Impaired glucose metabolism in nondiabetic patients with acute stroke

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Abstract

Introduction: Impaired glucose tolerance, an intermediate metabolic state between normal glucose levels and diabetes is associated with an increased stroke risk. The aim of this study was to determine the prevalence of impaired glucose metabolism in patients with acute stroke who had normal fasting plasma glucose.

Methods: Eligible subjects were non diabetic patients with ischemic stroke, from April 2005 to April 2006, who were evaluated eight weeks after their stroke event for FBS, GTT, HbA1C and serum insulin level (HOMA); the correlation of these tests with the number of stroke risk factors among the patients was assessed.

Results: Among 58 patients, 18 of them did not complete the study. In GTT evaluation in 40 patients, 26 of them (65%) had normal test values while 10 patients (25%) showed impaired tolerance and 4 (10%) were diabetic.

Overall, 35% of them had impaired glucose metabolism. In HbA1C analysis only 15% had abnormal test results. The mean of HOMA in our patients was 1.7 (1.64 to 2.16 in the normal group compared with the impaired one, respectively). In the FBS study, previously undiagnosed DM patients, impaired glucose tolerance patients and non diabetic ones account for 10, 25, and 65% of all cases respectively.

Discussion: Impaired glucose metabolism is one of the important risk factors for stroke and if only fasting plasma glucose is used for screening patients, at least 10% of patients prone to the side effects of hyperglycemia, will be missed.

Conclusion: This study shows that in patients with no history of diabetes who have an ischemic stroke, even moderately elevated glucose levels are associated with both a higher risk of short-term mortality and an increased risk of poor functional recovery compared with lower glucose levels.

Keywords: Impaired glucose tolerance, HOMA, Diabetes Mellitus, Ischemic Stroke

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Introduction

Stroke is considered as one of the most common causes of death and morbidity throughout the world. The presence of diabetes increases the risk of stroke and it is now estimated that there are more than 700,000 incident strokes annually and 4.4 million stroke survivors.[1,2] Diabetes mellitus doubles the risk of ischemic stroke[3] and worsens survival of patients with acute stroke.[4,5] Moreover, recent evidence that glucose lowering with insulin reduces ischemic brain damage in animal models of stroke.[6] However, the onset of diabetes may occur several years before the clinical diagnosis and its development is preceded by a prolonged period of insulin resistance with unfortunate side effects. In addition, insulin resistance has been shown to be independently associated with increased risk of cerebrovascular events in non-diabetic subjects.[7,8] There is also a positive link between mild plasma glucose elevation (even below the threshold for diabetes) and cardiovascular events[9] the risk of myocardial infarction, heart failure and cardiac death is already significantly increased in subjects with modestly elevated blood glucose.[10,11,12] Hyperglycemia during the acute phase of stroke occurs in about one third of patients without a prior diagnosis of diabetes.[13,14] Whether this raised plasma glucose concentration in non diabetic patients with acute stroke is a stress response or reflects the unrecognized diabetes is controversial.[15,16] Recent evidences suggest that insulin resistance may be one of the treatable risk factors for ischemic stroke. Epidemiological researches have shown a link between insulin resistance and risk of stroke and biologic research has associated it with metabolic and cellular events that promote hyperinsulinemia, atherosclerosis, hypertension, hyperglycemia, abnormal fibrinolysis, systemic inflammation, dyslipidemia and altered vascular endothelial function.[17]

Methods

This study was conducted in non-diabetic patients with acute ischemic stroke who were admitted to our hospital since April 2005 to April2006. Patients with previous diagnosis of DM, hemorrhagic stroke and that received steroids were excluded. The research protocol was approved by the local ethics committee. Acute stroke was defined according to WHO criteria: "rapidly developing clinical symptoms or signs of focal disturbance of cerebral function, lasting more than 24h with no apparent cause other than vascular origin".[18] The diagnosis of ischemic stroke and its subtypes was established by neurological examinations and confirmed by CT scan (TOAST criteria).[19]We measured fasting plasma glucose concentration, serum insulin and HbA1C two months after stroke events.

Because insulin sensitivity maybe perturbed by the physical stress of illness, patients could not enter the study before 2 months had elapsed since their stroke event.[20] A standardized oral glucose tolerance test with 75g of glucose dissolved in 200ml of water was performed after eight weeks. Plasma glucose was measured by the glucose oxidase method. The HbA1C was assessed by HPLC (high performance liquid chromatography) method with its normal upper limit set at 6; and insulin level was measured by ImmunoRadioMetricAssay (IRMA). The degree of insulin resistance in addition to criteria of GTT and FBS was estimated by the homeostasis model insulin resistance index (HOMA): Fasting Glucose (mmol/l) *Fasting insulin (mu/l)/22.5. A higher HOMA level indicates higher insulin resistance. Impaired glucose tolerance and diabetes were defined according to the American Diabetes Association (ADA) criteria 2004.[21] Hypertension was considered as blood pressure >140/90, hypertriglyceridemia as TG>250 and hypercholesterolemia as cholesterol>200. *(see table -1) for statistical analysis we used SPSS 14 software.

Table 1. Clinical and biochemical data of patients who completed the study

Parameter	value%
Age: <40 40-60 >60	10 35 55
Stroke type: Embolic Thrombotic	 55 45
Family hx of DM	12.5
Hypertension#	57
Cigarette smoking	20
Hyperlipidemia*	35

Results

Out of 58 non-diabetic patients who were admitted in our hospital with ischemic stroke, 40 cases completed the study. Demographic data of these non-diabetic patients has been demonstrated in table1. The majority of our patients were male (57.5% to 42.5%). Age distribution was 10% less than 40 years, 35% between 40-60 years and 55% above 60 years. Among these patients, 26 (65%) had normal test values (FBS,

GTT, HbA1C) after 8 weeks. 10 patients (25%) showed impaired GTT and overt diabetes was diagnosed in 4 (10%) patients (table2). Overall, 35% of the patients without history of diabetes, had abnormal glucose metabolism 8 weeks after stroke. 15% of the patients had abnormal HbA1C. Family history of diabetes was positive in 12.5% of the patients. Mean HOMA was 1.7 in our patients (1.64 in the normal group and 2.17 in patients with impaired levels).

Table-2.Glucose metabolism data in patients who completed the study

FBS:	%
Normal	75
Impaired	25
GTT:	
Normal	65
Impaired	25
DM	10
HbA1C	
Normal	85
Abnormal	15
HOMA:	
Total	1.7
Normal group	1.64
Impaired group	2.16

In GTT levels measured among 40 patients, 26 patients (65%) had normal results while 10 patients (25%) showed impaired tolerance test and 4 patients (10%) were diabetic. Overall, 35% of them had impaired glucose metabolism. In FBS analysis only 25% of patients had impaired fasting glucose. Considering ADA 2007 guideline for diabetes the 25% figure obtained in FBS study would rise to 40%. In HbA1C analysis only 15% had abnormal results. The frequencies of risk factors were 57% for hypertension, 35% for hyperlipidemia, and 20% for cigarette smoking. Family history of diabetes was positive in only 12.5% of patients. The mean of HOMA in our patients was 1.7 (1.64 in the normal group compared to 2.17 in the group showing impaired levels).

Discussion

Patients with acute ischemic stroke without previous diagnosis of diabetes had a high prevalence of abnormal glucose metabolism. Totally, 35% of our patients had abnormal glucose metabolism based on measurements of GTT and HOMA two months after their stroke events.

This value was 50% (36 of 72) in a study that used composite insulin sensitivity index for evaluation of insulin

resistance.[21] The gold standard for measuring insulin sensitivity is a hyperinsulinemic euglycemic clamp, a procedure that is technically difficult and inappropriate for epidemiologic work. Several convenient alternatives have been proposed, including measures based on fasting value for insulin and glucose, or values for insulin or glucose obtained during an oral glucose tolerance test. Generally speaking, measures derived from OGTT correlate more closely with the clamp than do those based only on fasting glucose or insulin. Of the methods available when we designed the study, in addition to OGTT, we selected the HOMA because it correlates closely with clamp results (correlation coefficient 0.56 to 0.88).

Conclusion

This impaired glucose metabolism was recorded when the effects of acute stress should have subsided, suggesting that in the majority of patients it is not as a result of stress during the acute phase of stroke. The oral glucose tolerance test we used to diagnose abnormal glucose metabolism is a better predictor of cardiovascular events and mortality than fasting plasma glucose. This fact was confirmed in a study by Vancheri et al.[22] The diagnosis of diabetes would have been missed at least in 10% of patients, if only tests of fasting glucose had been used. A criticism to our study in this regard is we presume that with a larger population, this 10% of discrepancy will increase. In the present study, patients with previously undiagnosed impaired glucose tolerance and diabetes were more insulin resistant after 2 months than patients with normal glucose metabolism. This result raises the possibility that the link between abnormal glucose metabolism and ischemic stroke is insulin resistance. In our patients, insulin resistance (expressed by HOMA) increased progressively with the impairment of glucose metabolism. As we mentioned before, the proportion of 15% of abnormal HbA1C indicates that this test is not an appropriate predictor of insulin resistance and cardiovascular events. Thus we proposed that, by use of insulin sensitizing drugs we can prevent the recurrence of ischemic stroke in non diabetic patients who are insulin resistant which has also been proposed by other studies.[23]

Acknowledgement

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اختلال متابولیسم گلوکز در بیماران غیر دیابتی مبتلا به سکته حاد مغزی

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چکیده

زمینه و هدف: دیابت از عوامل خطرزای شناخته شده و قابل کنتـرل در ابـتلا بـه سـکته هـای مغـزی ایـسکمیک میباشد. گروهی از افراد جامعه ممکن است قند خون ناشتای نرمال داشته اما تست تحمل گلوگز غیر طبیعی داشته باشند. این مطالعه به بررسی تست تحمل گلوکز در بیماران غیر دیابتی مبتلا به سکته ایسکمیک مغزی می پردازد.

روش بررسی: بیماران غیر دیابتی مبتلا به سکته ایسکمیک مغزی حاد وارد مطالعه شدند.
دراین بیماران هشت هفته پس از حادثه عروقی، قند خون ناشتا ، تست تحمل گلوکز و سطح سرمی انـسولین مـورد بررسی قرارگرفت.

نتیجه‌گیری: از ۵۸ بیماری که طی یکسال وارد مطالعه شده بودنـد ۱۸ بیمـار پـس از هـشت هفتـه جهـت انجـام آزمایش مراجعه ننموده واز مطالعه خارج شدند. از ۴۰ بیمار باقیمانده ده مـورد اخـتلال در تـست تحمـل گلـوگز را نشان دادند(۲۵٪).

یافته‌ها: اختلال متابولیسم گلوکز حتی بـا وجـود سـطح سـرمی نرمـال را بایـد یکـی از عوامـل خطـرزای حـوادث ایسکمیک مغز برشمردبنابراین انجام این تست در بیماران غیر دیابتی توصیه می‌گردد.

واژگان کلیدی: اختلال متابولیسم گلوکز، اندکس HOMA، دیابت ملیتوس، سکته ایسکمیک