Serum cortisol but not oxidative stress biomarkers are related to frailty: results of a cross-sectional study in Spanish older adults

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Abstract

Frailty is a multidimensional geriatric syndrome of loss of reserves and increased vulnerability to negative health outcomes. Cortisol, the major hormone of the hypothalamic pituitary adrenal (HPA) axis, and oxidative stress may be influenced by multiple endogenous and environmental factors throughout the lifespan, triggering changes in organism functioning. Association of elevated levels of cortisol and oxidative stress biomarkers with aging and several age-related diseases is well documented. However, the possible role of these factors on frailty status in older adults has not been extensively studied. Hence, the aim of this study was to conduct a cross-sectional study in 252 older adults (≥65 years old) classified according to their frailty status. Plasma cortisol and biomarkers related to oxidative stress including reactive oxygen/nitrogen species, oxidative DNA damage, and total antioxidant capacity were determined in non-frail, pre-frail, and frail subjects. Results showed significantly increasing cortisol concentrations with frailty burden, but no marked association between any oxidative stress biomarker and frailty status. In addition, dependence on activities of daily living and 10-year mortality risk were also correlated with elevated cortisol levels. Current results support the hypothesis that age-related HPA axis dysregulation is associated with frailty status, although further research is necessary to establish the role of cortisol in the pathophysiology of frailty.

Keywords:

Introduction

The world population is currently experiencing a rapid and unstoppable aging process and this trend is evident in most developed countries and also in developing countries (United Nations 2017). Since population aging is leading to important social and health-care challenges, there is an increasing interest of researchers and governments regarding aging and age-related diseases. Over the last decade, one of the most important concepts advanced in geriatrics has been the establishment of the notion of "frailty", a more precise approach to age-related conditions which may replace the obsolete concept of "chronological age" with the more accurate and person-tailored parameter of "biological age". Frailty may be defined as a progressive physiologic decline in multiple body systems, which is marked by loss of function, diminished physiologic reserve, and increased vulnerability to disease and death (Fulop et al. 2015). Frailty associated physiological dysregulation involves multi-organ systems including the musculoskeletal, immune, endocrine, hematologic, nervous, and cardiovascular systems (Fried et al. 2009; Leng et al. 2009). Prevalence of frailty is highly variable depending upon factors such as gender, age, race, or socio-economic conditions (Collard et al. 2012; Fried et al. 2001; Theou et al. 2015), and has been estimated to range from 4% to 59% (reviewed in Collard et al. 2012). According to the criteria for frailty identification proposed by Fried et al. (2001), frailty prevalence in Spain ranges from 3.7% to 16.3% in community-dwellings where older adults reside (Abizanda et al. 2011; Maseda et al. 2016), but reaches 68.8% in institutionalized older populations (González-Vaca et al. 2014).

Cortisol plays an important role in regulating the organism's response to stress through maintenance of homeostasis and regulation of salt and water balance, blood pressure, immune function and metabolism (Gardner et al. 2013). Environmental, physical, psychological and social stressors trigger alterations in the hypothalamic pituitary adrenal (HPA) axis reactivity, increasing cortisol levels or producing changes in circadian cortisol rhythms (Sapolsky, Romero, and Munck 2000). HPA axis dysfunction is one of several plausible candidate pathways contributing to biological aging (Varadhan et al. 2008). There is a growing interest in the possibility that this age-related hormonal change associated with high basal cortisol levels might also be related to frailty in older individuals. In this context, some investigators associated higher cortisol levels with different frailty-related phenotype features such as grip strength, or standing and walking performance (Peeters et al. 2008, 2007).

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are generated as a normal product of cellular metabolism. These reactive species are essential for survival attributed to involvement in several biological functions such as neurotransmission, blood pressure modulation, and control of the immune system (Pavelescu 2015). It is established that ROS/RNS may also originate from exogenous sources such as air and water pollution, cooking, tobacco smoke, drugs or alcohol consumption, UV light, ionizing radiation, and heat stress (Liguori et al. 2018). Adverse effects due to ROS/RNS are normally countered by antioxidant defenses, but during aging the balance between oxidative species production and antioxidant defenses may deteriorate, resulting in oxidative stress that may damage proteins, lipids, DNA and carbohydrates with consequent cellular structure and functional destruction (Czerska, Markery, and Oksydacyjnego 2015). Indeed, the role of oxidative stress in aging and in age-related diseases, such as atherosclerosis, inflammatory diseases, diabetes, vascular diseases, neurodegenerative diseases, or cancer is well known (reviewed in Liguori et al. 2018). Two recent systematic reviews concluded that frailty appeared to be associated with higher oxidative stress and possibly lower antioxidant parameters (Sánchez-Flores et al. 2017; Soysal et al. 2017), although several studies included in the reviews were based upon analysis of small sample sizes. Therefore, the objective of the present study was to provide support to the hypothesis that condition of frailty is related to increased cortisol basal levels and examine whether oxidative stress biomarkers were elevated to further enhance the body of evidence relating frailty with oxidative stress.

Methods

Study population

A cross-sectional study was undertaken in a population of Spanish older adults, classified according to frailty status criteria of Fried et al. (2001). In total, 252 individuals (82 males and 170 females) aged 65–102 years were included in the study. Participants were recruited from several associations of retired or older individuals, nursing homes, and daycare centers located in Galicia, Northwestern Spain. Participants were individually assessed at the centers, by professionals specially trained in clinical evaluation to unify criteria, and all completed a questionnaire to collect demographic, lifestyle, and medical information. All participants, or their relatives in case of inability, provided informed consent to be included in this study. The study protocol conformed to the principles embodied in the Declaration of Helsinki and was approved by the University of A Coruña Ethics Committee. Participants were excluded if the subjects (1) did not possess the necessary skills to be assessed, (2) had cancer or any chronic infection such as human immunodeficiency virus, hepatitis B virus or hepatitis C virus, (3) were taking medications known to affect the immune system, (4) denied participating in the study or (5) refused signing the informed consent.

Frailty status

Frailty status of each participant was determined according to the five phenotypic criteria proposed by Fried et al. (2001). These criteria are based upon the presence or absence of specific phenotypic components: (i) unintentional weight loss which is not due to dieting or exercise: at least 4.5 kg in the past year; (ii) self-reported exhaustion: identified by two questions from the Spanish version (Ruiz-Grosso et al. 2012) of the modified 10-item Center for Epidemiological Studies-Depression (CES-D) scale (Radloff 1977); (iii) weakness: grip strength in the lowest 20% at baseline, adjusted for gender and body mass index (BMI); (iv) slow walking speed: the slowest 20% at baseline, based upon time to walk 15 ft, adjusting for gender and standing height; and (v) low physical activity: the lowest 20% at baseline, based upon a weighted score of kilocalories expended per week, calculated according to the Spanish validation (Ruiz-Comellas et al. 2012) of the Minnesota Leisure Time Physical Activity Questionnaire (Taylor et al. 1978) according to each participant's report, and adjusting for gender. Frailty was defined as the presence of three or more of these characteristics, pre-frailty in case of one or two of them present, and the absence of all five determined a non-frail state.

Functional status

The functional status [i.e., the participant's capacity to perform basic activities of daily living (ADL)] was evaluated by an occupational therapist using the Barthel index (Mahoney and Barthel 1965) validated for the Spanish population (Baztán et al. 1993).

Ten-year mortality risk

General co-morbidity and number of co-morbid diseases were determined using the Charlson et al. (1987) co-morbidity index. An age-adjusted score was computed for each patient, coding co-morbid diseases as 1 to 6 = present and 0 = absent. In addition, this index was used to analyze whether the 10-year mortality rates from co-morbid disease differed significantly among frailty categories. A composite co-morbidity-age score was computed for each participant, evaluating the 10-year mortality by means of a theoretical low-risk population whose 10-year survival was 98% (Hutchinson, Thomas, and MacGibbon 1982).

Blood sample collection and storage

Whole blood samples were obtained in the early morning into Vacutainer tubes without anticoagulant or containing sodium heparin, and BD Vacutainer CPT Cell Preparation Tubes with sodium heparin (Becton Dickinson). Samples were transported immediately to the lab. CPT tubes were employed for isolation of peripheral blood mononuclear leukocytes (lymphocytes + monocytes) according to the manufacturer's instructions. Isolated leukocytes were cryopreserved at −80°C until analysis in 50% fetal calf serum, 40% RPMI 1640, and 10% dimethyl sulfoxide, at 107 cells/ml. Serum and plasma samples were obtained by centrifugation at 950 x g for 10 min, aliquoted, and stored at −80°C until analysis. All lab measurements were performed in a blinded manner since samples were coded at the moment of collection.

Serum cortisol levels

Cortisol was measured in serum samples by using a direct quantitative enzyme immunoassay (Diagnostics Biochem Canada Inc.), according to the manufacturer's instructions. Absorbance was measured at 450 nm in a Spectrostar Nano microplate reader (BMG Labtech) equipped with kinetic analysis software (Spectrostar Nano Control, BMG Labtech). A logistic four-parameter curve was utilized for the calculations. The sensitivity of the cortisol assay was 0.4 μg/dl.

Reactive oxygen and nitrogen species

Reactive oxygen and nitrogen species (ROS/RNS) in serum were measured by means of the OxiSelect In Vitro ROS/RNS assay kit (Cell Biolabs, Inc.), according to the manufacturer´s instructions. Hydrogen peroxide (H_2O_2), peroxyl radical (ROO·), nitric oxide (NO), and peroxynitrite anion (ONOO–) are detected in this assay. These free radical molecules are representative of both ROS and RNS, thus allowing for measurement of the totally free radical set within a sample. ROS and RNS species react with the assay fluorogenic probe, which is rapidly oxidized to the highly fluorescent 2′,7′-dichlorodihydrofluorescein (DCF). Fluorescence intensity was measured in a TECAN GENios plate reader equipped with XFluor4 analysis software at 480 nm excitation and 530 nm emission wavelengths. Results were expressed as DCF equivalents. The detection sensitivity limit of the assay was 10 pM DCF.

Oxidative DNA damage

In order to evaluate oxidative DNA damage a modified version of the alkaline comet assay was performed by incubating isolated mononuclear leukocytes with human 8-oxoguanine glycosylase (OGG1) repair enzyme following the protocol described by Smith, O'Donovan, and Martin (2006) with minor modifications (García-Lestón et al. 2012). For each individual sample, two slides were prepared. Mononuclear leukocytes incubated with enzyme on slides were compared with the corresponding slides incubated with just buffer to estimate the net oxidative DNA damage. Comet IV Software (Perceptive Instruments) was used for image capture and analysis. In all cases, 100 cells were scored blinded (50 from each replicate slide), and % DNA in the comet tail (%tDNA) was employed as a DNA damage parameter.

Total antioxidant capacity

Total antioxidant capacity was measured in plasma samples by using the Antioxidant assay kit (Sigma Aldrich), following manufacturer´s guidelines. The principle of the assay is the formation of a radical cation, a soluble chromogen that is green in color and determined spectrophotometrically. Antioxidants present in the plasma samples suppress the production of the radical cation in a concentration-dependent manner, and the color intensity decreases proportionately. TroloxTM, a water-soluble vitamin E analog, serves as a standard or control antioxidant. Absorbance at 405 nm was measured with a Spectrostar Nano microplate reader (BMG Labtech) equipped with kinetic analysis software (Spectrostar Nano Control, BMG Labtech). Results were expressed as TroloxTM equivalent antioxidant capacity (TEAC). The sensitivity of this method was 0.015 mM TEAC.

Statistical analysis

A general descriptive analysis of the study population, classified according to the frailty status, was carried out by univariate analysis. Socio-demographic, lifestyle, environmental, and clinical characteristics were compared in the three groups of subjects, applying the analysis of variance (ANOVA) for continuous variables and Chi-square test for categorical variables.

The effect of frailty status on cortisol and oxidative stress biomarkers determined was preliminarily assessed by ANOVA and Tukey's post-hoc test. Data from cortisol and ROS/RNS followed a normal distribution (Kolmogorov–Smirnov goodness-of-fit test). Since no improvement in the approximation to the normal distribution could be achieved by data transformation, antioxidant capacity and net oxidative DNA damage values were analyzed using the Kruskal–Wallis and Mann–Whitney U-tests.

Linear regression analysis was applied to estimate the effect of frailty status on cortisol and oxidative stress parameters. Models were adjusted for gender, age and tobacco consumption (never/ever smokers), and were run with log-transformed data. Models were also used to estimate the effect of dependence and mortality risk on the biomarkers determined. All results are shown as mean ratios (MR) and 95% confidence interval (95% CI). Statistical analyses were conducted by means of the STATA/SE software package V. 12.0 (StataCorp LP) and the IBM SPSS software package V. 20 (SPSS, Inc.). Statistical significance was set at $p < .05$.

Results

The study population comprised 252 older adults, aged from 65 to 102 years (mean age 79.3 ± 8.8 years) (Table 1). Female gender was less prevalent in the non-frail group (approximately 1:2), but gender proportions were opposite in the pre-frail and frail groups. Similar lack of balance, especially in favor of women, is frequent in studies in older adults (Sánchez-Flores et al. 2017). Percentage of smokers decreased with increasing frailty severity, although frail smokers consumed a higher amount of cigarettes per day than pre-frail and non-frail groups. Nevertheless, the number of years smoking was not significantly different among the three frailty groups. Individuals residing in the family home decreased with rising frailty burden with all non-frail subjects but only 6% of frail subjects lived in family homes. Further, dependence and co-morbidity rose with frailty severity. Depeneance occurred in 94% of frail group and co-morbidity was found in 40% of the same group. Similarly, mortality risk at 10 years showed an increasing trend ranging from 48% in non-frail individuals to 88% in frail individuals.

Figure 1. Results of the biomarkers analyzed in the study group, classified according to frailty status (univariate analysis). Bars represent the mean±standard error. *p < .05, statistically different from non-frail; #p < .05, statistically different from pre-frail.
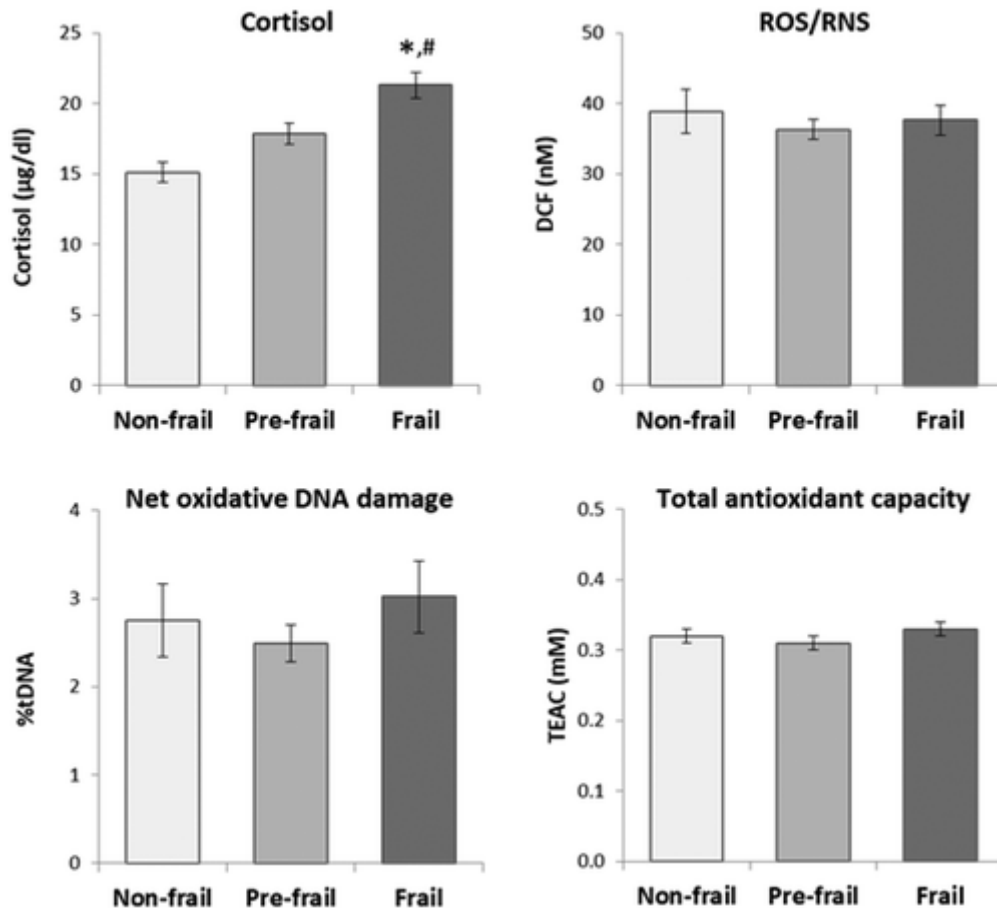
Table 1. Description of the study population.

	Total	Non-frail	Pre-frail	Frail	p
Total individuals N (%)	252 (100)	39 (15.5)	125 (49.6)	88 (34.9)	
Gender N (%)					
Males	82 (32.5)	26 (66.7)	34 (27.2)	22 (25.0)	**<0.001[c]**
Females	170 (67.5)	13 (33.3)	91 (72.8)	66 (75.0)	
Age (years-old)[a]	79.3 ± 8.8 (65–102)	73.3 ± 5.6 (65–85)	76.7 ± 7.6 (65–100)	85.8 ± 7.9 (65–102)	**<0.001[d]**
Smoking habits N (%)					
Non-smokers	196 (77.8)	22 (56.4)	98 (79.0)	76 (90.5)	**<0.001[c]**
Ever smokers	51 (20.2)	17 (43.6)	26 (21.0)	8 (9.5)	
No. cigarettes/day[a]	18.1 ± 13.8 (2–60)	16.1 ± 8.8 (3–40)	15.0 ± 13.9 (2–60)	31.4 ± 15.7 (20–60)	**0.016[d]**
Years smoking[a]	26.2 ± 16.7 (4–66)	19.4 ± 9.1 (10–34)	29.8 ± 19.3 (4–66)	29.3 ± 18.2 (6–52)	0.196[d]
Living conditions N (%)					
Family home	151 (59.9)	39 (100)	107 (85.6)	5 (5.7)	**<0.001[c]**
Family home+daycare center	27 (10.7)	–	4 (3.2)	23 (26.1)	
Nursing home	74 (29.4)	–	14 (11.2)	60 (68.2)	
Functional status N (%)					
No dependence	147 (58.6)	37 (94.9)	105 (84.0)	5 (5.7)	**<0.001[c]**
Dependence	104 (41.4)	2 (5.1)	20 (16.0)	82 (94.3)	
Comorbidity[b] N (%)					
No comorbidity	173 (68.9)	33 (84.6)	88 (70.4)	52 (59.8)	**0.036[c]**
Comorbidity	78 (31.1)	6 (15.4)	37 (29.6)	35 (40.2)	
Mortality risk 10 years (%)[a,b]	67.6 ± 30.5 (13.8–100)	48.3 ± 27.4 (15.0–100)	59.3 ± 30.7 (15.0–100)	88.3 ± 17.6 (13.8–100)	**<0.001[d]**

[a]mean±standard deviation (range); [b]according to Charlson's comorbidity index; [c]Chi-square test (bilateral); [d]ANOVA test (bilateral).

Figure 1 illustrates the univariate analysis comparisons of cortisol and oxidative stress biomarkers in the three groups of older adults classified according to frailty status. Cortisol was the only parameter exhibiting significant differences where the levels increased progressively and significantly with frailty burden. When compared with serum cortisol reference interval for adults in the early morning (171–536 nmol/l, equivalent to 6.2–19.43 μg/dl) (Addison 2012), 16.2% of non-frail subjects presented cortisol concentrations above the reference interval. In contrast, this prevalence was approximately 2-fold (36.4%) in pre-frail individuals and 3-fold (52.3%) in the frail group. It is noteworthy that no significant differences were observed in ROS/RNS levels, net oxidative DNA damage and total antioxidant capacity among all frailty groups in this study.

Results obtained from the multivariate statistical analysis are presented in Table 2. An increasing tendency with frailty severity was observed in cortisol concentration, although significance was detected only in the frail group compared to non-frail individuals. In addition, a significant influence of age was noted with positive for cortisol concentration accompanied by inverse for ROS/RNS levels and net oxidative %tDNA. No marked influence was found for gender or smoking habit with any parameter analyzed in this study.

Table 2. Effect of frailty status on the biomarkers analyzed; models adjusted by age, sex, and smoking habit.

	Cortisol		ROS/RNS		Net oxidative DNA damage		Total antioxidant capacity	
	Mean Ratio	95% CI	Mean Ratio	95% CI	Mean Ratio	95% CI	Mean Ratio	95% CI
Frailty status								
Non-frail	1.00		1.00		1.00		1.00	
Pre-frail	1.12	(0.95–1.31)	1.02	(0.82–1.29)	0.98	(0.73–1.33)	0.90	(0.74–1.10)
Frail	**1.23***	**(1.01–1.49)**	1.15	(0.88–1.51)	1.12	(0.86–1.77)	0.98	(0.78–1.24)
Gender								
Male	1.00		1.00		1.00		1.00	
Female	1.00	(0.88–1.15)	0.93	(0.77–1.12)	1.09	(0.85–1.39)	1.00	(0.85–1.18)
Age	**1.01***	**(1.00–1.02)**	**0.98***	**(0.97–0.99)**	**0.98***	**(0.97–1.00)**	1.00	(0.99–1.01)
Smoking habit								
Non-smokers	1.00		1.00		1.00		1.00	
Smokers	1.10	(0.94–1.28)	1.04	(0.84–1.28)	1.16	(0.87–1.54)	0.85	(0.70–1.02)

CI: confidence interval; *p< 0.05.

The influence of dependence in ADL and 10-year mortality risk on cortisol concentrations were also obtained by multivariate analysis, adjusted by age, gender, and tobacco consumption habit. Mean ratios were 1.21 (1.06–1.38 95% CI) for dependence and 1.01 (1.00–1.01 95% CI) for 10-year mortality risk.

Discussion

A growing body of evidence suggests the association between oxidative stress and aging. De la Fuente, and Miquel. (2009) suggested that the "free radical/oxidative stress theory of aging" and later the "oxidative-inflammatory theory of aging". Pandey and Rizvi (2010) proposed that aging is a loss of homeostasis due to chronic oxidative stress that affects especially the regulatory systems, such as nervous, endocrine, and immune systems. These hypotheses complemented with the revisited "nitric oxide theory of aging" (McCann et al. 2005), indicate that levels of oxidative stress and inflammatory cytokines gradually increase with age, whereas antioxidant defense mechanisms are diminished. Indeed, several investigators reported that ROS/RNS levels might play a critical role in a number of age-related diseases, including Alzheimer´s (Halliwell 2006), diabetes (Davì, Falco, and Patrono 2005), Parkinson´s (Wood-Kaczmar, Gandhi, and Wood 2006), atherosclerosis (Parthasarathy et al. 2008), cardiovascular (Aviram 2000), and rheumatoid arthritis (Hitchon and El-Gabalawy 2004).

Frailty syndrome corresponds to a combination of biological, physiological, social, and environmental changes that occur with advancing age (Nourhashémi et al. 2001). The activation of the immune system during aging induces an inflammatory state leading to chronic oxidative stress and further inflammatory reactions with a consequent increase in age-related morbidity and mortality (de la Fuente, and Miquel. 2009). Previously (Marcos-Pérez et al. 2018, 2017) reported an association of frailty in older adults with an additional degree of immune stimulation and inflammation, higher than expected to take only age into account. The possible relationship between frailty in older adults and oxidative stress biomarkers was also determined. Significant elevation in the concentration of derivate of reactive oxygen metabolites (Namioka et al. 2016; Saum et al. 2015), isoprostanes and lipoprotein phospholipase A2 (Liu et al. 2016), oxidized glutathione (Serviddio et al. 2009), malondialdehyde (MDA) and 4-hydroxy-2,3-nonenal-protein plasma adducts (Pereira et al. 2016; Serviddio et al. 2009), conjugated dienes and trienes (Pereira et al. 2016), serum 8-hydroxy-2′-deoxyguanosine (8-OHdG) (Wu et al. 2009), MDA formed from lipoperoxides and protein carbonylation (Inglés et al. 2014), and urinary 8-OHdG and 8-isoprostane (Namioka et al. 2016) were observed in frail subjects as compared with non-frail individuals. However, alterations in MDA levels and paraoxonase-1 were not detected by Goulet et al. (2009) in a small population (N = 54). (Collerton et al. 2012) in a large cohort (N = 845) found no marked changes in isoprostanes iPF2 alpha-III and iPF2 alpha-VI levels. Regarding antioxidant-related biomarkers, frailty was reported to be associated with significantly lower levels of total thiol levels (Saum et al. 2015), vitamin E (Ble et al. 2006), and total antioxidant potential (Namioka et al. 2016). In contrast, other investigators did not detect significant differences regarding frailty status for vitamin C and vitamin E (Goulet et al. 2009), or biological antioxidant potential (Namioka et al. 2016). In agreement, our results demonstrated no marked significant relationship between frailty and levels of oxidative stress biomarkers (ROS/RNS concentration and oxidative DNA damage) and total serum antioxidant capacity. At present, it is difficult to reconcile significant decreases obtained in the current study for both ROS/RNS levels and oxidative DNA damage, as previous findings reported an expected increase in oxidative stress parameters with age (Garm et al. 2013; Noren Hooten et al. 2012; Siomek et al. 2007). Inconsistent observations among results from different studies reflect the difficulty of assessing these types of biomarkers in humans, which may be due to the highly reactive nature of some of the metabolic parameters, which may be attributed to (1) short half-life, or (2) variation in exposure to environmental factors, including air pollution, UV radiation or heavy metals exposure, that may influence affect these parameters (Aseervatham et al. 2013). Further, limited sample sizes evaluated in several studies, confounders considered (or not) in the statistical analyses, and

different criteria used for the definition of frailty status across investigations may also account for differences in the results reported.

There is a significant consensus that HPA axis reactivity to external stressors, as evidenced by elevated cortisol level increases with age. Accordingly, higher cortisol concentrations were reported in patients with several age-related diseases such as Alzheimer´s (Lupien et al. 1999), diabetes (Buffington, Givens, and Kitabchi 1994), metabolic syndrome (Reynolds et al. 2003), depression (Rothschild 2003), hypertension (Al'Absi and Wittmers 2003), osteopenia (Dennison et al. 1999), sepsis (Sam et al. 2004), heart failure (Güder et al. 2007), and sarcopenia (Waters et al. 2008). Further, progressive and significant increases of cortisol concentrations with age were noted in the literature in wide age range populations (20–80 years) (Evans et al. 2011; Swaab, Bao, and Lucassen 2005), and in older adults (women aged 80–90 years) (Varadhan et al. 2008). In agreement with these previous findings, our results also demonstrate a significant positive age effect associated with serum cortisol levels.

Significant and progressive elevation in cortisol concentrations with frailty severity were obtained in the current study. In addition, the number of subjects out of the reference range established for serum cortisol for the whole adult population rose progressively from the non-frail to frail group. To our knowledge, only two previous studies addressed the possible relationship between frailty and cortisol levels where the hormone was measured in saliva samples. Varadhan et al. (2008) determined salivary cortisol levels over a 24 hr period and found significant positive associations of frailty burden with evening cortisol and 24 hr mean cortisol, but not with awakening cortisol concentrations. Holanda et al. (2012) found higher salivary cortisol values in the morning and before bedtime among frail-aged individuals.

Frailty in older adults was reported to be associated with higher concentrations of inflammatory parameters including, among others, interleukin 6 (IL6) and tumor necrosis factor alpha (TNFα) (Marcos-Pérez et al. 2018; Soysal et al. 2016). Since cytokines such as IL6 and TNFα are well-known activators of the HPA axis (Turnbull and Rivier 1999), elevation in cortisol concentrations related to frailty might involve chronic inflammation responses. It is noteworthy that catabolic effects of cortisol are related to loss of muscle strength and mass, weight loss, and decreased appetite and energy (Attaix et al. 2005). All these consequences, which are classic frailty phenotypic traits, provide additional reinforcement to the involvement of cortisol (and HPA axis) upregulation in frailty status.

Frailty is a predictor of a number of adverse health outcomes in the elderly including mortality, with an incidence of up to 45% per year in the frail group (Abizanda et al. 2013). In addition, several investigators related increased mortality risk with high cortisol concentrations in patients with different age-related diseases such as stroke (Christensen, Boysen, and Johannesen 2004), heart failure (Güder et al. 2007), sepsis (Sam et al. 2004), and sarcopenia (Waters et al. 2008). Our results are in agreement with these previous studies as evidenced by a significant association between serum cortisol and 10-year higher mortality risk in the older adult population. Impaired functional status (i.e., dependence for basic ADL) was also markedly associated with higher concentrations of cortisol with a 21% rise in individuals with dependence regarding those without dependence. This result provides additional evidence to the correlation between high cortisol levels and dependence reported in chronic heart failure patients (Anker et al. 1997).

In summary, although it was previously reported that frailty may be associated with higher oxidative stress and possibly lower antioxidant parameters, no such relationships were noted in the parameters analyzed in this study. However, higher serum cortisol concentration was found related to increasing frailty burden, thus supporting the hypothesis that age-related HPA axis dysregulation may be associated with frailty status in the elderly. These findings contribute to enhance our knowledge on the pathophysiology of frailty status, which is required for future implementation of therapeutic or, more importantly, preventive interventions in the older adult population.

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Conflict of interest declaration

The authors report no potential conflicts of interest.

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