ORIGINAL ARTICLE

Oral baclofen administration in persons with chronic spinal cord injury does not prevent the protective effects of spasticity on body composition and glucose homeostasis

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Study design: Correlation study.

Objectives: To determine the effects of oral baclofen on body composition (fat mass (FM), fat-free mass (FFM)), extra- and intracellular fluid compartments and glucose homeostasis (plasma glucose and plasma insulin concentrations) in individuals with spinal cord injury (SCI) after controlling for spasticity.

Settings: Laboratory settings at the University of Michigan, MI, USA.

Methods: Fifteen individuals with chronic motor complete SCI (32 ± 8 years old, 25 ± 5 kg/m², C6–T11, American Spinal Injury Association A and B) underwent multifrequency bioelectrical impedance analysis to measure body composition and body fluid compartments. Spasticity of the hip, knee and ankle flexors and extensors was measured using a modified Ashworth Scale and the dose of daily oral baclofen was recorded. After overnight fasting, plasma glucose and insulin sensitivity were measured in response to an oral glucose tolerance test.

Results: Oral baclofen dose was positively related to body mass index, but not to extensor or flexor spasticity. The dose of baclofen seemed to be correlated to extensor spasticity after considering spasticity per FFM. The increased dose of oral baclofen was positively associated with increased FFM, extra- and intracellular fluid compartments and total body water, but not with FM. Oral baclofen dose was negatively associated with the homeostatic model assessment index.

Conclusion: Administration of oral baclofen did not attenuate the protective effects of spasticity on body composition and metabolic profile after SCI. The possibility that oral baclofen could exert an independent protective effect needs to be further investigated.

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Introduction

Spinal cord injuries (SCI) predispose individuals to increased body fat mass (FM), decreased fat-free mass (FFM), impaired glucose tolerance, insulin resistance and abnormal lipid profile.^{1,2} The deterioration in body composition and metabolic profile has been strongly associated with higher risk of cardiovascular diseases (228%) and type II diabetes mellitus (50–75%).^{1,2} The above condition is accentuated by immobilization and rapid skeletal muscle atrophy that can start within a few weeks after injury.^{3,4} The decline in FFM and skeletal muscle atrophy can lead to abnormal fluid distribution, resulting in disturbances in the balance

between intracellular fluid (ICF) and extracellular fluid (ECF).⁵ Therefore, studying factors that can attenuate or contribute to changes in body composition and metabolic profile is of paramount significance after SCI.

Spasticity is a velocity-dependent increase in muscle tone associated with hyperreflexia and clonus.⁶ Spasticity commonly affects the paralyzed muscles below the level of injury and leads to contractures, impaired bed mobility and development of pressure ulcers. However, along with others, we have shown that spasticity could protect against skeletal muscle atrophy, impaired glucose tolerance and deterioration in body composition after SCI.^{7–9} Recently, spasticity was strongly associated with increased FFM in motor complete SCI; maintenance of FFM primarily resulted in improved energy expenditure, insulin sensitivity and lipid profile.⁹ In addition, spastic leg skeletal muscles have a three times higher glucose uptake than do controls.⁸

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Oral baclofen (a γ -aminobutyric acid (GABA) derivative) is an agonist-specific inhibitor to GABA_B receptors located in the spinal cord.^{6,10} It primarily restricts Ca⁺⁺ influx and reduces presynaptic neurotransmitter release in excitatory spinal pathways. Oral baclofen showed an improvement of spasticity in >70% of individuals with SCI.¹⁰ Therefore, oral baclofen administration could possibly prevent the protective effects of spasticity on body composition and metabolic profile. This may be especially true because oral baclofen has been reported to affect the tension-generating capacity of skeletal muscle in healthy participants, as well as cause adverse effects in people with SCI.¹⁰ Contrary to this claim, a low-dose administration of oral baclofen results in increased plasma insulin-like growth factor-1 (IGF-1), reduced body weight and improved glucose tolerance.^{11,12} An increased level of IGF-1 may result in a decrease in FM and an increase in FFM.¹¹

This cross-sectional study examined the effects of long-term administration of oral baclofen on body composition and glucose profile in individuals with chronic SCI. It was hypothesized that oral baclofen may cause a deterioration in body composition and glucose intolerance by inhibiting the protective effects of spasticity.

Materials and methods

Fifteen individuals with chronic traumatic motor complete SCI (13 men and 2 women, mean $\pm$ s.d. age 32 ± 8 years, body weight 77 ± 17 kg, height 176 ± 9 cm, body mass index (BMI) 25 ± 5 kg/m², C6-T11 and American Spinal Injury Association classification A and B) participated in this study. All participants were recruited from the University of Michigan SCI Model System and from the Spasticity Clinic. Detailed descriptions of all procedures and risks of participation in this study were given to each potential participant. All participants gave their written informed consent before the study. The institutional review board of The University of Michigan approved this study.

Inclusion criteria were (1) men or women between 18 and 45 years of age, to avoid any confounding effects of the aging process on body composition; (2) minimum of 1 year after injury and 1 year on the same dose of oral baclofen to ensure stability of spasticity at the time of measurements and (3) level of injuries C6-T11, as people with injuries above C6 have limited hand functions and become dependent on others to have their meals, or they eat less frequently, resulting in involuntary weight loss and influencing body composition in an unpredictable manner. A lower motor neuron injury is typically seen in those with an injury below T11 and leads to flaccid paralysis of the involved skeletal muscles.⁷

Exclusion criteria included cardiovascular diseases, hypertension, diabetes mellitus, hyperlipidemia, cigarette smoking and pressure ulcers of Grade II or above. All SCI individuals with a BMI >35 were excluded to avoid the potentially confounding effects of a greatly expanded FM. In addition, BMI underestimates %FM in people with SCI.⁵ Etiologies for

SCI other than trauma were excluded, as well as other populations with spasticity.

First visit

The first visit was performed at the Health and Human Performance Laboratory located at the Department of Physical Medicine and Rehabilitation. After ensuring eligibility to participate in the study, the frequency and dose of oral baclofen administration per day were recorded. Participants were asked to empty their bladder and received a general physical examination by a certified physician. The physical examination consisted of measuring vital signs and a resting 12-lead electrocardiogram performed to rule out any preexisting cardiac problems.

During the same visit, body weight (kg) and height (m) were measured to calculate BMI (kg/m²). The weight of the participant in a wheelchair was measured on a wheelchair scale (Tanita, USA). After the participant was transferred to the testing table, the wheelchair was weighed empty and the weight thus obtained was subtracted from total weight to obtain the weight of the participant. Height was measured in a lying position from the top of the head to the heel.

Modified Ashworth scale. A modified Ashworth scale (MAS) was used to evaluate musculoskeletal spasticity in the six muscle groups (hip, knee, ankle flexors and extensors).⁶ Spasticity was evaluated by the same investigator while the patient was in a supine position using standard procedures.¹³ Room temperature was maintained constant between 21 and 24 °C. Three scores were reported for each specific muscle group and were then averaged (Table 1). Extensor spasticity was determined as the average of hip, knee and ankle extensor muscle groups and the corresponding muscle groups for flexor spasticity.¹⁴ This approach was adopted to examine the effects of oral baclofen dose on extensor spasticity separate from that of flexor muscles, because extensor spasticity has been correlated to the adaptations in body composition and metabolic profile compared with

Table 1 Oral baclofen dose, spasticity, body composition and fluids and OGTT in individuals with motor complete SCI

	Mean $\pm$ s.d.	Range
Baclofen dose (mg per day)	82 $\pm$ 64	10–200
Extensor spasticity (MAS)	1.9 $\pm$ 1	1–4
Flexor spasticity (MAS)	1.4 $\pm$ 0.8	1–3
ICF (l)	17 $\pm$ 3	12–24
ECF (l)	16 $\pm$ 3	11–21
TBW (l)	33 $\pm$ 5	22–44
FFM (kg)	42 $\pm$ 11	14–58
FM (kg)	35 $\pm$ 14	20–62
% FM (FM/body weight)	45 $\pm$ 13	30–79
Glucose AUC	672 $\pm$ 127	486–856
Insulin AUC	408 $\pm$ 171	107–725
Homa index	2.9 $\pm$ 0.8	1.8–4.5

Abbreviations: AUC, area under the curve; ECF, extracellular fluid; FFM, fat-free mass; FM, fat mass; HOMA, homeostatic model assessment; ICF, intracellular fluid; MAS, modified Ashworth scale; OGTT, oral glucose tolerance test; SCI, spinal cord injury; TBW, total body water.

flexor spasticity.⁹ In addition, spasticity was adjusted to FFM to determine whether FFM could influence the relationship between oral baclofen dose and spasticity.

Bioelectrical impedance analysis. A multiple-frequency analyzer (HYDRA ECF/ICF Model 4200; XITRON) was used to measure whole-body impedance using a tetra-polar method. All participants were asked to remain in a supine position for at least 30 min to minimize the effects of fluid shifting. Arms and legs were comfortably placed at an angle of 15° from the body and all sites were cleaned with alcohol swabs. Two conductive gum based patches were placed on the dorsal surfaces of right hand- wrist and the other two were placed on the right ankle-foot. A harmless alternating current was delivered throughout the body, with frequencies ranging from 5 to 1000 kHz, to measure the impedance of ECF and ICF. FFM (kg) was determined as total body water (TBW) divided by 0.732, and FM (kg) was determined as body weight minus FFM, in which 0.732 is the lean tissue hydration constant.⁵ The validity of bioelectrical impedance analysis (BIA) in measuring body fluid (ICF, ECF and TBW) and body composition (FM, FFM) after SCI has been established earlier.⁵

Second visit

Ten of the 15 participants reported to the General Clinical Research Center at the University of Michigan hospital 7–10 days after the first visit. After an overnight fasting for 9 h, a Teflon catheter was inserted into an antecubital vein of one arm for blood sampling. At 0700, a 75 g oral glucose tolerance test (OGTT) was administered and blood was drawn at 0 min before and at 30, 60, 90 and 120 min. After allowing the blood samples to clot for 30 min, blood was centrifuged at 3000 rpm for 10 min and serum was transferred for analysis. A 4 ml sample of blood was drawn at each time point to measure plasma glucose and insulin concentrations. All blood samples were sent to the Chemistry Pathology Laboratory for analysis. Plasma glucose concentration was assessed using commercially available colorimetric assays (Thermo DMA). Plasma insulin concentration was measured using a commercially available radio-immunoassay kit (Linco Research; St Charles, MO, USA). Plasma glucose and insulin concentrations were calculated as the average of their respective concentrations at 0, 30, 60, 90 and 120 min. The homeostatic model assessment (HOMA) index was calculated as the product of the fasting plasma insulin level ($\mu\text{U ml}^{-1}$) and the fasting plasma glucose level (mmol l^{-1}), divided by 22.5. The areas under the curve for plasma glucose and insulin were computed by integration with trapezoidal rule.

Statistical analysis. Pearson's correlation coefficient was used to determine the relationship, if any, between the dose of oral baclofen, body fluid, body composition and outcomes of OGTT. A continuous design was used because the current population is characterized by many diverse factors that would make a matching design difficult to accomplish. Partial correlation was used to test the relationships between

oral baclofen dose (independent variable) and body fluid and composition (dependent variables) after accounting for variance in spasticity or time since injury. This statistical approach was adopted because the relationships could possibly be affected by variance in spasticity scores among participants.⁷ A cutoff of 60 mg per day of oral baclofen was used to determine the effect of high- vs low-dose administration on the magnitudes of body composition and fluid (ICF, ECF and TBW). All values were presented as mean $\pm$ s.d. and statistical significance was set at a level of $P < 0.05$.

Results

The outcomes of oral baclofen dose, spasticity, body composition, fluid compartments and OGTT are presented in Table 1. The average number of years since injury was 10 ± 8 years. ECF and ICF represent $49 \pm 2\%$ and $50 \pm 2\%$ of TBW, the ratio of ECF to ICF was 0.98 ± 0.1 .

BMI was strongly related to FFM ($r = 0.54$, $P = 0.03$; Figure 1a) and FM ($r = 0.76$, $P = 0.001$; Figure 1b), but not to %FM ($r = 0.46$, $P = 0.09$). Moreover, no relationship was found between BMI and flexor or extensor spasticity ($P = 0.7$), suggesting that BMI is not an accurate surrogate of body composition compartments in individuals with SCI.

The dose of oral baclofen was not related to either flexor spasticity ($P = 0.8$) or extensor spasticity ($P = 0.1$). However, partial correlation showed a relationship between oral baclofen dose and extensor spasticity ($r = 0.52$, $P = 0.057$), but not flexor spasticity ($r = 0.4$, $P = 0.15$), after accounting for the ratio of extensor spasticity to FFM. The relationship between oral baclofen dose and extensor spasticity became more evident after accounting for the ratio of flexor spasticity to FFM ($r = 0.67$, $P = 0.009$), with a trend toward flexor spasticity ($r = 0.51$, $P = 0.06$).

Figure 1 Relationship between BMI and (a) FFM ($r = 0.54$, $P = 0.03$) and (b) FM ($r = 0.76$, $P = 0.001$) in 15 individuals with motor complete SCI.

Figure 2 Relationship between oral baclofen dose and (a) BMI ($r=0.62$, $P=0.013$) and (b) FFM (0.57 , $P=0.02$) in 15 individuals with motor complete SCI.

Figure 3 Relationship between oral baclofen dose and HOMA index in 10 participants. The inverse relationship suggests that oral baclofen can improve insulin sensitivity in individuals with SCI ($r=-0.68$, $P=0.03$). The same relationship became more pronounced after log-transformation of the HOMA-index values because of its nonlinearity ($r=-0.74$, $P=0.014$).

Pearson's correlation revealed significant relationships between oral baclofen dose and body weight ($r=0.64$, $P=0.01$), BMI ($r=0.62$, $P=0.013$; Figure 2a), FFM (0.57 , $P=0.02$; Figure 2b), ECF ($r=0.48$, $P=0.06$), ICF ($r=0.69$, $P=0.004$) and TBW ($r=0.64$, $P=0.01$). The relationships were not evident with FM ($r=0.46$, $P=0.08$), %FM ($r=0.2$, $P=0.5$) or years since injury ($r=0.1$, $P=0.47$).

Approximately 47% of the sample size ($n=15$) received a dose of <60 mg per day ($n=7$). Those who were administered a dose >60 mg per day had a higher FFM (47.25 ± 8.4 vs 35.77 ± 10 kg, $P=0.031$), ICF (18.5 ± 3.7 vs 14.8 ± 0.971 , $P=0.024$) and TBW (35.77 ± 6.27 vs 29.86 ± 2.291 , $P=0.035$), but not FM (36 ± 16 vs 33 ± 13 kg, $P=0.2$).

Ten of the 15 participants enrolled in this study were able to complete the OGTT. Oral baclofen dose was negatively related to the plasma glucose area under the curve ($r=-0.58$, $P=0.07$) and to plasma glucose concentration ($r=-0.64$, $P=0.049$). The relationship between oral baclofen dose and HOMA is shown ($r=-0.68$, $P=0.03$; Figure 3). It should be noted that the increase in FFM was accompanied by a reduction in plasma glucose area under the curve ($r=-0.35$, $P=0.3$), but did not attain statistical significance, possibly because of the small sample size.

Discussion

Earlier findings showed that oral baclofen is effective in managing spasticity and may cause adverse effects such as muscle weakness, hypotonia, fatigue and dizziness,¹⁰ factors that may lead to further immobilization, weight gain, increased FM and altered glucose homeostasis. The claim was supported by findings of decreases in maximal knee torques and electromyography magnitude after ingestion of a single dose of oral baclofen.¹⁵ On the contrary, the administration of low-dose oral baclofen resulted in increased IGF-1, which is known to increase FFM and reduce FM.¹¹ We were unable to accept our hypothesis because our current findings showed that a long-term administration of the same dose of oral baclofen does not interfere with the protective effects of spasticity on body composition and metabolic profile that were noted earlier.⁷⁻⁹ Moreover, a potential protective effect was observed on glucose homeostasis.

It was earlier established that intrathecal baclofen resulted in weight gain in children with cerebral palsy.¹⁶ In this study, oral baclofen dose was found to be a function of body mass or FFM. In addition, oral baclofen dose was related to BMI, a finding that may erroneously suggest that those who are at a high dose of oral baclofen are fatter. However, the results document that BMI may reflect an increase in both FFM and FM after SCI (see Figure 1). A similar finding was earlier reported between BMI and FM in individuals with SCI.¹⁷ The increase in FFM is subsequently accompanied by an increase in spasticity and may lead to a high dose of oral baclofen to manage spasticity. A person with a large FFM compartment could have more skeletal muscle mass, greater spasms and spasticity. This study confirms earlier findings that BMI may inaccurately reflect body composition after SCI.^{5,17} Another significant finding that may highlight the importance of body composition assessment in this population is the lack of relationship between oral baclofen dose and either flexor or extensor spasticity. However, after accounting for spasticity to FFM, the relationship between oral baclofen dose and spasticity became stronger. Therefore, an accurate dose should be prescribed after considering body mass or FFM.

It is difficult to speculate the cause behind the lack of a direct relationship between oral baclofen dose and spasticity. Oral baclofen could possibly modulate the relationship between agonist and antagonist muscle groups by simply reducing co-contraction. Management of spasticity is subject specific; the dose of oral baclofen could possibly be

prescribed on the basis of the patient's observation or feedback and not on the severity of spasticity. Some patients have difficulty comprehending that the goal of treatment is spasticity control and not elimination, because a threshold level of spasticity is necessary to maintain muscle mass and enhance glucose homeostasis.^{7,8} For example, those with MAS >2 have a greater skeletal muscle cross-sectional area by >20%.⁷ Moreover, extensor spasticity has recently been shown to be correlated with a reduction in FM and increase in FFM after motor complete SCI.⁹ Averaging flexor and extensor spasticity has minimized the effects of extensor tone and the aforementioned relationships vanished, suggesting the importance of maintaining a certain threshold in the extensor tone to achieve a desirable effect on body composition.⁹

The use of multifrequency BIA allows for accurately distinguishing between ECF and ICF; frequencies >50 kHz are recommended for measuring ICF. This study confirmed earlier findings that there is diminished ICF and expanded ECF, and ECF is relatively increased compared with ICF, likely a response to the reduction in FFM and increase in FM.⁵ Compared with earlier reported values,⁵ BIA could have overestimated our values.¹⁸ However, it should be noted that small ionic changes can affect the calculated ECF by 1–2% and ICF by 4–5%.¹⁹ Moreover, skeletal muscle atrophy in the lower extremities can challenge the accuracy of prediction of ICF and ECF. One need not postulate the influence on fluid shifts because of baclofen administration, as the absolute sizes of ICF and ECF were not measured by a standard radioisotopic dilution technique. However, the relationship between oral baclofen dose, ECF, ICF and TBW could possibly be mediated, in part, through growth hormone- or IGF-1-dependent mechanisms. Growth hormone administration has been shown to result in an expansion of TBW and ECF by possibly causing sodium retention.¹⁸

The prevalence of oral glucose disorders exceeds 50% in paraplegics and 75% in quadriplegics.² The progression of insulin resistance to impaired glucose homeostasis precedes type II DM and is associated with cardiovascular disease. The HOMA index was used to determine the effect of oral baclofen on insulin resistance. Oral baclofen has been shown to reduce adiposity in mice with genetically deficient leptin receptors.¹² A reduction in adipocytes resulted in an improvement in insulin sensitivity.¹² Our findings did not support a reduction in FM or %FM; the lack of relationship between oral baclofen dose and %FM could be explained by the lack of difference in %FM between the high- vs low-dose groups. However, it is possible that oral baclofen may have inhibited the increase in FM in the high-dose group. In addition, maintenance of FFM may have improved insulin sensitivity through an insulin-independent mechanism. A recent study showed that spastic skeletal muscles have a three times higher glucose uptake compared with healthy controls.⁸

Earlier studies and our current findings aimed at highlighting the possible factors that could influence body composition after SCI. Body composition after SCI is a function of level of injury, time since injury and extent of physical activities. Current data are correlative and direct

inferences are unlikely to be made. Five of our participants dropped out after the first visit, most citing commitments for work. Despite the smaller sample size, we were able to document a significant relationship between oral baclofen dose and outcomes of OGTT. Although subjective, the use of a single MAS score could be an acceptable measure of spasticity,¹⁴ because of the strong relationship observed between a single score and repeated multiple scores.⁹

The current data show that administration of oral baclofen may have a potential protective effect against deterioration in body composition and glucose dysfunction in individuals with SCI. Oral baclofen was directly related to FFM, and was indirectly correlated with the HOMA score, which has been applied as an index of insulin sensitivity. Those administered a high dose of oral baclofen seemed to have greater FFM, and maintained their FM compared with the low-dose group. Although it was expected that baclofen would counter the salutary effect of spasticity and would have a negative effect on the variables studied because of its antispastic effects, it was in fact determined not to have deleterious but, rather, beneficial effects. Further studies are warranted to determine the exact mechanism by which oral baclofen could exert positive effects on body composition and the metabolic profile after SCI.

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