RELATIONSHIP BETWEEN BASAL PLASMA GLUCOSE LEVELS AND RECOVERING PROSPECTIVE OF PATIENTS WITH ACUTE STROKE

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Abstract

Introduction: Cardiovascular disease, especially coronary and cerebral, is the leading cause of death in diabetic patients. The aims of our study were to investigate carbohydrate metabolism disorders in patients with stroke, to analyze factors influencing stroke prognosis and to study the relationship between plasma glucose levels at admission and mortality rate after 14 days from the acute event in those patients.

Materials and Method: For this study we enrolled 208 subjects diagnosed with stroke. For all subjects plasma glucose level at admission and after 14 days from admission was measured. We investigated the relationship between glycemia at admission and mortality rate respectively glycemia after 14 days.

Results and discussion: From all patients involved in the study 31 had Type 2 Diabetes Mellitus (T2DM). In the patients group without previously diagnosed T2DM, 19 had plasma glucose level at admission > 125 mg/dL, 12 between 110-125 mg/dL and 146 below 110 mg/dL. In the group of patients not previously diagnosed with diabetes having plasma glucose level > 125 mg/dL at admission, 66.7% still had plasma glucose >125 mg/dL after 14 days from admission. We found a positive correlation between plasma glucose level at admission and mortality caused by stroke.

Conclusions: T2DM is a major risk factor for stroke. Plasma glucose level at admission was correlated positively with stroke mortality, both in patients with T2DM and in those without previously diagnosed T2DM, independently of other related factors.

Keywords: Acute stroke, Diabetes Mellitus, Mortality

Introduction

Atherosclerosis is the dominant etiologic factor for stroke. Cardiovascular disease, involving atherosclerosis, especially coronary and cerebral, as its morphophatologic substrate is the leading cause of death for T2DM patients.

Elevated blood glucose is common in the early phases of stroke. Although up to one third of acute stroke patients had either been diagnosed or newly diagnosed with diabetes, probably a major proportion of patients having stress hyperglycemia mediated partly by the release of cortisol and norepinephrine. It is also an outcome of relative insulin deficiency, which is associated with increased lipolysis. Even in nondiabetic patients, stress hyperglycemia may be a marker of defective glucose regulation in individuals with insulin resistance and developing T2DM (Perttu, 2004).

Experimental studies have demonstrated that hyperglycemia contributes to brain damage through different mechanisms: increasing blood brain permeability, producing cerebral edema, and promoting the release of inflammatory mediators (Garg, 2006; Marquardt, 2005; Godoy, 2010). An additional mechanism of injury, ischemia, is mediated by vasoconstriction and thrombosis in microcirculation (Garg, 2006; Godoy, 2010).

The prognostic value of hyperglycemia has been extensively evaluated; however, to date, it is not clear whether hyperglycemia contributes directly to worsen the outcome, or whether it just represents a surrogate marker of the stroke's severity (Garg, 2006; McCowen, 2001; Godoy, 2010). The management of hyperglycemia in this setting is still controversial and varies worldwide (Godoy, 2010; McCormick, 2008).

Blood glucose is usually increased immediately after the stroke, probably being the result of stress response to the stroke event (Yong, 2008; Allport, 2006; Gray, 2007; Walters, 2006). However, within at least a week, blood glucose usually declines and reaches a stable level (Allport, 2006; Gray, 2007; Walters, 2006; Szczudlik, 2001). Most studies are suggesting that an association between initial stroke severity and hyperglycemia on admission exists (Jørgensen, 1994; Wong, 2008; Stead, 2009). Fasting blood glucose (FBG) measured about one week after stroke (when the stress response has resolved) (Szczudlik, 2001) represents the patient's habitual blood glucose at the time of the stroke.

The aims of our study were to investigate carbohydrate metabolism disorders in patients with stroke, to analyze factors influencing stroke prognosis and to study the

relationship between plasma glucose levels at admission and mortality rate after 14 days from the acute event in those patients.

Main Text

Materials and Method

Study population: We conducted a hospital-based study, lasting one year, from January to December 2012, at the Neurology Department of the Timisoara Emergency Clinical Country Hospital.

The participants were selected from patients hospitalized in the Neurology Department, all of them admitted for an acute stroke event. The study protocol was approved by the ethics committee of the Timisoara Emergency Clinical Country Hospital, and the participants signed their informed consent at the time of recruitment. The study enrolled 208 subjects diagnosed with stroke, 16 (7.69%) hemorrhagic stroke and 192 (92.31%) with ischemic stroke, 52.7% men and 48.3% women, having an average age 57.2± 6.9.

Laboratory data: The venous blood samples were collected in the morning, after 12 hours of fasting. In all participants, FBG was measured at admission, and at 14 days from admission.

The diagnosis of stroke was established based upon neurological examination and laboratory investigation (including CT-scan and/or MRI). We investigated the relationship between admission glycemia and mortality rate respectively glycemia after 14 days.

Statistical methods: All patient data were summarized in the electronic health record. The mortality rate is expressed as a number of deceases per 100 patients in the studied interval. Fisher's exact test was used for assessing the significance level of differences between proportions (p value below 0.05 was considered to be significant). To evaluate the association between a factor and an outcome, odds ratio (OR) indicator was used, along with its 95% confidence interval (CI) and statistical significance.

Results

From the total of 208 patients diagnosed with stroke, 31 were previously diagnosed with T2DM. In the previously undiagnosed patients (177), 19 individuals (10.73%) had glycemic values at admission over 125 mg/dL; 12 (6.78%) had glycemic values between 110 - 125 mg/dL and 146 (82.49%) had normal glycemic values (<110 mg/dL), Figure 1.

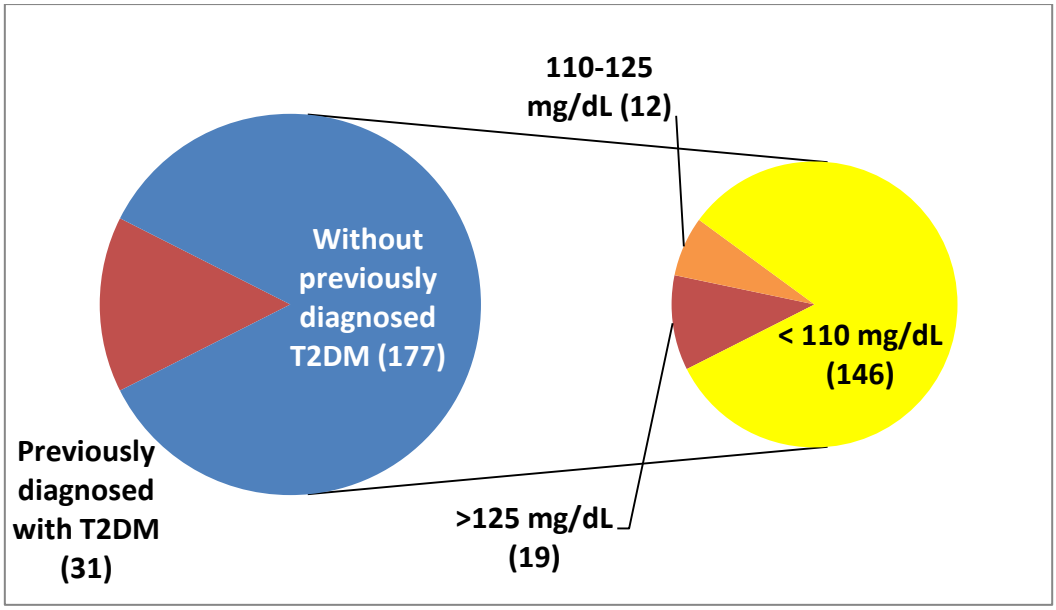

Figure 1. *Plasma glucose levels at admission*

In the entire group, the mortality rate at 14 days after admission was 10.1% (21 patients). The highest mortality rate was found in patients not previously diagnosed with T2DM but which had plasma blood glucose levels higher than 125 mg/dL. The group of patients having admission glycemia between 110-125 mg/dL had a 14 day mortality rate of 16.6 %, which was similar to the one found in previously diagnosed T2DM patients (16.13%). A significant decreased mortality rate was found in patients not diagnosed with T2DM which had glycemic values under 110 mg/dL (6.84%), Figure 2.

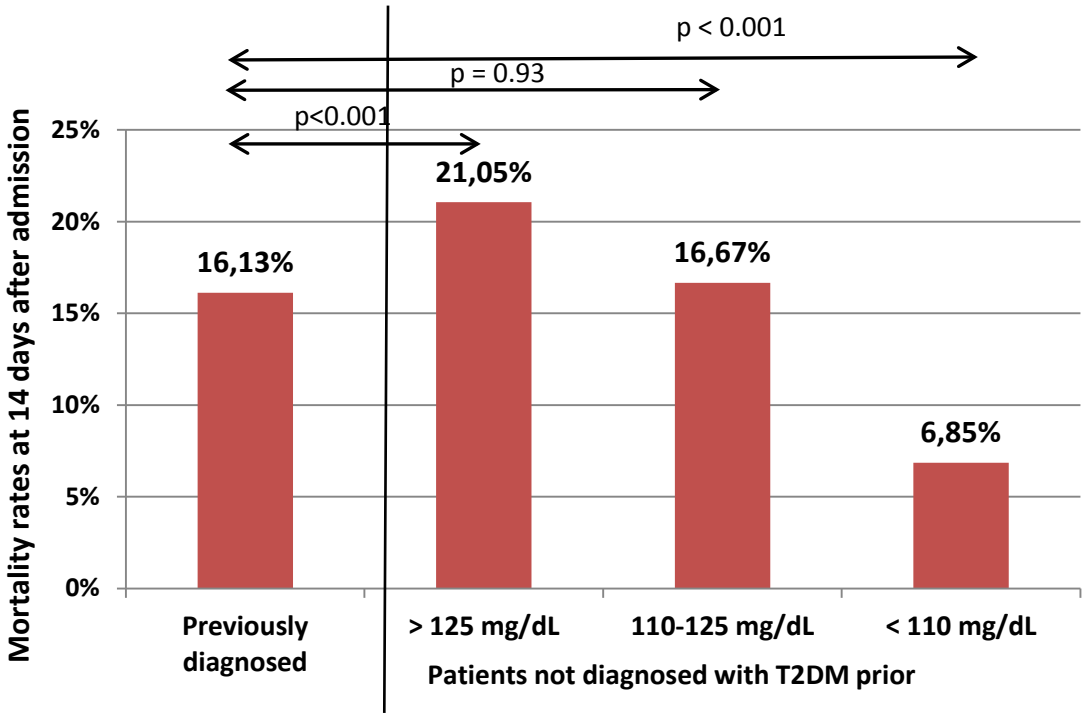

Figure 2. *Mortality rates at 14 days after admission in patients with stroke.*

We found an increased risk for decease (related to the group with glycemic values at admission <110 mg/dL) in all the other three studied groups. While significant increases in risk of death were found only in the group with plasma blood glucose levels higher than 125 mg/dL, the other two groups had increases but these rises in OR were not significantly statistical (Table 1).

Table 1. *ODDS RATIO vs. not previously diagnosed group and with plasma blood glucose at admission below 110 mg/dL*		ODDS RATIO for decease (95 % CI)
Patients previously diagnosed with DM		2.62 (0.83 – 8.28); p=0.102
Patients not diagnosed with T2DM prior admission	Glycemia at admission >125	3.63 (1.01 – 12.99); p=0.048
	Glycemia at admission: 110-125	2.72 (0.52 – 14.14); p=0.23

The repeated measurement of plasma glucose levels after 14 days from admission revealed that 66.7% (10 individuals out of 15 survivors) from the patients with initial glycemia higher than 125 mg/dL had also a glycemia higher than 125 mg/dL at the repeated measurement, the patients being now diagnosed with T2DM.

Discussion

Studies are revealing that even in the normal range of FBG there is a significant association between more severe strokes and higher FBG one week after the stroke. Because blood glucose was measured at a time when the stress-induced blood glucose was increased (Yong, 2008; Allport, 2006; Gray, 2007; Walters, 2006; Wong, 2008) event which had been resolved after 14 days from the acute event (Jørgensen, 1994; Wong, 2008; Stead, 2009), our study points to a significant association between higher glucose concentrations and more severe stroke-induced brain injury.

Most studies indicate a direct association between stroke severity and blood glucose concentrations at stroke onset (Yong, 2008; Jørgensen, 1994; Capes, 2001; Weir, 1997; Bruno, 1999; Kamouchi, 2011; Putaala, 2010). Blood glucose measured at that time cannot be assumed to reflect the patient's habitual blood glucose prior stroke onset (Rehncrona, 1981). At one week after the stroke, FBG concentrations have declined, stabilized, and the FBG concentration may then reflect the patient's habitual blood glucose concentration at the time of the stroke (Szczudlik, 2001). We consider this the most likely explanation for the strong association between stroke severity and FBG at one week after the event, seen in our study.

There is compelling experimental and clinical evidence of an association between hyperglycemia and poorer outcome after stroke (Yong, 2008; Jørgensen, 1994; Capes, 2001; Weir, 1997; Bruno, 1999; Kamouchi, 2011; Putaala, 2010). Our study now provides clinical evidence that indicates: higher FBG concentrations even within the normoglycemic range are

also associated with poorer outcome. This statement agrees with numerous animal studies which revealed a toxic effect of higher glucose concentrations in ischemic brain tissue, in particular those demonstrating glucose as the substrate for lactate production in the ischemic penumbra (Dietrich, 1993; De Courten-Myers, 1992; De Courten-Myers, 1989; Prado, 1988; Kawai, 1997).

Due to the encouraging results of the treatment regimens that used tight glucose control in the management of the critically ill patients (Van Den Berghe, 2001; Malmberg, 1995; Pittas, 2006), the current guidelines are recommending the lowering of blood glucose at least if it is high at admission (Kreisel, 2010). To date, the GIST-UK trial (Gray, 2007) is the only completed randomized study which analyses the glucose-lowering therapy in stroke. This trial's main aim was to determine whether treatment with glucose-potassium-insulin infusion for 24 hours, used in order to maintain normoglycemia within the range of 70–130 mg/dL, might reduce the mortality or the severe disability at 90 days after the stroke. The result of this study was negative; the investigators haven't found any evidence of insulin's treatment beneficial effect on reducing mortality or disability after stroke, and safety concerns were raised since a number of patients required rescue intravenous glucose treatment because hypoglycemic episodes occurred. However, the treatment was initiated in average after 13 hours from the stroke, at a time when most irreversible brain damage already had taken place. Hence, the negative outcome of the study is not excluding that higher blood glucose, at the time of stroke, may increase brain damage and initial stroke severity.

Conclusion

Our study provides clinical evidence regarding an association between more severe strokes and higher blood glucose even within the normoglycemic range following stroke. This recent evidence supports that acute, elevated, predominantly stress-related hyperglycemia is associated with poor outcomes. Through several different biochemical mechanisms, elevated glucose in the setting of cerebrovascular injury probably accelerates the course of ischemic damage, also in the boundary regions having milder perfusion deficit. However, obtaining normoglycemia as soon as possible should be encouraged, although conclusive evidence of decreased risk with this approach is lacking. Especially the nondiabetic patients may be at risk of further brain damage if hyperglycemia prevails.

T2DM is a major risk factor for stroke. Measuring the plasma glucose levels is mandatory at admission and should be repeated at least once more before discharge, in all patients with stroke. Plasma glucose levels at admission are correlated positively, both in

patients with T2DM and those without previously diagnosed DM with the mortality after stroke, independently of other factors.

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