- Mean survival after placement in a residential home is 30 months, and for a nursing home is 20 months.
- The lifetime cost of each such institutional care placement averages over £60,000.

Conflicts of interest

None declared.

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doi: 10.1093/ageing/afq074
Published electronically 28 June 2010

Muscle strength is associated with adipose tissue gene expression of inflammatory adipokines in postmenopausal women

SIR—Ageing is associated with declines in physical function that lead to physical disability and loss of independence [1, 2]. Traditionally, loss of muscle mass has been thought of as the most important factor leading to loss of physical function and onset of disability. However, the number of older persons with excess fat mass is increasing [3], and a growing body of evidence shows obesity is an independent risk factor for ageing-related disability. Cross-sectional data show a higher prevalence of frailty, low function and disability, with higher body mass index (BMI) and fat mass, even in older persons with a normal amount of lean mass [4–7]. Longitudinal data also support a greater decline in physical function in more obese older adults [7, 8]. Since most mechanistic studies focus primarily on skeletal muscle, little is known regarding the mechanisms by which excess adipose tissue contributes to loss of physical ability in older adults.

The relationship between excess fat and loss of function in older adults is, in part, mediated by biomechanical factors [9, 10]. However, increasing knowledge about the role of adipose tissue as an endocrine organ suggests there may also be biochemical effects of adipose tissue itself on properties of skeletal muscle that lead to loss of function, i.e. the association of excess adipose tissue with physical function decline may also be due to the secretion of inflammatory proteins by adipose tissue [11]. This premise is supported by evidence that muscle strength is lower in obese persons and in conditions characterised by chronic inflammation such as diabetes and metabolic syndrome [4, 12]. Our overall hypothesis is that adipose tissue contributes to ageing-related loss of physical function, in part, via its capacity to produce and secrete inflammatory mediators that subsequently affect skeletal muscle function. This study begins to test this hypothesis by determining whether adipose tissue gene expression of specific inflammatory adipokines, interleukin-6 (IL-6) and tumour necrosis factor-α (TNFα), is associated with clinical measures of muscle strength in overweight or obese, postmenopausal women.

Methods

Data are from women who volunteered for a randomised clinical trial as detailed elsewhere [13]. Briefly, women were (i) abdominally obese (BMI: 25–40 kg/m^2 and waist circum-

Table 1. Body composition, physical function and abdominal adipose tissue gene expression of adipokines

	Mean ± SD (n = 47)	Range
Body mass/composition		
Weight (kg)	91.5 ± 11.9	73.6–112.4
Body mass index (kg/m^2)	33.6 ± 4.4	26.2–45.5
Lean mass (kg)	52.7 ± 6.2	40.7–64.8
Fat mass (kg)	40.2 ± 7.2	25.4–54.1
Body fat (%)	43.0 ± 3.5	34.5–51.3
Muscle strength		
Grip strength (kg)	32.0 ± 7.1	22.0–48.0
Arm muscle quality (kg/kg arm lean mass)	12.0 ± 2.7	6.8–18.3
Knee strength (N m)	87.7 ± 34.3	26.7–175.6
Leg muscle quality (N m/kg leg lean mass)	10.8 ± 4.0	4.3–21.8
Abdominal adipose tissue gene expression[a]		
Tumour necrosis factor-α (10^{-3})	23.42 ± 19.58	3.93–88.08
Interleukin-6 (10^{-3})	19.90 ± 15.11	1.46–67.68

[a]All are expressed relative to β-actin mRNA.

ference >88 cm), (ii) 50–70 years old, (iii) postmenopausal, (iv) non-smoking for >1 year, (v) not on hormone therapy, (vi) sedentary (<15 min exercise two times a week in the past 6 months) and (vii) weight stable (<5% weight change) for at least 6 months. All women provided informed consent to participate in the study according to the guidelines of the Wake Forest University Institutional Review Board. We report data from 47 women from whom we obtained abdominal subcutaneous adipose tissue and muscle strength at baseline.

'Body composition' was measured by dual energy X-ray absorptiometry (Hologic Delphi QDR, Bedford, MA, USA). 'Hand grip strength' was measured using an adjustable, hydraulic dynamometer (Fred Sammons Inc., Burr Ridge, IL, USA). Two trials were conducted for each hand, unless there was reported tenderness or pain in her wrist or hand, or recent surgery of the upper extremity. The larger value of the two hands was used for our analysis.

'Isometric knee extensor strength' was measured using a portable, fully adjustable isometric chair (Bio Logic Engineering Inc., Dexter, MI, USA). The participant was instructed to sit in the chair with hips and knees flexed at 90°. She was asked to extend the knee, pushing as hard as she could against the dynamometer, which was positioned a few inches above the ankle. Both legs were tested unless participants reported recent knee or hip surgery, or a history of knee injuries. The larger value of the two legs was used for our analysis.

'Abdominal subcutaneous adipose tissue' was taken via aspiration with a 16-gauge needle under local anaesthesia after an overnight fast. The tissue was washed with warm saline to eliminate blood and connective tissue, and ~0.5 g was snap frozen in liquid nitrogen and then stored at −80°C. Total RNA was isolated from frozen samples with the RNeasy lipid tissue kit (Qiagen, Valencia, CA, USA). Real-time quantification of adipokine to β-actin mRNA was performed using TaqMan gene expression assay (Applied Biosystems, Foster City, CA, USA). Data were obtained as threshold cycle (C_T) value and gene expression of the target gene was calculated using the formula $(1/2)^{CT\ target\ gene\ -\ CT\ \beta\text{-}actin}$.

Table 2. Pearson's correlations between muscle strength and adipose tissue gene expression of tumour necrosis factor-α (TNFα) and interleukin-6 (IL-6)

Muscle strength	TNFα	IL-6
Grip strength (kg)	−0.13	−0.40*
Arm muscle quality (kg/kg arm lean mass)	−0.33**	−0.08
Knee strength (N m)	−0.08	−0.22
Leg muscle quality (N m/kg leg lean mass)	−0.26	−0.09

All gene expressions of adipokines are expressed relative to β-actin mRNA.
*$P < 0.01$.
**$P < 0.05$.

The SAS software version 9.1 (SAS Institute, Cary, NC, USA) was used to perform all statistical analyses. Three women's TNFα gene expression levels were ≥3 SD away from the mean, so they were not used. The remaining data approximate normal distributions. Relationships among muscle strength, adipose tissue gene expression and body composition variables were examined using multiple regression analyses. An alpha level of 0.05 was selected to denote statistical significance.

Results

All women were postmenopausal (age 58.7 ± 5.0 years; 13.6 ± 10.9 years after final menstruation) and 23.4% were Black. Table 1 shows descriptive statistics for body composition, muscle strength and abdominal adipose tissue gene expression of IL-6 and TNFα.

Examination of the relationship between muscle strength and adipose tissue IL-6 and TNFα gene expression showed that grip strength negatively correlated with adipose tissue gene expression of IL-6 and arm muscle quality (expressed as grip strength relative to arm lean mass) negatively correlated with gene expression of TNFα (Table 2). Using the average of left and right hand grip strength and knee strength showed similar results (data not shown) as using the larger values of left and right. Grip strength was still correlated with adipose tissue gene expression of IL-6 when arm lean mass was adjusted (partial $r = -0.32$, $P = 0.034$). Thus, women with higher adipose tissue gene expression of IL-6 and TNFα had lower absolute and relative arm strength, respectively.

We also examined the correlations between muscle strength and adipose tissue gene expression of IL-6 and TNFα after adjusting for total adiposity (fat mass or percent body fat), although only IL-6 correlated with fat mass ($r = -0.34$, $P = 0.019$). The abovementioned negative

correlations remained significant with either fat mass or percent body fat in the model (partial r values = −0.32 to −0.40, $P < 0.05$).

Discussion

The present study shows that women with higher gene expression of IL-6 and TNFα in abdominal fat had lower arm strength. These relationships were independent of total adiposity, suggesting that muscle function may be linked to adiposity through biochemical properties of adipose tissue.

Prior studies have demonstrated an association between physical function and circulating inflammatory biomarkers [14–20]. The present study extends the link between physical function and inflammation by showing that muscle strength is associated with adipose tissue gene expression of inflammatory biomarkers. The total amount of adipose tissue is a key regulator of its expression and secretion of inflammatory biomarkers [21]. With fat accumulation in obese persons, adipocytes become larger and the secretion of adipose-derived inflammatory proteins increase, possibly resulting in chronic systemic inflammation.

Adipose tissue production of adipokines may also exert a direct effect on skeletal muscle function. Adipokines can affect insulin action and fatty acid metabolism of muscle, thereby possibly affecting physical function. For example, IL-6 inhibits insulin action and increases lipid availability, which causes insulin resistance [22]; TNFα mediates insulin resistance via serine phosphorylation of insulin receptor substrate in skeletal muscle, which inhibits the ability of insulin to stimulate GLUT-4 translocation to the cell membrane [22]. Moreover, there is also evidence for a direct effect of adipokines on muscle catabolism and contractile function. For example, *in vivo* protein breakdown positively correlated with circulating TNFα concentrations [23], and myosin heavy chain protein synthesis rates inversely correlated with plasma IL-6 concentrations [24]. There may be biological differences in the effect of TNFα and IL-6 on muscle so that adipose tissue gene expression of IL-6 has a stronger association with muscle strength than mass and, thus, correlated with grip strength but not arm muscle quality, while TNFα was the opposite.

We did not find an association between leg muscle strength and adipose tissue gene expression of IL-6 and TNFα, perhaps due to a larger effect of body weight on strength of weight-bearing muscles. Increased body weight adds load to the supporting leg muscles, providing added stimulus to the development of force production in these muscles. Therefore, in obese individuals, this biomechanical effect may mask any effect of adipose tissue inflammatory factors on lower body muscle strength.

A few things should be noted to interpret the results. The cross-sectional nature of the study does not clarify whether adipose tissue expression of these adipokines is causally linked to physical function; yet, no prior study has examined these potentially important associations. Caution should be taken when generalising results of the study because only women 50–70 years of age were included. Physical function measures may be affected by factors such as cognition. The standard deviations for IL-6 and TNFα in this sample were large, which may affect their associations with physical function. IL-6 and TNFα produced from other sources including skeletal muscle itself may affect the correlations of adipose tissue-produced adipokines with physical function. Examining circulating and gene expression of adipokines in other tissues would help elucidate the mechanisms of their effect on physical function. Thus, additional studies are needed to confirm these associations and to investigate the underlying mechanisms.

Key points

- Women with higher gene expression of IL-6 and TNFα in abdominal fat had lower arm strength.
- These associations were independent of total adiposity.
- Muscle function may be linked to adiposity through biochemical properties of adipose tissue.

Acknowledgements

This study was supported by US National Institutes of Health grant R01-AG/DK20583, Wake Forest University Claude D. Pepper Older Americans Independence Center (P30-AG21332) and Wake Forest University General Clinical Research Center (M01-RR07122).

Conflicts of interest

None.

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doi: 10.1093/ageing/afq024
Published electronically 15 March 2010