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ORIGINAL COMMUNICATION

Ischemic stroke in prediabetic patients

Jaume Roquer · Ana Rodríguez-Campello · Elisa Cuadrado-Godia · Eva Giralt-Steinhauer · Jordi Jiménez-Conde · Irene R. Dégano · Angel Ois

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Abstract To describe the clinical characteristics of first-ever ischemic stroke (IS) patients with prediabetes, and to compare them with diabetes mellitus (DM) and non-DM patient characteristics. Retrospective analysis of a prospective series of first-ever acute IS patients. Patients were classified as non-DM (HbA1c during admission <5.7 % and no previous evidence of 2 or more fasting glucose >126 mg/dL), prediabetes (HbA1c from 5.7 to 6.4 %), and DM (previous DM diagnosis or HbA1c ≥6.5 % independently of current blood glucose). Demographic and clinical characteristics were compared between the three groups, along with outcome data [early neurological deterioration (END), 3-month poor outcome, 3-month mortality, outcome after rtPA treatment]. No demographic differences were observed. Prediabetic patients had more arterial hypertension ($p = 0.006$) and higher waist circumference ($p < 0.0001$) than non-DM patients, and DM patients had more hypercholesterolemia ($p < 0.0001$), body mass index ($p = 0.017$), and coronary artery disease ($p = 0.005$) than prediabetics. There were differences in TOAST subtype distribution ($p < 0.0001$). There were no differences in rtPA treatment success rate between groups. Multivariate analysis adjusted by age and stroke severity showed that DM but not prediabetes is an independent factor associated with END and 3-month poor outcome. Prediabetic patients with IS exhibit an "intermediate" vascular risk factor profile between that of non-DM and DM patients. In contrast to DM patients, IS prognosis in patients with prediabetes is similar to non-DM patients.

Keywords Ischemic stroke · Prediabetes · Outcome · Vascular risk factor · Epidemiology

Introduction

Prediabetes, defined as impaired fasting glucose and/or impaired glucose tolerance, indicates high risk for diabetes mellitus (DM) [1]. The diagnostic criteria changed in 2010,

J. Roquer (✉) · A. Rodríguez-Campello · E. Cuadrado-Godia · E. Giralt-Steinhauer · J. Jiménez-Conde · A. Ois
Servei de Neurologia, IMIM-Hospital del Mar, Passeig Marítim 25-29, 08003 Barcelona, Spain
e-mail: jroquer@hospitaldelmar.cat

A. Rodríguez-Campello
e-mail: arodriguezc@hospitaldelmar.cat

E. Cuadrado-Godia
e-mail: ecuadrado@hospitaldelmar.cat

E. Giralt-Steinhauer
e-mail: egiralt@hospitaldelmar.cat

J. Jiménez-Conde
e-mail: jjimenez@hospitaldelmar.cat

A. Ois
e-mail: aois@hospitaldelmar.cat

J. Roquer · A. Rodríguez-Campello · E. Cuadrado-Godia · E. Giralt-Steinhauer · J. Jiménez-Conde · I. R. Dégano · A. Ois
Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), Barcelona, Spain
e-mail: iroman@imim.es

J. Roquer · E. Cuadrado-Godia
DCEXS, Universitat Pompeu Fabra, Barcelona, Spain

A. Rodríguez-Campello · E. Giralt-Steinhauer · J. Jiménez-Conde · A. Ois
Departament de Medicina, Universitat Autònoma de Barcelona, Barcelona, Spain

when the American Diabetes Association recommended glycosylated hemoglobin A1c (HbA1c) to diagnose prediabetes (HbA1c levels from 5.7 to 6.4 %) [2]. The importance of prediabetes for cardiovascular diseases is supported by numerous studies. (1) Annually, 5–10 % of individuals with prediabetes will progress to DM [3]; (2) prediabetes is predictive of vascular mortality independent of vascular risk factor profile [4]; (3) prediabetes is associated with early forms of nephropathy, chronic kidney disease, small fiber neuropathy, diabetic retinopathy, and increased risk of macrovascular disease [3]; (4) prediabetes is considered a vascular risk factor for stroke, and cardiovascular disease [5]; (5) target organ damage precedes the diagnosis of DM, with both renal [6] and retinal [7] damage seen in patients with impaired glucose tolerance; (6) for prediabetics, lifestyle modification produced a reduction of 40–70 % in relative risk of DM [3].

Despite all these considerations, data on stroke epidemiology characteristics and outcome in prediabetic patients are scarce and controversial [8, 9]. The aim of the present study is to analyze these relationships in a large prospective cohort of patients with first-ever ischemic stroke (IS) in which HbA1c determination during acute phase permitted the diagnosis of prediabetes.

Methods

From January 2007 to December 2012, a total of 2,137 patients with acute IS were prospectively included in the BASICMAR database [10], an ongoing register of patients with acute IS at a single university tertiary hospital. Patients with intracerebral hemorrhage ($n = 292$), transient ischemic attack ($n = 289$), previous stroke ($n = 201$), and unusual cause of stroke ($n = 72$) were excluded. Of the remaining patients ($n = 1{,}283$), 1,088 had HbA1c testing during hospitalization (84.8 %). Missing HbA1c data were due to early discharge ($n = 94$), early death ($n = 35$), or no test ordered ($n = 66$).

All patients received a computed tomography (CT) scan in the emergency room. Stroke subtype was categorized using the TOAST classification [11], following a neurovascular study that included carotid and transcranial ultrasound or angio-magnetic resonance imaging (MRI), and 24-h electrocardiogram (EKG) monitoring. Patients were evaluated at hospital admission and at least twice a day during the first 3 days by a trained neurologist who established initial severity using the NIH stroke scale (NIHSS). Additional CT or MRI evaluations were done, if needed, during hospitalization. Transthoracic or transesophageal echocardiography was performed in patients with strokes of undetermined origin.

Following national and international guidelines, therapy included rtPA (first 4.5 h) and, beginning in 2010, endovascular treatment. Intravenous rtPA treatment was considered successful if patient achieved a modified Rankin scale (mRS) from 0 to 2 at 3-month follow-up. The first blood glucose (non-fasting) was obtained in the emergency room, and is the value used for this study. During hospitalization, additional glucose tests were done when indicated by a systematic protocol and according to the patient's clinical progress. HbA1c determination was obtained from fasting patients on the morning after admission or at some point during the first 7 days of hospitalization.

Vascular risk factors, as defined by international guidelines, were obtained from the patient, relatives, caregivers, or previous medical records. A structured questionnaire was used to record the following: arterial hypertension (evidence of at least two raised blood pressure measurements, systolic >140 mmHg or diastolic >90 mmHg, recorded on different days before stroke onset; a physician's diagnosis; or use of medication); diabetes (previous physician diagnosis or use of medication); hyperlipidemia [physician diagnosis, use of medication, serum cholesterol concentration >220 mg/dL, low-density lipoprotein cholesterol (LDL-c) >130 mg/dL or serum triglyceride concentration >150 mg/dL]; current smoking habits; ischemic heart disease (documented history of angina pectoris or myocardial infarction); and atrial fibrillation (AF) (physician diagnosis, use of medication, or conclusive electrocardiogram data). Body mass index (BMI) and waist circumference (WC) were obtained in 947 and 821 patients, respectively.

Glucose disturbance diagnosis: patients with previous physician diagnosis of DM or using DM medication were classified as previous DM, independently of HbA1c value during hospitalization. Using the HbA1c value obtained during hospitalization, patients with no previous history of DM were classified as follows: (1) non-DM if HbA1c <5.7 % and no evidence of two or more fasting blood glucose >126 mg/dL, (2) prediabetic if HbA1c from 5.7 to 6.4 % and no evidence of two or more fasting blood glucose >126 mg/dL, and (3) DM if Hb1Ac ≥6.5 % independently of current blood glucose.

Outcome data included early neurological deterioration (END), defined as an increase in the NIHSS score of ≥4 points in the first 72 h after stroke onset [12], and 3-month follow-up. Functional status (by mRS) and mortality was obtained by clinic visit or telephone contact. In the case of patients lost to follow-up after the 3-month visit, we consulted electronic medical records, the primary care physician, or hospital admissions records.

Statistical analysis

Age, NIHSS, glycemia at emergency room arrival, BMI, WC, and HbA1c presented a non-normal distribution and were expressed as medians and interquartile ranges 25–75 (IQR 25–75). Categorical data were expressed as counts and percentages. Differences in parametric and

nonparametric continuous variables were evaluated using the *t* test and Mann–Whitney *U* or Kruskal–Wallis test, respectively, and the Chi square test was used for proportional analysis. We compared vascular risk factor profile, stroke characteristics, outcome variables, and rtPA results between the three groups, between non-DM and prediabetics and between prediabetics and DM patients. Blood glucose and HbA1c values were also compared between patients treated with rtPA who achieved good vs. poor outcome. Finally, the impact of DM and prediabetes adjusted by age, stroke severity (NIHSS), and previous mRS on outcome (END, poor 3-month outcome, 3-month mortality) was estimated by logistic regression. Patients with previous mRS >2 were excluded from the analysis of poor stroke outcome (mRS 3–6) at 3 months. All analyses were two-tailed. The significance level was set at 0.05.

Ethics

The information used in this study was collected from the prospective BASICMAR register with the approval of our local ethics committee (CEIC-IMIM-Hospital del Mar, Barcelona, Spain). All patients gave their informed consent prior to their inclusion in the study.

Results

1. Baseline patient data (Table 1): no age or sex differences were observed between groups. Regarding vascular risk factors, there were differences in hypertension ($p < 0.0001$), hypercholesterolemia ($p < 0.0001$), BMI ($p < 0.0001$), WC ($p < 0.0001$), coronary artery disease ($p < 0.001$) and peripheral artery disease ($p < 0.0001$). The profile was similar for non-diabetics and prediabetics with differences only for arterial hypertension ($p = 0.006$) and WC ($p < 0.0001$). Patients with DM were more likely to have hypercholesterolemia ($p < 0.0001$), coronary artery disease ($p = 0.005$), and increased BMI ($p < 0.017$) than prediabetics.
2. Stroke characteristics (Table 2): the study groups differed in TOAST subtype distribution ($p < 0.005$), with more atherothrombosis cases in DM patients and more undetermined cases in non-DM patients. There were no differences in stroke severity between non-DM, prediabetic, and DM patients. Patients with DM suffered more END ($p = 0.005$) and worse 3-month outcome than the prediabetic patients (nonsignificant trend, $p = 0.059$). There were no differences in the rtPA success rate between non-DM, prediabetic and diabetic patients. Glycemia was significantly greater in rtPA patients with poor outcome vs. good outcome [134 (108, 166) vs. 115 (100, 148); $p = 0.012$], but no differences were observed in HbA1c values [5.80 (5.34, 6.60) vs. 5.78 (5.20, 6.30); $p = 0.346$].
3. Multivariate analysis adjusted by age and stroke severity (Table 3) showed that DM is an independent factor associated with END and 3-month poor outcome but not with mortality, whereas prediabetes has no influence on outcome variables.

Table 1 Demographic and vascular risk factors in non-diabetic, prediabetic, and diabetic first-ever ischemic stroke patients

	Non-DM ($n = 394$)	Prediabetes ($n = 273$)	DM ($n = 421$)	*p*	*p**	*p***
Age, median years (q1, q3)	77 (67, 83)	77 (67, 84)	76 (68, 82)	0.355	0.885	0.213
Sex (male), *n* (%)	188 (47.7 %)	135 (49.5 %)	216 (51.3 %)	0.591	0.694	0.642
Arterial hypertension, *n* (%)	254 (65.0 %)	204 (75.0 %)	333 (79.5 %)	0.0001	0.006	0.190
Hypercholesterolemia, *n* (%)	147 (37.5 %)	107 (39.2 %)	230 (54.9)	0.0001	0.685	0.0001
Body Mass Index, median (q1, q3)	26.1 (23.7, 29.1)	26.7 (24.2, 29.8)	27.5 (25.0, 30.5)	0.0001	0.131	0.017
Waist circumference, median cm (q1, q3)	96 (87, 104)	100 (92, 109)	101 (92, 110)	0.0001	0.0001	0.673
Coronary artery disease, *n* (%)	46 (11.7 %)	33 (12.1 %)	85 (20.3 %)	0.001	0.903	0.005
Peripheral artery disease, *n* (%)	20 (5.1 %)	23 (8.5 %)	50 (12.0 %)	0.0001	0.108	0.164
Atrial fibrillation, *n* (%)	144 (36.5 %)	100 (36.6 %)	150 (35.6 %)	0.950	1.0	0.808
Current smoking, *n* (%)	87 (22.4 %)	61 (22.8 %)	74 (17.9 %)	0.113	0.924	0.140
Current alcohol overuse, *n* (%)	71 (18.3 %)	57 (21.3 %)	79 (19.2 %)	0.778	0.368	0.556
Glucose, median mg/dl (q1, q3)	107 (96, 123)	113 (101, 131)	160 (124, 206)	0.0001	0.001	0.0001
HbA1c, median % (q1, q3)	5.1 (4.8, 5.4)	5.9 (5.7, 6.0)	7.4 (6.6, 8.5)	0.0001	0.0001	0.0001

DM diabetes mellitus

* *p* value for comparison between non-DM and prediabetic patients

** *p* value for comparison between prediabetic and DM patients

Table 2 Stroke characteristics and outcome data in non-diabetic, prediabetic, and diabetic first-ever ischemic stroke patients

	Non-DM ($n = 394$)	Prediabetes ($n = 273$)	DM ($n = 421$)	p	p*	p**
Stroke type						
Atherothrombotic, *n* (%)	41 (10.4 %)	37 (13.6 %)	73 (17.3 %)		0.578	0.350
Lacunar, *n* (%)	87 (22.1 %)	62 (22.7 %)	95 (22.6 %)			
Cardioembolic, *n* (%)	156 (39.6 %)	98 (35.9 %)	157 (37.3 %)			
Undetermined, *n* (%)	110 (27.9 %)	76 (27.8 %)	96 (22.8 %)	0.005		
Outcomes						
NIHSS median points (q1, q3)	6 (3, 13)	5 (3, 13)	5 (3, 11)	0.063	0.096	0.957
END, *n* (%)	51 (12.9 %)	29 (10.6 %)	78 (18.5 %)	0.008	0.398	0.005
3-month mortality, *n* (%)	59 (15.0 %)	29 (10.6 %)	60 (14.3 %)	0.785	0.105	0.201
3-month mRS 3–6***, *n* (%)	128 (37.1 %)	80 (33.3 %)	146 (41.1 %)	0.267	0.380	0.059
rtPA successful, *n* (%)	42 (53.2 %)	36 (61.0 %)	29 (46.8 %)	0.509	0.389	0.145

NIHSS National Institutes of Health Stroke Scale, *END* early neurological deterioration

* p value for comparison between non-DM and prediabetic patients

** p value for comparison between prediabetic and DM patients

*** Patients with previous mRS = 3 were excluded from this analysis ($n = 148$)

Table 3 Multivariate logistical regression analysis of the impact of DM and prediabetes for poor outcome variables [early neurological deterioration (END), 3-month poor outcome, and 3-month mortality] adjusted by age and stroke severity (NIHSS)

	END OR (95 % CI), p value	3-month poor outcome OR (95 % CI), p value	3-month mortality OR (95 % CI), p value
Non-DM	Index	Index	Index
Prediabetes	0.82 (0.50–1.34), $p = 0.430$	0.86 (0.56–1.32), $p = 0.486$	0.66 (0.38–1.17), $p = 0.152$
DM	1.67 (1.12–2.87), $p = 0.012$	1.51 (1.03–2.21), $p = 0.036$	1.09 (0.65–1.71), $p = 0.838$
Previous mRs 0	Index	Index	Index
Previous mRs 1	0.96 (0.57–1.62), $p = 0.888$	1.84 (1.18–2.86), $p = 0.007$	1.18 (0.63–2.22), $p = 0.609$
Previous mRs 2	0.95 (0.54–1.67), $p = 0.846$	3.77 (2.34–6.07), $p < 0.0001$	1.88 (0.99–3.57), $p = 0.054$
Previous mRs 3	1.08 (0.65–1.79), $p = 0.764$	–	2.29 (1.31–4.02), $p = 0.004$
Age	1.02 (1.01–1.04), $p = 0.009$	1.05 (1.03–1.06), $p < 0.0001$	1.07 (1.04–1.10), $p < 0.0001$
NIHSS	1.07 (1.04–1.09), $p < 0.0001$	1.21 (1.17–1.24), $p < 0.0001$	1.21 (1.17–1.25), $p < 0.0001$

DM diabetes mellitus, *END* early neurological deterioration, *NIHSS* National Institutes of Health Stroke Scale

Discussion

The frequency of prediabetes in first-ever IS is high (25.1 %), exceeding the 10 % observed in general population [13] and similar to previous reports in IS patients ranging from 23.1 to 26.4 % [14, 15], emphasizing the importance of glucose disturbances in IS: 63.8 % of patients from our cohort were diabetics or prediabetics. The main finding of our study is that demographic and clinical characteristics of prediabetic patients with first-ever IS are not significantly different from non-diabetic patients. However, some differences were observed between prediabetic patients and DM patients (Tables 1, 2). Prediabetic patients occupy an "intermediate" situation regarding vascular risk factors: they have significantly higher WC and prevalence of arterial hypertension than non-DM patients, and significantly lower BMI and prevalence of hypercholesterolemia and coronary artery disease than DM patients. Furthermore, the TOAST subtype distribution differed between the three groups: atherosclerotic etiology increased from 10.4 % in non-DM patients to 13.6 % in prediabetics and 17.3 % in diabetics. This finding suggests some kind of relationship to be explored in future research, particularly in light of the fact that, DM and insulin resistance accelerate atherosclerosis by several mechanisms that lead to vascular injury [16].

Multivariate analysis showed that DM is an independent factor for poor outcome and END, but has no impact on 3-month mortality, agreeing with previous reports [17, 18]. However, prediabetes has no independent influence on any outcome measure. This finding agrees in part with a recent study [19] showing that both diabetes (significantly) and prediabetes (nonsignificant trend) were associated with END and early poor outcome. Our results confirmed these relationships for DM patients, but showed no relationship between prediabetes and END or poor outcome. It is

important to note that these studies were quite different regarding sample size (52 prediabetic cases in the published study vs. 273 in the present study), diagnostic criteria of prediabetes (impaired glucose tolerance or impaired fasting glucose test vs. HbA1c determination), END criteria (increase in the NIHSS of $\geq$2 points during the first 14 days vs. $\geq$4 points in the first 72 h after stroke onset), and definition of poor outcome (mRS score 2–6 vs. mRS score 3–6), respectively.

Finally, we found no differences in the success of rtPA treatment between DM, prediabetics, and non-diabetics. Patients with poor rtPA response had higher blood glucose levels in acute stroke phase than those with good response ($p = 0.012$), but there was no difference for HbA1c, agreeing with a previous study [20].

Limitations

The diagnosis of glucose disturbance was based on only one HbA1c value obtained during hospitalization. Despite normality of glucose levels and Hb1Ac determinations during admission, a small proportion of patients will actually have DM or prediabetes. Regarding the results of rtPA treatment, we have outcome data (mRS at 3 months) but no data on recanalization.

In conclusion, despite the important role of prediabetes for cardiovascular diseases, prediabetic patients with first-ever IS had few differences when compared with non-diabetics. The vascular risk factors profile was "intermediate", between that of non-diabetic and DM patients, and outcome parameters were similar to non-diabetics and better than DM cases.

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Ethical standard The information used in this study was collected from the prospective BASICMAR register with the approval of our local ethic committee (CEIC-IMIM-Hospital del Mar, Barcelona, Spain). All patients gave their informed consent prior to their inclusion in the study.

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