylated hemoglobin on the risk of 30-day readmission was differentially affected by the type of treatment (P for interaction $< .01$). Glycosylated hemoglobin (per 1% decrease) was inversely associated with higher risk in those receiving insulin (hazard ratio = 1.45; 95% confidence interval, 1.13-1.86; $P = .003$) or insulin/sulfonylurea/meglitinides (hazard ratio = 1.44; 95% confidence interval, 1.16-1.80; $P = .001$). Conversely, glycosylated hemoglobin (per 1% increase) had no effect in non-insulin dependent diabetes (hazard ratio = 1.01; 95% confidence interval, 0.87-1.17; $P = .897$) or even a positive effect in patients not receiving insulin/sulfonylurea/meglitinides (hazard ratio = 1.12; 95% confidence interval, 1.03-1.22; $P = .011$).
Conclusions: In acute heart failure, glycosylated hemoglobin showed to be inversely associated to higher risk of 30-day readmission in insulin-dependent or those treated with insulin/sulfonylurea/meglitinides. A marginal effect was found in the rest. Whether this association reflects a treatment-related effect or a surrogate of more advanced disease should be clarified in further studies.

Efecto diferencial de la glucohemoglobina y el tratamiento antidiabético sobre el riesgo de reingreso a 30 días después de un ingreso por insuficiencia cardiaca aguda

Palabras clave:
Glucohemoglobina
Control de la glucemia
Tratamiento de la diabetes
Insuficiencia cardiaca aguda
Riesgo de reingreso

RESUMEN

Introducción y objetivos: En los pacientes con insuficiencia cardiaca y diabetes tipo 2, las cifras bajas de glucohemoglobina se han relacionado con un riesgo más elevado de mortalidad, pero la información relativa a la morbilidad es escasa. El objetivo de este estudio fue evaluar la asociación existente entre la glucohemoglobina y el reingreso en un plazo de 30 días en los pacientes con diabetes tipo 2 e insuficiencia cardiaca aguda.
Métodos: Se determinó la glucohemoglobina antes del alta en 835 pacientes consecutivos con insuficiencia cardiaca aguda y diabetes tipo 2. Se utilizó un análisis de regresión de Cox adaptado para eventos competitivos.
Resultados: La media de edad fue de 72,9 ± 9,6 años y la mediana de la glucohemoglobina fue de 7,2% (6,5-8,0%). Los pacientes tratados con insulina o con insulina/sulfonilurea/meglitinidas constituyeron un 41,1 y un 63,2% de la cohorte, respectivamente. A los 30 días del alta, 109 (13,1%) pacientes habían tenido un reingreso en el hospital. El análisis multivariante reveló que el efecto de la glucohemoglobina sobre el riesgo de reingreso en 30 días se veía afectado de manera diferente según el tipo de tratamiento (p para la

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interacción < 0,01). La glucohemoglobina (por cada 1% de disminución) presentaba una asociación inversa con un mayor riesgo en los pacientes tratados con insulina (*hazard ratio* = 1,45; intervalo de confianza del 95%, 1,13-1,86; p = 0,003) o con insulina/sulfonilurea/meglitinidas (*hazard ratio* = 1,44; intervalo de confianza del 95%, 1,16-1,80; p = 0,001). En cambio, la glucohemoglobina (por cada 1% de aumento) no tenía efecto alguno en la diabetes no insulinodependiente (*hazard ratio* = 1,01; intervalo de confianza del 95%, 0,87-1,17; p = 0,897) o mostraba incluso un efecto positivo en los pacientes no tratados con insulina/sulfonilurea/meglitinidas (*hazard ratio* = 1,12; intervalo de confianza del 95%, 1,03-1,22; p = 0,011).

Conclusiones: En la insuficiencia cardiaca aguda, la glucohemoglobina mostró una asociación inversa con el riesgo de reingreso en 30 días en los pacientes insulinodependientes o en los tratados con insulina/sulfonilurea/meglitinidas. En el resto de pacientes se observó un efecto marginal. En futuros estudios deberá esclarecerse si esa asociación refleja un efecto relacionado con el tratamiento o bien es un indicador indirecto de una enfermedad más avanzada.

Abbreviations

AHF: acute heart failure
DM2: type 2 diabetes mellitus
HbA_{1c}: glycosylated hemoglobin
HF: heart failure
Ins/SU/MG: insulin/sulfonylurea/meglitinides

INTRODUCTION

Risk of early readmission in patients recently discharged for acute heart failure (AHF) remains prohibitively high.[1,2] Readmissions are usually associated to increased mortality and constitute an excessive health-care burden.[1] Contemporary heart failure (HF) programs and institutional initiatives set reduction in the rate of early readmissions as a main target.[3–5] Unfortunately, there are no well-established risk factors to identify patients at higher/maximum risk.[6] Diabetes mellitus is a common comorbidity in HF and its optimal management remains unclear. Recent studies and current guidelines have stressed the potential deleterious effects of intensive glucose-lowering strategies and subsequent higher risk of hypoglycemic events in certain subgroups, such as those with advanced cardiovascular (CV) diseases.[7–10] In accordance with these statements, some epidemiological and observational studies have shown a U-shape pattern or inverse relationship between glycosylated hemoglobin (HbA_{1c}) and mortality in patients with HF and diabetes mellitus.[11–13] Nevertheless, no data are available regarding the effect of HbA_{1c} on the risk of readmission, especially after an episode of decompensation and according to the type of antidiabetic treatment.

Hypoglycemia occurs mainly through activation of the sympathoadrenal system, but also by promoting endothelial dysfunction and inflammation. Among the effects are increased systolic blood pressure, heart rate, risk of arrhythmias, myocardial ischemia, and fluid accumulation/redistribution, conditions that are well known as precipitating factors for HF decompensation.[8,14,15] Along this line, we postulate that lower HbA_{1c} values in type 2 diabetes mellitus (DM2) patients with a recent hospitalization for AHF, especially those treated with antidiabetic drugs that increase the risk of hypoglycemia, could possibly identify those at higher risk of early readmission.

The aim of this study was to evaluate the association of HbA_{1c}, measured during an index admission for AHF, and the risk of 30-day unplanned readmission, and determine whether the type of antidiabetic treatment differentially modifies this association.

METHODS

Study Sample

We included 2079 consecutive patients admitted to the cardiology department of a tertiary center (*Hospital Clínico Universitario de Valencia*, Spain) from January 1, 2006, to December 31, 2013 with a principal diagnosis of AHF. This was defined as rapid onset of symptoms and signs of abnormal cardiac function together with objective evidence of structural or functional abnormality of the heart at rest (cardiomegaly, third heart sound, cardiac murmur, abnormal echocardiogram, or increased natriuretic peptides).[16–18] In all patients, intravenous treatment with furosemide was prescribed, at least during the first 48 h of admission. By design, patients without prior diagnostic of DM2 at the index hospitalization (n = 1173) were excluded. Additionally, hospital deaths (n = 34) and patients with final diagnosis of acute coronary syndrome (n = 20) and pneumonia (n = 16) were also excluded from this analysis. The final sample included 835 individuals (Figure of the supplementary material).

Before discharge, information related to demography, medical history, vital parameters, 12-lead electrocardiogram, standard laboratory, echocardiographic parameters, and pharmacologic therapies were routinely recorded using pre-established registry questionnaires. Standard laboratory tests were obtained before discharge (median of 4 days [interquartile range, 3-6 days]). Treatment with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, aldosterone antagonists, anticoagulants, diuretics, and other therapeutic strategies were individualized following established guidelines in effect at the time the patient was recruited in the registry.[16–18]

Diabetes Treatment and Glycosylated Hemoglobin Measurement

Antidiabetic treatment (insulin, sulfonylureas, meglitinides, metformin, thiazolidinedione, inhibitors of dipeptidyl peptidase 4 and alpha glucosidase inhibitors) was recorded at discharge. Blood HbA_{1c} along with standard laboratory tests were measured during hospitalization (median of 4 days [interquartile range, 3-6 days] after admission). For analysis purposes, patients were categorized in 2 groups, according to the hazard of hypoglycemic events: *a)* high risk of hypoglycemic events (insulin/sulfonylurea/meglitinides [Ins/SU/MG], and *b)* low risk of hypoglycemic events (dipeptidyl peptidase 4 and alpha glucosidase inhibitors).