

## Inflammation Biomarkers Are Independent Contributors to Functional Performance in Chronic Conditions: An Exploratory Study

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### Abstract

Chronic health conditions are accompanied by low-grade systemic inflammation and increased blood concentrations of pro-inflammatory cytokines, such as tumor necrosis factor (TNF). Blood levels of soluble receptors for tumor necrosis factor (TNF) can influence functional performance in patients with chronic conditions such as fibromyalgia, chronic obstructive pulmonary disease, and Chagas disease. However, a gap remains with regard to the association between systemic inflammation biomarkers and functional performance in chronic conditions. The aim of this

study was to verify the association of soluble receptors for TNF with functional performance in chronic conditions. One hundred and forty-six volunteers with chronic conditions (52.4 years, 49.8% males) were assessed to verify the association between blood levels of soluble receptors for tumor necrosis factor 1 (sTNF-R1) and 2 (sTNF-R2) and functional performance. Simple and multivariate linear regression, adjusted for body mass index and age, were used as appropriate. High sTNFR-1 plasma level was associated with a lower functional performance regardless of BMI adjustment ( $R^2 = 0.235$ ;  $\beta = -0.380$ ;  $p = 0.000$ ) or age adjustment ( $R^2 = 0.763$ ;  $\beta = -0.148$ ;  $p = 0.002$ ). High sTNFR-2 plasma level was associated with a high functional performance regardless of age adjustment ( $R^2 = 0.763$ ;  $\beta = 0.147$ ;  $p = 0.001$ ). In brief, high sTNFR-1 plasma level and low sTNFR-2 plasma level predicted a reduction of approximately 76.3% in functional performance in chronic conditions. Thus, the findings showed that the soluble receptors for TNF-alpha are determinants of functional performance in chronic conditions.

**Keywords:** blood-based biomarkers, chronic condition, functional performance

## 1. Introduction

According to the World Health Organization (2018), 71% of worldwide deaths in 2016, affecting 41 million people, were related to chronic conditions including fibromyalgia, chronic obstructive pulmonary disease, and Chagas disease (Macfarlane et al., 2017). Studies have demonstrated that chronic conditions are accompanied by low-grade inflammation that can precede the development of the chronic condition (Dandona et al., 2007) (Darval et al., 2007). Moreover, low-grade inflammation is also related to age and obesity.

In the literature, a two to four-fold increase in plasma levels of cytokines due to the aging process has been described, including pro-inflammatory cytokines such as Tumor Necrosis Factor alpha (TNF- $\alpha$ ) (Wang, 2010) (Felicio et al, 2014). TNF- $\alpha$  binds to two receptors, i.e., tumor necrosis factor soluble receptor 1 (sTNF-R1) and tumor necrosis factor soluble receptor 2 (sTNF-R2). These receptors have different kinetics for their ligands and mediate different effects (Brockhaus, 1997).

Studies by our team have shown that endurance exercise training improved blood levels of the soluble receptors for tumor necrosis factor (TNF-  $\alpha$ ) and functional performance in chronic conditions. However, a gap remains in regard to the association between systemic inflammation biomarkers and functional performance in chronic conditions. In addition, since our research group has a database including inflammation biomarkers and data on functional performance tests in chronic conditions, the feasibility and need for this investigation is justified.

Thus, the present study aimed to evaluate the association of soluble receptors for TNF with functional performance in chronic conditions.

## **2. Method**

This is a retrospective study, in which a database of research from the Laboratory of Exercise Physiology (LAFIEX) and the Laboratory of Inflammation and Metabolism (LIM) from 2010 to 2020 was used.

This research was approved by the Research Ethics Committee of UFVJM and followed all the precepts for carrying out experiments with chronic conditions (4.648.410). Thus, the sample consisted of a database of patients with chronic conditions of fibromyalgia, chronic obstructive pulmonary disease, and Chagas disease.

The investigated parameters in the chronic conditions were sTNFR's inflammation biomarkers (sTNFR1 and sTNFR2) (independent outcomes), and functional performance as dependent outcome (distance covered during the six-minute walk test) (6MWT). In addition, the linear regression model was adjusted for body mass index (BMI) and age. The inclusion criteria were patients with chronic conditions with data on sTNFR's plasma levels and distance in meters covered, obtained from a functional performance test.

The data were analyzed using the SPSS statistical package, version 20.0 (SPSS Inc., USA). The normality and homoscedasticity of the data were evaluated using specific tests. The association between the independent outcomes (plasma level biomarkers) and dependent outcome (functional performance) was investigated using simple and multivariate linear regression. As BMI and age were associated with functional performance in the simple linear regression, they were adjusted in the model of multiple linear regression. Significance level was set at 5%.

## **3. Results**

The sample was composed of 146 patients with chronic conditions (Table 1). In the simple linear regression, higher sTNFR1 plasma level and age were associated with lower functional performance, while higher sTNFR2 plasma level was associated with higher functional performance.

In the multivariate linear regression, adjusted for BMI, only sTNFR-1 was associated with functional performance. Thus, high sTNFR-1 plasma level was associated with a lower functional performance regardless of BMI adjustment and high sTNFR-1 plasma level and low sTNFR-2 plasma level were associated with lower functional performance regardless of age adjustment. In brief, high sTNFR-1 plasma level and low sTNFR-2 plasma level predicted a reduction of around 76.3% in functional performance in chronic conditions (Table 2).

Table 1. Baseline characteristics of the sample (n=146)

Variable	Value
Age (years)	54.3 (31 – 76)
Males, n (%)	63 (43.15)
BMI (kg/cm <sup>2</sup> )	25.80 (14.3 – 41.1)
Blood Biomarkers	
sTNF-R1 (pg/mL)	958.77 (154.07 – 2816.67)
sTNF-R2 (pg/mL)	2166.24 (663.66 – 4500.32)
Functional Performance	
6MWT (m)	491.66 (202 – 664)

Data presented as mean (95% CI) or absolute number (percentage). BMI: body mass index; sTNF-R1: soluble tumor necrosis factor receptor-1; sTNF-R2: Soluble tumor necrosis factor receptor-2; 6MWT: six-minute walk test.

Table 2. Results of simple linear regression analysis and stepwise multiple linear regression analysis (n=146).

Independent Variable	Dependent Variable Functional Performance (distance covered during 6MWT)		
	$\beta$	p value	R <sup>2</sup>
Log <sub>10</sub> sTNF-R1	-0.472	0.000*	0.217
Log <sub>10</sub> sTNF-R2	0.276	0.001*	0.070
Model			
Log <sub>10</sub> sTNF-R1	-0.428	0.000*	0.225
Log <sub>10</sub> sTNF-R2	0.122	0.122	
Adjusted Model			
Log <sub>10</sub> sTNF-R1	-0.380	0.000*	0.235
Log <sub>10</sub> sTNF-R2	0.094	0.240	
BMI	-0.140	0.090	
Adjusted Model			
Log <sub>10</sub> sTNF-R1	-0.148	0.002*	0.763
Log <sub>10</sub> sTNF-R2	0.147	0.001*	
Age	-0.779	0.000	

Legend:  $\beta$ , standardized regression coefficient. R<sup>2</sup>, adjusted coefficient of determination. Unit measure for soluble tumor necrosis factor receptor-1 (sTNF-R1): pg/mL; soluble tumor necrosis factor receptor-2(sTNF-R2): pg/mL. Body mass index (BMI): kg/cm<sup>2</sup>. Six-minute walk test (6MWT): m.\*Significant difference (p<0.05).

#### 4. Discussion

The present study demonstrates that the increase in the sTNFr-1 biomarker is associated with impaired functional capacity in chronic diseases. This points that biomarkers can be used as a complementary tool to the assessment of functional capacity for the management and treatment adjustment in rehabilitation in various chronic health conditions. For this purpose, studies that assess, in a different way, the relationship between chronic health conditions and functional capacity were used. It is believed that it creates a paradigm for future studies associating other chronic health conditions and functional capacity through these and other biomarkers of inflammation.

Evidence demonstrates that chronic conditions are often accompanied by low-grade systemic inflammation, characterized by higher levels of systemic inflammatory cytokine (Angelis et al., 2014)(Rodriguez-Pintó et al., 2014)(Ribeiro et al., 2018)(Silva et al., 2020). In this sense, our data showed that high systemic sTNFR-1 plasma level was associated with a low covered distance during the 6MWT. Thus, each increase of around 0.45 pg/mL in sTNFR-1 plasma level resulted in a decrease of around one meter in covered distance.

Soluble TNF receptors seem to have opposite effects on functional performance (Brockhaus, 1997) (Bradley, 2008)(Oliveira et al., 2011), whereby in some situations they can be inhibiting, while in others they increase their effect, prolonging their function (Aderka, 1992). Our findings corroborate this idea and although a higher sTNFR-1 plasma level was associated with lower functional performance, there was a direct association in regard to sTNFR-2 level, i.e. the lower the sTNFR-2 plasma level, the lower the functional performance. Our results are in line with other studies, which showed elevated levels of sTNFR-1 associated with lower functional performance in chronic conditions (Penninx et al., 2004)(Simão et al., 2012)(Braz et al., 2016), due to decreased protein content in the skeletal muscle and consequent loss of muscle mass and strength (Llovera, 1993). Regarding sTNFR-2 plasma levels, the modulatory role of sTNFR2 on TNF plasma levels has been demonstrated in another study (Aderka et al., 1992). Thus, high sTNFR2 plasma levels may indicate an active inflammatory process attempting to control or inactivate the action of TNF (Aderka et al., 1992)(Petersen & Pedersen, 2005), rather than the cause of the inflammation.

High BMI was associated with low functional performance in simple linear regression, probably due to the decrease in muscle performance and biomechanical disadvantages (overweight/obese) (Acaröz Candan, 2020)(Pataky, 2020). Thus, considering that BMI was an independent outcome negatively associated with functional performance, we adjusted for BMI in the multiple linear regression. Our results reinforced high systemic sTNFR-1 plasma level as a predictor of lower functional performance in chronic conditions. Considering that advancing age was also associated with low functional performance in simple linear regression, we adjusted age in the multiple linear regression. The aging process implies a chronic subliminal inflammatory state (Felicio et al., 2014), where high levels of cytokines contribute to the appearance of sarcopenia

and subsequent impairment of functional performance (Brinkley et al., 2009) (Bano et al., 2017).

Our results showed the sTNFR-1 and sTNFR-2 blood levels as determinant factors of functional performance in chronic conditions. This study has both limitations and strengths. The study has a cross-sectional format, which does not enable the inference of a cause-and-effect relationship, which would require more longitudinal studies. However, as far as is known, this is the first study to investigate a large, heterogeneous sample composed of a wide range of chronic conditions including fibromyalgia, chronic obstructive pulmonary disease, and Chagas disease.

### 5. Conclusion

The increase in sTNFR-1 plasma level is an independent contributor to functional performance in chronic conditions and sTNFR-2 plasma level directly contributes to functional performance in chronic conditions. Thus, the control of systemic inflammation biomarkers may improve functional performance in patients with chronic conditions.

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