



The relationship between selected body fatness indices and the level of blood interleukin-6 in female nursing home residents aged 80+ years without inflammation: A pilot study[☆]



Ryszard Zarzeczny^{a,*}, Agnieszka Nawrat-Szołtysik^b, Anna Polak^b, Ahmed Manasar^c, Jakub Maliszewski^d, Adam Kiełtyka^e, Beata Matyja^f, Magdalena Dudek^b, Joanna Zborowska^b, Adam Wajdman^b

^a Institute of Physical Education, Tourism and Physiotherapy, Jan Długosz University in Częstochowa, 13/15 Armii Krajowej St., 42-200 Częstochowa, Poland

^b The Jerzy Kukuczka Academy of Physical Education in Katowice, 72A Mikołowska St., 40-065 Katowice, Poland

^c Silesians Analytical Laboratories in Katowice, 1 Żelazna St., 40-851 Katowice, Poland

^d TECHNOMEX - Trade and Service Company, 15 Szparagowa St., 44-100 Gliwice, Poland

^e BetaMed Medical Center, 100A/802 Mikołowska St., 40-065 Katowice, Poland

^f Saint Elisabeth Nursing Home in Ruda Śląska, 30 Wolności St., 41-700 Ruda Śląska, Poland

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ABSTRACT

Background: Interleukin-6 (IL-6) production facilitates a shift from acute to chronic inflammation that may induce the development of some diseases and aging. Several studies have suggested that adiposity is closely related to serum IL-6 level, but their authors examined relatively young older adults (aged 60–80 years), so it is not clear whether this association would also occur in people at a more advanced age.

Objective: to assess whether in elderly women without inflammation the widely used anthropometric obesity indices are associated with serum IL-6 level and, if so, to determine the best anthropometric predictor of this inflammatory biomarker.

Methods: The sample consisted of 12 women (85.1 ± 3.9 years; 58.1 ± 8.7 kg; 151.9 ± 6.3 cm), the residents of nursing homes, who did not use anti-inflammatory drugs, statins or diuretics and whose blood C-reactive protein (CRP) concentration was lower than 3 mg/l. To determine CRP and IL-6 concentrations, venous blood samples were collected in the morning in a fasted state. The following anthropometric measurements were made in all participants: body weight, body height, the circumferences of waist, hip and neck. Body fat percentage and visceral fat rating (VFR) were determined by bioelectrical impedance analysis. The measurements were then used to calculate body mass index (BMI), body fat mass index (BFMI), body adiposity index (BAI), the waist-hip ratio (WHR) and the waist-height ratio (WHtR). In the statistical analysis, Pearson's correlation coefficients and stepwise multiple regression analysis with backward elimination were used.

Results: A direct relationship was established between IL-6 and CRP levels ($r = 0.639$; $p < 0.05$). Moreover, IL-6 significantly and positively correlated with hip and neck circumferences, BMI, BFMI, and BAI, as well as with VFR (r range 0.597–0.704; $p < 0.05$). The multiple regression analysis for IL-6 showed that the neck circumference was the only statistically significant independent variable ($r^2 = 0.496$; $p < 0.05$; $SEE = 0.554$ pg/ml).

Conclusions: The results suggest that of all popular indices of adiposity neck circumference is the best predictor of serum IL-6 concentration in the oldest old women without inflammation.

[☆] **Authors' contributions:** Ryszard Zarzeczny – study conception and design; Agnieszka Nawrat-Szołtysik, Ahmed Manasar, Jakub Maliszewski, Adam Kiełtyka, Beata Matyja, Magdalena Dudek, Joanna Zborowska, Adam Wajdman – data collection; Ryszard Zarzeczny, Agnieszka Nawrat-Szołtysik, Anna Polak, Ahmed Manasar, Jakub Maliszewski, Adam Kiełtyka, Beata Matyja, Magdalena Dudek, Joanna Zborowska, Adam Wajdman – research execution; Ryszard Zarzeczny, Agnieszka Nawrat-Szołtysik – statistical analysis; Ryszard Zarzeczny, Agnieszka Nawrat-Szołtysik, Anna Polak – interpretation of the data; Ryszard Zarzeczny, Anna Polak – preparation of the manuscript.

* Corresponding author at: Institute of Physical Education, Tourism and Physiotherapy, Jan Długosz University in Częstochowa, 13/15 Armii Krajowej str., 42-200 Częstochowa, Poland.

E-mail address: r.zarzeczny@ajd.czest.pl (R. Zarzeczny).

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1. Introduction

Most countries face the problem of aging populations. It is estimated that between 2005 and 2030 the number of European citizens aged 80 years or older will increase from 18.8 million to almost 35 million (Han et al., 2011). These numbers indicate that the proportion of the octogenarian, nonagenarian and centenarian adults is and will be rising. As a result, new social, economic and health challenges can be expected.

A higher incidence of chronic diseases, mental illnesses, physical disabilities and other co-morbidities in an aging population (Boutayeb and Boutayeb, 2005) seems to be due to reduced physiological functions combined with predominantly sedentary behaviors and limited physical activity of the elderly (Lara et al., 2015; Wirth et al., 2017). Given that life expectancy increases faster than the period of life spent in good health, a need arises to identify measures (biomarkers) for predicting the length of healthy aging (Lara et al., 2015; Wirth et al., 2017).

A growing body of evidence points to a decline in immune function as the main cause of aging. It is reported that most older adults are diagnosed with a chronic low-grade inflammation manifested by moderate increases in systemic levels of pro-inflammatory cytokines (e.g. interleukin-6 (IL-6)) and C-reactive protein (CRP) (Franceschi, 2007). The elders are also more likely to experience increased and prolonged inflammatory response following acute infections (Krabbe et al., 2001). Although acute inflammation related to infection that in most cases progresses at a fast rate is a necessary healing response, chronic inflammation can be detrimental to health (Gabay, 2006; Tracy, 2003). In a recent study by Tomeleri et al. (2018), raw bioelectrical impedance measurements showed an inverse relationship between phase angle and the levels of inflammatory biomarkers in older women, which suggests that prolonged inflammation may lead to tissue damage (Gabay, 2006).

CRP and IL-6 are the most frequently investigated inflammatory biomarkers in studies with older adults (Wirth et al., 2017). CRP is synthesized in liver in response to microbial sensing and circulating inflammatory cytokines (Pepys and Hirschfield, 2003). In the healthy adults, the median CRP concentration is 0.8 mg/l (Shine et al., 1981). Its elevated level (> 3.0 mg/l) has been found to be associated with many risk factors for cardiovascular diseases including hypertension, insulin resistance and obesity (Pearson et al., 2003). IL-6 is a pleiotropic cytokine exerting a variety of effects on the central and peripheral organs (Hoene and Weigert, 2008). It is also a key factor regulating the body's defense mechanisms (Akira et al., 1993) and the primary stimulator of the hepatic production of most acute phase proteins (Gauldie et al., 1987). IL-6 is mainly secreted by macrophages and monocytes, but under inflammatory and non-inflammatory conditions it is also secreted by different tissue cells, such as adipocytes, endothelial cells, fibroblasts, keratinocytes, osteoblasts, myocytes or pancreatic b cells (Kamimura et al., 2003; Van Snick, 1990). In contrast to CRP, a "normal" IL-6 concentration range has not been established. According to research, the serum level of IL-6 in resting elders varies from approximately 1.4 pg/ml for individuals in good physical and cognitive health (Ridker et al., 2000) to 26.3 pg/ml in institutionalized, geriatric patients (Maurel et al., 2007). In most studies with healthy older adults, the resting IL-6 concentration did not exceed 10 pg/ml (Hoene and Weigert, 2008), typically ranging from 2 to 4 pg/ml (Giovannini et al., 2011; Harris et al., 1999; Puzianowska-Kuźnicka et al., 2016). The differences in the basal concentration of IL-6 may result from interactions between pro- and anti-inflammatory agents (Minciullo et al., 2016), which can be modified by subjects' age, diet, body fat content, the level of physical activity, smoking, and other disease risk factors, including genetic background (Baylis et al., 2013; Candore et al., 2010; Roubenoff et al., 1998; Yudkin et al., 2000). It is interesting to note that IL-6 acts as an anti-inflammatory mediator when its serum concentration is "normal", but overproduction of IL-6 has a pro-inflammatory

effect leading to chronic inflammation (Gabay, 2006) and greater susceptibility to pathologies. A higher concentration of IL-6, compared with controls, has been reported for patients with obesity (mean IL-6 level - 7.7 pg/ml) (Roytblat et al., 2000), type II diabetes (mean IL-6 level - 6.2 pg/ml) (Dekker et al., 2007), cardiovascular diseases (mean IL-6 level in mild - 2.9 pg/ml and severe congestive heart failure - 20.9 pg/ml) (Tsutamoto et al., 1998), Alzheimer disease (mean IL-6 level - 6.5 pg/ml) (Licastro et al., 2000), rheumatoid arthritis (mean IL-6 level - 41.8 pg/ml) (Chung et al., 2011), as well as for the frail subjects (IL6 level > 4.6 pg/ml) (Fried et al., 2009). A strong correlation has also been established between the serum level of IL-6 in older adults and increased risk for cardiovascular events (Cesari et al., 2003), physical disability (Penninx et al., 2004) and mortality (Harris et al., 1999; Maurel et al., 2007). It is also noteworthy that in older adults IL-6 may be a better predictor of cardiovascular morbidity (Cesari et al., 2003) and mortality (Harris et al., 1999) than C-reactive protein (CRP).

More and more attention is being given to the role of adipose tissue mass in the etiology of age-related low-grade inflammation. In addition to the aforementioned link between systemic IL-6 concentration and increased adiposity, positive correlation has also been found between the level of this pro-inflammatory mediator and body mass index (BMI), total body fat and abdominal fat (Cesari et al., 2005; Kern et al., 2001). It is also suggested that fat deposits in some parts of the body (e.g. abdominal viscera, thigh muscle) are associated with a higher serum IL-6 concentration independent of total fat mass (Beasley et al., 2009; Fain et al., 2004; Fried et al., 1998). On the other hand, a pharmacologically induced lowering of visceral fat content has been shown to significantly reduce systemic inflammatory markers concentration in both animals and humans (Finelli et al., 2013). It is important to note that all these findings come from studies conducted with middle-aged individuals and relatively young older adults (aged 60–80 years). This fact may be of relevance, because after the age of 80 years both fat tissue and muscle mass decrease (Mathus-Vliegen, 2012). Given that the body composition changes with aging, whether or not body fat indices in the oldest old are still related to serum IL-6 concentration is not clear. Hence, our study with a sample of female nursing home residents aged 80 years and older aimed to determine whether the widely used anthropometric obesity indices are associated with serum IL-6 level and, if so, to identify the best anthropometric predictor of concentration of this pro-inflammatory mediator. Since inflammation is related to age (Roubenoff et al., 1998), here we present the first study investigating the relationship between body fat indices and IL-6 concentration in the oldest old without this confounding factor.

2. Methods

2.1. Participants and ethics approval

Sixty nine women, the residents of nursing homes in Upper Silesia, Poland, were invited to take part in this study. They were screened based on medical history questionnaires and physical examinations performed by a geriatric physician. The inclusion criteria were: aged 80 years or older, able to perform the basic activities of daily life without help (scoring a 6 on the Katz ADL scale (Wallace and Shelkey, 2008)), capable of logical verbal interaction, without medical contraindications to physical exercise. The exclusion criteria included cancer, uncontrolled high blood pressure, the use of diuretics, atrial fibrillation, a cardiac pacemaker, amputations, epilepsy, neurodegenerative disorders, the use of walking aids, pain or aching in the joints felt at the time of screening or on most days of at least one month during the prior year, acute or chronic inflammatory illness, the use of non-steroidal anti-inflammatory drugs or corticoids, and elevated circulating C-reactive protein (CRP > 3 mg/l according to the CDC & AHA recommendations (Pearson et al., 2003)). The final sample consisted of twelve women, because five declined to participate in the study, forty were excluded for reasons other than a failure to meet the CRP

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