REVIEW ARTICLE

Body composition in multiple sclerosis

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Abstract
Multiple sclerosis affects central nervous system leading to disability. Among other complications the deterioration of body composition is usually neglected and increases the risk for diseases such as coronary heart disease, non-insulin dependent diabetes mellitus, lipid abnormalities and bone loss leading to fractures in this population. Body mass index values, the effect of spasticity, the increased number of drugs used and the relationship between skeletal muscle and bone which interacts with impaired motor function leading to body composition alterations in multiple sclerosis are reviewed.

Keywords: Multiple sclerosis, body composition, bone, muscle, fat, rehabilitation

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Introduction

Multiple sclerosis (MS) leads to muscle weakness, co-ordination and balance problems, as well as sensation disorders, visual and cognitive deficits and gradual limitation of functioning[1]. All these disability conditions lead further to immobilisation associated with profound changes in body composition. The potential risks involved in these changes i.e. loss of lean tissue mass (LM) and bone mineral density (BMD) vs. gain in fat mass (FM) in body composition have implications for the health of the disabled individuals[2].

Body fat has been identified as a significant predictor of mortality in humans making body composition measurement to quantify nutritional and health status an important issue for human health[3-5]. Moreover, some disorders such as carbohydrate intolerance, insulin resistance, lipid abnormalities, and heart disease occur prematurely and at a higher prevalence in disabled populations and may be related to adverse changes in body composition that result from immobilization and skeletal muscle denervation[6].

Generally, among lesions of the central nervous system (CNS) there are differences on the evolution or not of the disease (i.e. progressive multiple sclerosis vs. complete paraplegia), the type of injury (i.e. spinal lesion with a level of injury vs. upper motor neuron lesion), life expectancy, the residual mobility and functionality, the ability to walk and stand (i.e. incomplete paraplegia-paraparesis vs. quadriplegia-tetraparesis) and drug treatment (i.e. frequent corticosteroid therapy in multiple sclerosis vs. long-term therapy with anticoagulants in paraplegia). In addition, there are differences in the degree of spasticity which is likely to play a regulatory role in maintaining bone density[7,8]. Moreover, another issue is the element of fatigue and muscle weakness in disabilities, especially in diseases like multiple sclerosis, which significantly reduces the mobility of these patients[9].

There is an inverse relationship between activity levels in disabled subjects depending on the degree of mobility impairment leading to reduced physical activity[10]. This is the case in MS: the reduced activity need to be accompanied by a reduction in energy intake otherwise body fat will increase[11]. Individuals with MS were reported to have a poor exercise tolerance, which was related to an increased energy cost when exercising on a treadmill, depending mainly on spasticity[12]. In individuals with MS who walked at their own preferred walking speed using assistive devices although functional electrical stimulation reduced the metabolic energy cost of walking, the cost remained significantly greater compared to that of controls[13]. Conversely, others found that the energy cost was not increased[14] and oxygen costs did not differ in persons with MS and mild disability from healthy subjects during a graded exercise on a cycle ergometer[15]. Recently published data are showing that the energy cost of self-paced walking in mildly disabled individuals with MS was higher, inversely related to the walking speed and directly related to the degree of disability, than that of control subjects[16]. The relative difference in energy expenditure between individuals with multiple sclerosis (MS) and able-bodied subjects is probably lower than the relative difference in

physical activity, because individuals with MS have a higher energy expenditure of physical activity[10].

Subjects with those motor disorders often face problems of depression and limit mobility[17]. The dependency on mobility devices, common in all disabilities, and the frequent periods of immobilization after multiple operative procedures contribute to the hypoactivity status of such subjects. It could be assumed that, under these conditions, body composition may be significantly compromised[18].

On the other hand the clinical manifestations of a disease such as MS could be variable; i.e. a severe form of MS can result in a wheelchair bound patient vs. patient with a more appropriate walking gait pattern vs. patient unable to walk at all and most of the time of the day bedridden[19,20].

Therefore, the purpose of this review is to present body composition alterations of ambulatory and non-ambulatory subjects with MS.

Body composition alterations in multiple sclerosis

In patients with MS not many studies investigated body mass index (BMI), which is a person's weight in kilograms divided by his height in meters squared. Nevertheless, BMI was found statistically less as to age comparable controls[21]. Both total body fat and mass percent showed consistent significant dependence on BMI, as among normal subjects. Multiple linear regression analysis of bone mineral percent at all studied sites showed consistent dependence on BMI (increased with higher BMI) for both MS and control subjects[22]. Recently, a Swedish population-based case-control study which investigated subjects' BMIs regarding MS risk found that subjects whose BMI exceeded 27 kg/m^2 at age 20 had a two-fold increased risk of developing MS compared with normal weight subjects. This result suggests a connective link between the obesity and the increasing MS incidence as recorded in some countries[23]. In line with these results another study found that obesity at age 18 (BMI>30 kg/m^2) was associated with a greater than twofold increased risk of MS in women[24].

In disabled conditions, the accuracy of skeletal muscle measured by DXA may be compromised when muscle atrophy is present. A lower ratio of muscle to adipose-tissue-free mass indicates a lower proportion of muscle in the fat-free soft tissue mass[14]. This is confirmed from studies in spinal cord injured (SCI) subjects: cross sectional area of skeletal muscle in the thighs after SCI is extensively reduced[25]. If this is the case, muscle mass would be overestimated by prediction models that assume that muscle represents all or a certain proportion of the fat-free soft tissue mass, i.e. in spinal cord injured subjects[26].

No significant difference between ambulatory MS patients and non MS controls in body composition was found despite lower physical activity in ambulatory MS patients[11]. In MS subjects, there was no significant relation between any of the body composition measures and the level of disability as measured by the Expanded Disability Status Scale (EDSS), a method of quantifying disability in MS[27]. Others found no difference in body fat percent between ambulatory MS patients and lower physical activity in ambulatory MS patients vs. controls[21,28]. A possible explanation for the similar body composition may be lower energy intake in MS individuals who are ambulatory and greater energy cost of physical activity (walking) in MS than it is with non MS controls[11].

A significant inverse relation between free fat mass (FFM) and EDSS score when ambulatory and non ambulatory MS subjects were combined was found[21]. On the contrary, when only ambulatory subjects were included no significant inverse relation between FFM percent and EDSS score was found[11]. It would seem apparent that non ambulatory patients with MS and controls would strengthen the inverse relation between FFM and EDSS score. In ambulatory MS subjects the finding of no relation between EDSS score and body fat percent was also explained in the study of Sioka et al which showed that ambulatory patients with MS had similar body composition compared with control individuals in respect to fat and lean mass, except in the lower extremities of female patients, where increased percentage of fat and reduced lean mass was found. According to the authors, a possible etiology for the gender difference observed includes the generally work related increased habitual mobility of male compared with female patients[22]. Moreover, studies suggested that worsening of MS symptoms was associated with significantly and moderately lower levels of self-reported physical activity independent of EDSS scores[29]. All these findings suggest that the level of disability in ambulatory individuals with MS does not predict body composition because MS would likely have a much greater effect on physical activity than on energy intake. This suggests that a significant level of disability does not force these individuals to be physically inactive and does not result in a greater body fat content. On the other side, there is inconsistent evidence of an inverse association between the neurological factor and cardio respiratory fitness in the MS population. According to Motl and Goldman the researchers have not examined the possibility that neurological disability is associated with cardio respiratory fitness independently of physical activity. This is important as physical inactivity has been associated with neurological disability in persons with MS[30].

There are many detrimental manifestations of excess body fat, such as hyperlipidemia, insulin resistance, and type II diabetes[11]. The largest component of FFM is muscle mass[31]. If muscle mass is lower in individuals with MS than in controls, this might explain the impaired ability to ambulate and perform other activities of daily living. Muscle fiber size from biopsy specimens of the tibialis anterior was 26% smaller than that from specimens of control subjects[32]. Thus, at least for this small muscle, muscle mass was lower in MS. This relationship may not hold true for other muscle groups or for whole-body muscle mass[11].

Another reason for skeletal muscle alterations is glucocorticoid usage. The prolonged duration of of glucocorticoid use causes catabolism of skeletal muscle. Decreased amino acid transport into muscle and increased glutamine synthesis with resultant muscle atrophy are some of the concomitant effects of glucocorticoid use on skeletal muscle. Endogenous glucocorticoid excess also produces generalized osteoporosis, most prevalent in trabecular-rich skeletal regions[21].

Beside corticosteroids, immunomodulatory, antiepileptic and antidepressant drugs usually used in individuals with MS, high incidence of vitamin D deficiency, molecular mechanisms and disuse-loss of mechanical stimuli in bone all have an impact on bone integrity (most believe that immobilization of these patients is a minor factor in the etiology of osteoporosis as compared to the remaining factors)[17].

Subjects with MS have multiple risk factors for osteoporosis, a disease characterized by low bone mass and destruction of the microarchitecture of bone tissue, resulting in increased bone fragility and susceptibility to fractures[33]. Although, there are several studies of bone mass in women with multiple sclerosis, higher rates of osteopenia and osteoporosis have been reported in women with spina bifida or spinal cord injury with lower T-scores compared to women with other types of disability. The finding that women with serious disabilities have low bone density is not surprising and is probably related to the lack of activity (reduced mobility, reduced loading on bone) and worsening of the disability[34].

There is a high incidence of vitamin D deficiency in MS patients and is determined by levels of 25-hydroxy vitamin D <20ng/ml[35]. The reasons might be due to a combination of low dietary vitamin D intake and avoidance of sun exposure, because MS symptoms may worsen resulting from fatigue upon heat exposure in these patients.

Reduced mobility has been implicated as an important factor in bone loss in patients suffering from multiple sclerosis (MS) and it seems to greatly influence the BMD of the femur[36,37]. Immobilization due to motor paralysis caused by lesion of the central nervous system contributes to bone changes which are: (a) the lack of the normal load applied to bone in the upright position and (b) the reduced number and intensity of muscle contractions. A severe form of MS can result in a wheelchair bound patient a clinical manifestation equivalent to paraplegia but another MS patient may have an appropriate walking gait pattern (i.e. using ankle foot orthosis) or may also be bedridden[19]. However, the high proportion of ambulatory patients with bone loss suggests additional non-mechanical factors[38]. So far, spasticity is considered by many researchers, to play a regulatory role in maintaining bone density[7]. Only one MS study assessed the relation of spasticity and bone strength, measured by quantitative ultrasound of cortical bone, using tibial speed of sound (SOS, m/sec) parameter at midpoint of the tibial shaft and found preserved bone strength in MS patients and increased SOS related to spasticity in a subgroup of female patients[39].

Low testosterone alone in these populations does not explain bone loss and no clear impact of smoking or alcohol abuse on decreased bone mass could be established[40]. Molecular mechanisms could also be the case in inflammatory or autoimmune disorders like MS: receptor activator of nuclear factor kappa B ligand (RANKL) stimulates osteoclastogenesis and the same do cytokines, such as TNF-α, IL-1, or IL-11, all produced by T-cells activation, leading to bone destruction. On the contrary, osteoprotegerin (OPG) is an osteoclastogenesis inhibitory factor preventing the function from RANKL. In MS this system is disturbed in favour of RANKL[41,42]. The effects of immunomodulatory therapy (IMT) on bone mineral density (BMD) measured by dual energy X-ray absorptiometry (DXA) in patients with MS who received different IMTs (interferon beta-1a, interferon beta-1b, and Glatiramer in 3% combined with high-dose pulse corticosteroid therapy) suggested that IMT may have a protective effect on bone in patients with MS even in the presence of pulse steroid therapy[43]. The RANK-RANKL interaction plays an important role in bone remodelling and immune function and mammary gland development. There is a link between bone turnover regulation and inflammatory immune cells in conjunction with various cytokines and hormones which induces endogenous interferon beta (IFN-beta) and osteoclastogenesis via induction of the c-fos gene [44,45]. The bond of IFN-beta to its biological receptor causes finally an inhibition of c-fos protein production and osteoclast proliferation and differentiation[46].

Glucocorticoid (GC)-induced osteoporosis (OP-GC) is the main type of secondary osteoporosis[47-52]. The mechanisms of GCs action in bone has been studied extensively. Prolonged treatment with glucocorticoids results in increased risk of fractures, evident at 3 months, regardless of changes in BMD. High dose, short-term i.v. treatment with GCs leads directly to reduction of bone formation and increased bone resorption, as indicated by markers of bone turnover[53,54]. In the study of Zorzon et al, osteopenia was found especially in MS women who received high dose methylprednisolone pulses (HDMP) in relapses period[55]. On the contrary, another study disputed the aforementioned result. This study, investigating the effect of intravenous (i.v.) administration of glucocorticoids in MS patients, found no clear effect on bone loss: besides, they reported an increase in BMD of the lumbar spine[51]. Moreover, with the use of enzyme-inducing antiepileptic drugs (AEDs) bone loss is accelerated by the metabolism of vitamin D3 leading to decreased calcium absorption, secondary hyperparathyroidism, greater bone resorption, and a continuous negative feedback. Studies support a relationship between selective serotonin reuptake inhibitors (SSRI) use in depression and lower BMD/change in BMD both in cross-sectional and longitudinal analyses[56]. Other important issues determining the alterations of body composition are the completeness of lesions (an absence of sensory or motor function below the neurologi-

cal level, including the lowest sacral segment), because body composition seems to be better in subjects with incomplete lesions (partial preservation of motor and/or sensory function below the neurological level, including the lowest sacral segment) i.e. in MS most subjects having a clinical outcome equivalent to incomplete tetraplegia or paraplegia and aging which contributes to major detrimental alterations of body composition[57-59].

Dietary changes, individualized physical activity programs and medication should be taken into account in therapy when we deal with this subgroup of subjects. However, self-management of dietary changes to improve weight control and disease should be the case, which means that the patients need to follow diets with lower energy intake and at the same time to eat regularly foods rich in nutrients[60].

Conclusion

We need to keep in mind that healthy BMI values often underestimate body fat and may mask the adiposity, and spasticity did not defend skeletal muscle mass and bone, supporting the concept that in neurologic disabilities, the myopathic muscle could not recognize correctly the stimulation because of the neurogenic injury.[8] The relationship between skeletal muscle and impaired motor function in MS subjects remains still unclear. According to Kent-Braun et al, it seems that chronically reduced maximum discharge rates and altered or incomplete motor unit activation may induce changes in skeletal muscle characteristics[33].

Moreover, disabled subjects mostly transfer much of the weight-bearing demands of daily activities to their upper extremities reducing the weight-bearing of the affected paralyzed muscles triggering a cycle of added muscle atrophy which interacts with the continuous catabolic action caused by the neurogenic factor.

Although the ranking system of the World Health Organization (WHO) created for postmenopausal osteoporosis focused mainly on healthy people, most authors classify disabled subjects according to the WHO criteria. At the same time, despite the increased number of risk factors in people with multiple sclerosis there aren't guidelines on the BMD measurements. An explanation about the problem of terminology according bone loss was given in a recently published paper for SCI [17]: "bone loss" is probably not specific enough, and might imply that the change in bone status is being recorded over time, while "osteoporosis" below the level of injury must be used with caution, especially in quadriplegia, paraplegia and/or equivalent diseases, a concept supported by the maintenance of bone in the spine in regions below the level of the lesion because of weight bearing in the seated position (i.e. in a wheelchair), and compressive stress of the fusion materials used following injury in the injured area (i.e. in traumatic paraplegia).

Further research about body composition in MS is needed and more longitudinal studies to quantitate and monitor body composition changes and to modify our therapeutic interventions. The most important issue related to body composition is how to promote optimal body weight to reduce risk of diseases such as coronary heart disease, non-insulin dependent diabetes mellitus, lipid abnormalities and fractures because of bone loss.

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Conflict of Interest

There was no conflict of interest related to this manuscript.

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