Metabolic disturbances after acute vascular events: A comparative study of acute coronary syndrome and ischaemic atherothrombotic stroke

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Abstract

Objective. – This pilot study aimed to compare metabolic disturbances, particularly insulin resistance (IR) and cardiovascular risk factors (CRFs), following two types of acute vascular atherothrombotic disease events: ischaemic atherothrombotic stroke (AS); and acute coronary syndrome (ACS).

Design and methods. – A total of 110 non-diabetic patients presenting with either AS (\(n=55\)) or ACS (\(n=55\)) were included in our prospective comparative study, and matched for age and gender. IR was determined using the homoeostasis model assessment of insulin resistance (HOMA-IR) method, and each patient’s personal and family history were also recorded.

Results. – IR was significantly higher in the ACS vs AS group (HOMA-IR index 2.17 ± 1.90 vs 1.50 ± 0.81, respectively; \(P=0.03\)). The AS group had a significantly higher prevalence of personal history of hypertension (51% vs 31%; \(P=0.03\)), while current smoking was more prevalent in the ACS group (30% vs 18%; \(P=0.04\)). There were no significant differences between the two groups as regards any other CRFs.

Conclusion. – The distribution of CRFs varied depending on the vascular event, and metabolic disturbances differed according to the atherothrombotic disease. IR was greater after ACS than AS.

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Keywords: Metabolic syndrome; Insulin resistance; Acute coronary syndrome; Stroke; Atherothrombotic disease

Résumé

Perturbations métaboliques après un accident vasculaire aigu : étude comparative entre syndrome coronaire aigu et accident vasculaire cérébral ischémique d’origine athérothrombotique.

Objectif. – Comparer les perturbations métaboliques, en particulier la résistance à l’insuline (IR) et les facteurs de risque cardiovasculaire (FRCV) après deux événements vasculaires aigus de la maladie athérothrombotique : accident vasculaire cérébral ischémique athérothrombotique (AVC-IA) ou syndrome coronaire aigu (SCA).

Méthodes. – Dans une étude pilote, 110 patients non diabétiques qui avaient présenté une AVC-IA (\(n=55\)) ou un SCA (\(n=55\)) ont été inclus dans une étude prospective, comparative, appariés pour l’âge et le sexe. L’IR a été déterminée en utilisant la méthode du modèle d’homéostasie de l’insuline (HOMA-IR) et, les antécédents personnels et familiaux ont été enregistrés.

Résultats. – L’IR était significativement plus élevée dans le groupe SCA que dans le groupe AVC-IA (HOMA-IR 2,17 ± 1,90 versus 1,50 ± 0,81, \(P=0,03\)). Dans le groupe AVC-IA, il y avait une prévalence significativement plus élevée d’antécédents personnels d’hypertension (51 versus 31 %, \(P=0,03\)). Le tabagisme actif était plus fréquent dans le groupe SCA (30 versus 18 %, \(P=0,04\)). Il n’y avait pas de différence significative entre les deux groupes pour les autres FRCV.

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Conclusion. – La distribution des FRCV varie en fonction de l’événement vasculaire, les perturbations métaboliques sont différentes selon la maladie athérothrombotique, l’insulinorésistance étant plus importante après un SCA qu’à la suite d’un AVC-IA.

Mots clés : Syndrome métabolique ; Insulinorésistance ; Syndrome coronaire aigu ; Accident vasculaire cérébral ; Maladie athérothrombotique ; Facteurs de risque cardiovasculaire

1. Introduction

Cerebro- and cardiovascular events are the leading cause of morbidity and mortality in industrialized countries. While acute coronary syndromes (ACSs) are caused by coronary atherosclerosis in a vast majority of cases, the risk factors for acute ischaemic atherothrombotic stroke (AS) include mainly carotid atherosclerosis as well as the presence of cardioembolic disease.

Numerous factors contribute to the development of atherosclerosis. The main ones are hypertension, dyslipidaemia, smoking, diabetes, age, male gender and abdominal obesity. There is a difference in the distribution of cardiovascular risk factors (CRFs) according to the site of the atherothrombotic complications, with hypertension more significant in the onset of ischaemic stroke [1], whereas dyslipidaemia plays a greater role in coronary patients [2]. Although the role of the metabolic syndrome (MetS) in the onset of a cardiovascular event is still being debated [3] and there are several different definitions of the syndrome, its pathophysiology is primarily linked to insulin resistance (IR). Several cohort studies have demonstrated that the MetS is associated with an increased risk of stroke [4] and coronary heart disease [5]. However, the relationship between atherothrombotic disease in the acute phase and IR is less well known. To our knowledge, no study has compared the metabolic disturbances following the two principal types of acute atherothrombotic events.

For this reason, the main objective of the present study was to compare metabolic disturbances in patients who had suffered two different consequences (AS and ACS) of a single disease (atherothrombosis). The hypothesis was that the two groups differed not only in ‘conventional’ CRFs, but also at the level of IR, as determined by homoeostasis model assessment (HOMA-IR), with possible prognostic implications.

2. Design and methods

This was a prospective, comparative, single-centre pilot study conducted at Grenoble University Hospital between November 2005 and November 2009. A total of 110 patients of both genders, aged 40 to 70 years (to avoid selection of a particular atherothrombotic profile) and presenting with completed AS (n = 55) or ACS (n = 55), were enrolled. As a pilot study, calculation of the number of patients in both groups could not be based on a dataset. Taking into account the capacity to recruit patients at our institution, it was decided that a total of 110 patients (55 in each group) should be included in the study. Matched for age and gender, none of them had diabetes mellitus. Diagnosis of ischaemic stroke was made on the basis of the patients’ interview data, physical examination and imaging examinations (computed tomography [CT] and/or magnetic resonance imaging [MRI] scans) showing the absence of haemorrhage, but with direct signs of ischaemia. Conventional neurological tests, including ultrasound of the supra-aortic arteries, electrocardiography (ECG) monitoring and cardiac ultrasound, identified an atherothrombotic mechanism as defined by:

1. the presence of atherosclerotic thrombosis or stenosis (≥ 50% diameter reduction, or < 50% but with plaque ulceration) in the clinically relevant extracranial or intracranial artery;
2. the absence of acute cerebral infarction in a vascular territory other than the one pertaining to the stenosed or occluded artery;
3. the absence of any other possible mechanism particularly in the light of normal 48-h ECG monitoring, normal transthoracic and transesophageal echocardiography, and the absence of coagulopathy.

Patients with an arterial disease other than atherosclerosis (such as arterial dissection, vasculitis or arterial spasm) were excluded. Also excluded were patients presenting with lacunar stroke.

These criteria were inspired by the Causative Classification of Stroke system, an evidence-based classification algorithm for acute ischaemic stroke [6]. An ACS with persistent ST-segment elevation was diagnosed on the basis of patient interview data and ECG signs of acute myocardial ischaemia. Calculation of the US National Institutes of Health Stroke Scale (NIHSS) was done for each AS patient to evaluate the severity of the ischaemic stroke [7]. Ethical approval was obtained from the local ethics committee, and all participants gave their informed consent. The registration (ClinicalTrials.gov) trial number for this study was NCT00926874.

The non-inclusion criteria were:

1. for patients in the ACS group, stroke within the previous 6 months (to diminish the role of acute biological and vascular modifications arising in the initial phase of the two types of atherothrombotic events) or coronary bypass performed between the start of hospitalization for ACS and inclusion;
2. for patients in the AS group, cardioembolic disease (diagnosis left to the assessment of the neurologist who treated the stroke) or ACS within the previous 6 months;
3. for all patients, haemodynamic instability, atrial fibrillation or flutter, frequent extrasystoles (> 10/min, to obtain valid 24-h ambulatory blood pressure monitoring [ABPM]) and
reduced mobility preventing the patient from maintaining a standing position.

When patients were admitted as an emergency to hospital, their personal and family histories were recorded along with their CRFs and concomitant treatment. All patients also underwent physical examination at inclusion, including cardiovascular and neurological assessment, recording of weight, height, abdominal circumference, blood pressure (BP) and heart rate (HR), and an ECG. All patients gave a fasting blood sample for measurement of lipid parameters, creatinine, insulin (no patient was being treated by insulin) and glucose, plus an echocardiogram for the ACS group. The HOMA-IR index was calculated as fasting insulin (U/mL) times fasting glucose (mmol/L) divided by 22.5 [8]. HOMA-IR values ≥ 2.4 (75th percentile for the study population) indicated IR. In the 48 hours after the acute event, transthoracic and/or transesophageal echocardiography was performed in the AS group, and all patients provided urine samples for measurement of microalbumin over a 24-h period. For both patient groups, 24-h ABPM was performed after a classical period of post-stroke hypertension (one week after the acute event).

Statistical analyses were carried out using SPSS version 11.0 software (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as means ± standard deviation (SD), and categorical variables as percentages. Data comparisons between the two patient groups (AS and ACS) were made by Student’s t test for parametric series, a non-parametric Mann–Whitney test in the event of non-normal distribution for continuous variables and a χ² test for categorical variables. Values of P<0.05 were considered significant.

3. Results

The general characteristics of our patients are summarized in Table 1. In the ACS group, all patients had ST-elevation myocardial infarction; the mean peaks of creatine kinase and troponin T values were 2118 ± 1876 U/L and 5.51 ± 3.88 μg/L, respectively. In all patients, cerebral infarction included the middle cerebral artery territory. In the 55 patients with stroke, 55 had undergone CT, 40 had CT angiography, 45 had MRI, 30 had MR angiography and 55 had transthoracic and/or transesophageal echocardiography. Diagnostic investigations revealed moderate-to-severe arterial stenosis or thrombosis secondary to atherosclerosis in the territory of the internal carotid or middle cerebral artery, consistent with cerebral imaging.

There were no significant differences between the two groups for the majority of CRFs. In the AS vs ACS group, there was a significantly higher prevalence of a personal history of hypertension (51% vs 31%, respectively; P = 0.03), while current smoking was more prevalent in the ACS vs AS group (30% vs 18%, respectively; P = 0.04). In the AS group, there was a tendency towards higher prevalence of a personal history of ischaemic stroke (P = 0.06) and a significantly higher prevalence of a family history of ischaemic stroke (P = 0.02). Prevalence of a history of coronary heart disease was identified as stable angina in two-thirds of patients and as myocardial infarction in one-third, with the same distribution in both groups. Table 2 lists the cardiovascular treatment before the acute atherothrombotic event that could have had an influence on metabolism. Statins were more frequently prescribed in the ACS vs AS group (34% vs 16%; P = 0.02), whereas calcium-channel blockers were more frequently prescribed in the AS group (21% vs 7%; P = 0.03). There were no significant differences between the two groups regarding other treatments. Standard treatments were used in both groups, including ten (18%) cases of thrombolysis in the AS cohort, and 49 (89%) percutaneous coronary interventions and 12 (22%) cases of thrombolysis in the ACS cohort. Laboratory parameters are summarized in Table 3. Insulin levels and HOMA-IR indices (Fig. 1) were higher in the ACS group, and triglycerides also tended to be higher in that group (P = 0.08). In the study population overall, 25 patients (22%) had IR, with a prevalence that was significantly higher in the ACS than in the...
Clinical parameters at inclusion according to vascular event.

<table>
<thead>
<tr>
<th></th>
<th>ACS (n = 55)</th>
<th>AS (n = 55)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.06 ± 1.29</td>
<td>5.31 ± 0.98</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>3.82 ± 1.99</td>
<td>3.25 ± 1.73</td>
<td>0.08</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.39 ± 0.57</td>
<td>1.39 ± 0.36</td>
<td>NS</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>2.94 ± 1.06</td>
<td>3.23 ± 0.83</td>
<td>NS</td>
</tr>
<tr>
<td>Blood creatinine (µmol/L)</td>
<td>83 ± 23</td>
<td>81 ± 16</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary microalbumin (mg/L)</td>
<td>16.3 ± 15.1</td>
<td>20.5 ± 25.4</td>
<td>NS</td>
</tr>
<tr>
<td>Blood glucose (mmol/L)</td>
<td>5.1 ± 0.95</td>
<td>5.0 ± 0.95</td>
<td>NS</td>
</tr>
<tr>
<td>Blood insulin (µIU/mL)</td>
<td>9.1 ± 3.9</td>
<td>6.6 ± 3.5</td>
<td>0.002</td>
</tr>
<tr>
<td>HOMA-IR index</td>
<td>2.09 ± 0.82</td>
<td>1.50 ± 0.81</td>
<td>0.001</td>
</tr>
</tbody>
</table>

ACS: acute coronary syndrome; AS: atherothrombotic stroke (ischaemic); HDL/LDL: high-density/low-density lipoprotein; HOMA-IR: homoeostasis model assessment of insulin resistance; NS: not significant.

Values are expressed as means ± SD or percentages.

AS group (31% vs 14.5%, respectively; P = 0.04). There was no difference between the two groups in low-density lipoprotein (LDL) cholesterol.

Patients in the AS group had higher BP values on both clinical examination (systolic BP: 136 ± 19 mmHg vs 122 ± 19 mmHg [P < 0.001]; diastolic BP: 81 ± 11 mmHg vs 74 ± 11 mmHg [P < 0.001]) and with ABPM (systolic BP: 135 ± 16 mmHg vs 113 ± 14 mmHg [P < 0.001]; diastolic BP: 82 ± 10 mmHg vs 69 ± 8 mmHg [P < 0.001]) than those in the ACS group. Left ventricular ejection fraction (LVEF) was also significantly higher in the AS vs ACS group (63 ± 7% vs 54 ± 10%; P = 0.04), and there was a significant correlation between LVEF and IR level (r = –0.28, P = 0.05) in the ACS patients. No correlation was found between disease severity (by NIHSS) and IR levels (r = –0.21, P = 0.24) after atherothrombotic stroke. In the ACS group, there was no correlation between troponin and HOMA-IR (P = 0.48). All patients in the AS group had normal troponin levels (< 0.01 µg/L).

4. Discussion

In the present pilot study, metabolic disturbances differed according to the atherothrombotic disease, IR was higher after ACS than AS, and the distribution of CRFs varied depending on the vascular event. Moreover, correlation between prognostic parameters and IR was found only in the ACS group.

Impaired insulin sensitivity has emerged as a potential risk factor for vascular disease following an acute atherothrombotic event. Caccamo et al. [9] showed the important prognostic role of IR after ACS. Subdividing their study population into tertiles of HOMA-IR index values, they found that patients with elevated HOMA-IR had a higher incidence of cardiovascular and cerebrovascular events at the 1-year follow-up. Likewise, Stubbs et al. [10] demonstrated that an IR index measured in patients admitted with myocardial infarction provides an important predictive measure of poor outcome, although the mechanism behind this poor outcome is not yet completely understood. Iozzo et al. [11] suggested that IR at the level of the myocardium could precede and possibly cause the development of cardiovascular disease. Indeed, the preferred substrate for ischaemic myocardium is glucose, and insulin is necessary to increase glucose entry into muscle cells. So, in the context of myocardial infarction, patients with IR may be exposed to double jeopardy. First, there is rapid depletion of glycogen stores due to IR and, second, the reactions that increase glycolysis in ischaemic tissue may be counterproductive due to accumulation of protons and lactate [12]. Tenerz et al. [13] revealed that patients with ACS and no previous diagnosis of diabetes have a high prevalence of IR both during their hospital stay and for 3 months thereafter. In the same study, IR remained unchanged after hospital discharge and throughout 3 months of follow-up, with further prognostic implications. Thus, it is of interest to note that metabolism disturbances persist after the acute event.

In our present study, IR appeared to be more prevalent after ACS. However, the prognostic role of IR was also evident following AS. Indeed, Urabe et al. [14] designed a study to define the relationship between IR and ischaemic stroke using HOMA-IR. Their data showed that IR appears to be an important factor for thrombotic ischaemic stroke. Following an ischaemic stroke, IR could be due to a stress response of brain origin [15]. There is also accumulating evidence that IR is associated with the activation of coagulation and fibrinolysis, which are also present in the acute phase of an ischaemic event such as ACS or ischaemic stroke [16,17].

Our present study supports the importance of a more vigorous screening strategy for the early detection of IR in patients with ACS. Indeed, because the prevalence of IR is high in ACS patients, early treatment of IR could be important for secondary coronary prevention. In terms of daily practice, myocardial protection could also be improved. In the presence of IR, the heart rapidly modifies its energy metabolism, resulting in increased fatty acid and decreased glucose consumption during stress such as ischaemia. In addition, accumulating evidence suggests that this alteration of cardiac metabolism plays an important role in the development of heart failure [18]. Theoretically, early...
identification of metabolic disturbances to optimize the metabolic milieu of ischaemic myocardium via normalization of IR may be warranted to improve outcomes before a revascularization procedure [19]. Multiple pathways can act on cardiac metabolism, but their clinical relevance remains to be demonstrated [18].

As shown in the present pilot study, the distribution of CRFs varies depending on whether the patient has presented with AS or ACS. Thus, hypertension plays a significant role in cases of stroke, whereas metabolic abnormalities such as dyslipidaemia are more frequent after ACS. Hypertension is known to be a major factor for ischaemic stroke, whereas metabolic abnormalities take second place, along with smoking. Recently, this was demonstrated yet again by the Interheart and Interstroke studies [1,2].

4.1. Study limitations

The results of our study need to be confirmed by others and in larger numbers of patients. Also, matching only for age and gender exposed our study to potential bias. In addition, it is difficult to say whether the abnormalities found are a cause or a consequence of the ischaemic phenomenon. Baseline differences, such as statin or beta-blocker treatment and smoking, may have favoured IR in the ACS group.

Nevertheless, despite these limitations, our study had several strong points:

(1) it was the first comparative study of ACS and ischaemic AS;
(2) the inclusion of only non-cardioembolic and non-lacunar ischaemic stroke patients allowed comparisons of CRFs in the same disease — atherosclerosis — but following two different atherothrombotic complications (ACS and AS);
(3) metabolic values were measured on the patients’ arrival in hospital at the time of the vascular event, thus avoiding the therapeutic effects of drugs, which differed depending on the disease presented.

5. Conclusion

In this pilot study, atherothrombotic disease was associated with a different distribution of CRFs depending on whether the patient presented with ACS or ischaemic AS. Metabolic disturbances — especially IR — are more common following ACS. Better identification of IR following an atherothrombotic event should enable better secondary cardio- and cerebrovascular prevention as well as the development of new therapeutic targets.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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