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Changes in Senescence Markers after a Weight Loss Intervention in Older Adults with Obesity

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Abstract

Background: Understanding how weight loss interventions in older adults with obesity impact aging biology can lay the foundation for targeted, ‘geroscience-based’ interventions. This study examines the association between changes in the senescence-associated secretory phenotypes (SASP) and changes in function in response to a weight loss intervention.

Methods: We conducted a post-hoc biomarker analysis on adults aged ≥ 65 years with body mass index [BMI] ≥30kg/m2 enrolled in a six-month, non-randomized telemedicine-delivered weight loss intervention. We assessed 16 SASP cytokines using serum samples collected pre-and post-intervention. Clinical outcomes include anthropometric and physical function measurements. A weight loss responder was defined as a loss of ≥5% of body weight.

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Authorship contributions

All listed authors had full access to all the data in the study, take responsibility for the integrity of the data and the accuracy of the data analysis, and had authority over manuscript preparation, the decision to submit the manuscript for publication, and approved its current contents. All authors meet the criteria for authorship stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.’

Conflicts of Interest-

No personal or financial conflicts of interest

Results: Mean age was 73.2±3.9 years (73% female), and BMI was 36.5±5.2kg/m2. Responders lost 7.6±2.5%, while non-responders lost 2.0±2.3% of weight (n = 16 per group, p<0.001). We observed several significant associations between SASP cytokines and physical function and anthropometric measurement outcomes in age- and sex-adjusted linear models. These included grip strength and Interleukin-8 (IL-8) (b=9.07) and Insulin-like Growth Factor 1 (IGF-1) (b=2.6); gait speed and Thymus and Activation-Regulated Chemokine (TARC) (b=0.46) and IL-7(b =61 0.11); weight IL-6 (b=−6.77) and IL-15 (b=−2.53); BMI and IL-15 (b=−0.95); waist-to-hip ratio and osteopontin (b=−0.07) (p<0.05 for all).

Conclusions: Our pilot data demonstrated an association between changes in select SASP biomarkers and increased functional ability with intentional weight loss in older adults with obesity. However, findings must be replicated in prospective randomized trials with a control group and additional SASP biomarkers.

INTRODUCTION

The prevalence of obesity is increasing globally, including among those aged 65 years and older (Mathus-Vliegen, 2012). This has important implications for patients and health systems, as obesity in older adults is associated with an increased risk of chronic low-grade inflammation, frailty, disability, and a lower quality of life (QOL).(Batsis & Villareal, 2018; G. Chen & Yung, 2019; Fulop et al., 2023; Villareal et al., 2017). When considering QOL in context of aging, there are a multitude of factors at play. For instance, maintaining healthy relationships with family, having a reinforced social support system, as well as a strong sense of control over one's health and wellbeing are key for achieving a high QOL among older adults (Martinez-Martin et al., 2012). Among the most recommended non-pharmacological strategies for improving QOL in older adults is physical exercise. (Rizo, 2020). For instance, strength training not only improves physical function and reduces falls, but it also works to improve one's sense of autonomy and reduce their fear of injury, improving their QOL (Miranda et al., 2024; Rizo, 2020). Weight loss interventions (e.g., diet and exercise) in older adults with obesity are also feasible, safe, and can lead to improved physical function and QOL (Carson et al., 2013; Villareal et al., 2017). However, mechanisms underlying the improvements observed with weight loss interventions are not fully understood. Thus, increasing our understanding of how changes in baseline levels of biological cytokines are associated with response to weight loss intervention can help improve targeted intervention strategies. For instance, those with a favorable profile may be prescribed a more straightforward program with less oversight, while those with a less optimal phenotype could be assigned a more intensive intervention.

The geroscience hypothesis offers a mechanism for conceptualizing the interplay between obesity, aging biology, and response to weight loss interventions. This hypothesis theorizes that aging results from the dysregulation of biological aging processes (G. Chen & Yung, 2019). Cellular senescence and the associated senescence-associated secretory phenotype (SASP) are biological pillars of aging that produce a bioactive secretome (i.e., proteins and metabolites that cells express and release to communicate with and influence other cells) (Aird et al., 2016; Birch & Gil, 2020; Schafer et al., 2020). While the production and effects of inflammatory cytokines is a natural process and crucial for maintaining

protective inflammation, senescence can accelerate detrimental hallmarks of ageing—such as elevating baseline persistent or chronic inflammation. Senescence can be induced by pathophysiological mechanisms such as metabolic dysfunction and can in turn accelerate the ageing process past what is considered “normal” (McHugh & Gil, 2018; Shapouri-Moghaddam et al., 2018). Specifically, induction of senescence can result in the generation of the senescence associated secretory phenotype (SASP) which is a programmed phenotype in which these senescent cells release inflammatory cytokines and chemokines (Coppé et al., 2010; McHugh & Gil, 2018; T & Ds, 2009). Prolonged effects resulting from high levels of these SASP metabolites has been shown to trigger age-related disorders such as metabolic syndrome, reduced physical function, frailty, and a lower QOL (Birch & Gil, 2020). And although this mechanism serves to protect the body, it nevertheless canalso trigger the development of age-related disorders, (Birch & Gil, 2020). Further, obesity in older adults increases the senescent cell burden, which has been implicated in obesity-related functional decline in older adults (Hernandez-Segura et al., 2018; Palmer et al., 2019). Thus, weight loss interventions may reduce this burden leading to improved health outcomes for older adults with obesity. Additionally, baseline biological profiles may predict response to a given intervention, or biological changes post initiation of an intervention may proceed with changes in weight and physical function, presenting an opportunity to tailor the intervention to maximize an individual’s response. This is the central tenant of precision medicine – the right treatment, for the right patient, at the right time.

While fluctuations in SASP cytokines are normal in healthy people, an elevation of SASP markers has been shown to be a hallmark for ageing. SASP is a quantitative array of cytokines, chemokines that is reflective of an individual’s cellular senescence burden. SASP cytokines are important because they can estimate senescence burden based on blood biomarkers, as opposed to analyzing whole tissues for senescence, which is difficult to apply to human subjects. Thus, SASP is important in that it can perhaps inform precision medicine, identifying how patients may respond to a certain treatment—based on their specific bodily level of cellular senescence—while also serving as an endpoint variable to analyze how an intervention affects senescence (Schafer et al., 2020).

In this study, we aim to expand on the existing knowledge base by examining if changes in SASP cytokines (either increasing or decreasing) are positively or negatively correlated with respective changes in physical function and anthropometric measurements leveraging data and samples from a six-month single-armed weight loss intervention in older adults with obesity. The selection of SASP cytokines used in this study was based on work by Shafer et al. that established a panel of 24 blood-measurable SASP proteins (Schafer et al., 2020). Shafer et al’s demonstrated that SASP cytokines were associated with age, frailty status and adverse surgical outcomes (Schafer et al., 2020).

METHODS

Description of Study

This study analyzes pre/post biological data from blood collected as part of a six-month single-arm pilot intervention for weight management among older adults with obesity (n=44). A detailed description of this clinical trial and its impact on clinical outcomes has

been previously published (NCT# 03104205) (Batsis et al., 2021). Briefly, there were no significant differences in demographic characteristics (i.e. marital status, smoking status, income, etc.) between groups and the 44 participants that completed the study had a mean age of 73.2±3.9 years and 73% of completers were of female sex. The intervention consisted of weekly dietitian visits, twice weekly group exercise sessions, and prescribed asynchronous aerobic exercise. The intervention was delivered using video conference sessions, remote monitoring via a Fitbit Alta HR, and face-to-face interactions. The primary outcome of the parent study was weight loss. We previously defined intervention responders as participants losing ≥5% of baseline body weight.

SASP Cytokines

Of the 53 individuals enrolled in the study, 32 had blood drawn before and after the intervention by a trained phlebotomist. We used a RayBiotech Cytokine Array G5 to analyze cytokine levels in serum samples to assess circulating SASP cytokines pre-and post-intervention. This cytokine array detects 80 human cytokines Of the 24 proteins from Shafer et. Al, 16 were included in the RayBiotech Cytokine Array G5: Vascular endothelial growth factor (VEGF), Tumornecrosis factor alpha (TNF-α), Thymus- and activation-regulated chemokine (TARC), regulated on activation, normal T cell expressed and secreted (RANTES), Osteopontin, macrophage inflammatory protein 1 beta (MIP1b), macrophage-derived chemokine (MDC), Interleukin (IL) 8, IL7, IL6, IL2, IL1b, IL15, Insulin-like growth factor 1 (IGF-1), interferon-gamma (IGFγ), and Glial cell line-derived neurotrophic factor (GDNF) (6). This study used the raw fluorescence unit measurement of each cytokine. Raw fluorescence unit measurements represent a relative cytokine signal intensity that has only been background-corrected and positive control-normalized.

Clinical Outcomes

This study evaluated validated measures of physical function and anthropometrics. For anthropometrics, we measured weight, BMI, waist-to-hip ratio, and waist circumference. A standard A+D digital scale was used to measure weight. No shoes, jackets, or other heavy clothing were worn during any of the measurements. Height was measured with a standard stadiometer and BMI was calculated using weight in kg divided by height in m^2. 30-second-sit-to-stand (30STS) was assessed by having participants sit in a chair with a back and stand up/sit down with folded arms for 30 seconds. A JAMAR handheld dynamometer was used to measure grip strength in both hands (three measurements per hand) with a 30 second gap between measurements. To measure 6-minute walk (6MW) time, participants walked for 6 minutes down a 70 m corridor (Batsis et al., 2021).

Statistical analysis

All data was analyzed using R version 4.2.1 (https://www.R-project.org/). Descriptive statistics included means ± standard deviations, and counts (%), with t-tests of unequal variances and chi-squares comparing responder vs. non-responder groups. All SASP cytokine data were log transformed due to non-normal distributions. Spearman correlation coefficients evaluated the changes in cytokine parameters and changes in physical function or anthropometrics. Linear regression models adjusted for age and sex were used to assess

the association between a change in SASP cytokines and a change in clinical outcome. A p-value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

The mean age of participants in this study was 73.2±3.9 years and 73% were female. There were no significant differences in baseline characteristics between responders and non-responders (Table 1). Baseline physical function, anthropometrics and SASP cytokines, were not significantly higher in responders relative to non-responders.

Association between Changes in SASP Cytokines and Changes in Physical Function
Changes in SASP cytokines observed after the intervention, regardless of responder status, were generally positively associated with changes in physical function (Figure 1). Changes in SASP cytokines observed after the intervention were generally positively associated with changes in physical function (Figure 1). A change in maximal gait speed had the most consistent and strongest correlation with changes in SASP cytokines. Specifically, changes in TARC and IL7 had strongest positive association with change in maximum gait speed (Spearman's correlation coefficients of 0.51 and 0.49, respectively) (Figure 1). In age- and sex-adjusted linear models there were several significant associations between SASP cytokines and physical functional measures: grip strength and IL8 (b = 9.07, p = 0.020) and IGF-1 (b=2.6, p=0.006); gait speed and TARC (b=0.46, p=0.018) and IL7(b=0.11, p=0.044) (Figure 1). There were no significant associations between 30-second sit to stand or six min walk tests and SASP.

Association between Changes in SASP Cytokines and Changes in Anthropometrics

We found that changes in SASP, regardless of responder status, were on average negatively associated with changes in anthropometrics (Figure 1).. The change in waist circumference had the strongest correlation with changes in SASP cytokines. We found that IL1b, IL15, IGF1, and GDNF had the strongest individual associations (Spearman's correlation coefficients of 0.45–0.49) (Figure 1). Additionally, changes in three cytokines (IL7, IL1b, and IL15) were negatively associated with changes in the waist-to-hip ratio. Furthermore, changes in IL6 had the strongest negative correlation with changes in weight and BMI.
In age and sex adjust linear models there were several significant associations between SASP cytokines and changes in anthropometrics: weight was associated with IL6 (b=−6.77, p=0.012) and IL15 (b=−2.53, p=0.007); BMI with IL15 (b=−0.95, p=0.028); waist-to-hip ratio with osteopontin (b=−0.07, p=0.025) (Figure 1). There were no significant associations between waist circumference and SASP.

DISCUSSION

In this exploratory analysis using biospecimens collected as part of a single arm pilot study we found an association between changes in SASP cytokine levels, and anthropometrics and physical function. Given the pilot nature of this study, our findings cannot be interpreted definitively; however, this highlights the need for future studies that examine a potential threshold of increase in SASP markers that demarcates between normal pro-inflammatory

effects designed to heal the body or enhance performance, versus excessive inflammation contributing to accelerated ageing and functional decline (Coppé et al., 2008).

Existing literature suggests that SASP contributes to age-related functional decline in older adults with obesity (Englund et al., 2021; Palmer et al., 2019). Little research explores SASP and its relationship with response to multicomponent weight loss interventions in this population. In this study, IL-6 and IL-7 had a significant positive association with 6MW and gait speed respectively. While these cytokines are associated with the SASP, in isolation, studies have shown these markers increase in response to exercise to assist in immune function and repairing damage induced by exercise among younger adults, yet the change in interleukin levels among older adults in response to exercise is more heterogenous (D. Chen et al., 2021; G. Chen & Yung, 2019; Małkowska & Sawczuk, 2023; Windsor et al., 2018). This notion that pro-inflammatory markers may show increases in response to exercise to initiate tissue repair and activate the immune system could also explain the inverse association we found between SASP markers and anthropometrics such as BMI and waist-hip ratio (G. Chen & Yung, 2019; Małkowska & Sawczuk, 2023). Further, the relatively short study period may also have impacted our results as the SASP markers may been high in the responder group, reflecting the effects of exercise, as opposed to the anti-inflammatory effects of weight loss (Petersen & Pedersen, 2005).

Declining physical function is one of the most evident phenotypic changes that occur with aging. Despite the impact of a loss of function on older adults, the biological drivers of this decline have not been fully elucidated (Ubaida-Mohien et al., 2019). Furthermore, adequate nutrition and physical activity are the only interventions that are known to slow age-related decline in physical function (Ubaida-Mohien et al., 2019). Advances in our understanding of aging biology have demonstrated that declining muscle strength, mass, and function (i.e., sarcopenia) are complex, and likely impacted by a combination of hormonal, inflammatory, and myocellular changes that occur with age. This pathophysiology is complicated further by obesity (i.e., sarcopenic obesity) which exacerbates inflammatory and hormonal changes to accelerate myocellular changes and functional decline (Batsis & Villareal, 2018). In recent years, the geroscience hypothesis has led to a paradigm shift in aging research and has turned toward understanding the fundamental drivers (e.g., cellular senescence and pro-inflammatory SASP cytokines) of these upstream pathophysiological changes. In preclinical and early pilot studies calorie restriction has been effective in modifying SASP cytokines and improving physical function suggesting that weight loss interventions may be effective in modifying fundamental pillars of aging to reduced age related morbidity i.e., improve healthspan. The findings in our study add to the emerging body of literature linking SASP cytokines, and declines in physical function in older adults. These findings can further develop the emerging field of precision medicine, specifically by understanding characteristic patterns in cytokines that ultimately heed reductions in physical performance (Sisodiya, 2021). Moreover, patients can perhaps be classified based on their cytokine profile, and by understanding how each specific profile effects function, physicians can preemptively treat these foreseen effects on physical function to improve patient outcomes (de Toro-Martín et al., 2017; Roos & Arden, 2016). However, the inconsistency seen in the links between individual SASP markers and measures of physical function, and anthropometrics in our study highlight the need for larger prospective randomized studies.

Studies with a greater sample size will allow for better characterization and examination of the links between individual SASP cytokines or groups of cytokines (e.g., composites based on primary role of cytokines) and clinical outcomes for older adults. For example, in this study we saw an association between SASP cytokines and change in grip strength but not sit-to-stand or six-minute walk however, in this study, this is hypothesis generating only given our small sample size.

While the emerging link between SASP and physical function is promising it remains unclear if the changes in SASP cytokines drive improvements in clinical outcomes or if changes in physical function and anthropometrics are improving SASP. Several recently published and relatively large prospective studies suggest that changes in SASP cytokines may be one of the fundamental drivers of declines in physical function (Fielding et al., 2022). Alternatively, adipose tissue is an important endocrine organ and a major source of pro-inflammatory cytokines and other related adipokines. These overlap with "SASP" factors. Thus, alterations to adiposity, will alter the secretion of adipose-derived inflammatory factors - which may mimic SASP factors. This could be independent of any effect on cellular senescence. There is no way to prove causation in this pilot study. Furthermore, there is no way disentangle the role of adipose dysfunction and signaling in a weight loss intervention - especially without a period of weight maintenance after weight / adipose loss. Randomized trials with a priori geroscience-based outcomes may help to shed light the interplay between weight loss, SAPS, adipose tissue and physical function.

Strengths and Limitations

This study provides several strengths in advancing the understanding of SASP cytokines within a human model. Unlike many review narratives and in-vitro analyses, we explored the link between SASP cytokines and exercise response in humans, an area that has not been previously studied (Coppé et al., 2008, 2010). Another key strength is our use of multiple SASP-related cytokines, rather than focusing on just one or two, as commonly done in other studies (Ding & Xu, 2022; Petersen & Pedersen, 2005; Su et al., 2022). This is the first study to evaluate SASP cytokines in a multicomponent weight loss intervention for adults over 65, assessing changes in body weight and function. Despite the small number of cytokines examined, we established robust associations with cellular senescence, physical function, and anthropometrics. However, the study's small sample size (32 participants) is a limitation, and further research, including randomized controlled trials (RCTs), is needed to clarify the relationships between aging, SASP, physical function, and weight loss in older adults (Batsis et al., 2021). The results should be replicated in larger, fully powered RCTs before drawing definitive conclusions (Wiley & Campisi, 2021). Future studies could use SASP cytokines to identify high-risk populations and differentiate responders from non-responders, allowing for tailored interventions. Incorporating nutrition interventions and further refining SASP cytokine analysis could advance precision medicine in this field. The exploratory nature of this study highlights the need for more detailed trials to confirm these findings and understand the biological mechanisms behind these preliminary associations, particularly their overlap with metabolic processes (Coppé et al., 2010; Loo et al., 2020).

In this single-armed pilot of a multicomponent weight loss intervention in older adults with obesity we found that changes in pro-inflammatory cytokines that may be related to SASP were associated with changes in physical function and anthropometrics. To examine whether these factors are mediators of the change in physical function observed with the weight loss intervention independent of effects on adiposity, a larger randomized intervention trial for older adults with obesity is needed. Additional tissue-level and circulating biomarkers of cellular senescence, and composite indices of SASP factors should be evaluated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

BMI	Body Mass Index (kg/m^2)
GDNF	Glial Cell Derived Neurotrophic Factor
IFNγ	Interferon Gamma
IGF1	Insulin-like Growth Factor 1
IL15	Interleukin 15
IL1β	Interleukin 1-Beta
IL2	Interleukin 2
IL6	Interleukin 6
IL7	Interleukin 7
IL8	Interleukin 8
MDC	Macrophage-Derived Chemokine
MIP1β	Macrophage Inflammatory Protein 1-Beta

TARC	Thymus- and Activation-Regulated Chemokine
TNFα	Tumor Necrosis Factor Alpha
VEGF	Vascular Endothelial Growth Factor
RANTES	Regulated upon Activation, Normal T Cell Expressed and Presumable Secreted

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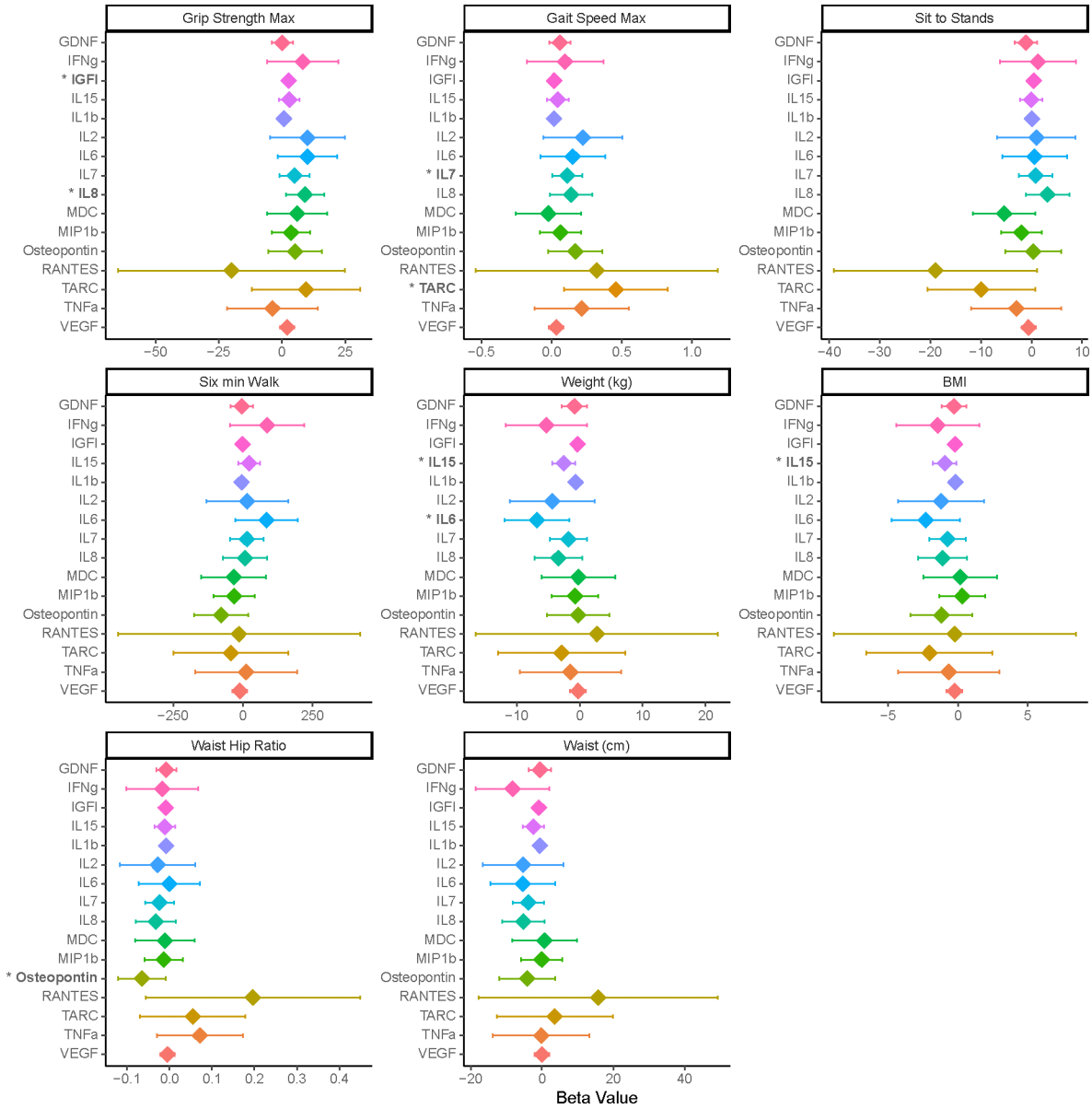

Figure 1. Association between change in cytokine and change in outcome.

BMI: Body Mass Index (kg/m^2), GDNF: Glial Cell Derived Neurotrophic Factor, IFNγ: Interferon Gamma, IGF1: Insulin-like Growth Factor 1, IL15: Interleukin 15, IL1β: Interleukin 1-Beta, IL2: Interleukin 2, IL6: Interleukin 6, IL7: Interleukin 7, IL8: Interleukin 8, MDC: Macrophage-Derived Chemokine, MIP1β: Macrophage Inflammatory Protein 1-Beta, TARC: Thymus- and Activation-Regulated Chemokine, TNFα: Tumor Necrosis Factor Alpha, VEGF: Vascular Endothelial Growth Factor, RANTES: Regulated upon Activation, Normal T Cell Expressed and Presumable Secreted

Figure 1 depicts age- and sex-adjusted linear models examining the association between changes in SASP cytokines, changes in physical function, and changes in anthropometrics. Each panel depicts either a physical function measurement or anthropometrics; the specific SASP cytokine is displayed on the vertical axis while the beta value (average change in

the dependent variable per unit change in the independent variable) is displayed on the horizontal axis with it's 95% confidence interval. SASP biomarkers that are bolded and starred on the vertical axis elicited a significant change in physical function/anthropometric ($p<0.05$).anthropometric

Table 1.

Baseline Characteristics

	Non-responder (n=16)	Responder (n=16)	Overall (n=32)	p-value
Age, years	74.3 (4.2)	72.3 (4.5)	73.3 (4.4)	0.22
Female Sex	14 (87.5%)	10 (62.5%)	24 (75.0%)	0.10
Smoking Status				0.72
Former	7 (43.8%)	6 (37.5%)	13 (40.6%)	
Never	9 (56.2%)	10 (62.5%)	19 (59.4%)	
Physical Function				
Grip Strength (kg)	22.5 (6.4)	24.7 (11.9)	23.6 (9.5)	0.52
Gait Speed (m/s)	1.0 (0.2)	1.1 (0.3)	1.1 (0.3)	0.85
Sit to Stand (sec)	12.5 (3.2)	14.5 (8.3)	13.5 (6.3)	0.38
Six Minute Walk (meters)	363.6 (64.1)	388.3 (119.2)	376.0 (95.0)	0.47
Anthropometrics				
Weight (kg)	93.4 (17.7)	101.7 (14.9)	97.6 (16.6)	0.16
BMI (kg/m^2)	36.6 (4.6)	37.3 (6.4)	36.9 (5.5)	0.75
Waist Hip Ratio	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.61
Waist Circumference (cm)	112.9 (12.3)	116.9 (14.6)	114.9 (13.4)	0.40