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Age-dependent differences in diabetes and acute hyperglycemia between men and women with ST-elevation myocardial infarction: a cohort study

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Abstract

Background: Both acute hyperglycemia as diabetes results in an impaired prognosis in ST-elevation myocardial infarction (STEMI) patients. It is unknown whether there is a different prevalence of diabetes and acute hyperglycemia in men and women within age-groups.

Methods: Between 2004 and 2010, 4640 consecutive patients (28% women) with STEMI, were referred for primary PCI. Patients were stratified into two age groups, < 65 years (2447 patients) and ≥65 years (2193 patients). Separate analyses were performed in 3901 patients without diabetes. Diabetes was defined as known diabetes or HbA1c ≥6.5 mmol/l at admission.

Results: The prevalence of diabetes was comparable between women and men in the younger age group (14% vs 12%, p = 0.52), whereas in the older age group diabetes was more prevalent in women (25% vs 17% p < 0.001). In patients without diabetes, admission glucose was comparable between both genders in younger patients (8.1 ± 2.0 mmol/l vs 8.0 ± 2.2 mmol/l p = 0.36), but in older patients admission glucose was higher in women than in men (8.7 ± 2.1 mmol/l vs 8.4 ± 2.1 mmol/l p = 0.028). After multivariable analyses, the occurrence of increased admission glucose was comparable between men and women in the younger age group (OR 1.1, 95%CI 0.9-1.5), but increased in women in the older age group (OR 1.3, 95% CI 1.1-1.7). Both diabetes and hyperglycemia were associated with a higher one-year mortality in both men and women.

Conclusions: The differences between men and women in hyperglycemia and diabetes in patients with STEMI are age dependent and can only be observed in older patients. This may have implications for medical treatment and should be investigated further.

Keywords: STEMI, Gender, Diabetes, Acute hyperglycemia

Background

Both hyperglycemia and diabetes are independent predictors of impaired prognosis after ST elevation myocardial infarction (STEMI) [1-4]. Prevalences of both hyperglycemia and diabetes in STEMI are increased in women, which in part may explain their higher mortality rates [1,5,6]. Moreover, diabetes has been associated with a higher cardiovascular mortality in women compared to men [7-9]. In the general population however, only in elderly people diabetes is more often present in women than in men [10]. Until now, data with regard to the impact of age on the difference in prevalence of hyperglycemia and diabetes between men and women with STEMI are lacking. We investigated whether the differences in both hyperglycemia and diabetes are age-dependent within a large registry of patients with STEMI, treated with primary percutaneous coronary intervention (PCI).

Methods

We performed an observational study including all consecutive patients admitted with STEMI, referred for primary PCI to our hospital between 2004 and 2010.

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Within these time frames, HbA1c and glucose were routinely measured on admission in all STEMI patients. Patients were diagnosed with STEMI if they had chest pain longer than 30 minutes and ECG changes with ST elevation greater than 2 mm in at least two precordial leads or greater than 1 mm in the limb leads. All patients were directly transported to the catheterization 4laboratory on arrival, and acute coronary angiography was performed with subsequent PCI when indicated as part of the routine treatment for all STEMI patients. The interventional strategy was at the operator's discretion. All patients were pretreated with aspirin, heparin, and clopidogrel during transportation to the hospital according to protocol, or these drugs were administered at the emergency ward. Cardiac biomarkers were elevated in all patients. Diabetes was defined as known diabetes or a HbA1c ≥ 6.5 at admission. This HbA1c value was identified by the American Diabetes Association as diagnostic for diabetes mellitus [11]. We performed additional analysis on a group without diabetes in order to concentrate on acute hyperglycemia due to stress. We conducted a multivariate analysis with gender as a predictor of a higher than median glucose levels. We corrected for confounders based on previously described variables in the literature [1,8]. Therefore, the multivariate model consisted of gender, TIMI flow, Killip class and age.

Data collection
Patient characteristics were registered into a dedicated database. Thrombolysis in Myocardial Infarction (TIMI) [12] flow was scored according to the TIMI flow grading system before and after PCI. Follow-up information was obtained with pre-defined time intervals of 30 days and one year using the outpatient files or by direct telephone interview by independent research nurses not involved in patient treatment., The HbA1c levels were measured on the Primus Ultra 2 affinity chromatography-HPLC (Primus Diagnostics, Kansas City, MO) with a within-run coefficient of variation of < 0.5%. The reference normal values in non diabetics were 4.0% to 6.5%. Glucose levels were measures with a Modular device (Roche Diagnostics). The reference values did not change during the study period and yearly numeric quality control data revealed that the coefficient of variation remained < 2%.

Statistical analysis
Statistical analysis was performed using SPSS version 17.0 (SPSS Inc, Chicago, IL). Continuous data were expressed as median and inter quartile range and categorical data as percentages. In order to examinate differences in women and men, we performed the Chi^2 test for categorical variables and one-way Anova for continuous variables. The test for significance were two-sided

with an α of < 0.5%. Multivariate analyses were performed using binary logistic regression. Predictors were identified using forward, stepwise logistic regression with the likelihood ratio test of all baseline variables with an α ≥ 0.1. The three most significant values and gender were entered into the final multivariate model. Kaplan Meier was performed with the log rank test for the p-values.

Results
A total of 4640 patients with STEMI were admitted between 2004 and 2010. Mean age of the total population was 64 ± 13 years, including 1291 women (28%). In the total population, the prevalence of hypertension was 36%, smoking 41% and hypercholesterolemia 21%. A total of 464 (10%) patients had a previous myocardial infarction.

Effect of age
In older women, a higher killip class was observed compared to men. This difference was not present in the younger age group. The prevalence of known diabetes was 10% in men en 16% in women in the total study group (p < 0.001). Undetected diabetes was observed in 4% of men and in 5% of women (p = 0.80), resulting in a significantly different prevalence of diabetes between both genders (p < 0.001). Diabetes was associated with an increased one-year mortality in both men (OR 1.9, 1.4-2.8 95% CI) and women (OR 2.1, 1.4-3.2 95% CI).

In the older age group the prevalence of diabetes was higher in women, while in the younger age group the prevalence was comparable (Table 1 and Figure 1).

Hyperglycemia in patients without diabetes
A total of 3901 patients had no diabetes, consisting of 1029 women (26%). Of the total group, 1761 patients (45%) were aged ≥65 years. Mean admission glucose was associated with both age and gender. Mean admission glucose was 8.2 ± 2.2 mmol/l in men and 8.5 ± 2.1 in women (p = 0.001). The mean admission glucose was 8.3 ± 2.6 mmol/l in younger patients and 8.9 ± 2.6 mmol/l in older patients (p < 0.001).

Baseline characteristics of the 3901 patients, stratified to age group and gender are summarized in Table 2. Besides differences in history of hypertension and smoking there were no significant differences in risk factors between men and women in the patient group below 65 years of age. In the older patient group however, men had more often a previous history of cardiovascular disease (prior PCI, CABG, myocardial infarction or stroke) while women were more often known with hypertension.

Glucose level at admission was comparable between men and women in the younger age group, but higher in women at older age (Table 2) Also, the prevalence of

Table 1 Prevalence of diabetes in the total study population (n = 4640) according to gender and age group

	Women	Men	p-value	Women	Men	p-value
	<65	<65		≥65	≥65	
	N = 508	N = 1939		N = 783	N = 1410	
History of diabetes	54(11%)	157(8%)	0.15	155(20%)	184(13%)	<0.001
Newly detected diabetes*	13(3%)	77(4%)	0.16	35(4%)	51(4%)	0.17
Total without chronic diabetes	439(86%)	1701(88%)	0.52	590(75%)	1171(83%)	<0.001
Missing	2	4		3	4	

* Patients without previously known diabetes and HbA1c ≥ 6.5% mmol/L.

admission glucose above the median was comparable within both genders at younger age in the multivariate model (OR 1.1, 0.9-1.5 95% CI) while in the older age group, admission glucose above the median was more frequent in women. (OR 1.3, 1.1-1.7 95% CI) This age-related difference remained after multivariate analyses.

In patients without diabetes, acute hyperglycemia was associated with an increased one-year mortality in both men (OR 2.2, 1.5-3.4 95% CI) and women (OR 2.9, 1.6-5.4 95% CI).

Mortality curves for patients without a history of diabetes are dichotomized into higher and lower than median glucose in women (8.1 mmol/l) and men (7.8 mmol/l) are depicted in Figure 2.

Discussion

In our present study of patients treated with primary PCI for STEMI the prevalence of diabetes was higher in older women compared to similarly aged men. In younger patients, however, we found no differences between men and women. Also, in patients without diabetes, a higher admission glucose could only be demonstrated in older women as compared to older men. Both diabetes and increased admission glucose in patients without

Figure 1 Prevalence diabetes in STEMI patients according to age and gender.

diabetes, were associated with a higher one-year mortality in both women and men.

Our study confirmed the increased prevalence of diabetes and acute hyperglycemia in women compared to men [5-7]. A new finding however in STEMI patients is that this association is age-dependent and only present in the older age-group. Diabetes (both known and unknown) confers to a greater risk for adverse cardiovascular events in women than in men [6,7]. Therefore, the increased risk induced by diabetes in patients presenting with STEMI is predominantly observed in older women.

In assessing the risk of adverse events in patients presenting with STEMI, both age and gender are important factors to consider. Importantly, the increased prevalence of diabetes in older women compared to older man is part of a different risk profile. Consistent with the literature, we found that men more frequently had ischemic heart disease in the medical history [6,7]. Hypertension however was more common in both older and younger women, and this is interesting because hypertension has been associated with the development of diabetes [13-15]. Hypertension may be an early sign of microvascular disease and increased risk of pre-diabetes and STEMI in (aging) women. The association between hypertension and diabetes is also important, since both risk factors induce microvascular and more diffuse coronary artery disease, which is more prevalent in older women [16-19].

Our findings may have implications for medical treatment for patients with STEMI, since it has been shown that some antiplatelet drugs are more effective in patients with diabetes [20,21]. Particularly since older women with abnormal glucose metabolism have a worse prognosis, optimal medical treatment is mandatory in this subgroup.

It is important to discriminate diabetes from acute hyperglycemia at admission [1,22]. High admission glucose in patients with diabetes is mainly due to glucose intolerance in the setting of diabetes. Whereas in patients without diabetes, hyperglycemia is probably associated with acute stress, induced by abnormal hemodynamics [1,23,24].

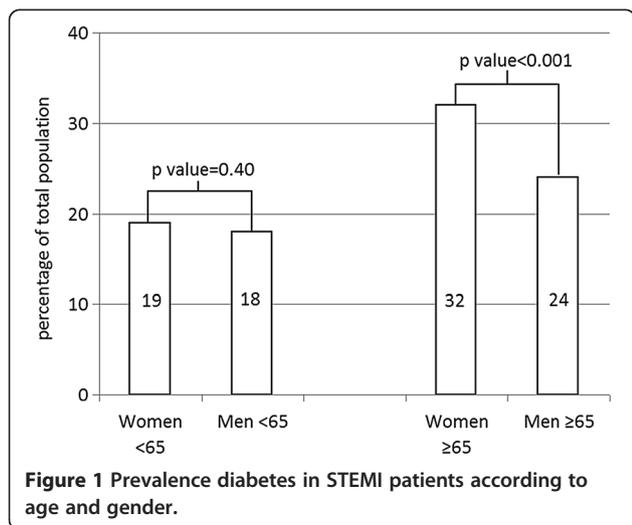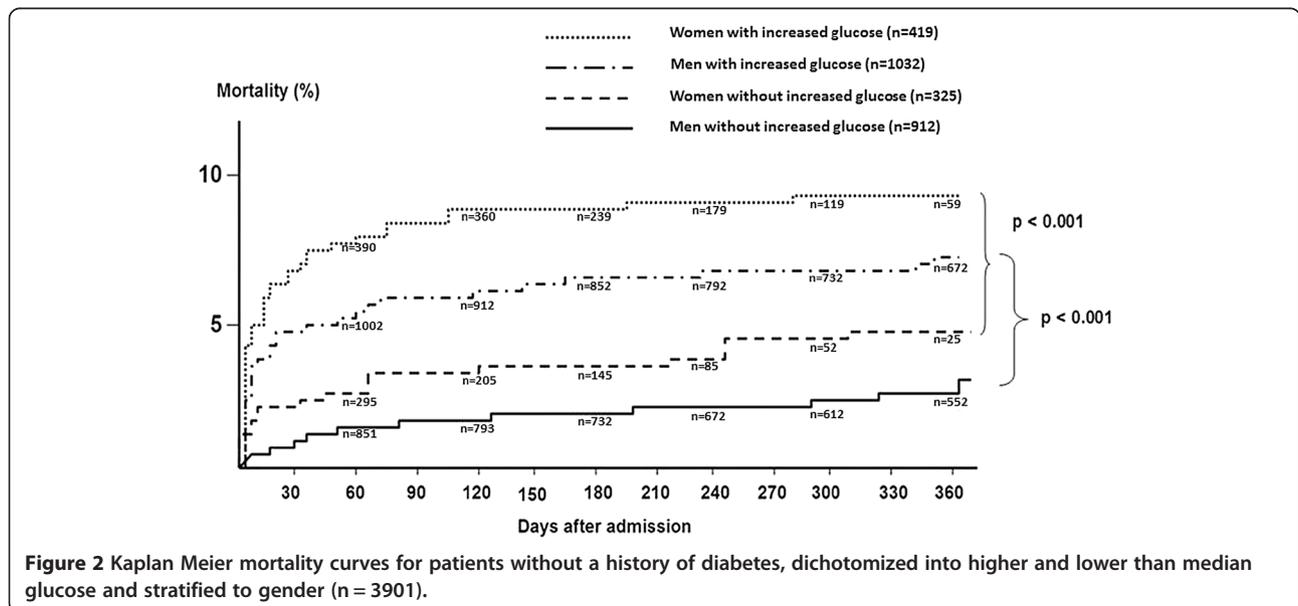There are several explanations for the increased prevalence of acute hyperglycemia in older women without

Table 2 Baseline Characteristics according to gender and age groups <65 and ≥65 years in 3901 patients admitted for primary angioplasty for ST-segment elevation myocardial infarction (STEMI) without diabetes

	Women <65 N = 439	Men <65 N = 1701	p-value	Women ≥65 N = 590	Men ≥65 N = 1171	p-value
Age (year)	55(48–60)	54(49–59)	0.41	75(70–81)	73(69–78)	<0.001
History of, n (%)						
MI	19(4%)	113(7%)	0.07	39(7%)	176(15%)	<0.001
CABG	5(1%)	30(2%)	0.36	13(2%)	67(6%)	0.001
PCI	21(5%)	117(7%)	0.11	36(6%)	141(12%)	<0.001
Stroke	5(1%)	21(1%)	0.87	17(3%)	57(5%)	0.05
Risk factors						
History of hypertension	142(32%)	431(26%)	0.004	267(45%)	432(37%)	0.001
Positive family history	227(53%)	841(51%)	0.43	170(30%)	310(27%)	0.34
Current smoking	280(65%)	963(57%)	0.004	123(21%)	263(23%)	0.41
Hypercholesterolemia	65(15%)	320(19%)	0.06	99(17%)	205(18%)	0.66
Admission data						
Glucose (mmol/l)	8.2 ± 2.2	8.0 ± 2.2	0.36	8.7 ± 2.1	8.4 ± 2.1	0.03
Killip class = 1	412(94%)	1619(96%)	0.22	519(88%)	1066(91%)	0.05
TIMI-3 before PCI	105(27%)	335(22%)	0.06	116(24%)	219(22%)	0.36

Continuous variables are displayed as median and interquartile range.

diabetes. Firstly, although we excluded patients with increased HbA1c, several older women may have had abnormal chronic glucose metabolism. Therefore, women are more susceptible for hyperglycemia in response to a stressor, as compared to patients with completely normal glucose metabolism. Secondly, older women with STEMI may have had more acute stress as there is evidence that women more often present with cardiogenic shock compared to men [25]. Also, in our study population older women had more often signs of heart failure on admission as compared to older men, whereas in the younger age group there was no difference in heart failure between men and women. However, after adjustment for the observed differences in heart failure, we found that older women still had increased admission glucose levels. Finally, gender-differences to stress in STEMI patients may be more present in elderly woman than in similarly aged men.

Figure 2 Kaplan Meier mortality curves for patients without a history of diabetes, dichotomized into higher and lower than median glucose and stratified to gender (n = 3901).

Our study has several limitations. The number of patients in some subgroups were small, and the study was not powered to detect small differences between these subgroups. Also, the sample size was too small to demonstrate survival differences between men and women within the different age groups. Information regarding renal failure, liver failure, obesity, physical activity, inflammatory markers and socioeconomic status were lacking. Therefore, we were unable to adjust for these potential confounders. Finally, our data cannot be extrapolated to non-STEMI patients,non-cardiac patients admitted to intensive care wards, or unstable patients since our study included only STEMI patients and only 8% of these patients had a killip class higher than 1.

Conclusion

In STEMI, diabetes and hyperglycemia on admission is more prevalent in older women compared to similarly aged men. This association was not prevalent in younger patients. We observed an independent increased risk of acute hyperglycemia in older women without diabetes and therefore, older women may have an increased stress response. Both acute hyperglycemia and diabetes are associated with a worse prognosis in both women and men. More research is needed to elucidate these age-dependent gender differences and to explore whether tailored treatment can improve prognosis.

Abbreviations

LDH: Lactaatdehydrogenase; NSTEMI: Non ST Elevation Myocardial Infarction; PPCI: Primary Percutaneous Coronary Intervention; STEMI: ST Elevation Myocardial Infarction; TIMI: Thrombolysis In Myocardial Infarction.

Competing interest

The authors declare that they have no competing interest.

Authors' contributions

AO participated in the design of the study, drafting of the manuscript, analysis and interpretation of the data. JPO participated in the design of the study, data collection drafting of the manuscript and interpretation of the data. JT participation in design of the study and interpretation of the data. AH participated in data collection and revised the manuscript. JD participated in data collection and revised the manuscript MG participated in data collection and revised the manuscript. JH participated in data collection and revised the manuscript. HS participated in data collection and revised the manuscript. AM participated in the design of the study and drafting of the manuscript. All authors read and approved the final manuscript.

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