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INFLAMMATORY CYTOKINES AND APPETITE IN HEALTHY PEOPLE

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Abstract: *Background and Objectives:* Inflammation has been associated with reduced appetite and body composition changes in populations with established diseases. However, it is not known if an association exists between appetite, body composition and inflammation in healthy people. *Design:* To explore associations of appetite with markers of inflammation and body composition, data from the Cytokines, Adiposity, Sarcopenia and Ageing (CASA) study was analysed. *Setting:* Western suburbs, Adelaide, Australia. Participants: 180, population representative, healthy participants, aged 18 – 82 years, were studied. *Measurements:* Body composition was measured by both Dual X-ray absorbiometry (DXA) and bioelectrical impedance analysis (BIA). Appetite was assessed by the Simplified Nutritional Appetite Questionnaire (SNAQ). Circulating cytokine concentrations were measured. *Results:* Multiple regression analysis showed appetite scores were increased in non-smokers (P = 0.031) and men (P = 0.024), negatively associated with serum levels of the pro-inflammatory IL-1β (β coefficient = - 0.379, P = 0.007), and positively associated with serum levels of the anti-inflammatory cytokine IL-10 (β coefficient = 0.25, P = 0.010). There was no association between appetite and body composition. *Conclusions*: Appetite loss may reflect background inflammation even in apparently healthy people, and probably occurs before consequent changes in body composition. Further explorations of longer term appetite changes with respect to inflammation and body composition changes are needed.

Key words: Appetite, body composition, cytokine, inflammation.

Introduction

Under-nutrition is common among older people, even in developed countries (1-4) and is associated with serious consequences, including more frequent and prolonged hospital admissions (5), increased infection risk (6), functional decline (7) and reduced life expectancy (3). It is important to identify factors that might predict those older people more likely to lose weight and become under-nourished, so prevention and early treatment measures can be implemented.

Multiple methods have been used to define and diagnose under-nutrition in older people, but features commonly seen in this condition are weight loss (particularly muscle loss), reduced body weight, reduced appetite and sometimes cachexia (8). Aging is associated with decline in appetite and food intake which is probably physiological, but may contribute to the development of pathological anorexia and under-nutrition. Indeed, reduced appetite is a reliable predictor of future weight loss in the elderly; appetite scores obtained from the Simplified Nutritional Appetite Questionnaire (SNAQ) have been found to predict future weight loss in older people (9).

Appetite loss may be caused by inflammation. Inflammation is the immune system's response to an acute infection or illness and is the result of the production of several pro-inflammatory cytokines including interleukin-1 (IL-1), IL-2, IL-6, IL-8, tumour necrosis factor-α (TNF-α) and interferon-γ (IFNγ) (10). These pro-inflammatory cytokines, when persistently elevated, can reduce appetite by actions on the hypothalamus and other neural centres, by altering gastric function and by modifying the regulation of appetite controlling hormones (10). Anti-inflammatory cytokines, such and IL-4 and IL-10 act to down-regulate pro-inflammatory cytokine production (11). An imbalance between pro-inflammatory and anti-inflammatory cytokines is thus thought to lead to the cachexia of many chronic diseases (12).

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Ageing itself may be a low-level pro-inflammatory state (13). It might therefore be that the anorexia of ageing is due, at least in part, to increased inflammation. If so, it might be expected that there would be a positive connection between pro-inflammatory markers and reduced appetite even in apparently healthy individuals across the adult age range. Little is known about these possible connections.

This study explored the associations of appetite with markers of inflammation and body composition in healthy adults. It was hypothesised that there would be associations between increased inflammation and reduced appetite even in this group of healthy individuals, but probably not between markers of inflammation and adverse body composition changes, as these are likely to be later effects of under-nutrition.

Methods

Participants

Healthy subjects (ages 18 to 82 years) were recruited from the western suburbs of Adelaide into the Cytokine, Adiposity, Sarcopenia and Ageing Study (CASA). The recruitment methodology is similar to that described for other larger population studies conducted in the same catchment area, the North West Adelaide Health Study (14). Telephone numbers from the Electronic White Pages were randomly selected, and willing subjects, aged 18 or over, with no exclusion criteria, were invited to participate. Subjects able to comply with the study protocol and who reported weight stability over the preceding 3 months were included in the study. Those with confirmed inflammatory diseases, pregnant and those who had been ill in the preceding 3 months or in the 2 weeks following blood sampling, were excluded. This study had ethics approval from the Central Northern Adelaide Health Service Ethics of Human Research Committee and all participants provided written informed consent.

Body Composition Measures

Body composition was assessed by measurement of height; weight; waist circumference; Fat Mass (FM) and Fat Free Mass (FFM) by Dual X-Ray absorbiometry (DXA) (Lunar PRODIGY whole body scanner; GE Medical Systems, Madison, WI) scan; and Biolectrical Impedence Analysis (BIA) (Quantum II BIA Analyser, RJL system).

Appetite

Participants completed the SNAQ questionnaire, giving one of five responses to four questions regarding appetite, satiety, taste and meal frequency (11). SNAQ gives a score out of 20, with higher scores indicating greater appetite. SNAQ has been found to predict weight loss over a six month period with 81.6 % sensitivity and 84.6 % specificity for people over 60 years of age (9).

Exercise Score

Exercise was assessed using Australian National Health Survey questions (12). Scores for exercise intensity were 3.5 for walking, 5.0 for moderate activity and 7.5 for high intensity activity. Exercise intensity score was multiplied by minutes per fortnight for each exercise intensity to give total exercise level. This total level was classified as "sedentary" (< 100), "low level" (100 <1600), "moderate level" (1600 – 3200 or > 3200 and less than 2 h of vigorous exercise) or "high level" (> 3200)".

Data Collection

Fasting blood samples were collected and body composition measured by BIA in the morning, and body composition by DXA was measured either the afternoon of the same day or on another day but within 2 weeks. Plasma samples were stored at –80°C until analysis. Cytokine concentrations were measured using LINCOplex kits. Trace values < 0.08 pg/L for cytokines were recorded as zero values.

Statistical Analysis

SNAQ scores were normally distributed. Other continuous study variables were non-normally distributed and are presented as medians (inter-quartile range). Categorical variables are presented as frequencies.

Relationships between the total SNAQ score and the study variables were assessed using Spearman rank correlation tests for non-parametric variables. Cytokines and anthropometric variables were included in a multiple regression analysis along with for age, gender and smoking status. Continuous data were log transformed prior to inclusion in this analysis. Statistical analysis was carried out using SPSS statistical program (17.0, SPSS, Chicago, USA) with statistical significance set at $P < 0.05$.

Results

180 subjects with complete results were included in the study. Median age was 52 years with a range of 18-82 years. SNAQ total scores ranged from 12-20 (out of 20), with a median score of 17. 15 participants (7.8%) had low SNAQ scores (defined as ≤ 14). Table 1 shows baseline subject characteristics.

The results of the univariate regression analysis of the relationship between SNAQ appetite scores and continuous study variables are shown in Table 2. Both IL-6 and IL-10 concentrations were positively related to appetite. There were also strong significant associations between concentrations of a number of cytokines,

including IL-6 with both IL-1β (r = .353, P <0.001) and IL-10 (r = .410, P<0.001). By multivariate analysis (Table 3) non-smokers had higher appetite scores than smokers and men higher scores than women. IL-1β concentrations were negatively and IL-10 concentrations positively associated with appetite. None of the body composition variables showed any association with SNAQ score from either the univariate or multivariate analyses.

Table 1
Baseline Participant Characteristics (n=180)

Continuous Variables	Median (Inter-Quartile Range)
Background Variables	
Age (years)	52 (40-62)
SNAQ appetite scores	17.0 (16.0-18.0)
Circulating Cytokine Concentrations	
IL-1β (pg/ml)	0.50 (0.0-1.8)
IL-2 (pg/ml)	1.46 (0.0 - 8.0)
IL-4 (pg/ml)	0.0 (0.0 - 15.8)
IL-6 (pg/ml)	1.95 (0.25-5.9)
IL-10 (pg/ml)	3.9 (0.0-13.8)
TNF-α (pg/ml)	3.5 (1.9 - 5.4)
HS-CRP (mg/L)	1.2 (0.6 - 2.3)
Anthropometric Measures	
BMI (kg/m²)	25.6 (23.0 - 28.7)
Waist Circumference (cm)	87.2 (76.3 - 96.7)
Total Lean Mass DXA (kg)	44.5 (38.1 - 56.8)
Total Fat DXA (Kg)	24.1 (17.1 - 30.2)
Nutritional Biomarkers	
Haemoglobin (g/L)	140.0 (129.0 - 150.0)
Lymphocyte (g/L)	1.8 (1.6-2.2)
Albumin (g/L)	39.0 (37.0 - 41.0)
Categorical Variables	**n (%)**
Background Variables	
Gender	106 (58.9 %) females; 74 (41.1%) males
Smoking Status	19 (10.6%) smokers
Exercise Level	
Sedentary	31 (17.2 %)
Low Level	75 (41.7%)
Moderate Level	39(21.7%)
High Level	35(19.4%)

Table 2
Univariate Regression Analysis of relationships between total SNAQ appetite score and Continuous Study Variables (n=180)

Variable	R	P
Background Variables		
Age (years)	0.016	0.836
Exercise Score	0.062	0.407
Nutritional Biomarkers		
Haemaglobin (g/L)	0.053	0.463
Lymphocyte (g/L)	0.040	0.585
Albumin (g/L)	0.038	0.601
Cytokines		
IL-1β (pg/ml)	0.033	0.637
IL-2 (pg/mL)	0.034	0.652
IL-4 (pg/mL)	0.041	0.584
IL-6 (pg/mL)	0.153	0.041
IL-10 (pg/mL)	0.210	0.005
TNF-α (pg/mL)	0.089	0.222
HS-CRP (mg/mL)	0.086	0.239
Anthropometric Measures		
BMI (kg/m²)	0.039	0.599
Waist Circumference (cm)	0.058	0.425
Total Lean Mass DXA (kg)	0.064	0.374
Total Fat DXA (kg)	0.050	0.494

Table 3
Multivariate Analysis of relationship between Study Variables and total SNAQ score (n=180)

Variable	β Coefficient	t	P
Background Variables			
Age (years)	0.042	0.472	0.638
Gender	-0.367	-2.287	0.024★
Smoking Status	-0.172	-2.176	0.031†
Cytokines			
IL-1β	-0.379	-2.739	0.007
IL-2	0.157	1.018	0.310
IL-4	0.057	0.535	0.593
IL-6	0.085	0.806	0.422
IL-10	0.248	2.598	0.010
TNF-α	0.035	0.392	0.696
CRP	-0.165	-1.868	0.064
Anthropometric Measures			
BMI	-0.227	-0.971	0.333
Waist	0.372	1.739	0.084
Lean	0.281	1.631	0.105
Fat	-0.058	-0.255	0.799
Exercise Score	0.117	1.471	0.143

★SNAQ scores higher in men than women; †SNAQ scores higher in non-smokers than smokers.

Discussion

In this novel study of appetite in healthy people, appetite as measured by the SNAQ questionnaire was associated negatively with circulating serum levels of IL-1β and positively with IL-10 levels, but was not associated with any measure of body composition or nutritional biomarker – albumin, lymphocyte count and haemoglobin.

The negative association between IL-1β and appetite found in this study is consistent with previous reports in humans with inflammatory conditions such as cancer (15), renal failure (16) eating disorders (17) and depression (18). Our finding is also consistent with the known pro-inflammatory effects of IL-1β and the results of animal studies. In rodents, food intake is suppressed in a dose-dependent manner by IL-1β (10, 19). Additionally, IL-1β knock-out mice are of normal size and weight, but resistant to inflammation-induced weight loss (10). Of interest older mice lose more weight in response to IL-1 administration than young adult mice (20).

The positive association between IL-10 and appetite is consistent with the anti-inflammatory actions of this cytokine. IL-10 is believed to suppress immune responses by inhibiting pro-inflammatory cytokine production (11, 21). For example, IL-10 has been found to be protective against weight loss induced by both pro-inflammatory cytokines (22) and bacteria-mimicked infection (23) in rodent studies.

The finding that IL-6 was associated with appetite in the univariate analysis, but not associated in the multivariate analysis is probably because IL-6 concentrations are significantly associated with those of other cytokines, such as IL-1β and IL-10 which have more powerful effects on appetite. Consistent with the strong association observed between IL-6 and IL-10 concentrations (r = 0.353, P <0.001), IL-6 has been found to up-regulate IL-10 during acute inflammation (24).

In the present study there was no association between appetite and circulating levels of either TNF-α or, CRP. TNF-α is a pro-inflammatory cytokine which has been associated with reduced appetite in patients with chronic diseases such as renal failure (25) and levels of CRP, an inflammatory marker, have been associated with appetite decline in patients with chronic disease (26, 27). The lack of an association with appetite in the present study is perhaps because our subjects were healthy and TNFα and CRP effects on appetite occur later in the pathways of chronic and inflammatory diseases.

Low appetite leads to reduced food intake, which in turn, often results in weight loss (9). Loss of appetite due to inflammation might therefore result in reduced lean tissue stores. We found, however, no such association in our study, a finding supported by a recent study of community elders in Malaysia, where appetite was also not associated with body composition (28).

Our results may provide some insight into the order in which changes leading to under-nutrition occur. It is not known if the muscle mass loss that often follows appetite reduction in older people leads to a pro-inflammatory state, or if inflammation leads to reduced appetite and food intake and subsequently to adverse body composition changes. Our findings support the latter sequence, at least in certain circumstances. In apparently healthy people there appears to be already present an association between inflammation and reduced appetite, without adverse effects on body composition, which we postulate would only occur with more prolonged and severe effects on food intake and nutrition.

This study was limited by a relatively small sample size. Nevertheless, subjects were randomly chosen from the community and thus reflect the situation in apparently healthy adults. A further limitation is that dietary background was also not assessed in this study and that SNAQ has not yet been validated against objective food intake (28), although it has been shown to predict future weight loss (9). Dietary intake was not assessed in this study. Because it is possible that body composition and weight loss may reflect long term nutrition, whereas appetite and inflammation reflect short term nutrition (29), it would be interesting to follow these subjects to assess longer-term relationships between inflammation, appetite, body weight change and nutritional status and we are now planning such a follow-up study.

In summary, the major finding of the present study is that appetite in healthy people is associated with several inflammatory markers but not with any measures of body composition or nutritional bio-markers. Further follow-up is needed to explore the possibility that this may predict future weight loss and increased likelihood of developing under-nutrition.

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