**Measures of Adiposity Differentially Correlate with C-Reactive Protein Among Persons with Multiple Sclerosis**

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**Abstract**

*Background:* While MS is considered, in part, an inflammatory disease, the relationship between measures of adiposity and MS have not been well studied. This is important considering the strength of the association between adiposity and inflammation reported in the general population, and the resultant increased risk for cardiovascular and metabolic disease. Evidence demonstrates MS is associated with higher prevalence rates of cardiovascular disease than the general population, which provides an impetus to examine how measures of adiposity and systemic inflammation are related in individuals with MS.

*Objective:*  To examine the association between measures of adiposity and systemic inflammation, specifically using the global marker C-reactive protein (CRP), among persons with MS compared with a control group without MS.

*Methods:*  Persons with MS and a control group (n=33/group) had measures of adiposity (body mass index, total body fat, and trunk fat) correlated and regressed to CRP.

*Results:* Differential relationships between CRP and adiposity measures were observed between the MS group and the control group. Within the MS group, when adjusted for sex, age, and physical activity level, only whole body percent fat explained a significant portion of the variance in CRP (adjusted R2 =0.095, p<0.05), whereas all of the adiposity measures explained a significant degree of variance within the control group (p<0.05), with trunk fat mass having the strongest correlation.

*Conclusions:* The differential relationships observed between the MS and control groups suggests that whole body fat may be a more important factor related to whole body inflammation in MS, rather than other adiposity markers, such as BMI or trunk fat. This differential association should be taken into account in future research examining body fatness/obesity and CRP.

**Key Words:** multiple sclerosis, obesity, inflammation, C-reactive protein, anthropometrics, body fat

1. **Introduction**

Over one-third (over 78 million individuals) of the U.S. adult population is classified as obese (Ogden et al., 2014). Obesity status is strongly associated with chronic diseases, such as cardiovascular disease or type 2 diabetes (Bhupathiraju and Hu, 2016; Hubert et al., 1983; Mokdad et al., 2003), believed to tied together through the common link involving systemic inflammation (Lumeng and Saltiel, 2011; Wang and Nakayama, 2010). This might be particularly relevant in multiple sclerosis (MS). MS is an immune-mediated disease of the CNS, and is described by inflammatory demyelination of axons within the brain, spinal cord, and optic nerve. Furthermore, obesity is common among persons with MS (Bronnum-Hansen et al., 2004; Goodin et al., 2014). To date, the association between obesity status and inflammation in MS has not been well characterized. Yet, data on inflammation and markers of cardiovascular disease (CVD) in MS does exist, with this population having higher rates of CVD-related mortality than the general population (Mincu et al., 2015), suggesting studying inflammation stemming from all potential sources will help us understand the interaction between inflammation and MS. Importantly, body fat, particularly trunk fat, may be a more influential factor than obesity status alone (via body mass index [BMI]) on inflammation (Stepanikova et al., 2017). The inflammation stemming from adipose tissue and other sources may, in turn, act synergistically with the CNS inflammation in MS, creating a larger inflammatory footprint in overweight and obese individuals with MS. The present study examined the association between measures of adiposity and systemic inflammation, specifically using the global marker C-reactive protein (CRP), among persons with MS compared with a control group without MS. We expected adiposity measures and CRP to have a stronger relationship among persons with MS compared to the control group.

1. **Methods**

*2.1 Participants & Research Design*

The current paper represents an analysis of secondary outcomes from a previously published cross-sectional study on arterial stiffness and physical activity (Ranadive et al., 2012). Participants between 18-64 yrs of age with and without MS (n=33/group) were matched for sex (27 females/6 males) and BMI and enrolled in the study after providing written informed consent. MS participants were relapse free for a minimum of 30 days. Diagnosis of MS was confirmed by each participant’s physician/neurologist according to McDonald’s criteria (Polman et al., 2011). Relapsing-remitting MS was reported among 29 individuals, with 3 diagnosed with secondary progressive, and 1 with primary progressive. Use of disease-modifying treatments was recorded. All participants were ambulatory (single-point assistance allowed for MS participants), non-smokers (6 mo minimum), and were tested following an overnight fast of 10-12 h. The study was approved by the University of Illinois Institutional Review Board.

*2.2 Anthropometric Measurements*

Height and weight were measured using a stadiometer and digital scale, respectively, while the participants wore a hospital gown. Body mass index was calculated (kg∙m-2). Dual energy x-ray absorptiometry (DEXA) was used to assess body composition (Hologic QDR 4500A, Waltham, MA). Following manufacturer guidelines, fat mass, lean mass and percent body fat were determined and regional analysis was conducted to determine truncal fat mass.

*2.3 Inflammatory Marker—C-Reactive Protein*

Standard venipuncture was performed following a 10-12 h overnight fast. Whole blood collected in EDTA tubes was centrifuged at 4°C at 1100*g* for 15 min and then stored at -80°C until batch analyses were performed. Samples were measured in duplicate. C-reactive protein (CRP) was assayed using ELISA kits (R&D Systems, Minneapolis, MN), with a sensitivity of 0.010 ng∙mL-1. CRP data were non-normally distributed, therefore were log transformed (logCRP) for correlation and regression analyses. Raw values are reported in Table 1.

*2.4 Physical Activity*

To control for physical activity, seven days of physical activity were collected using the ActiGraph single-axis accelerometer (model 7164; Manufacturing Technology Inc., Fort Walton Beach, FL). The device was worn during all waking hours except during any exposure to water (e.g. showering, swimming, etc.). Participants were considered compliant if they wore the monitor for (at least 10 hours/day on at least 4 of the 7 days). One-minute epochs of the physical activity counts were utilized during waking hours, with these epochs averaged over the 7-day period. Accelerometry data among individuals with MS has been reported to be both reliable (Motl et al., 2007) and valid (Gosney et al., 2007).

*2.5 Statistics*

Between-group characteristics were assessed using Chi-Square (sex) and independent Student *t-*tests (age, physical activity, all obesity variables and logCRP). Then, bivariate correlations were calculated between all independent (age, sex, physical activity, BMI, truncal fat, total body fat) and dependent (logCRP) variables to check for multicollinearity. Next, age, sex and physical activity were entered in a multivariate linear regression analysis as confounders (i.e., these variables are known to influence both anthropometric measures and inflammation), together with any single anthropometric variable (i.e. BMI, truncal fat or total body fat mass or percentage), to determine the additional value of that anthropometric measure with regards to explaining the dependent variable logCRP. This was repeated for every anthropometric measure. Separate analyses were then completed for the MS-only group and the control group. Only participants with complete data were included in the regression analyses. IBM Statistics SPSS 22.0 (Armonk, New York) was used to perform these analyses and an alpha level <0.05 was considered statistically significant.

1. **Results**

Table 1 includes descriptive characteristics, and shows that the groups are similar on all variables except activity level, which is substantially higher in the control group than the MS group. Of the adiposity measures, only body fat yielded significant correlations between logCRP within the MS group (Table 2). In contrast, the control group did have significant correlations between logCRP and all anthropometric variables (Table 2).

*3.1 Regression Analyses*

Table 3 contains the regression analyses for the MS group, the control group, and the whole group. Within the MS group, when adjusted for sex, age, and physical activity level, only whole body percent fat significantly explained logCRP (adjusted R2 = 0.096, p<0.05). Within the control group, when adjusted for sex, age, and physical activity level, all of the obesity variables explained a large degree of variance in logCRP (p<0.05). Of the obesity variables, trunk fat mass had the strongest correlation with logCRP for the control group. In contrast, BMI had the smallest association to logCRP for the control group. Within the whole group, when adjusted for sex, age, and physical activity level, all of the obesity variables explained a large degree of variance on logCRP (p<0.05), which appears to be driven by the control group when examining the groups separately.

1. **Discussion**

To our knowledge, this is the first paper investigating the association between obesity and CRP, an important marker of systemic inflammation in persons with MS. Interestingly, we observed differential associations between individuals with and without MS, although not in the direction we expected! Among those with MS, only whole body fat percentage was associated with CRP, whereas all anthropometric measures were related with CRP in the control group, after adjustment for age, sex, and physical activity. We further note that there were no bivariate associations between measures of adiposity and CRP in MS, but all measures of adiposity were associated with CRP in controls. This appears to be indicative of a different relationship between adiposity and inflammation (as indicated by CRP) in persons with MS than another group without MS.

Inflammatory markers are increased in obese individuals in comparison to their lean counterparts due to increased macrophage activation, and therefore greater cytokine secretion (Fantuzzi, 2005). Often measured by CRP and IL-6, one may expect an additive effect with the addition of a diagnosis of MS, as this is associated with elevated inflammation (Stadelmann et al., 2011). Our data suggest this may not be the case. Strong relationships between different markers of obesity and CRP in MS were not seen and the evaluation of the variance explained by each regression in persons with MS is suggestive that some other unknown factor may be playing a larger role in the inflammation associated with the disease than adiposity. We did not see increased levels of inflammation in MS compared to the control group, which has been previously reported (Oliveira et al., 2014; Soilu-Hanninen et al., 2005). A possible explanation may be that individuals with MS exhibited good systemic inflammatory control from the application of disease modifying therapies.

The differential relationships between measures of adiposity and CRP between the two groups in the current study are very interesting given that the overall body composition of ambulatory persons with MS compared with controls did not differ in our study, or in previous reports (Formica et al., 1997; Lambert et al., 2002; Pilutti and Motl, 2016; Sioka et al., 2011; Ward et al., 2013). It has previously been shown that females with MS have greater fat mass percentage, however, they have reduced lean mass in the lower extremities compared with healthy controls, which is not related to severity of neurological disability (Sioka et al., 2011; Ward et al., 2013). Previous studies in healthy individuals have suggested central obesity is most strongly related to inflammation (Lapice et al., 2009; Lemieux et al., 2001; Perry et al., 2008; Valentine et al., 2009), potentially due to the greater expression of adipokines, such as IL-6 and TNFα (Fantuzzi, 2005). These data were used to recommend waist-to-hip ratio be measured to identify individuals with higher cardiovascular or metabolic risk, and, that these measurements may be potential surrogate markers for subclinical inflammation (Lapice et al., 2009). As such, total trunk fat mass and truncal fat percentage had the strongest relationship with inflammation in our healthy controls but this was not observed in the sample of individuals with MS. A more global measure of obesity, whole body fat mass, was significantly related in MS. This suggests that central adiposity measures may not be as useful in MS for risk detection. Furthermore, simple measures such as BMI, also were not associated with inflammation in persons with MS. Instead, more accurate measures of adiposity need to be used individuals in MS.

BMI is a commonly used marker for classifying obesity status and is subsequently used for the assessment of health risk. Although BMI is easy to use, it does not assess lean or fat mass, nor central adiposity, and therefore is not a direct measure of adiposity. Despite its previous associations with inflammation (Visser et al., 1999), our data further suggest BMI is not a significant predictor of inflammation in a population with inflammation largely present, such as MS. This is not a surprising result, as a recent study determined BMI underestimates adiposity in both individuals with MS and controls (Pilutti and Motl, 2016).

Further exploration of the specific mechanisms and pathophysiology through which obesity is interacting with inflammation in MS is required, as well as further study of the association between obesity and inflammation. Future studies need to incorporate more ‘obesity-specific’ markers, such as adiponectin or leptin; measures of more inflammatory markers, such as TNFα or IFNγ; or study ‘simulated situations’ on a cellular level. Potentially, inflammation in MS would be positively influenced by a weight reduction program, but controlled intervention studies are needed to determine the effect of these clinical treatment applications. It would be expected for CRP to increase in patients with MS as the disease progresses if not well controlled or during a relapse. All of our subjects were stable, and therefore the normal levels of CRP are not surprising and support the use of their disease-modifying, anti-inflammatory therapies (Soilu-Hanninen et al., 2005), as well as statins, which are known to reduce CRP (Ridker et al., 2008).

Strengths of this study are the range of different anthropometric variables measured, including the gold standard measurement with a DEXA scan. Sample sizes of both groups were reasonably large, but the inclusion and exclusion criteria of the study resulted in a selected sample, with a relatively small range of outcomes on obesity and inflammation, thus making it harder to detect relationships. Limitations include the use of only one marker of inflammation, CRP, and no direct measure of visceral adiposity. Future research would benefit from a larger sample size, and allowing for a broader range of participants. This would also allow for the inclusion of other and more confounding factors, and provide more insight in the mechanism in MS.

1. **Conclusion**

In individuals with MS, only whole body fat percentage was associated with inflammation. The implication of this outcome is that the choice of the obesity marker measured is crucial when studying obesity and inflammation in MS. Based on our data whole body fat percentage should be used instead of BMI or trunk fat (mass or percentage). Differences in the pathway of how adipose tissue may impact inflammation in MS requires further research. Further research addressing this gap in knowledge are important for clinical practice, such as for the relevance and application of weight management programs in treating inflammation in MS.

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**Table 1**—Descriptive Characteristics

|  |  |  |
| --- | --- | --- |
|  | **MS** | **Control** |
| **Males/Females (n)** | 6/24 | 6/25 |
| **Age (yrs)** | 47 ± 11 | 47 ± 11 |
| **Height (cm)** | 166.4 ± 10.4 | 167.1 ± 9.3 |
| **Weight (kg)** | 71.6 ± 13.8 | 70.5 ± 12.4 |
| **BMI (kg∙m-2)** | 26.0 ± 5.0 | 25.3 ± 4.4 |
| **Trunk fat (kg)** | 11.9 ± 5.1 | 10.2 ± 5.6 |
| **Trunk fat (%)** | 32.6 ± 8.3 | 28.2 ± 11.2 |
| **Whole body fat (kg)** | 25.3 ± 9.0 | 22.5 ± 9.9 |
| **Whole body fat (%)** | 34.4 ± 7.7 | 30.5 ± 10.4 |
| **CRP (mg∙L-1)** | 1.54 ± 1.30 | 1.35 ± 1.29 |
| **Accelerometry counts/day\*^** | 172 ± 119 | 363 ± 221 |
| **Disease Modifying Treatments (%)** | 83 | -- |

MS: multiple sclerosis; BMI: body mass index; CRP: C-Reactive protein

Mean ± SD

\*p<0.05, MS different from control group

^data divided by 1000

**Table 2**—Spearman correlation tables for the group with multiple sclerosis (MS) (top table) and the control group (bottom table).

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ***MS Group*** | **log**  **CRP** | **Sex** | **Age (yrs)** | **PA (counts/1000)** | **BMI (kg/m2)** | **Trunk mass (kg)** | **Trunk fat (%)** | **Whole body fat mass (kg)** | **Whole body fat (%)** |
| **logCRP** |  | -0.23 | 0.01 | -0.10 | 0.34 | 0.32 | 0.35 | 0.39\* | 0.44\* |
| **Sex** |  | -0.07 | -0.17 | -0.20 | -0.28 | -0.53\* | -0.42\* | -0.67\* |
| **Age (yrs)** | -0.37 | 0.20 | 0.31 | 0.26 | 0.16 | 0.12 |
| **PA (counts/1000)** | -0.10 | -0.08 | -0.01 | -0.06 | -0.13 |
| **BMI** | 0.88\* | 0.74\* | 0.89\* | 0.70\* |
| **Trunk mass (kg)** | 0.90\* | 0.89\* | 0.76\* |
| **Trunk fat (%)** | 0.83\* | 0.88\* |
| **Whole body fat mass (Kg)** | 0.87\* |
| **Whole body fat (%)** |  |

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ***Control Group*** | **log**  **CRP** | **Sex** | **Age (yrs)** | **PA (counts/1000)** | **BMI (kg/m2)** | **Trunk mass (kg)** | **Trunk fat (%)** | **Whole body fat mass (kg)** | **Whole body fat (%)** |
| **logCRP** |  | -0.27 | -0.06 | -0.29 | 0.52\* | 0.69\* | 0.64\* | 0.65\* | 0.58\* |
| **Sex** |  | -0.14 | -0.14 | -0.14 | -0.42\* | -0.55\* | -0.51\* | -0.66\* |
| **Age (yrs)** | -0.09 | 0.15 | 0.17 | 0.22 | 0.18 | 0.18 |
| **PA (counts/1000)** | -0.57\* | -0.59\* | -0.50\* | -0.54\* | -0.43\* |
| **BMI** | 0.86\* | 0.77\* | 0.81\* | 0.52\* |
| **Trunk mass (kg)** | 0.97\* | 0.96\* | 0.90\* |
| **Trunk fat (%)** | 0.97\* | 0.96\* |
| **Whole body fat mass (Kg)** | 0.95\* |
| **Whole body fat (%)** |  |

\*p<0.05, significant 2-tailed correlation.

CRP: C-Reactive protein; PA: physical activity; BMI: body mass index

**Table 3**—Multivariate linear regression results for the total group, as well as the MS and control groups, respectively.

|  |  |  |  |
| --- | --- | --- | --- |
| Independent Variable | Dependent Variable--**logCRP** (n=56) | | |
| **Model 1** | **Model 2** | |
| Adjusted R2 | Adjusted R2 | Obesity p-value |
| ***TOTAL GROUP*** | | | |
| **BMI** | 0.066 | 0.164 | 0.010 |
| **Trunk fat mass** | 0.066 | 0.237 | 0.001 |
| **Trunk fat %** | 0.066 | 0.285 | <0.001 |
| **Whole body fat mass** | 0.066 | 0.230 | 0.001 |
| **Whole body fat %** | 0.066 | 0.283 | <0.001 |
| ***MS GROUP*** | | | |
| **BMI** | -0.068 | -0.032 | 0.193 |
| **Trunk fat mass** | -0.068 | -0.032 | 0.191 |
| **Trunk fat %** | -0.068 | 0.039 | 0.072 |
| **Whole body fat mass** | -0.068 | -0.014 | 0.149 |
| **Whole body fat %** | -0.068 | 0.096 | 0.033 |
| ***CONTROL GROUP*** | | | |
| **BMI** | 0.048 | 0.198 | 0.025 |
| **Trunk fat mass** | 0.048 | 0.358 | 0.001 |
| **Trunk fat %** | 0.048 | 0.348 | 0.002 |
| **Whole body fat mass** | 0.048 | 0.328 | 0.003 |
| **Whole body fat %** | 0.048 | 0.291 | 0.005 |

Model 1: age, sex, physical activity counts

Model 2: age, sex, physical activity counts, obesity value (BMI or Trunk fat mass or Trunk fat % or Whole body fat mass or Whole body fat %)