Myocardial infarction and prevalence of diabetes mellitus

Is increased casual blood glucose at admission a reliable criterion for the diagnosis of diabetes?

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Aims To investigate the prevalence of diabetes mellitus in patients with acute myocardial infarction and to determine whether casual blood glucose and haemoglobin A₁c measured at admission could be used to diagnose diabetes mellitus.

Methods and Results A prospective study that included all patients with acute myocardial infarction hospitalized during a one-year period at a coronary care unit. Casual blood glucose was measured at admission, fasting blood glucose during the hospital stay and, if necessary for classification, 2–3 months after discharge. Haemoglobin A₁c was measured once at admission. Of 305 patients included in the study, 285 could be classified into three groups: 21% of these had previously diagnosed diabetes, 4% had newly diagnosed diabetes and the remaining patients were categorized as non-diabetic. Casual blood glucose ≥11.1 mmol·l⁻¹ at admission was found in 12 patients with no previously known diabetes, but diabetes mellitus was confirmed in only six of these patients. Haemoglobin A₁c showed considerable overlapping of values between the three groups of patients (i.e. patients with known diabetes mellitus, patients with newly diagnosed diabetes mellitus and non-diabetics).

Conclusion One of four patients with acute myocardial infarction had diabetes mellitus. Increased casual blood glucose at admission was not a reliable measure to establish a diagnosis of diabetes and thus follow-up measures were necessary. Haemoglobin A₁c was found to be an unreliable measure in the verification of diabetes.


Key Words: Diabetes mellitus, acute myocardial infarction, prevalence, casual blood glucose, stress-induced hyperglycaemia.

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Introduction

Diabetes mellitus is a strong risk factor for cardiovascular disorders, including coronary heart disease[1,2]. In previous studies, diabetes mellitus has been diagnosed in 10 to 24% of patients with acute myocardial infarction[3–5]. Furthermore, the age-adjusted prevalence of diabetes among patients with acute myocardial infarction has increased significantly over the past two decades. A true increase in diabetes, improved documentation in medical records and longer survival of diabetic patients are all factors underlying this increase[6].

Intensive insulin treatment and intensive secondary prevention measures may improve the outcome of acute myocardial infarction in diabetic patients[7]. Therefore, it is important to identify patients with and without a previous diagnosis of diabetes mellitus at admission for acute myocardial infarction. In non-diabetic patients the magnitude of the rise in plasma glucose during the early phase of acute myocardial infarction has been attributed to the severity of heart failure[8]. A casual plasma glucose level ≥11.1 mmol·l⁻¹ at admission for acute myocardial infarction in non-diabetic patients occurs in about 20% of the patients; however, in only about 20% of these cases is it likely to be a manifestation of pre-existing diabetes when a clearly
elevated haemoglobin A1c is used as a diagnostic criterion for diabetes mellitus[9]. Consequently, stress-induced hyperglycaemia at admission for acute myocardial infarction may overestimate the frequency of diabetes mellitus[9]. Earlier reports have shown that, in patients with acute myocardial infarction, casual blood glucose >10·0 mmol·l⁻¹ at admission is likely to identify undiagnosed diabetes[10]. In the DIGAMI study, casual blood glucose ≥11·1 mmol·l⁻¹ at admission to hospital identified, with reasonably high precision, undetected diabetes in patients with suspected acute myocardial infarction[11], whereas haemoglobin A1c had limited value as a diagnostic tool[12].

One purpose of this study was to estimate the prevalence of diabetes mellitus in an unselected patient population with acute myocardial infarction. A further goal was to study whether casual blood glucose at admission could be used to diagnose earlier undiagnosed diabetes mellitus in these patients. Finally, we sought to determine whether haemoglobin A1c could be used to identify acute myocardial infarction patients with previously unknown diabetes mellitus.

Material and Methods

Patients

The Central Hospital in Västerås, Sweden, serves a population of about 150 000 inhabitants. All patients admitted to the Central Hospital with suspected acute myocardial infarction were observed in the coronary care unit. During a 1 year period (October 1995–September 1996), 337 patients fulfilled the diagnostic criteria for acute myocardial infarction. Of these 337 patients, 13 were excluded because of their unwillingness to participate in the study. In addition, 19 patients had more than one acute myocardial infarction during the study period; in these patients, only the first acute myocardial infarction was included in the subsequent data analysis. Thus, the final sample consisted of 305 acute myocardial infarction patients.

Method

Casual blood glucose and haemoglobin A1c were both analysed at admission and fasting blood glucose was measured on the 2nd and 5th days after admission. Admission blood glucose values in patients with ongoing intravenous glucose infusion were excluded. A specially trained nurse collected all medical data from each patient’s medical records. At follow-up, haemoglobin A1c was measured once and fasting blood glucose twice and if at least one fasting blood glucose was between 5·6 and 6·6 mmol·l⁻¹, a 75 g oral glucose tolerance test was performed. Laboratory examinations were carried out according to the laboratory routines of the Central Hospital in Västerås.

Blood glucose

Venous sampling was used for blood glucose analysed in the ward and capillary blood glucose was taken during the 75 g oral glucose tolerance test. The blood glucose samples were treated with a haemolysis reagent (Merck Diagnostica, 64271 Darmstedt, Germany) and glucose was determined enzymatically with glucose dehydrogenase on a Cobas Mira analyser (Roche Diagnostica, Basel, Switzerland).

Haemoglobin A1c

Haemoglobin A1c was measured with high performance liquid chromatography using Mono S ion-exchange resin (Beckman System Gold, Beckman Instruments Inc., Fullerton, CA, U.S.A.). The reference range was <5·3%.

Creatine kinase-B

Creatine kinase-B was determined by an immunoinhibition method (Merck Diagnostica, 64271 Darmstedt, Germany) on a Cobas Mira analyser (Roche Diagnostica, Basel, Switzerland). The method automatically compensated for adenylate kinase activity.

Diabetes mellitus

Manifest diabetes mellitus was established if the patient had been informed of the diagnosis by a physician before the admission or was undergoing treatment (diet, oral antidiabetic agents or insulin). Diabetes was defined according to the World Health Organisation (WHO) criteria from 1985 as fasting venous or capillary blood glucose ≥6·7 mmol·l⁻¹ on two occasions or a 75 g oral glucose tolerance test with a 2 h capillary blood glucose ≥11·1 mmol·l⁻¹[13]. The prevalence of diabetes was also analysed using the criteria suggested by the WHO working group 1998[14] (see Table 1) as well as the criteria from the American Diabetes Association (ADA) 1997[15] (see Table 2).

Myocardial infarction

A diagnosis of myocardial infarction was established if at least two of the following criteria were fulfilled: chest pain ≥15 min; serum creatine kinase-B value above the normal range 10–16 h after onset of symptoms; and development of new Q waves or ST elevations typical of myocardial infarction in at least 2 of the 12 standard ECG leads.

Study criteria for the diagnosis of diabetes mellitus

The scheme for diagnosing diabetes mellitus, based on the 1985 WHO criteria, is illustrated in Fig. 1. Patients without previously known diabetes mellitus and with a
Diabetes mellitus

2. Fasting plasma glucose <6.1 mmol·L⁻¹ (110 mg·dl⁻¹)

3. 2 h plasma glucose <7.8 mmol·L⁻¹ (140 mg·dl⁻¹) after a 75 g oral glucose load or both

Table 1 WHO criteria from 1998 for the diagnosis of diabetes mellitus and other categories of hyperglycaemia

<table>
<thead>
<tr>
<th>Glucose concentration (mmol·l⁻¹ (mg·dl⁻¹))</th>
<th>Whole blood</th>
<th>Plasma Venous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous</td>
<td>Capillary</td>
<td></td>
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<tr>
<td>Diabetes mellitus</td>
<td></td>
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<tr>
<td>Fasting</td>
<td>≥6.1 (≥110)</td>
<td>7 (≥126)</td>
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<tr>
<td>or</td>
<td></td>
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<tr>
<td>2-h post glucose load or both</td>
<td>≥10.0 (≥180)</td>
<td>11 (≥200)</td>
</tr>
<tr>
<td>Impaired glucose tolerance (IGT)</td>
<td>&lt;6.1 (&lt;110)</td>
<td>≤7.8 (&lt;140)</td>
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<tr>
<td>Fasting concentration (if measured)</td>
<td></td>
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<tr>
<td>and</td>
<td>&lt;6.1 (&lt;110)</td>
<td>&lt;7.0 (&lt;126)</td>
</tr>
<tr>
<td>2-h post glucose load</td>
<td>≥6.7 (&gt;120)and &lt;10.0 (&lt;180)</td>
<td>≥11 (≥200)</td>
</tr>
<tr>
<td>Impaired fasting glycaemia (IFG)</td>
<td>≥5.6 (≥100)and &lt;6.1 (&lt;110)</td>
<td>≥7 (≥140)</td>
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<tr>
<td>Fasting</td>
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<tr>
<td>or</td>
<td>&lt;6.7 (&lt;120)</td>
<td>≤7.8 (&lt;140)</td>
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<td>2-h (if measured)</td>
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</table>

*Corresponding values for capillary plasma are: for diabetes mellitus, fasting ≥7.0 (≥126), 2 h ≥12.2 (≥220); for IGT, fasting <7.0 (<126) and if measured, 2 h <8.9 (<160). For epidemiological or population screening purposes, the fasting or 2 h value after 75 g oral glucose may be used alone. For clinical purposes, the diagnosis of diabetes should always be confirmed by repeating the test on another day unless there is unequivocal hyperglycaemia with acute metabolic decompensation or obvious symptoms.

Table 2 ADA criteria for the diagnosis of diabetes mellitus

1. Symptoms of diabetes plus casual plasma glucose concentration ≥11.1 mmol·l⁻¹ (capillary blood glucose ≥11.1 mmol·l⁻¹). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.

2. Fasting plasma glucose ≥7.0 mmol·l⁻¹ (fasting venous or capillary blood glucose ≥6.1 mmol·l⁻¹). Fasting is defined as no caloric intake for at least 8 h.

3. 2 h plasma glucose ≥11.1 mmol·l⁻¹ during an oral glucose tolerance test (capillary blood glucose ≥11.1 mmol·l⁻¹). The test should be performed as described by WHO using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

In the absence of unequivocal hyperglycaemia with acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day. The third measure (oral glucose tolerance test) is not recommended for routine clinical use.

If the two fasting blood glucose values were <5.6 mmol·l⁻¹ at the follow-up, the patient was classified as non-diabetic. The patient was categorized as newly diagnosed diabetes if the two fasting blood glucose values at the follow-up were ≥6.1 mmol·l⁻¹ based on the suggested 1998 WHO criteria and ADA criteria or ≥6.7 mmol·l⁻¹ according to the WHO criteria from 1985. If at least one fasting blood glucose value was between 5.6–6.6 mmol·l⁻¹, a 75 g oral glucose tolerance test was performed.

Patients were diagnosed as being diabetic if they had constantly elevated blood glucose levels during the hospital stay and the diagnosis could be confirmed on a follow-up 2–3 months after discharge from hospital. Patients without known diabetes according to previous medical records, who could not be investigated because of early death or difficulties in participating in the follow-up were classified as non-diabetic if fasting blood glucose levels during the hospital stay were <6.1 mmol·l⁻¹ (as suggested by new WHO criteria and ADA criteria) or <6.7 mmol·l⁻¹ (1985 WHO criteria). Patients without known diabetes and in whom only one casual blood glucose sample at admission had been obtained were classified as non-diabetic if the value was <8.0 mmol·l⁻¹. For blood samples taken between 04.00 and 08.00 h, we used blood glucose <6.1 mmol·l⁻¹ (suggested new WHO criteria and ADA criteria) or <6.7 mmol·l⁻¹ (1985 WHO criteria).

Figure 1  Flowchart of patients recruited to the study. FBg = fasting blood glucose; CBg = casual blood glucose; ND = non-diabetic; NDD = newly diagnosed diabetes.
because these values could be considered to represent a fasting value. Casual blood glucose >20 mmol/l in one patient without known diabetes who died before follow-up was classified as newly diagnosed diabetes.

**Statistical analysis**

Statistical analysis of HbA1c was done using the Wilcoxon–Mann–Whitney tests because distributions in the samples were not gaussian. Between-group comparisons of casual blood glucose, body mass index and age were performed by a one-way ANOVA followed by Scheffe’s F test.

**Results**

**Patient characteristics (Table 3)**

Of the 305 patients, 285 (94%) were eligible for investigation to establish a diagnosis of diabetes based on the 1985 WHO criteria. In the remaining 20 patients the classification was incomplete: 18 because of death in hospital and two because the patient failed to participate in the follow-up. Sixty-one of the 305 patients had a previous diagnosis of diabetes mellitus. Over 90% of the diabetic patients could be classified as type 2 (non-insulin dependent) diabetes. Among all the diabetic patients, three were diagnosed before 40 years of age while 54 had been diagnosed after 40 years of age. For the remaining four patients, no information about age at the time of diagnosis was available (two were treated with diet and two with oral antihyperglycaemic agents).

Non-classified patients were older compared with the classified patients ($P<0.001$). No statistically significant differences in body mass index were observed between the groups. The drop out rate was low. Practical problems, including a 7 week strike by nurses, or death of the patient resulted in the lack of admission of blood glucose in 8% of the patients and the lack of haemoglobin A1c in 36% of the patients.

**Prevalence of diabetes mellitus based on the 1985 WHO criteria (Fig. 1)**

Of 305 patients, 285 (94%) could be classified: 61 (21%) of these had a history of diabetes, 12 patients (4%) had newly diagnosed diabetes and 212 patients (75%) were non-diabetic.

**Prevalence of diabetes mellitus based on the 1998 suggested WHO and the 1997 ADA criteria**

Of 305 patients, 269 (88%) patients could be classified. Thirty-six patients (12%) remained unclassified because follow-up was not possible or the criteria for classification were not fulfilled. Of the 269 classified patients, 61 (23%) had previously known diabetes, 13 (5%) had newly diagnosed diabetes and 195 (72%) were classified as non-diabetic. The percentage of known and newly diagnosed diabetes according to the WHO 1998 criteria was identical to the ADA criteria.

**Prevalence of fasting blood glucose $\geq 6.1$ mmol/l in patients without known diabetes mellitus on the 2nd and 5th hospital day**

On the second day, 48% (83 of 172 samples) of the patients without previously known diabetes mellitus had fasting blood glucose $\geq 6.1$ mmol/l. On the 5th
day, 21% (43 of 204 samples) of the patients without previously known diabetes mellitus had fasting blood glucose $\geq 6\cdot 1 \, \text{mmol} \cdot \text{l}^{-1}$.

Casual blood glucose at admission (Tables 3, 4 and 5)

Casual blood glucose at admission was significantly higher among the diabetic patients ($P<0.001$) although there was an overlap between non-diabetics, newly diagnosed diabetics and known diabetics.

Twelve patients without previously known diabetes had casual blood glucose $\geq 11\cdot 1 \, \text{mmol} \cdot \text{l}^{-1}$. Only six of these met the diagnostic criteria for diabetes mellitus at follow-up, in accordance with the 1985 WHO criteria, or the suggested WHO criteria of 1998, or the ADA criteria. Of the six patients with casual blood glucose $\geq 11\cdot 1 \, \text{mmol} \cdot \text{l}^{-1}$ who were non-diabetic at follow-up, two had reinfarctions during the study period and the reinfarctions were not included in the results. One of these two patients had two reinfarctions, and in one the casual blood glucose at admission was $\geq 11\cdot 1 \, \text{mmol} \cdot \text{l}^{-1}$; the other patient had one reinfarction and again the casual blood glucose was $\geq 11\cdot 1 \, \text{mmol} \cdot \text{l}^{-1}$. One patient with casual blood glucose at admission $\geq 11\cdot 1 \, \text{mmol} \cdot \text{l}^{-1}$ had impaired glucose tolerance.

In patients who escaped the oral glucose tolerance test despite casual blood glucose $\geq 11\cdot 1 \, \text{mmol} \cdot \text{l}^{-1}$ at admission, three had a fasting blood glucose $<5\cdot 6 \, \text{mmol} \cdot \text{l}^{-1}$ and a normal haemoglobin A1c, either during the hospital stay or at the follow-up; two patients had fasting blood glucose $<5\cdot 6 \, \text{mmol} \cdot \text{l}^{-1}$ but haemoglobin A1c was just above the reference limit. Eight percent of the patients admitted to the coronary care unit for acute myocardial infarction had no admission blood glucose measures taken.

Haemoglobin A1c (Tables 3, 5 and 6)

Patients with a history of diabetes, had higher mean haemoglobin A1c values than those with newly
diagnosed diabetes, and patients with newly diagnosed diabetes (WHO criteria 1985) had higher mean haemoglobin A1c values than those without diabetes mellitus.

Considerable overlap in the haemoglobin A1c values among these three groups of patients was noted; however, in patients with casual blood glucose ≥11·1 mmol·l⁻¹ at admission and with no previous history of diabetes, haemoglobin A1c failed to discriminate between those with a new diagnosis of diabetes mellitus and those who were non-diabetic during the follow-up period. Of 155 patients categorized as non-diabetic at follow-up according to the WHO criteria of 1985, 17 (11%) had haemoglobin A1c value above 5.74%, which is the upper reference range for the laboratory.

**Limitation of the study**

It would have been preferable to retest individuals with normal blood glucose and perform oral glucose tolerance test in all patients. However, our approach is in line with the recommendation from the ADA not to use oral glucose tolerance tests for routine clinical use\cite{15}. In 45 patients (Fig. 1) follow-up was not possible and 24 of those patients had to be classified as non-diabetic after a casual blood glucose <8·0 mmol·l⁻¹ or fasting blood glucose <6·7 mmol·l⁻¹ but without a fasting value <5·6 mmol·l⁻¹ during hospital stay. Some of these patients may have met the diagnostic criteria for diabetes. However, none of the 12 patients with casual blood glucose at admission ≥11·1 mmol·l⁻¹ were included in this group. One patient was classified as diabetic based on casual blood glucose >20·0 mmol·l⁻¹.

Another 20 patients were not possible to classify and were excluded from the calculation of diabetes prevalence. They had no known diabetes according to previous medical records, but were older and their casual blood glucose (if measured) were higher compared to the non-diabetics and it is reasonable to expect that some of them were diabetic.

Finally, a nurse's strike led to the absence of some data, which were not vital for the overall result of the study.

**Discussion**

In the present population-based investigation every fourth patient hospitalized with acute myocardial infarction had diabetes mellitus. Although this is a considerably higher rate of occurrence than those reported by others\cite{3,5,16}, it is comparable to that found in an earlier Swedish study\cite{4}. If an oral glucose tolerance test had been performed in all patients a slightly higher figure is likely to have been obtained. The prevalence rate of diabetes in the same age category of the population as our group of individuals with acute myocardial infarction was close to 12%\cite{10}. Consequently, our data indicate that diabetes mellitus is about twice as common in acute myocardial infarction patients as compared with the general population.

Our model for follow-up was able to classify 94% of all patients into diabetic or non-diabetic categories based on the 1985 WHO criteria. When our study was first initiated in the mid-1990s, we chose a fasting blood glucose level of <5·6 mmol·l⁻¹ as the cut-off point for follow-up patients without previously known diabetes. Our cut-off is in line with the suggested 1998 WHO criteria for diabetes mellitus, which states that a fasting blood glucose level of <5·6 mmol·l⁻¹ is an appropriate upper limit for normality\cite{14}. Using the 1998 WHO and the 1997 ADA criteria, only one more new diabetic patient was noted relative to the 1985 WHO criteria; on the other hand, there were another 16 patients who could not be classified by the 1998 WHO and the ADA standards.

The absolute risk of cardiovascular deaths is three times higher for diabetic than for non-diabetic men after correction for other risk factors\cite{17}. The risk for acute myocardial infarction in diabetic subjects without previous myocardial infarction is comparable to the risk of reinfarction in non-diabetic patients with previous acute myocardial infarction\cite{18}. Reduction of heightened blood pressure and elevated serum cholesterol has been shown to reduce the incidence of cardiovascular disease in patients with type 2 diabetes\cite{19,20}. One study suggests a linear association between glycaemia and the risk of coronary heart disease in middle-aged and elderly patients with type 2 diabetes\cite{21}. The recent demonstration in the UK Prospective Diabetes Study that effective intervention to improve glycaemic control and
blood pressure reduces the rate of complications[19,22], together with indications that the time from onset of elevated glucose to diagnosis may take many years[23], suggests that it is important to diagnose diabetes earlier in order to permit intervention. Further, the DIGAMI study suggests that identification and optimal metabolic treatment may improve the prognosis in diabetic patients with acute myocardial infarction[7].

In the present study only 50% of the patients with casual blood glucose ≥11.1 mmol·l−1 at admission, which is the cut-off for intervention in the DIGAMI, met the 1985 WHO, the suggested 1998 WHO and the ADA criteria for diabetes mellitus after follow-up[7,13-15]. This finding convincingly indicates that high casual blood glucose in patients with acute myocardial infarction was not a reliable parameter in establishing a diagnosis of diabetes and supports the assumption that many patients without known diabetes and with hyperglycaemia at admission for acute myocardial infarction do not have diabetes[9]. Casual capillary blood glucose values ≥11.1 mmol·l−1 are considered as diabetic by ADA criteria if, in addition, clinical symptoms of diabetes exist[15]. However, in the clinical setting of an acute myocardial infarction the clinical symptoms of diabetes may easily be overlooked.

In comparison with the follow-up after 2–3 months, the fasting blood glucose taken on the 5th day in hospital had resulted in three times as many patients with a value ≥6.1 mmol·l−1. This finding supports the notion that stress related to myocardial infarction, including the acute stress response involving insulin-antagonistic hormones (e.g. cortisol and catecholamines), is a major determinant of plasma glucose during acute myocardial infarction and, to a lesser extent, the previous glycaemic control[9].

Hemoglobin A1C has been used as indicative of a prior diabetes when used in patients with acute myocardial infarction and hyperglycaemia[10,24], however, the measure does not have the capacity to establish the diagnosis of diabetes with any higher degree of certainty[12]. This problem is illustrated in the present study where 11% of the non-diabetic patients, in whom a diagnosis of diabetes was not confirmed at follow-up, had a haemoglobin A1C value above the upper reference limit of 5.3%. Two patients with a casual blood glucose ≥11.1 mmol·l−1 at admission and without diabetes mellitus had haemoglobin A1C around the upper reference level. During a later hospitalization, their casual blood glucose was again ≥11.1 mmol·l−1. This observation strengthens the assumption that glucose and haemoglobin A1C in the upper ranges of normal represent an impaired glucose metabolism, a notion which is supported by a 6-year follow-up showing that an elevated fasting blood glucose within 72 h of acute myocardial infarction is a good marker for future diabetes mellitus[25].

Our results emphasize the difficulty in establishing a diagnosis of diabetes in patients with acute myocardial infarction. There is a great need to investigate glucose metabolism further in patients with acute myocardial infarction and without earlier evidence of diabetes mellitus.

### Conclusion

One of four patients admitted for acute myocardial infarction was found to have diabetes mellitus. Sixteen percent of these patients had no prior diagnosis of diabetes. Increased casual blood glucose at admission was not a reliable method of establishing a diagnosis of diabetes and a follow-up was necessary. Considerable overlap in haemoglobin A1C values was noted between patients with known diabetes mellitus, newly diagnosed diabetes mellitus and non-diabetics.

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### References


