

## Title: **Inflammatory Cytokines and Physical Frailty in Obese Elderly Subjects**

PI: Dennis T Villareal, Associate Professor, Division of Geriatrics and Nutritional Sciences

### Introduction/Brief Literature Review

The number of obese elderly persons in the United States is rapidly increasing because of an increase in the elderly population and the percentage of elderly persons who are obese. Obesity has important functional implications in elderly persons because it worsens the age-related decline in physical function, which can lead to frailty and loss of independence. In fact obesity may be the single greatest cause of disability in elderly persons<sup>1</sup> and is associated with increased rates of nursing home admissions<sup>2</sup>

Aging is associated with a decrease in skeletal muscle mass (sarcopenia) and an increase in body fat. Disability occurs when the diminished muscle mass is unable to perform normal daily activities. We recently found that most community-living obese elderly persons (age > 65 y, BMI  $\geq$  30) met our criteria for physical frailty (low scores in the physical performance test, peak endurance power, and functional status questionnaires)<sup>3</sup>. Furthermore we found that physical frailty in obese elderly persons was associated with lower skeletal muscle mass and poorer muscle quality<sup>3</sup>. Moreover, obese elderly persons had lower leg strength, poorer gait and balance (e.g. assessed by walking speed, obstacle course), and poorer quality of life (e.g. assessed by SF-36) compared to nonobese elderly persons. Thus, contrary to common belief, obesity in the elderly does not protect against sarcopenia (but in fact, predisposes to it!), which is associated with physical frailty that leads to loss of independence and premature institutionalization. The mechanism/s for our finding of sarcopenia in obese elderly persons need to be investigated, as these could lead to effective interventions to maintain independence and improve quality of life in the increasing elderly population.

Aging is associated with increase in the circulating levels of proinflammatory cytokines, tumor necrotic factor (TNF)-  $\alpha$  and interleukin (IL)-6 but elevations are not very marked and levels are much lower than those observed during acute infections<sup>4</sup>. Low-grade inflammatory activity, however, may play a pathogenetic role in several age-associated diseases. Although causal relationships remain to be demonstrated, high plasma levels of TNF- $\alpha$  and IL-6 have been associated with insulin resistance, muscle wasting, and high mortality risk in elderly<sup>5,6</sup>. The origin of elevated TNF- $\alpha$  and IL-6 levels observed during ageing has not been clarified. Many different cell types, particularly adipose tissues, can produce both cytokines. In fact, increased levels of TNF-  $\alpha$  and IL-6 have been reported in obese subjects and have been associated with visceral adiposity and type 2 diabetes<sup>7</sup>.

### Hypothesis and how the project might lead to further research

We hypothesized that obesity would be associated with a further increase in the levels of CRP, TNF  $\alpha$ , and IL-6 in the elderly, which in turn would be associated with an exacerbation of the age-related decline in physical function and quality of life. **The results of our proposal should stimulate interventions that have the potential to decrease cytokine levels and prevent or slow the decline in physical function and quality of life in obese elderly persons (e.g. weight loss and exercise).** They will also provide evidence for the importance of

measuring inflammatory cytokines as predictors of physical dysfunction and quality of life in the elderly.

### Methods.

We studied a random sample of 33 obese elderly subjects and 30 nonobese frail elderly subjects. Subjects were well matched in age and gender distribution. We measured and compared the levels of adipokines/cytokines such as Leptin, CRP, and IL-6 between these two groups of subjects. We also measured cytokine levels in a subgroup of obese elderly subjects who just completed a six month randomized study of weight loss and exercise training.

### Results

1. Obese frail elderly subjects had significantly higher levels of Leptin, CRP, and IL-6 than nonobese elderly subjects.

	Obese Frail Elderly (n=33)	Nonobese Elderly (n=30)	<i>P</i> value
Age, yr	70.0 ± 4.5	70.9 ± 4.2	NS
BMI, kg/m <sup>2</sup>	38.3 ± 5.1	25.7 ± 3.0	<.001
Weight, kg	102.3 ± 17.7	73.8 ± 13.3	<.001
Physical performance test score	34.0 ± 2.0	29 ± 2	<.001
Adipokines/cytokines			
Leptin, ng/mL	35.1 ± 14.3	25.7 ± 3.0	.001
CRP, mg/L	5.9 ± 5.0	1.4 ± 0.9	<.001
IL-6, pg/mL	3.7 ± 3.3	1.5 ± 0.7	.001

2. Intensive Lifestyle Intervention (weight loss and exercise training) resulted in a reduction of Inflammatory Cytokines in Frail Obese Elderly Subjects. Subjects in the treatment group lost ~9% of body weight.

	Control group (n=10)	Treatment group (n=17)	Between-Group Comparison of Change	
			Difference (95% CI)	<i>P</i> value
<b>C-reactive Protein, mg/L</b>				
Baseline	5.8 ± 4.5	6.1 ± 5.4		
6 months	6.6 ± 4.5	3.5 ± 3.6*		
Change	0.8 ± 2.8	-2.5 ± 4.3	-3.3 (-0.2 to -6.4)	.003
<b>Interleukin-6, pg/mL</b>				
Baseline	3.3 ± 1.6	4.6 ± 4.5		
6 months	4.8 ± 4.1	2.3 ± 1.2†		
Change	1.6 ± 4.3	-2.4 ± 4.7	4.1 (-0.3 to -7.7)	<.001

\**P*=.04 for the comparison with baseline value. †*P* =.05 for the comparison with baseline value

Implications, intended next steps, and potential long-term extensions.

The findings in this mini-grant provide evidence that obesity is associated with a further increase in the levels of proinflammatory cytokines in the elderly. The data suggest that the excess production of cytokines may contribute to the development of physical dysfunction and frailty in obese elderly persons. We previously demonstrated that weight loss and exercise can ameliorate frailty in obese elderly persons.<sup>3</sup> In this minigrant, we have expanded these findings by demonstrating that the reduction in frailty is associated with a reduction in inflammatory cytokines. Therefore, lifestyle intervention is particularly important to reduce frailty, possibly by reducing proinflammatory state in obese elderly persons. A manuscript is currently being completed and will be submitted for publication. We have obtained further funding from NIH to examine the independent and combined effects of one year intervention of weight loss and exercise in frail obese elderly subjects. The data generated will be used to establish appropriate treatment guidelines for the increasing number of frail obese elderly men and women.

## Lay Summary:

There has been a marked increase in the number of obese elderly persons in the United States. Obesity worsens the age-related decline in physical function leading to impairment in ability to perform normal daily activities of living (frailty). In fact obesity may be the single greatest cause of disability in older persons. Obesity may worsen physical function in older persons by causing an excess production of cytokines. Cytokines are proteins that normally form part of the body's response to infection and cancer. However, in obese elderly persons, cytokines may be produced in excess and contribute to physical dysfunction and frailty. The aim of this study was to compare the levels of cytokines in physically limited obese older persons with those in healthy nonobese older persons. We found that obese older persons have much higher levels of cytokines such as C reactive protein and Interleukin 6 than nonobese older persons. These findings suggest that interventions to decrease cytokines (e.g. weight loss and exercise) may be beneficial in obese older persons to improve physical function and maintain functional independence in the community.

## Reference List

- (1) Himes CL. Obesity, disease, and functional limitation in later life. *Demography* 2000 February;37(1):73-82.
- (2) Zizza CA, Herring A, Stevens J, Popkin BM. Obesity affects nursing-care facility admission among whites but not blacks. *Obes Res* 2002 August;10(8):816-23.
- (3) Villareal DT, Banks M, Sinacore D, Siener C, Klein S. Weight loss and exercise ameliorates frailty in obese elderly men and women. *Arch Intern Med*. In press 2006.
- (4) Bruunsgaard H, Pedersen M, Pedersen BK. Aging and proinflammatory cytokines. *Curr Opin Hematol* 2001 May;8(3):131-6.
- (5) Reid MB, Li YP. Tumor necrosis factor-alpha and muscle wasting: a cellular perspective. *Respir Res* 2001;2(5):269-72.
- (6) Harris TB, Ferrucci L, Tracy RP et al. Associations of elevated interleukin-6 and C-reactive protein levels with mortality in the elderly. *Am J Med* 1999 May;106(5):506-12.
- (7) Bertin E, Nguyen P, Guenounou M, Durlach V, Potron G, Leutenegger M. Plasma levels of tumor necrosis factor-alpha (TNF-alpha) are essentially dependent on visceral fat amount in type 2 diabetic patients. *Diabetes Metab* 2000 May;26(3):178-82.