Effectiveness of intensive neurorehabilitation in obese subacute stroke patients

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Summary

The relationship between abdominal subcutaneous adipose tissue thickness (aSAT), body fat percentage (BFP), waist-to-hip ratio (WHR) and body mass index (BMI) and outcome measures of neurological deficit and functional recovery was evaluated in obese subacute stroke patients before and after neurorehabilitation. Decreased National Institutes of Health Stroke Scale ($p = 0.0001$) and modified Rankin Scale (mRS) ($p = 0.002$) scores, as well as increased Barthel Index ($p = 0.0001$) scores were detected after neurorehabilitation. Decreased BMI, aSAT, BFP and WHR observed after neurorehabilitation did not penalize the overall functional recovery as shown by correlations between the clinical measure scores and fat mass indices. The correlation observed after neurorehabilitation between BMI and mRS ($rho = 0.4526$, $p < 0.05$) suggests that a high BMI may compromise functional recovery. Monitoring of body fat mass indices may provide information aimed at improving the disability of obese stroke patients.

KEY WORDS: ischemic stroke, neurorehabilitation, obesity.

Introduction

It is widely known that obesity is an important risk factor for stroke, both first-ever and recurrent ischemic events (Niewada and Michel, 2016; Bailey, 2016). The mechanism by which obesity induces a sequelae of events triggering brain ischemia remains to be clarified completely, even though the chronic elevation of inflammatory markers released by the visceral component of adipose tissue, metabolically more active than subcutaneous adipose tissue, seems to play a key role (Suk et al., 2003).

Although there is unanimous agreement that obesity is an important risk factor for many diseases, including stroke, and that it is essential to reduce excess weight (Adams et al., 2006; Nguyen et al., 2011; Foulds et al., 2012), some clinical findings indicate a lower risk of stroke and stroke recurrence in obese or overweight patients, the so-called obesity paradox effect (Doehner et al., 2013; Zhao et al., 2014; Andersen and Olsen, 2015).

On the basis of this hypothesis, several studies set out to evaluate whether obesity is a favourable condition for stroke functional recovery by examining the response to post-stroke rehabilitation interventions in sub-acute or chronic stroke patients with a higher body mass index (BMI). Accordingly, there emerged some evidence of more positive outcomes in overweight stroke patients undergoing inpatient rehabilitation with respect to normal-weight and underweight patients (Doehner et al., 2013; Burke et al., 2014; Nishioka et al., 2016). This claimed influence of obesity/high BMI in favouring a positive functional recovery is, however, far from clearly accepted, and the existence of a protective effect of high BMI on survival and/or rehabilitation outcome is still debated (Sheffler et al., 2012; Dehlendorff et al., 2014; Kim et al., 2019).

A recent study (Morone et al., 2019) offers an interesting interpretation of the relationship between functional outcome and obesity. The Authors showed that decreases in BMI in subacute hemiparetic stroke patients, overweight or obese at rehabilitation admission, were associated with less effectiveness of neurorehabilitation, suggesting that rehabilitation outcomes may be influenced by modifications in BMI during the rehabilitation intervention. It is worth considering that most of the studies aiming to investigate the implications of obesity on clinical and functional outcomes have used BMI measures on the assumption that post-stroke impairment in body composition can compromise the patient's independence in activities of daily living (Bouziana and Tziomalos, 2011).

However, BMI assessment as the sole indicator of stroke functional recovery may present some limits as this parameter does not allow a proper evaluation of the distribution of fat mass and fat free mass, and thus makes the evaluation of body composition too simplistic. For a more accurate investigation on the possible involvement of obesity/high BMI in favouring a positive functional recovery, it could be of interest to perform a detailed evaluation of body composition in order to identify which body component is most involved in the effectiveness of the rehabilitation intervention and may possibly be taken as a prognostic indicator. It is worth noting that bioelectrical impedance analysis can be used to measure body districts directly, and the ultrasound technique to detect the thickness of abdominal fat mass (Ha et al., 2010; Wagner et al., 2013; Wagner et al., 2018).

This study set out to evaluate the effectiveness of intensive multifunctional neurorehabilitation in obese subacute stroke patients and to assess the relationship between several body composition parameters and outcome measures of functional recovery before and after an inpatient neurorehabilitation intervention.

Materials and methods

Study design and participants

In this observational clinical study (repeated measures study), subacute stroke patients assigned, between October 2017 and December 2018, to in-hospital neurorehabilitation at the Nova Salus Rehabilitation Center for neurological sequelae of first-ever ischemic stroke confirmed by brain computed tomography and/or magnetic resonance imaging were screened as potential subjects. The Adult Comorbidity Index-27 and Mini-Nutritional Assessment Short-Form (MNA®-SF) were used to screen for comorbidities and to assess nutritional status, respectively (Rubenstein et al., 1991; Kaiser et al., 2009). Stroke patients were excluded if they presented a history of cardio- and/or cerebrovascular events before the index stroke, chronic inflammatory diseases, cancer, chronic renal failure, lower limb orthopaedic disorders, pain syndrome, psychiatric disorders or dysphagia. The inclusion criteria were Class I obesity [obesity, computed by BMI [(body mass (kg) divided by height squared (m^2)], was categorized as Class I (BMI: 30-34.00 kg/m^2), Class II (BMI: 35-39.99 kg/m^2), and Class III (BMI: > 40 kg/m^2) (World Health Organization, 2000)], subacute stroke phase, Mini-Mental State Examination scores > 18 (Folstein et al., 1975), autonomous locomotion before index stroke, right or left hemiparesis and preserved trunk control (i.e. in the sitting position for at least 10 seconds). Twenty stroke patients [10 males and 10 females, aged 76.7 ± 1.3 (standard deviation) years] fulfilled all the inclusion criteria and were enrolled in the study. The stroke patients' characteristics and clinical data are reported in Table I. Pharmacological treatment for hypertension and dyslipidaemia was not interrupted during the inpatient rehabilitation in any patient. As shown by their scores on the National Institutes of Health Stroke Scale (NIHSS) (12.6 ± 0.6) (Adams et al., 1999), modified Rankin Scale (mRS) (4.2 ± 0.2) (Bonita and Beaglehole, 1998), and Barthel Index (BI) (42.3 ± 1.2) (Mahoney and Barthel, 1965), the stroke patients were moderately disabled on admission, and required assistance with activities of daily living (ADL). All the study parameters were measured before and at the end of the neurorehabilitation treatment.

On the stroke patients' admission to hospital, they or their caregivers gave their written informed consent to all the rehabilitation procedures. The study design, approved by the local ethics committee and complying with the Declaration of Helsinki of 1975, as revised in 2008 (http://www.wma.net/en/20activities/10ethics/10helsinki/), was explained in advance to the stroke patients and caregivers who gave their written informed consent to the study.

Neurorehabilitation protocol

As reported in our previous studies (Ciancarelli et al., 2012, 2015), the protocol, focusing on improving global motor control, dexterity and fine motor skills, was designed to promote recovery of post-stroke neurological deficits and to restore lost functional abilities relevant to ADL and self-care management. The inpatient neurorehabilitation intervention lasted 8 weeks and consisted of twice daily sessions, six days a week. Each rehabilitation session lasted about 45 minutes. The effectiveness of the neurorehabilitation, expressed as the percentage improvement obtained after the rehabilitation intervention compared with the maximum achievable improvement, was calculated as suggested by previous studies (Shah et al., 1990; Morone et al., 2019).

Body fat measurements

We used the BMI cut-offs recommended by the World Health Organization (2000). The BMI ranges reported by the WHO are: 18.5-24.9 kg/m^2 for normal weight, 25.0-29.9 kg/m^2 for overweight, and > 30 kg/m^2 for obesity. On hospital admission, the standing height of each patient, wearing light clothes and no shoes, was measured to the nearest 0.1 cm using a standard stadiometer. BMI, body fat percentage (BFP), and waist-to-hip ratio (WHR) measurements were performed using a multi-frequency bioelectrical impedance analysis device (InBody720, InBody Italia, Carasmed s.r.l., Baranzate, Mi-

Table I - Subacute stroke patients' clinical characteristics and medications on admission.

Age (years)	76.7±5.8
Time from stroke onset	< 20 days
SBP (mmHg)	140.57±27.63
DBP (mmHg)	81.40±9.74
METs	< 4
Creatinine	1.2±1.34
Antiaggregants (patients %)	70%
Statins (patients %)	40%
Total cholesterol (mg/dl)	220±2.68
Triglycerides (mg/dl)	131.02±54.6
HDL-C (mg/dl)	47.97±14.00
LDL-C (mg/dl)	149.27±11.25
C-reactive protein (mg/dl)	0.7±0.62
Serum albumin (mg/dl)	3.7±0.89

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; METs, metabolic equivalent of task; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

lan, Italy), in which a precision balance is associated with a multi-frequency tetra-polar bio-impedance meter that, using eight tactile electrodes, measures the impedance that the body opposes to the passage of an alternating current by evaluating both the resistance and the reactance separately (Shafer et al., 2009).
The wide frequency band, from 1 KHz to 1 MHz, makes it possible to monitor the smallest changes in body composition. A portable ultrasound device (BX2000 Ultrasonic BodyMetrix, HOSAND Technologies s.r.l., Italy) with a 2.5 MHz transmitter was used to measure uncompressed abdominal subcutaneous adipose tissue thickness (aSAT) (Ripka et al., 2016; Wagner 2013; Wagner et al., 2018). The aSAT values were obtained automatically using the BodyView software that accompanies the portable BodyMetrix device.
The patient was placed in the supine position and the transducer was situated approximately 2 cm to the right of the umbilicus to within 8 cm of the iliac bone without any pressure of the transducer on the abdomen. A sufficient amount of water-soluble transmission gel was applied to the skin to enhance acoustic coupling.

Statistical analysis

All variables were tested for normal distribution using the Shapiro-Wilk test, and given the non-normal distribution of some of them, we adopted the Wilcoxon matched-pairs signed-rank test for the comparison between the first recording (before neurorehabilitation) and the last one (performed after the eight-week multifunctional intensive neurorehabilitation intervention).

Spearman's correlation coefficient (rho) was computed to evaluate correlations between anthropometric indices and clinical scores, i.e., NIHSS, mRS and BI scores. A value of $p \leq 0.05$ was considered statistically significant for the Wilcoxon test and for the Spearman correlation coefficients.
All data are given as means ± standard deviation. Statistical analysis was performed using STATA for Windows, version 15 (Stata Corp, College Station, Texas, USA).

Results

Applying the BMI (kg/m^2) cut-off points recommended by the World Health Organization (2000), Class I obesity status was confirmed in all the stroke patients included in this study. The various anthropometric indices evaluated in the study showed decreases at the end of the neurorehabilitation intervention, even though all patients continued to show Class I obesity (Fig. 1). More specifically, BMI values were 31.3 ± 1.2 on admission, and decreased to 30.2 ± 1.0 after neurorehabilitation ($p = 0.0001$). The same trend after neurorehabilitation was observed for aSAT, which decreased by 1.5 mm (before 27.0 ± 10.0, $p = 0.0001$; after 25.5 ± 10.7, $p = 0.0001$), BFP, which showed a 1.1% decrease (before 37.3 ± 4.5, $p = 0.0001$; after 36.2 ± 4.5, $p = 0.0001$), and WHR, which decreased by 0.03 (before 0.96 ± 0.6, $p < 0.0001$; after 0.93 ± 0.1, $p < 0.0001$). All the patients completed the entire scheduled rehabilitation program without sig-

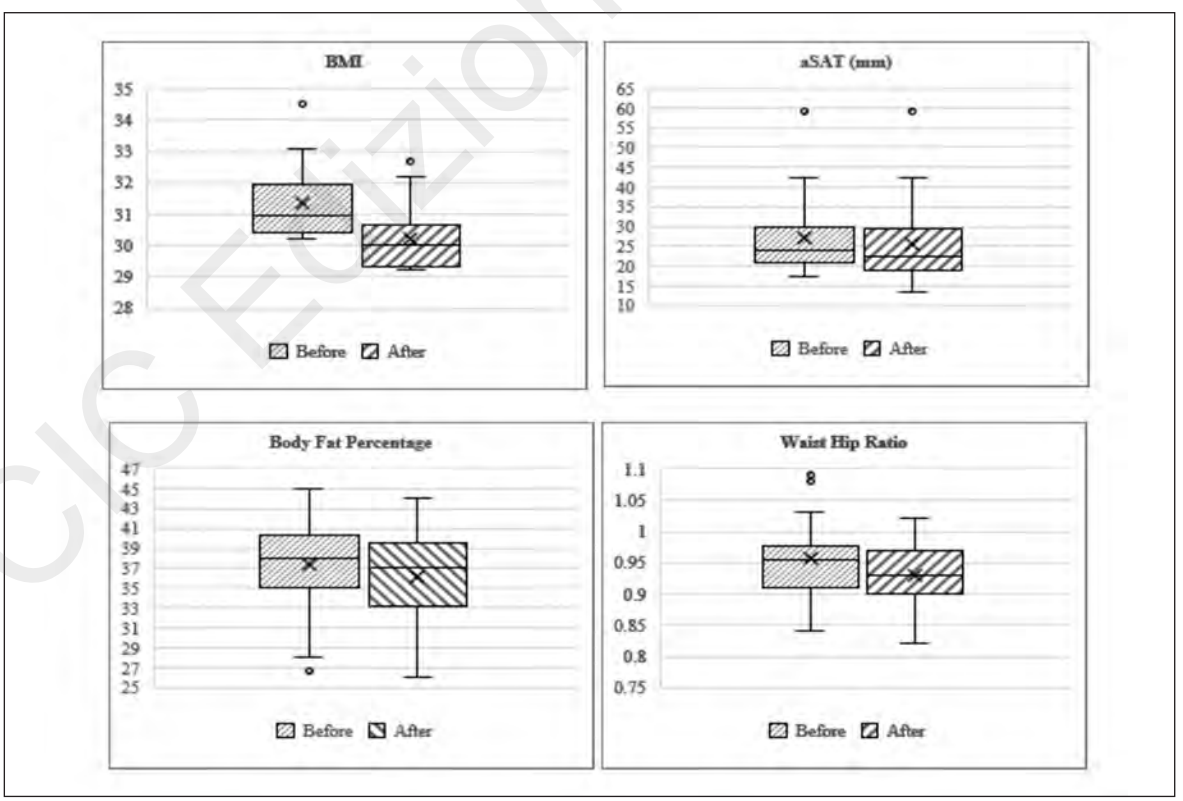

Figure 1 - Modifications of anthropometric indexes before and after neurorehabilitation.

nificant negative events. Analysing functional recovery after neurorehabilitation, we observed improvements in all measures (Table II). In detail, we found a decrease in the mean NIHSS score, from 12.6 ± 2.8 before neurorehabilitation to 6.6 ± 1.8 after it, a reduction of 6.0 points (p = 0.0001), and in the mean mRS score, from 4.2 ± 1.0 before neurorehabilitation to a final score of 3.1 ± 1.1 (p = 0.0019). The Barthel Index also showed a significant improvement (p = 0.0001) at the end of the neurorehabilitation treatment (before: 42.3 ± 5.2; after: 65.2 ± 8.0). Figure 2 illustrates the effectiveness of the neurorehabilitation intervention expressed as the percentage of patients achieving a positive outcome. BMI showed no correlation, before or after neurorehabilitation, either with NIHSS score (before: rho = -0.1552, p = 0.5258; after: rho= -0.2265, p = 0.6885) or with BI (before: rho = -0.0527, p = 0.8304; after: rho = 0.2265, p = 0.3368). A moderate positive correlation was detected between BMI and mRS only after neurorehabilitation (before: rho = -0.3298, p =0.1679; after: rho = 0.4526, p = 0.0451), suggesting that increased BMI may be positively associated with higher mRS scores. Observing the scatter-

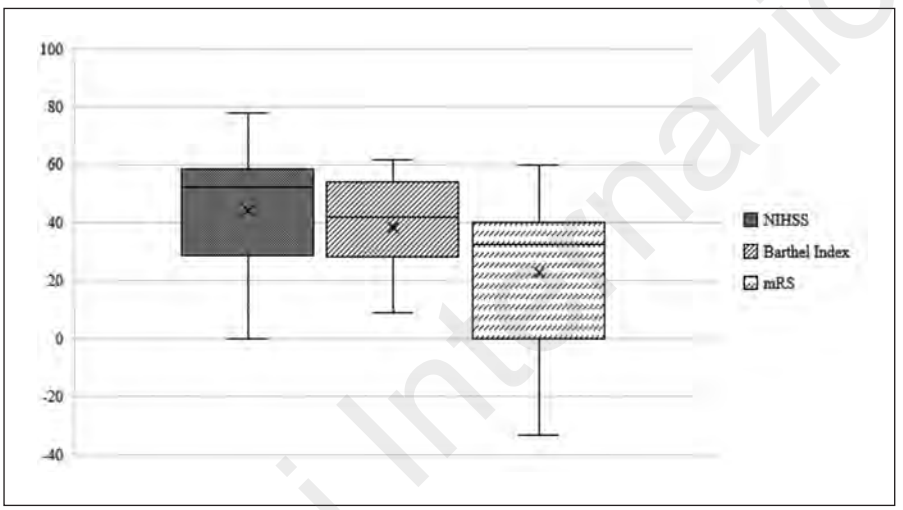

Figure 2 - Effectiveness of neurorehabilitation intervention, expressed as the percentage of stroke patients achieving a positive outcome.

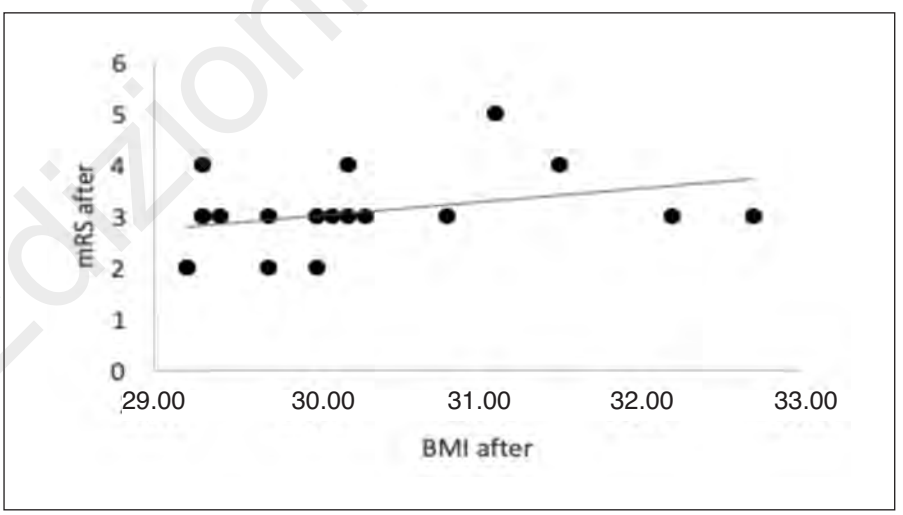

Figure 3 - Correlation between BMI and mRS after rehabilitation.

Table II - Evaluation of neurological deficits and related disability before and after 8-week multifunctional intensive neurorehabilitation.

Clinical and functional outcome measures	Before rehabilitation	After rehabilitation	Δ scores	p
NIHSS	12.6 ± 2.8	6.6 ± 1.8	6	0.0001
mRS	4.2 ± 1.0	3.1 ± 1.1	1.1	0.0019
BI	42.3 ± 5.2	65.2 ± 8.0	22.9	0.0001

plot shown in Figure 3, the two variables tend to be distributed on a straight line. It is worth noting that the change in BMI observed after neurorehabilitation (Δ BMI) did not correlate with the changes recorded on the functional recovery scales (Δ NIHSS, Δ BI and Δ mRS). In particular, Δ BMI did not correlate with Δ NIHSS (rho = -0.0983, p = 0.6890), with Δ BI (rho = -0.1100, p = 0.6540), or with Δ mRS (rho = -0.1429, p = 0.5594). BFP did not correlate with NIHSS score before the neurorehabilitation intervention (rho = 0.1089, p = 0.6477), while a moderate negative correlation was detected after neurorehabilitation (rho = -0.4777, p = 0.0332), thus suggesting that a higher BFP could be associated with lower NIHSS scores. While BFP did not correlate with BI before the neurorehabilitation intervention (rho = 0.274, p = 0.253), a moderately negative correlation (rho = -0.5033; p = 0.0237) was observed between BFP and BI after neurorehabilitation, therefore suggesting that higher BFP is associated with lower BI scores. BFP did not correlate with mRS either before or after neurorhehabilitation (before: rho = 0.0241, p = 0.9195; after: rho = -0.1141, p = 0.6318). No statistically significant correlation was found either before or after neurorehabilitation between WHR and NIHSS (before: rho = 0.0485, p = 0.8438; after: rho = -0.2121, p = 0.3693), BI (before: rho= 0.0621, p = 0.8007; after: rho = -0.1255, p = 0.5981) or mRS (before: rho = -0.3865, p = 0.1021; after: rho = 0.2184, p = 0.355) scores. Furthermore, no statistical significance either before or after neurorehabilitation was found for the correlations between aSAT and NIHSS (before: rho = 0.0675, p = 0.7837; after: rho = -0.3003, p =0.1984), BI (before: rho = -0.1010, p = 0.6807; after: rho = -0.1702, p = 0.4731), or mRS (before: rho = -0.1244, p = 0.6118; after: rho =-0.0624, p =0.7938) scores.

Discussion

The observation of a better prognosis for overweight or obese patients after stroke, as well as in chronic diseases (Kalantar-Zadeh et al., 2005), has underlined the need not only to understand the mechanism that underlies the "obesity paradox" phenomenon but also to identify with greater accuracy which body composition parameters might be involved in it. Obesity is defined by the WHO as a condition in which the percentage of body fat is increased to an extent that health and well-being are impaired (World Health Organization, 2000). The currently used WHO BMI cut-off values for overweight and obesity status are based on morbidity and mortality studies, however, the BMI, which reflects nutritional status *per sé*, does not provide a valid index of body compartments, nor it is able to estimate the actual body fat mass, a reference component for the definition of obesity (World Health Organization, 2000). Therefore, it is not possible to know, through BMI measurement alone, whether any changes in it correspond to losses or gains in body fat mass or fat-free mass. To date, limited data are available on the impact of obesity on post-stroke rehabilitation outcomes (Sheffler et al., 2012; Jang et al., 2015; Morone et al., 2019), and, to the best of our knowledge, no studies have evaluated the potential involvement of specific adipose tissue indices on the functional recovery of obese subacute stroke patients undergoing a rehabilitation intervention. In the current study, aSAT, BFP and WHR, as specific indices of body fat mass, were evaluated, together with BMI, in a very homogeneous cohort of obese subacute stroke patients in order to evaluate the effectiveness of a scheduled protocol of intensive neurorehabilitation in improving neurological deficits and functional capabilities, as well as to assess the relationship between BMI, body fat mass indices and outcome measures before and after the neurorehabilitation intervention. Obesity is known to diminish quality of life, predisposing to an increased risk of disability in ADL (Backholer et al., 2012; Himes and Reynolds, 2012), and guidelines have thus been proposed to reduce the disability of obese patients (Capodaglio et al., 2017). Obese patients are prevalent among individuals who have suffered an ischemic stroke (Lu et al., 2009; Mozaffarian et al., 2015). Available data on how obesity might potentially affect clinical outcomes following an ischemic stroke are heterogeneous and conflicting. As shown by the findings of our study, intensive neurorehabilitation performed for 8 consecutive weeks by the obese subacute stroke patients enrolled, in whom no negative events occurred, was effective in improving neurological deficits and functional independence in ADL, thus confirming the strategic role of neurorehabilitation in boosting neuronal plasticity (Zorowitz and Brainin, 2011; Ciancarelli et al., 2015). Indeed, the finding of lower NIHSS and mRS scores at the end of the rehabilitation intervention suggested an improvement of the neurological deficits and a reduction of the related disability, while the higher BI scores suggested a significant improvement in the overall functional autonomy of these stroke patients. Furthermore, in accordance with clinical data showing, in stroke survivors, a general loss of body weight, both within a short-term and also a medium-term period after the ischemic event (Jönsson et al., 2008), our patients showed a statistically significant decrease in their BMI values at the end of the 8-week rehabilitation intervention, even though they still showed Class I obesity. A decrease in BMI may occur if the single components contributing to the total body mass, namely body fat mass as well as fat-free mass, decrease, individually or together. In this study, we did not show whether the patients' total body fat-free mass was lower at the end of neurorehabilitation intervention. Instead, the results of our study provide evidence of marked decreases in all the obesity indices taken into consideration. In detail, we observed post-neurorehabilitation decreases in aSAT (p = 0.0001), BFP (p = 0.0001) and WHR (p < 0.01). Accordingly, the observed decrease of these obesity indices may contribute, probably in a prevalent way, to the decrease of BMI values, albeit remaining within the range of cut-off values that define Class I obesity. As suggested by the correlations we found between BI scores and BFP, reducing the body's global fat mass percentage is effective in improving the overall functional autonomy of stroke patients in ADL. As a consequence, the prerequisite for better clinical outcomes is not an increased fat mass, which, on the contrary, may impair functional recovery. Moreover, the significant decreases in WHR and aSAT, the indices usually used to estimate abdominal fat distribution, did not penalize the observed favourable recovery shown by the clinical measures after neurorehabilitation, nor could their base-

line (admission) values be taken to have prognostic significance as indicators of positive clinical outcomes. It should be noted that centrally located fat, as indicated by the WHR, is one of the more important determinants of elevated blood pressure.

The concomitant presence of obesity and hypertension, as in the stroke patients enrolled in this study, is associated with sympathetic activation, and there exists evidence that the degree of sympathetic activation is greater in patients with abdominal body fat distribution (Krzesiński et al., 2016). Therefore, as is well known, and as we also found, an overall decrease in body fat mass not interfering with positive functional outcomes may, because of decreased inflammatory effects of obesity, be favourable to counteract the developmental pathway leading to major cardiovascular disease events. Interestingly, the correlation observed between BMI and mRS score values observed at the end of the rehabilitation intervention suggests that excessive fat mass presumably accounting for an excessively high BMI could compromise the recovery in terms of functional independence in ADL, at least in subacute stroke patients with obesity status in Class I. As a consequence, high BMI values may not offer real advantages for functional recovery in inpatient neurorehabilitation, and the so-called obesity paradox, if based on the use of BMI as the sole index of obesity, demands a more prudent interpretation.

The lack of correlation between changes in BMI values observed before and after neurorehabilitation (Δ BMI) and positive changes in the scores recorded on the clinical measures (Δ NIHSS, Δ BI and Δ mRS) seems to support the hypothesis that BMI cannot be considered a prognostic index of neurological and functional recovery. An unexpected result was the moderate negative correlation between BFP and NIHSS, both measured after neurorehabilitation, which showed that an increase in BFP could be associated with a lower severity of neurological deficit, as suggested by the decrease in NIHSS score values. A possible explanation for this relationship may, in our opinion, be linked to the protective effect of Class I obesity status on neuromotor performance (Schnitzer et al., 2012). It could be important to verify whether this protective effect of obesity is valid in Class III obese patients too.

The current study has some limitations that should be taken into account in assessing its results. The main one is the size of the sample, which could reduce the power of the study. Indeed, the selected criteria, aimed at increasing the sensitivity of the study, resulted in a small but very homogeneous cohort of stroke patients (Class I obesity status). This could preclude the generalization of the results to all kinds of stroke patients. Furthermore, evaluation of rehabilitation outcomes in Class III obese stroke patients could provide useful data on the effectiveness of neurorehabilitation in stroke patients with major skeletal muscle impairments, often evident clinically as osteoarthritis of the hip or knee, and severe metabolic dysfunction.

Taken as a whole, findings of the current study showed that multifunctional intensive neurorehabilitation in subacute obese stroke patients with Class I obesity status produced positive effects, improving the disability due to catabolic changes of body composition induced by the acute stroke event. Tracking fat and fat-free mass in obese stroke patients receiving neurorehabilitation may provide useful information for clinical practice aimed at improving the disability and quality of life of obese stroke patients.

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