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Research Article

Glucose Tolerance at Hospital Discharge as a Prognostic Marker in Acute Heart Failure Patients

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Abstract

Background: Because patients with Heart Failure (HF) and diabetes have a poorer prognosis compared to HF patients without diabetes, it is important to understand the prognostic value of glycaemic control in this population. This study investigated the association between different markers of glycaemic control and outcome in 192 HF patients on the day of hospital discharge.

Methods: All-cause mortality combined with hospitalization for cardio-renal cause during follow-up was defined as the primary outcome.

Results: A history of diabetes was present in 94 patients (32%). From the remaining 98 patients, 3% was classified as having normal glucose tolerance, 41 (42%) prediabetes and 54 (55%) newly diagnosed diabetes. During the median follow-up time of 470 days, there were 23 deaths (24%) among the previously known diabetic patients, compared to 18 (18%) in the group of newly diagnosed (pre)diabetic patients. 2h glucose was a significant predictor for outcome, with a hazard ratio (95% CI) of 1.080 (1.00-1.17) while neither fasting plasma glucose nor HbA1c were associated with outcome.

Conclusions: The majority of HF patients have impaired glucose regulation on the day of hospital discharge. Elevated 2h glucose during OGTT, but not fasting plasma glucose nor HbA1c, demonstrated a higher risk for worse outcome.

Keywords: Prognosis; Hemoglobin A1c protein; Glucose tolerance test; Hyperglycemia

Introduction

Diabetes is recognized as an independent predictor of worse prognosis in patients with Heart Failure (HF) [1]. In chronic HF, the reported prevalence of diabetes varies from 8% to 41% [2]. Similarly, in acute HF, the reported prevalence of diabetes during hospital admission varies widely (16-46%) [3]. The large variation in prevalence of diabetes in different studies can at least partly be explained by differences in study design and inclusion criteria, geographic/ethnic characteristics of study subjects, and different diagnostic criteria for diabetes.

In non-HF populations it has been shown that the progression from prediabetes (the presence of insulin resistance, hyperinsulinemia, impaired fasting glucose or impaired glucose tolerance) to diabetes can be prevented through lifestyle changes and increased physical activity [4,5]. Therefore, in order to prevent diabetes and its complications in HF, early diagnosis of abnormalities in glucose regulation is important. The World Health Organization and American Diabetes Association recommend the use of fasting glucose, oral glucose tolerance testing and HbA1c in the diagnostic process [6,7]. Specifically for the HF population, the use of a 2 hour Oral Glucose Tolerance Test (OGTT) is promoted for diagnosing impaired glucose tolerance [8-10]. However, while most studies in acute HF report admission blood glucose levels [11-16], only Matsue and colleagues used oral glucose tolerance testing to identify impaired glucose tolerance in relation to adverse events [17]. Besides a dramatic prevalence of impaired glucose regulation (63%) in patients without previously diagnosed diabetes, they reported an increased risk for adverse cardiovascular and cerebral events during follow-up in patients with known diabetes as well as in patients with impaired glucose tolerance [17]. However, they did not include glycated hemoglobin (HbA1c) as a marker of prolonged glycaemic state in their analyses [4].

We were interested in describing the prevalence of (pre)diabetes as well as the importance of different markers for diagnosis of (pre) diabetes at the end of a hospital stay for acute HF. Moreover, this study aimed at determining the prognostic implications of the different diagnostic markers for (pre)diabetes regarding all-cause mortality and hospitalization for cardio-renal causes.

Methods

Subjects and study design

Between September 2012 and September 2013, all patients admitted to Jessa hospital (Hasselt, Belgium) with congestive HF were screened for diabetes and for participation in OGTT. Heart failure was diagnosed according to the European Society of Cardiology criteria [18]. Both patients with new-onset HF and with decompensated chronic HF were eligible for inclusion. Exclusion criteria for inclusion in the study were (1) acute myocardial infarction, (2) malignant disease (cancer) with treatment at the time of admission, (3) missing or unknown vital status. Exclusion for glucose tolerance

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testing were (1) corticosteroid treatment, (2) cognitive impairment (e.g. dementia), (3) unstable condition with transfer to another department (not included in flowchart) and (4) sudden unplanned discharge preventing the planning of the OGTT. Three groups were defined: patients who underwent a glucose tolerance test, patients with ongoing antidiabetic therapy and patients who fulfilled exclusion criteria for glucose tolerance testing. Ethical approval was obtained from the committees of the Jessa hospital and Hasselt University.

Outcome parameters

Death from any cause combined with the first rehospitalization for cardio-renal causes during follow-up was defined as the primary endpoint. Other endpoints of interest were death, number of rehospitalizations, days spent in rehospitalization and days lost (for reasons of hospitalization and death). Days lost to death was calculated as follows: in case of death before the end of follow-up, the remaining days until the study end were counted as 'days lost to death'. These days were added to the number of days the patient stayed in hospital to obtain 'days lost'.

Data regarding death and hospital admissions were collected by contacting family doctors, by searching hospital files and through an online registry of death announcements from national papers. Follow-up was completed in June 2014.

Oral glucose tolerance test and blood parameters

A 2 hour OGTT was performed immediately before hospital discharge. Following an overnight fasting period, baseline blood glucose (in fluoride-oxalate tubes) and HbA1c (in EDTA tubes) were determined *via* a venous blood sample. Hereafter, 75g glucose (B. Braun Melsungen AG, Melsungen, Germany) dissolved in 250ml water was ingested and venous blood samples were taken for blood glucose analysis at 30, 60, 90 and 120min. Plasma glucose was determined with an Olympus AU analyzer (Beckman Coulter, Switzerland) and HbA1c with Hi-AutoA1C Analyzer (Menarini Diagnostics, Italy). Combining the results of OGTT and HbA1c, patients were classified as having Normal Glucose Tolerance (NGT), Prediabetes was defined as fasting plasma glucose 5.6-6.9 mmol/L or 2h plasma glucose 7.8-11.0 mmol/L or HbA1c 5.7-6.4 %, and diabetes mellitus as fasting glucose ≥7.0 mmol/L or 2h glucose ≥ mmol/L or HbA1c ≥6.5 % [4].

Patient characteristics

Clinical data, including Body Mass Index (BMI), history of Ischaemic Heart Disease (IHD) and Left Ventricular Ejection Fraction (LVEF) at the end of hospital admission were retrieved from hospital records.

Statistics

Statistical analyses were performed using SAS Enterprise Guide 4.3 and SAS 9.2 (SAS Institute Inc.) software. Patient characteristics were compared using unpaired t-tests or one-way analysis of variance (ANOVA) with Bonferroni post-hoc analysis for continuous variables and Fisher's exact test for categorical variables. The distributions of number of hospitalizations, days spent in hospital and total days lost were skewed, and therefore non-parametric ANOVA was used for these variables. Event free survival curves were constructed using the Kaplan-Meier method; differences were tested using Wilcoxon statistics because of crossing curves. Univariate and multivariate

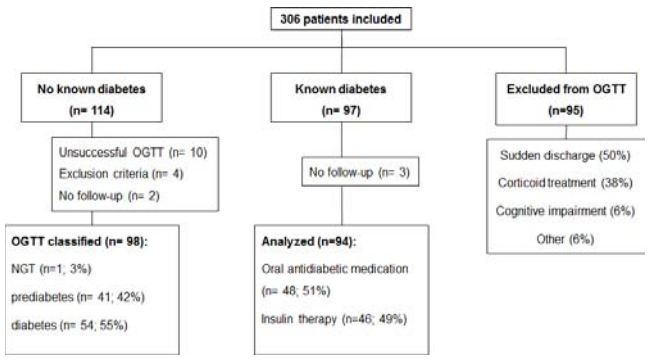

Figure 1: Patient flow diagram.

Table 1: Patients characteristics according to glucometabolic state.

	Total group n=192	NGT n=3	Pre-diabetes n=41	Diabetes n=54	*P**	Known diabetes n=94	*P***
Age (years)	74 ± 11	66 ± 14	74 ± 14	78 ± 10	0.15	73 ± 11	0.09
Sex (% male)	103 (54%)	3 (100%)	21 (51%)	26 (48%)	0.33	53 (56%)	0.37
BMI (kg/m²)	28.1 ± 5.2	24.5 ± 1.9	26.1 ± 4.0	26.7 ± 4.6	0.60	29.8 ± 5.6	0.0001
Aetio-logy (IHD, %)	96 (50%)	1 (33%)	14 (34%)	24 (44%)	0.64	57 (61%)	0.02
LVEF (%)	44 ± 15	34 ± 23	44 ± 15	43 ± 14	0.49	45 ± 16	0.56

NGT: Normal Glucose Tolerance; BMI: Body Mass Index; IHD: Ischeamic Heart Disease; LVEF: Left Ventricular Ejection Fraction. Continuous variables are presented as mean ± SD, categorical variables as number and percentage. *denotes $p<0.05$ in the comparison of 3 groups with OGTT; **denotes $p<0.05$ in the comparison of 3 groups with OGTT and patients with known diabetes.

Cox proportional hazard analyses were performed to determine the independent predictors of survival and event free time. In addition to glucometabolic parameters, the following variables were tested for possible association with survival and event free time: age, gender, BMI, IHD and LVEF. Parameters significant to $p<0.1$ in univariate analysis were entered in the multivariate model. Results are presented as mean ± one standard deviation. All tests were two-sided with a *P*-value of 0.05 as the threshold for statistical significance.

Results

A patient flow diagram is presented in Figure 1. Among 306 patients admitted with acute HF in the study period, 32% were taking anti-diabetic medication and 31% were excluded from glucose tolerance testing. Among 114 patients who underwent OGTT, ten patients could not be classified because of discomfort during glucose load (n=5) or missing results from blood analyses (n=5). From two patients in the OGTT group and three patients in the diabetic group, no follow up data after hospitalization were available. Finally, analyses were performed on 98 patients who underwent OGTT and 94 patients with known diabetes.

The total cohort (n=192) had a mean age of 74±11 years old and consisted of 54% male patients (Table 1). Furthermore, mean LVEF was 44±15% with 50% of patients having a LVEF under 45%, indicating an equal proportion of patients with reduced and preserved systolic function. In patients undergoing OGTT, the median hospital duration was 7 days (range 1-109 days), compared to 9 days (range 1-70 days) in patients previously diagnosed with diabetes ($p>0.05$).

Table 2: Importance of 2h glucose values during OGTT for glucometabolic classification.

	Prediabetes n=41	Diabetes n=54
FPG	1 (2%)	1 (2%)
FPG + 2hPG	3 (7%)	5 (9%)
FPG + Hba1c	7 (17%)	-
FPG + 2hPG + HbA1c	15 (37%)	5 (9%)
2hPG	2 (5%)	39 (72%)
2hPG + HbA1c	10 (24%)	3 (6%)
HbA1c	3 (7%)	1 (2%)

FPG: Fasting Plasma Glucose; 2Hpg: 2h plasma glucose during OGTT. Figures represent the amount of patients (%) fulfilling a certain combination of diagnostic markers for prediabetes or diabetes.

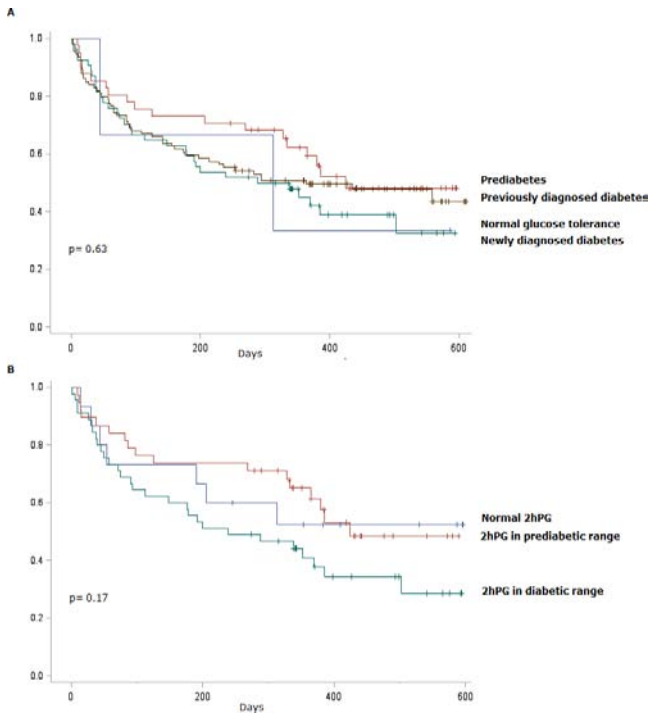

Figure 2: Kaplan-Meier curves for survival combined with freedom from cardiorenal hospitalization according to general ADA classification (A) and classification based on 2h glucose during OGTT only (B). 2hPG, 2h glucose value during OGTT; | denotes a censored value.

According to ADA criteria, only 3 patients showed NGT (3%), 41 patients (42%) were classified as prediabetic and 54 patients (55%) were classified as diabetic. Baseline patient characteristics of the study population stratified by glucometabolic state are presented in Table 1. Age, sex, BMI, LVEF and proportion of patients with IHD were comparable between patients classified in different ADA groups based on OGTT. In contrast, patients with prior diagnosis of diabetes were distinguished from (pre)diabetic patients undergoing OGTT by higher BMI and a larger proportion of patients with IHD.

Importance of OGTT in the diagnosis of prediabetes and diabetes

Mean Fasting Plasma Glucose (FPG) from patients with a successful OGTT was 6.0±0.7 mmol/L, with 25% of FPG values in the normal range. Similarly, mean HbA1c was 5.8±0.4%, with 28% of HbA1c values in the normal range. As illustrated in Table 2, if an OGTT had not been performed, two patients in the prediabetic group (5%) and the majority of patients in the diabetic group (72%) would have been misclassified based on FPG combined with HbA1c.

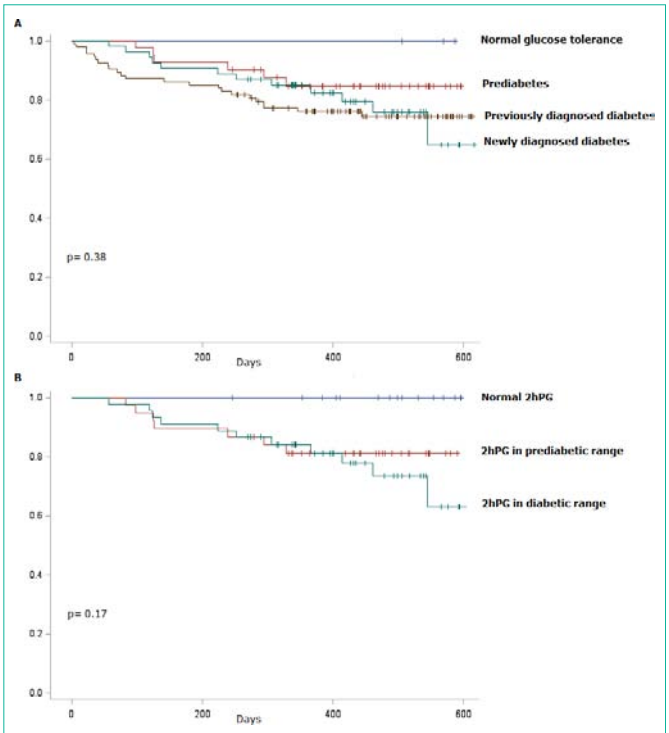

Figure 3: Kaplan-Meier curves for survival according to general ADA classification (A) and classification based on 2h glucose during OGTT only (B). 2hPG, 2h glucose value during OGTT; | denotes a censored value.

Outcome

The median (interquartile range) follow-up time in survivors was 470 days (384-546 days).

Mortality combined with readmission for cardio-renal cause

In the group of patients with previously diagnosed diabetes, 23 (24%) died during follow-up, compared with 18 (18%) in the group with no prior diagnosis of diabetes (p=0.13). When mortality data were combined with (re)hospitalization for cardio-renal cause, Kaplan-Meier curves for the 4 groups (3 ADA groups and previously diagnosed diabetics) were comparable (p=0.63, Figure 2). Also when focusing on prediabetic patients and newly diagnosed diabetic patients, there was no significant difference (p=0.17). Looking into the separate markers for glucometabolic diagnosis, 2h plasma glucose during OGTT (2hPG) was the best predictor for outcome (p=0.17; Figure 3) compared to FPG (p=0.66) and HbA1c (p=0.72).

Univariate analyses of hazard ratio showed that 2hPG was a near-significant predictor for events with an increased risk of 8% per mmol increase in 2hPG (p=0.05; Table 3). Further analyses searching for confounding factors revealed that age was an important confounder, next to history of IHD, while sex, BMI and LVEF were not. The first multivariate model containing 2hPG, age and IHD revealed that

Table 3: Hazard ratios for all-cause death and CR hospitalization.

Predictor	Hazard Ratio (95% Confidence Interval)	*P* value
According to ADA classification ADA classification Prediabetes vs newly found diabetes	1.50 (0.85-2.65)	0.16
Impaired fasting glucose Per classification level increase		0.60
Impaired glucose tolerance Per classification level increase		0.16
Elevated HbA1c Per classification level increase		0.59
Glucometabolic parameters **0 min glucose** per mmol/L increase	0.83 (0.55-1.26)	0.39
30 min glucose per mmol/L increase	1.01 (0.86-1.19)	0.88
60 min glucose per mmol/L increase	1.03 (0.93-1.14)	0.58
90 min glucose per mmol/L increase	1.04 (0.96-1.14)	0.32
120 min glucose per mmol/L increase	1.08 (1.00-1.17)	0.05
HbA1c per 0.1% increase	1.01 (0.99-1.02)	0.44
Confounding factors		
Age per year increase	1.04 (1.02-1.06)	<.0001
Male sex	1.33 (0.90-1.97)	0.16
BMI	0.98 (0.94-1.02)	0.30
History of IHD **LVEF** per 5% increase	1.59 (1.07-2.36) 1.01 (0.95-1.08)	0.02 0.75
Multivariate models		
120 min glucose + Age + IHD 120 min glucose Age IHD	1.04 (0.95-1.13) 1.04 (1.01-1.07) 1.32(0.76-2.29)	0.40 0.02 0.33
120 min glucose + Age 120 min glucose Age	1.04 (0.96-1.13) 1.04 (1.01-1.07)	0.34 0.01

BMI: Body Mass Index; IHD: Ischaemic Heart Disease; LVEF: Left Ventricular Ejection Fraction.

only age remained an independent predictor. The second model, containing only 2hPG (p=0.34) and age (p=0.01) confirmed that no significant relationship remained between 2hPG and mortality and readmission for cardio-renal causes.

Mortality

Although some trends are visualized in the survival curves for patients stratified by ADA classification and prior diagnosis of diabetes (early mortality seems to be higher in patients with prior diagnosis of diabetes and late mortality seems to be higher in patients with newly diagnosed diabetes), these were not statistically significant (p=0.38, Supplemental data Figure 2S-A). Interestingly, there was no mortality in the group of 15 patients with normal 2hPG and patients with 2hPG in the diabetic range seem to have a worse outcome (Supplemental data Figure 2S-B). However, differences were not significant (p=0.17).

Similar to the primary outcome summarized above, univariate analyses investigating the predictive effect of glucometabolic parameters showed that only 2hPG was a predictor for mortality with hazard ratio (95% Confidence Interval) =1.19 (1.04-1.37; p=0.01). However, after model building to investigate the independent effects, the influence of age (hazard ratio=1.06 (1.02-1.10); p<0.01) reduced the significance of 2hPG (p=0.09) as a predictor for mortality.

From the group of patients with no previous diagnosis of diabetes, survivors were younger during hospitalization compared to deceased patients (74±13 *vs* 83±6 years old, p<0.05), while BMI and LVEF were comparable. Surprisingly, FPG was higher in survivors (6.0±0.7 *vs* 5.7±0.5 mmol/L, p<0.05) and HbA1c was equal in both groups (5.8±0.4 *vs* 5.8±0.4%, p>0.05). Again, 2hPG was able to demonstrate a difference between survivors and non-survivors (10.7±3.2 *vs* 12.5±3.2 mmol/L, p<0.05).

Rehospitalizations and days lost

The median of the number of rehospitalizations for all reasons of the total group was one (range: 0-9), and was not different between groups. However, patients newly diagnosed with diabetes spent more days in hospital (7 [0-126]) compared to prediabetic patients (2 [0-42]; p<0.05). Furthermore, there was a trend towards more days lost in the former group (11 [0-614] *vs* 2 [0-499], p=0.07).

Discussion

Our results showed that impaired glucose regulation at hospital discharge, is omnipresent and under recognized in patients admitted with acute HF. Furthermore, this study indicates that from all three markers for diagnosis of (pre)diabetes (fasting glucose, 2h glucose during OGTT and HbA1c), elevated 2h glucose during OGTT is the better predictor for mortality combined with rehospitalization for cardio-renal causes.

Glucose regulation is severely disturbed in acute heart failure

In our study population, the prevalence of diabetes was 32% based on glucose-lowering therapy and known history in patient files, and was increased to 49% when the results of the OGTT and HbA1c were taken into account. A further 13% was identified as prediabetic and an insignifant proportion of patients undergoing OGTT showed

normal glucose tolerance. It is safe to assume that glucose regulation is also impaired in a large proportion of the patients excluded for OGTT in this study, because this group also contains patients with corticosteroid treatment, which is known to increase glucose values [19]. The prevalence of impaired glucose regulation in our patient population is clearly higher compared to patients hospitalized with an acute coronary event: from 164 patients undergoing OGTT on the day of discharge in the study of Norhammar *et al*, classification of normal glucose tolerance-prediabetes and diabetes was assigned in 34%, 35% and 31% respectively [20]. Furthermore, the proportion of patients with newly diagnosed diabetes in the present patient population (55% of patients undergoing OGTT) is increased when compared to patients with stable chronic HF, as described by Egstrup et al (18%) and by our own research group (25%) [8,10]. In comparison, in the study of Matsue *et al*, the OGTT on the day of discharge revealed only 9% newly diagnosed diabetics and 34% prediabetic patients. The use of the stringent ADA criteria in our study can probably partly account for the differing results.

We showed that the OGTT had a significant contribution in the diagnosis of diabetes, as the majority of the newly diagnosed diabetic patients were identified because of glucose values after glucose loading. This finding is comparable to studies in chronic HF patients [8,10]. Glycated hemoglobin in particular showed limited sensitivity for diagnosis of diabetes in the context of this study, which could mean that the disturbed glucose regulation is an acute reaction on illness and stress from hospitalization which is not yet reflected in this marker of prolonged glycaemia.

Elevated glucose levels at the end of a hospital admission for acute HF can have several reasons, of which three are highlighted below. (1) Hyperglycaemia and other abnormal metabolic factors are commonly found in seriously ill patients, caused by a highly complex interplay of counter-regulatory hormones such as catecholamines, growth hormone, cortisol, and cytokines [21]. In this respect, it is a question of debate whether elevated glucose values are deleterious and increase mortality, or if they are rather another marker of a serious disease. (2) It is known that diuretic therapy is associated with hyperglycaemia [22]. Therefore, increased glucose values in acute HF patients could also be the result of the intensive diuretic therapy to relieve congestion during their hospital stay. (3) In our study, as well as in the study of Matsue *et al* [17], patients were tested for glucose tolerance at the end of their hospital stay, which is a period of severely reduced physical activity or worse, immobilization. Hamburg and colleagues showed that even a short period of 5 days bed rest can induce insulin resistance in healthy subjects. This was illustrated by a 67% increase in the insulin response to glucose loading as well as increased glucose curves during OGTT [23]. Possibly, the insulin resistance resulting from bed rest during HF admissions is even worse, as the median length of hospital stay in our study was 7 days in patients undergoing OGTT and 9 days in patients previously diagnosed with diabetes. This figure is concordance with the EuroHeart Failure Study II, where the median duration of hospitalization was 9 days [24]. In order to prevent worsening of insulin resistance induced by bed rest during hospital admissions for HF, early mobilization should be even more emphasized and promoted.

Outcome

Our data show that increased 2hPG is significantly associated with an adverse prognosis, while FPG and HbA1c values were not able to identify patients at risk. This effect was more apparent on a continuous scale, as opposed to comparison of patients with normal-prediabetic-diabetic 2hPG values on a categorical scale. With every increase of 1 mmol/L in 2hPG, mortality risk combined with hospitalization for cardio-renal causes increased with 8% and risk for mortality with 19%. The study of Matsue and colleagues was similar to the present study in respect to patient population (inclusion of acute HF patients with reduced as well as preserved systolic dysfunction in the same age range) and assessment of glucose regulation at the day of discharge [17]. However, our data could not confirm the results of Matsue et al, who reported a 3-4 fold higher risk in patients classified as glucose intolerant [17]. Conversely, literature reporting the prognostic impact of non-fasting glucose levels at the start of the hospitalization period does not provide an unequivocal answer. A large multicentre trial showed a powerful association between admission glucose and short term (30 day) mortality [15]. Barsheshet and colleagues reported similar results for 60 day mortality [11]. Two other studies concluded that admission glucose was also an important predictor for long-term prognosis in acute HF [13,16]. On the other hand, the largest study of Kosiborod *et al* [14], which included more than 50,000 elderly patients hospitalized with HF, found no association between admission glucose levels and mortality after 30 days and 1 year of follow-up. A more recent study of Barsheshet showed similar results [12]. As admission glucose levels reflect the glycaemic state during acute and critical illness, these findings cannot directly be compared to our findings from the time of discharge.

The predictive effect of 2hPG disappeared when corrected with age in our study population. The influence of older age on increasing short-and long term mortality has been shown by Gustafsson *et al* [25]. In addition, age has been described as an independent predictor of mortality in studies investigating the prognostic impact of known diabetes [11-13,26], and admission glucose [11,12,15]. However, it is also known that glucose regulation is impaired in the elderly without HF, through a combination of decreased insulin secretion and increased insulin resistance [27]. Furthermore, in contrast with the results of Dries and colleagues in a chronic HF patient population, the negative influence of ischemic heart disease on event rate also disappeared in our multivariate model with age as the most powerful predictor [28].

While a significantly increased risk for worse outcome was described for elevated 2hPG, but not for FPG nor for HbA1c, the clinical relevance of this finding is not clear. Especially because the predictive effect was reduced when age was taken into account, our results do not promote the use of the OGTT when looking for prognostic parameters. However, it is clear that clinical follow-up is necessary in patients with elevated 2hPG in order to prevent worsening of glucose regulation as well as comorbidities associated with diabetes mellitus.

Limitations

Our study did not include some factors that could add information to our predictive model. First, comprehensive echocardiographic parameters were not available for all patients. Second, severity of HF was not illustrated with BNP values, because they were not available at the moment of glucose tolerance testing.

Conclusions

The majority of HF patients suffer from impaired glucose regulation on the day of hospital discharge. From all three markers for diagnosis of (pre)diabetes (fasting glucose, 2h glucose during OGTT and HbA1c), elevated 2h glucose during OGTT is the better predictor for mortality combined with rehospitalization for cardio-renal causes.

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