Admission Blood Glucose Level as Risk Indicator of Death After Myocardial Infarction in Patients With and Without Diabetes Mellitus

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Background: High admission blood glucose levels after acute myocardial infarction (AMI) are common and associated with an increased risk of death in subjects with and without known diabetes. Recent data indicate a high prevalence of abnormal glucose metabolism in patients with unknown diabetes at the time of AMI. We investigated the predictive value of admission blood glucose levels after AMI for long-term prognosis in patients with and without previously diagnosed diabetes mellitus, particularly in those with unknown diabetes but with blood glucose levels in the diabetic range.

Methods: In a retrospective study with prospective follow-up, 846 patients (737 without and 109 with known diabetes) were eligible for follow-up during a median of 50 months (range, 0-93 months).

Results: During follow-up, 208 nondiabetic patients (28.2%) and 47 diabetic patients (43.1%) died (P = .002). An increase of 18 mg/dL (1 mmol/L) in glucose level was associated with a 4% increase of mortality risk in nondiabetic patients and 5% in diabetic patients (both P < .05). Of the 737 previously nondiabetic subjects, 101 had admission blood glucose levels of 200 mg/dL (11.1 mmol/L) or more, and mortality in these patients was comparable to that in patients who had established diabetes (42.6% vs 43.1%).

Conclusions: Admission blood glucose level after AMI is an independent predictor of long-term mortality in patients with and without known diabetes. Subjects with unknown diabetes and admission glucose levels of 200 mg/dL (11.1 mmol/L) or more after AMI have mortality rates comparable to those of subjects with established diabetes. Admission blood glucose level may serve to identify subjects at high long-term mortality risk, in particular among those with unknown diabetes.

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abnormalities clustered in the insulin resistance syndrome, which is associated with a high risk of cardiovascular disease.\textsuperscript{18-20} Alternatively, it was proposed that blood glucose constitutes a risk factor for cardiovascular disease over a wide array of values, even in the normoglycemic range.\textsuperscript{21,22} At present, the cause and significance of hyperglycemia after AMI are not fully understood, but intensive insulin therapy in both diabetic and nondiabetic subjects reduces long-term mortality.\textsuperscript{24,25} Because most studies have focused on short-term prognosis, we investigated the predictive value of admission blood glucose levels after AMI for long-term prognosis in a large number of patients. In addition, outcome was compared between patients with known diabetes and those with unknown diabetes at the time of AMI, but with glucose levels in the diabetic range.

METHODS

PATIENTS AND DATA COLLECTION

In this retrospective study with prospective follow-up, 1027 consecutive patients admitted to the coronary care unit with a clinical diagnosis of AMI between January 1, 1989, and December 31, 1996, whose data were recorded in a research database, were eligible. Baseline and admission characteristics were extracted from this database. The end point of this study, all-cause mortality during follow-up, was obtained retrospectively. Survival status was assessed from written replies to inquiries to the Municipal Civil Registration Service. A maximum of 3 mailings was sent out to each community, and if no response was obtained, information regarding the vital status was requested from the patients’ general physicians. From 181 patients (17.6%), relevant data were missing, and these subjects were excluded. However, the available data of this subject group did not differ significantly from those of the included group (data not shown). Finally, the study population consisted of 946 patients who were followed up for a median of 50 months (range, 0-93 months).

DEFINITIONS

The diagnosis of AMI was based on World Health Organization criteria.\textsuperscript{26} Previous infarction was considered present if a patient had been admitted previously because of AMI or if there were signs of an old infarction outside the area of the index infarction. Previous congestive heart failure was present if mentioned in the hospital or general practitioner records. Known diabetes mellitus was defined as a history of diabetes obtained from hospital records, when the patient confirmed to be informed about the diagnosis or when pharmacologic treatment was started. A similar definition was used for previous hypertension and lipid disorders. The location of the infarction was based on electrocardiogram recordings (inferior, anterior, or undefined, eg, in the presence of a left bundle-branch block). The wall motion score (WMS) was determined by echocardiography as described previously.\textsuperscript{27} In short, the left ventricle was divided into 13 segments (6 basal, 6 distal, and 1 apical). Each segment was scored on a 4-point scale ranging from 0 (normal contraction) to 3 (dyskinesia). The WMS was calculated by adding the score of all segments. For discrimination between preserved and poor left ventricular function, patients were divided into a group with WMS of 7 or less and WMS greater than 7, respectively.\textsuperscript{28}

The diagnosis of in-hospital congestive heart failure was based on the presence of at least 2 of the following criteria: bilateral basal pulmonary rales, dyspnea, a third heart sound, or radiographic evidence of pulmonary congestion. Second- and third-degree atrioventricular blocks on the electrocardiogram were combined as high-grade atrioventricular block. A reinfection was defined as a new AMI with an onset more than 72 hours after the index infarction.

LABORATORY DETERMINATIONS

Venous blood for plasma glucose determinations was collected routinely directly after admission, before administration of any intravenous medication. Samples were analyzed in the hospital’s central laboratory by means of a glucose oxidase method (Beckman Glucose Analyzer 2; Beckman Instruments, Fullerton, Calif).

DATA ANALYSIS AND STATISTICAL METHODS

All statistical analyses were performed with SPSS statistical software (SPSS Inc, Chicago, Ill). Data are presented as mean (±SD), numbers, or proportion. An unpaired, 2-tailed t test, \( \chi^2 \) test, and analysis of variance were used to test the significance of the difference between the various groups. To assess the relationship between admission glucose levels and mortality, the following approach was applied. First, admission blood glucose levels were evaluated as a continuous variable in subjects with (n=737) and without (n=109) previously diagnosed diabetes mellitus by means of a univariate model. Then, the Cox proportional hazards regression model (multiple analysis) was used to estimate the association between mortality and admission glucose levels and correct for possible influencing variables. Risk factors entered into the Cox regression model were as follows: age greater than 65 years, sex, previous infarction, previous heart failure, smoking, diabetes mellitus, hypertension and lipid disorders, location of infarction, WMS greater than 7, acute treatment (conservative treatment, thrombolysis, or percutaneous transluminal coronary angioplasty), and in-hospital occurrence of congestive heart failure, reinfection, ventricular fibrillation, atrial fibrillation, or high-grade atrioventricular block.

Second, the 737 previously nondiabetic subjects were divided on the basis of their admission plasma glucose levels into group 1 (blood glucose level, <141 mg/dL [<7.8 mmol/L]), group 2 (141-199 mg/dL [7.8-11.0 mmol/L]), and group 3 (≥200 mg/dL [≥11.1 mmol/L]). In this analysis, patients with known diabetes at the time of AMI were designated group 4. The 4 groups were compared with regard to their baseline and admission characteristics, in-hospital events, and mortality at follow-up. In these groups, the association between admission glucose levels and mortality was tested by means of a similar univariate model and multiple analysis approach as indicated previously. Kaplan-Meier survival analysis was performed. \( P<.05 \) was considered statistically significant.

RESULTS

SUBJECT CHARACTERISTICS AT BASELINE

Table 1 lists baseline characteristics at admission of patients with and without known diabetes. The mean age of the study population was 64.6±11.9 years; 70% was male and 13% had preexisting diabetes. In comparison with subjects without known diabetes, patients with known diabetes were older, were more likely to have a history of congestive heart failure and hypertension, and
During a median follow-up of 50 months (range, 0-93 months), 255 subjects died. The mortality rate among diabetic subjects was 43.1% as compared with 28.2% in nondiabetic patients (P = .002; Table 1). The number of in-hospital deaths was 43 (5.1%), and this was comparable in nondiabetic (5.3%) and diabetic (4.6%) subjects (data not shown).

An increase of 18 mg/dL (1 mmol/L) in blood glucose in previously nondiabetic subjects was associated with an increase in mortality risk of 3% in univariate analysis and 4% in adjusted analyses. This increase in mortality risk was 6% and 5%, respectively, in the diabetic group (Table 2).

STATIFICATION OF SUBJECTS WITHOUT DIAGNOSED DIABETES ACCORDING TO ADMISSION GLUCOSE LEVELS

After the 737 previously nondiabetic subjects were divided into classes on the basis of admission blood glucose levels, 314 subjects were in group 1, 322 were in group 2, and 101 were in group 3 (Table 3). All variables were comparable in subjects with known diabetes (group 4) and those with admission glucose levels within the diabetic range (group 3; Table 3). Subjects without diagnosed diabetes who had admission glucose levels of 200 mg/dL (11.1 mmol/L) or more showed a higher incidence of in-hospital congestive heart failure (40.6%) as compared with undiagnosed diabetic patients with lower admission glucose levels. In-hospital mortality in the 4 groups was 2.5%, 7.1%, 6.9%, and 4.6%, respectively (P = .02; data not shown). The Kaplan-Meier survival curves for the respective groups are presented in the Figure. The long-term prognosis for subjects from groups 1 and 2 was comparable, whereas the prognosis for patients from group 3 was significantly worse and comparable to that of patients with previously known diabetes. Indeed, mortality rates in groups 3 and 4 were 42.6% and 43.1%, respectively.

In adjusted analyses, admission blood glucose level appeared as an independent predictor of death in both groups 3 and 4 (relative risk, 1.04; 95% confidence interval, 1.01-1.08; P = .03; and relative risk, 1.05; 95% confidence interval, 1.00-1.11; P = .048, respectively) (Table 4).

**MAJOR FINDINGS**

The present study not only confirms the relationship between admission blood glucose level and mortality after AMI, but further expands the evidence of the significance of this variable as a predictor of long-term mortality in diabetic and nondiabetic subjects, as both a continuous and a strata-lying variable. We showed that subjects who were not diagnosed as having diabetes mellitus at the time of AMI but had admission glucose levels within

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**Table 1. Clinical Characteristics of Patients With and Without Previously Known Diabetes**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Nondiabetic</th>
<th>Known Diabetic</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission blood glucose level, mean ± SD, mg/dL</td>
<td>160.4 ± 70.3 275.7 ± 124.3</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>Demographic data, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>64.1 ± 11.9 67.9 ± 11.5</td>
<td>.002</td>
<td></td>
</tr>
<tr>
<td>Age &gt;65 y</td>
<td>394 (53.5) 70 (64.2)</td>
<td>.04</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>525 (71.2) 68 (62.4)</td>
<td>.06</td>
<td></td>
</tr>
<tr>
<td>Previous heart failure</td>
<td>23 (3.1) 12 (11.0)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>136 (18.5) 21 (19.3)</td>
<td>.84</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>410 (55.6) 41 (37.6)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>252 (34.2) 48 (44.0)</td>
<td>.045</td>
<td></td>
</tr>
<tr>
<td>Lipid disorders</td>
<td>129 (17.5) 13 (11.9)</td>
<td>.15</td>
<td></td>
</tr>
<tr>
<td>AMI characteristics at admission, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location of infarction</td>
<td></td>
<td></td>
<td>.75</td>
</tr>
<tr>
<td>Inferior</td>
<td>332 (45.0) 46 (42.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>290 (38.3) 47 (43.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>115 (15.6) 16 (14.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMS &gt;7</td>
<td>483 (65.5) 78 (71.6)</td>
<td>.21</td>
<td></td>
</tr>
<tr>
<td>Treatment, No. (%)</td>
<td></td>
<td></td>
<td>.21</td>
</tr>
<tr>
<td>Conservative</td>
<td>304 (41.2) 54 (49.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombolytic</td>
<td>418 (56.7) 52 (47.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary PTCA</td>
<td>15 (2.0) 3 (2.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-hospital deaths, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>181 (24.6) 45 (41.3)</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>20 (2.7) 3 (2.8)</td>
<td>.98</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>76 (10.3) 11 (10.1)</td>
<td>.94</td>
<td></td>
</tr>
<tr>
<td>High-grade AV block</td>
<td>49 (6.6) 9 (8.3)</td>
<td>.54</td>
<td></td>
</tr>
<tr>
<td>Recurrent myocardial infarction</td>
<td>34 (4.6) 6 (5.5)</td>
<td>.68</td>
<td></td>
</tr>
<tr>
<td>Deaths, No. (%)</td>
<td>208 (28.2) 47 (43.1)</td>
<td>.002</td>
<td></td>
</tr>
<tr>
<td>Follow-up, mean ± SD, mo</td>
<td>46.1 ± 26.2 38.3 ± 26.6</td>
<td>.004</td>
<td></td>
</tr>
</tbody>
</table>

*Unpaired, 2-tailed t test for continuous variables and χ² test for categorical variables.

**Table 2. Univariate and Multiple Analysis of Admission Blood Glucose Levels to Predict Mortality in Patients With Myocardial Infarction**

<table>
<thead>
<tr>
<th>Analysis of Continuous Glucose Levels</th>
<th>Nondiabetic (n = 737)</th>
<th>P Value</th>
<th>Known Diabetic (n = 109)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate</td>
<td>1.03 (1.02-1.05)</td>
<td>.001</td>
<td>1.06 (1.02-1.10)</td>
<td>.004</td>
</tr>
<tr>
<td>Multiple</td>
<td>1.04 (1.02-1.06)</td>
<td>&lt;.001</td>
<td>1.05 (1.00-1.11)</td>
<td>.048</td>
</tr>
</tbody>
</table>

*Data are given as relative risk (95% confidence interval) unless otherwise indicated.
The diabetic range had a similarly high risk of death as subjects with previously diagnosed diabetes.

POSSIBLE MECHANISMS UNDERLYING ASSOCIATION BETWEEN BLOOD GLUCOSE LEVEL AND MORTALITY

The relationship between admission hyperglycemia and short-term (in-hospital) mortality in both subjects with and without known diabetes after AMI has been well established. Several possible mechanisms underlying this relationship were proposed. These include stress-related relative insulin deficiency, increased lipolysis, elevated levels of circulating free fatty acids, and decreased myocardial glucose utilization, all of which may have adverse effects on myocardial energy metabolism and function in the presence of ischemia. Also, hyperglycemia may cause dehydration leading to volume depletion, decreased stroke volume, and output failure of the compromised left ventricle. Moreover, acute hyperglycemia may induce oxidative stress, adversely affecting platelet function, coagulation, and fibrinolysis as well as various endothelial functions and increasing the risk of reinfarction, congestive heart failure, or death. Alternatively, hyperglycemia may be regarded as an indicator of stress, which correlated with more extensive cardiac damage after AMI. In our study, no association was found between admission blood glucose levels and myocardial infarction size (data not shown).

In a recent meta-analysis of studies assessing the association between stress hyperglycemia and risk of death after AMI, different thresholds were used to define admission hyperglycemia. However, admission glucose levels even in the nondiabetic range between 110 and 144 mg/dL (6.1 and 8.0 mmol/L) conferred an almost 4-fold risk of death to subjects without known diabetes after AMI, as compared with subjects with lower glucose concentrations.

Early studies have demonstrated that intravenous infusion of potassium-glucose-insulin solution results in more rapid resolution of electrocardiographic changes of infarction and increased myocardial contractility. More recently, it was shown that restoring euglycemia by intensive insulin therapy significantly reduces morbidity and mortality in patients after AMI and in critically ill subjects admitted to an intensive care unit. At present, however, it is unclear whether blood glucose lowering per se, insulin therapy, or both are responsible for the observed beneficial effects.
ASSOCIATION BETWEEN ADMISSION BLOOD GLUCOSE LEVEL AFTER AMI AND LONG-TERM MORTALITY

An AMI may unmask preexisting insulin resistance and pancreatic β-cell dysfunction and identify subjects with a cluster of cardiovascular risk factors associated with dysglycemia, who may not only have more extensive coronary artery disease but have a higher absolute risk of cardiovascular death. This latter mechanism may explain the findings from an increasing number of studies showing that high admission blood glucose level is associated not only with short-term but also with long-term death after the index AMI in subjects with and without known diabetes.25 In subjects with known diabetes at the time of AMI, a continuous relationship between admission glucose levels and risk of long-term mortality was observed.25 Admission hyperglycemia was of borderline significance as an independent predictor of death in subjects with unknown diabetes during an average follow-up of 2.5 years after AMI, but the study may not have had enough power to detect significance.9

Our study included a substantially larger number of subjects with a considerably longer follow-up. We found a relationship between admission blood glucose level and long-term mortality not only in subjects with known diabetes but also in those without diagnosed diabetes at the time of the AMI. The latter association may be related to a prolonged deleterious effect of high admission glucose levels that should be sustained over several years, which seems unlikely, or rather to undiagnosed insulin resistance or metabolic syndrome, compatible with prediabetes or frank type 2 diabetes mellitus in many subjects with high admission glucose levels but without known diabetes at the time of the AMI.

ABNORMAL GLUCOSE METABOLISM IN PATIENTS WITH AMI AND NO PREVIOUS DIAGNOSIS OF DIABETES

Previous studies suggested a prevalence of about 4% of undiagnosed diabetes among patients with AMI.15,36 Another study found that 24 (8.1%) of 295 patients without known diabetes at the time of AMI had blood glucose levels of 200 mg/dL (11.1 mmol/L) or higher at admission, but these subjects were not studied for diabetes at follow-up.25 Only recently it was shown that when previously nondiabetic subjects with AMI and admission blood glucose levels less than 200 mg/dL were tested by an oral glucose tolerance test after discharge, 40% of these subjects had impaired glucose tolerance and 25% had undiagnosed diabetes.31 Since subjects without known diabetes and blood glucose levels of 200 mg/dL and higher were excluded in that study, the authors estimated the true prevalence of diabetes among subjects with AMI to be as high as 43%. In the present study, we did not set out to diagnose impaired glucose tolerance or diabetes, and no formal testing was performed at follow-up. However, using the World Health Organization criteria for postload glucose levels to stratify subjects with previously unknown diabetes,13 we found that 44% had blood glucose levels in the range of impaired glucose tolerance (group 2) and 14% within the diabetic range (group 3). The relevance of this finding was substantiated by the observed increase in in-hospital mortality in group 2 and the long-term mortality in previously undiagnosed subjects with admission glucose levels of 200 mg/dL or higher, which was identical to that of patients with a confirmed diagnosis of diabetes at the time of AMI. Therefore, although no definite conclusions can be drawn from the admission blood glucose level regarding the glycometabolic diagnosis after discharge, it may serve to identify subjects, in particular among those without known diabetes, at high long-term mortality risk. We have no definite explanation for the observed increased in-hospital mortality among subjects from group 2. However, since these subjects had no history of diabetes, it is likely that less attention was paid to their glycometabolic regulation during admission, in terms of additional blood glu-

Table 4. Univariate and Multiple Analysis of Admission Blood Glucose Levels to Predict Mortality After Classification According to Admission Blood Glucose Levels*

<table>
<thead>
<tr>
<th>Analysis of Continuous Glucose Levels</th>
<th>Group 1 (n = 314)</th>
<th>P Value</th>
<th>Group 2 (n = 322)</th>
<th>P Value</th>
<th>Group 3 (n = 109)</th>
<th>P Value</th>
<th>Group 4 (n = 109)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate</td>
<td>0.85 (0.64-1.15)</td>
<td>.30</td>
<td>0.98 (0.73-1.33)</td>
<td>.91</td>
<td>1.01 (0.98-1.04)</td>
<td>.14</td>
<td>1.06 (1.02-1.10)</td>
<td>.001</td>
</tr>
<tr>
<td>Multiple</td>
<td>0.97 (0.71-1.31)</td>
<td>.82</td>
<td>0.90 (0.66-1.22)</td>
<td>.51</td>
<td>1.04 (1.01-1.08)</td>
<td>.03</td>
<td>1.05 (1.00-1.11)</td>
<td>.048</td>
</tr>
</tbody>
</table>

*Data are given as relative risk (95% confidence interval). See Table 3 for explanation of groups.
Glucose measurements and initiation of insulin treatment, than in patients with known diabetes. Future studies should establish whether insulin therapy in patients with undiagnosed diabetes improves long-term outcome after AMI.

It is known that in the general population up to 50% of all subjects with type 2 diabetes mellitus are undiagnosed. Since type 2 diabetes as well as the associated cardiovascular risk factors are asymptomatic, the disease remains undetected for years and its duration cannot be readily assessed. Indeed, patients may experience cardiovascular events before the diagnosis of type 2 diabetes. This is in line with the reported absence of a strong association between the duration of diabetes and macrovascular disease, in contrast to the relationship observed between diabetes duration and microvascular complications. Subjects with unknown diabetes and admission glucose levels of 200 mg/dL (11.1 mmol/L) or higher had baseline characteristics similar to those with known diabetes, suggesting that not only glucose but also other conventional risk factors should be evaluated in subjects admitted because of AMI. Total risk assessment may disclose potentially modifiable risk factors that may offer therapeutic options and should be followed up after discharge.

Norhammar et al found that hemoglobin A1c concentration at admission and fasting blood glucose level at discharge were independent predictors of abnormal glucose metabolism at 3 months of follow-up. Others have argued that hemoglobin A1c concentration may not be a suitable measure to diagnose diabetes unless it is clearly abnormal, because of low sensitivity and lack of standardization of the determination method. We were unable to obtain hemoglobin A1c or fasting glucose levels in our study population and therefore cannot assess the predictive value of these variables.

STUDY LIMITATIONS

Because of the partly retrospective character of this study, it was impossible to relate admission blood glucose levels to factors such as time between onset of symptoms and arrival at the hospital or preinfarction variables as time since last meal. As far as the latter aspect is concerned, it is unlikely that the patients were in the fasting state on admission; if so, the finding of high blood glucose levels would be even more suggestive of the presence of a disturbed glucose metabolism or frank diabetes. Previous congestive heart failure was considered present if mentioned in the hospital or general practitioner records; no data were available on the accuracy of this diagnosis. It is well known that this diagnosis may both be overestimated and underestimated in general practice. In this study, however, it was not possible to estimate the true prevalence of heart failure because of the index infarction.

No information was available on the duration and the type (type 1 or 2) of known diabetes. However, in the case of type 2 diabetes, which in general constitutes the vast majority of the diabetic population, the exact duration of diabetes cannot be determined, since the disease is initially asymptomatic and can remain undetected for years. As stated before, no hemoglobin A1c concentrations at admission or fasting blood glucose levels at discharge were determined. More important, we did not have the opportunity to formally test subjects after recovery from AMI to establish or rule out the diagnosis of impaired glucose tolerance or diabetes. Finally, no information was available on revascularization interventions that may have been performed during the posthospitalization follow-up period and their possible influence on prognosis.

CONCLUSIONS

In view of the findings by Norhammar et al and our observation that subjects from group 2 had the highest in-hospital mortality while those from group 3 had mortality rates at follow-up comparable with those of known diabetic subjects, we conclude that admission blood glucose level after AMI may be an important tool for risk stratification at follow-up and a potential point of impact for therapeutic measures.

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REFERENCES


