

Relationship between perceived academic stress and Interleukin 6 levels in health students

Relación entre el estrés académico percibido y los niveles de Interleucina 6 en estudiantes de salud

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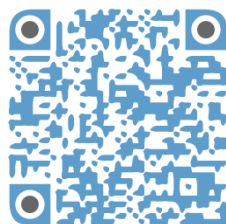
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ABSTRACT

Background: Academic stress is an important research topic due to the effect it has on the quality of life of students, future professionals and therefore, adult contributors in a society. It has been shown that students in the health field face additional stressors specific from their careers, and suffer greater stress than the general population of the same age.

Methods: 52 students, 23 from Physiotherapy and 29 from Medicine programs were surveyed with Academic Stressors Academic Scale (SAS) to know academic stress level and IL-6 was quantified in serum.

Results: It was found that students who perceive the academic semester as stressful "fairly often" and "many times", increases in 50%, 75% and 76.9% during the semester; while "anxiety/distress" feeling was predominant. The most frequent SAS scale factors were "methodological deficiencies", "student overload", "beliefs about performance", "lack of content value", "participation" and "exams"

Conclusion: The study revealed an IL-6 increment, and their association with "Methodological Deficiencies" at 1st moment. This study showed the importance of academic stressors identification at same time that it is a call to construct strategies to reduce stressors in University context.

RESUMEN

Introducción: El estrés académico es un tema de investigación importante debido al efecto que tiene sobre la calidad de vida de los estudiantes, futuros profesionales y, por lo tanto, los contribuyentes adultos en una sociedad. Se ha demostrado que los estudiantes en el campo de la salud enfrentan factores estresantes adicionales específicos de sus carreras y sufren un mayor estrés que la población general de la misma edad.

Métodos: 52 estudiantes, 23 del programa de fisioterapia y 29 del programa de medicina fueron encuestados con la Escala de Estresores Académicos del Cuestionario de Estrés Académico (E-CEA) para conocer el nivel de estrés de los estudiantes; la citoquina IL-6 se cuantificó en suero.

Resultados: Se encontró que la frecuencia de estudiantes que perciben el semestre académico como estresante "con bastante frecuencia" y "muchas veces", aumenta en un 50%, 75% y 76.9% durante el semestre; mientras que el sentimiento de "ansiedad / angustia" era predominante. Los factores de la escala E-CEA más frecuentes fueron "deficiencias metodológicas", "sobrecarga de estudiantes", "creencias sobre el rendimiento", "falta de valor de contenido", "participación" y "exámenes".

Conclusión: El estudio reveló un incremento de IL-6 y su asociación con "Deficiencias metodológicas" en el 1er momento. Este estudio mostró la importancia de la identificación académica de estresores al mismo tiempo que hace un llamado a construir estrategias para reducir los estresores en el contexto universitario.

Keywords Academic stress; IL-6; Physiotherapy; Psychoneuroimmunology

Palabras clave Estrés académico; IL-6; Fisioterapia; Psiconeuroinmunología

I. INTRODUCTION

Academic stress is an important research topic due to the effect it has on the quality of life of students, future professionals and therefore, adult contributors in a society. It has been shown that students in the health field face additional stressors specific from their careers, and suffer greater stress than the general population of the same age (Compton, Carrera, Frank, 2008; Dyrbye, Thomas, Shanafelt, 2006). Among these stressors have been mainly identified, the awareness of having in their hands people's health and life, extended work hours, difficult work places (emergency rooms or intensive care) and continuous assessment of large volumes of knowledge. In response to these stress circumstances, students can develop depression (Dahlin, Joneborg, Runeson, 2005) drug dependence (Jalilian, Karami, Ahmadpanah, Ataee, Ahmadi, Eslami, et al., 2015), suicidal tendencies (Dyrbye, Thomas, Massie, Power, Eacker, Harper, et al., 2008), difficulty in establishing interpersonal relationships (Hojat, Vergare, Isenberg, Cohen, Spandorfer, 2015), as well as associated pathologies such as musculoskeletal disorders (Ekpenyong, Daniel, Aribio, 2013), infections (Sarid, Anson, Yaari, Margalith, 2004), oral diseases (Deinzer, Hilpert, Bach, Schawacht, Herforth, 2001), and autoimmune disorders (Dube, Fairweather, Pearson, Felitti, Anda, Croft, 2009), among others.

Research on the association between stress and students in health areas is extensive (Abdulghani, AlKanhal, Mahmoud, Ponnampuruma, Alfaris, 2011; Gomathi, Ahmed, Sreedharan, 2013; Walsh, Feeney, Hussey, Donnellan, 2010) Survey-type tools to elucidate the problem qualitatively, have noted that time available to perform academic activities, fear of failure, interactions within the classroom, economic problems and social and global problems, are the most frequent stressors within this population, while the consequences are associated with these factors: high burnout index, fatigue and depersonalization, emotional exhaustion, depression and suicidal ideation (Dyrbye, West, Satele, Boone, Tan, Sloan et al., 2014).

Of these studies, few inquire students' health status through their own biological indicators for this purpose. In this sense, the relationship between stress and the immune system has been explored; for example, it has been shown that in situations of acute stress, health science undergraduate students have an increase in the concentration of cortisol in their blood (Tseng, Iosif, Seritan, 2011), leukotriene in nasal fluids (Trueba, Ryan, Vogel, Ritz, 2016). It is also related to an increase of the adrenocorticotropic hormone (ACTH), which in turn generates an increase in the IL-4, IL-10 and IL-13 cytokines that have anti-inflammatory effects, and a decrease in the pro-inflammatory IL-1 β , IL-6, TNF- α , IFN- γ , IL-2 and IL-12 cytokines (Koelsch, Boehlig, Hohenadel, Nitsche, Bauer, Sack, 2016). On the other hand, when stress is chronic, fatigue of the hypothalamus-adrenal pituitary axis occurs, which attenuates the response of cortisol, causing resistance to glucocorticoids due to the low expression of its receptors; therefore,

the effect of cortisol on the inflammatory response loses its effect and increases IL-6, TNF- α and IFN- γ levels (Murali, Hanson, Chen, 2007) so that chronic stress is related to a pro-inflammatory profile (Tian, Hou, Li, Yuan, 2014) which can become an etiological factor of pathologies of an inflammatory nature.

Considering the above, this research aimed to identify the circumstances of academic stress in a population of Physiotherapy and Medicine students of the Faculty of Health Sciences of the University, through the application of the Academic Stressors Scale SAS and the pro-inflammatory cytokine IL-6 quantification.

II. METHODS

Study Population

An observational, longitudinal and descriptive study was carried out. The selected population was obtained from the students of the Faculty of Health Sciences of the University of Cauca, enrolled in the seventh semester of the Medicine Program and from the sixth semester of the Physiotherapy Program; who were chosen due to their higher academic load according to their study plans.

The following aspects were taken into account as inclusion criteria: Academic enrollment with 100% of the academic credits required for the corresponding semester, signature of the informed consent, presence in the three moments of the survey administration and in peripheral blood samples collection, students who were not consuming any type of drugs or hallucinogenic substances, and as an indication of the peripheral blood samples collection, who had followed a minimum fast of 8 hours. 52 students participated, 23 students from the Physiotherapy Program and 29 students from the Medicine Program; however, the quantification analysis of IL-6 was performed on 51 students given the dispersion of 1 case between the first and the second moment. All the procedures were approved by the Ethics Committee of the University of Cauca, the project was registered with ID 4624 in the Research System of the University of Cauca.

Measurement of stressors

The stressors were measured through a survey of sociodemographic characteristics and the academic stressors questionnaire, which was formulated and validated in 2016 by Cabanach and collaborators (reliability of $\alpha=0.96$)

(Cabanach, Souto-Gestal, Franco, 2016). From this questionnaire, the Stressors Academic Scale (SAS) was used, consisting of 54 questions with Likert-type answers (Never =1, Sometimes= 2, Fairly Often =3, Many times =4 and Always =5).

The survey was first administered on the first week of the semester (“1st Moment”), where the survey of sociodemographic characteristics (age, gender, socioeconomic status, marital status, economic stability and academic program) was also administered. The survey was administered again in week 13, where the 70% evaluation of the academic content takes place, and in week 16, where final exams are taken, defined as the “2nd Moment” and the “3rd Moment”, respectively. The SAS was entirely assessed and grouped into 8 factors: teacher’s methodological deficiencies (12 items); student’s overload (10 items); public interventions (5 items); bad social relationships in the academic context (6 items); lack of control over one’s academic performance (5 items); lack of content value (4 items); low academic esteem (5 items); exams (4 items); inability to participate in decisions regarding one’s own academic work (3 items).

IL-6 determination in serum of peripheral blood

IL-6 determination in serum of peripheral blood was performed by means of peripheral venous blood samples, which were obtained by direct venipuncture with the Venoject system (Terumo Europe NV Eschborn Germany), using Vacutainer® tubes without additives (BD Franklin Lakes red cap tubes, NJ, USA). 6 mL of blood was collected from each person in the established times (1st, 2nd and 3rd moments). The serum was separated by centrifugation and the samples were labeled and stored at -70°C until the cytokine IL-6 was quantified. The cytokine IL-6 was quantified from peripheral blood serum by the sandwich ELISA method using the Human IL-6 ELISA MAX™ kit (Biolegend), the procedure was performed according to the manufacturer’s instructions.

Data analysis

The data from the SAS and the Cytokine IL-6 quantification were included in an Excel-type electronic sheet in which each student was assigned a code; once the data were entered, the electronic sheet was exported to the statistical program SPSS.19 for its corresponding analysis.

The sociodemographic variables were analyzed using frequency and percentage tables, as well as the variables of the academic stressor questionnaire, which were analyzed first by question and then by groups or factors, comparing the average behavior by factor in each of the programs. To classify the results by average, it was decided to group them in ranks to facilitate the interpretation of the final results: 0 to 0.9 “Never”, 1 to 1.9 “Sometimes”, 2 to 2.9 “Fairly often”, 3 to 3.9 “Many times” and 4 to 5 “Always”. Finally,

the questionnaire questions which presented the highest response rate represented in the final average were selected; as a selection criterion, it was taken into account that the question obtained a frequency greater than or equal to 20 in the answers, except for the ones answered as "never", and that it would be repeated in the results of each moment of the questionnaire administration.

For the analysis of the IL-6 quantification, the ANOVA test was performed for repeated samples and the Dunn's multiple comparison test, with a value of $p < 0.05$. Finally, a Pearson correlation was conducted between the higher frequency academic stressors by academic program and the IL-6.

III. RESULTS

Analysis of socio-demographic variables

The average age of the surveyed students was 21.54 years, with a minimum age of 19 years and a maximum of 27 years; 38.5% (20/52) of the respondents were men, while 61.5% (32/52) were women; regarding the socioeconomic level classified in Colombia by 5 strata, being stratum 1 the lowest income and stratum 5 the highest income; 78.8% (41/52) belonged to 1, 2 and 3 strata. 73.1% (38/52) considered having a good economic stability. Regarding marital status, 98.1% (51/52) reported being single. Among the respondents, 44.2% (23/52) were enrolled in the Physiotherapy program and 55.8% (29/52) in the Medicine program. [Table I](#) describes the socio-demographic characteristics.

VARIABLE	PHYSIOTHERAPY n (%)	MEDICINE n (%)
Age	21.54±v2.8	21±1.6
Gender		
Male	6 (26.1)	14 (48.3)
Female	17 (73.9)	15 (51.7)
Socioeconomic stratum		
One	6 (26.1)	0 (0)
Two	8 (34.8)	8 (27.6)
Three	6 (26.1)	13 (44.8)
Four	3 (13.0)	7 (24.1)
Five	0 (0)	1 (3.4)
Marital status		
Single	22 (95.7)	29 (100)
Common law marriage	1 (4.3)	0 (0)
Economic stability		
Regular	6 (26.1)	7 (24.1)
Good	16 (69.6)	22 (75.9)
Excellent	1 (4.3)	0 (0)

Table 1. Bivariate analysis of the socio-demographic variables of Physiotherapy and Medicine students.

Analysis of the survey on perceived academic stress

Regarding the level of perceived stress, it was found that at the 1st moment 48.1% (25/52) perceive stress “sometimes”, however 50% (26/52) perceive it “fairly often” and “many times”. When administering the survey at the 2nd moment, the level of stress perceived by the students was 75% (44/52) for a stress level between “fairly often” and “many times”, as well as the level of stress perceived by students at the 3rd moment with a percentage of 76.9% (27/56). Having said that, regarding the predominant feeling, the “anxiety / distress” was the main emotion that produced stress, this tendency was reiterative in the three moments of the study.

Concerning the factors of the SAS survey, it was found that in the studied population, 6 out of 8 factors, namely “methodological deficiencies”, “student’s overload”, “beliefs about one’s academic performance”, “lack of content value”, “participation” and “exams”, presented a rising variability, in the three moments of the study, going from experiencing stress manifestations “sometimes” to “fairly often” (Table 2).

FACTOR	1st	2nd	3rd
	MOMENT □ ± DE	MOMENT □ ± DE	MOMENT □ ± DE
Methodological deficiencies	2.9 ± 0.8	3.0 ± 0.8	3.1 ± 0.9
Student overload	3.0 ± 0.8	3.3 ± 0.9	3.3 ± 0.9
Beliefs about performance	2.7 ± 0.8	2.9 ± 0.9	3.1 ± 1.0
Public interventions	2.7 ± 0.9	2.6 ± 0.8	2.7 ± 0.8
Negative social climate	2.1 ± 0.9	2.0 ± 0.8	2.2 ± 0.9
Lack of content value	2.4 ± 0.9	2.6 ± 0.9	2.8 ± 1.0
Participation	2.0 ± 0.7	2.2 ± 0.9	2.6 ± 0.9
Exams	3.0 ± 0.9	3.1 ± 0.8	3.4 ± 0.9

Quantitative and qualitative values of academic stressors according to the SAS. 0-0.9 = never; 1.0-1.9 = Sometimes; 2.0-2.9 = Fairly often; 3.0-3.9 = Many times; 4.0-5 = Always

Table 2. Average of each SAS factor for academic programs.

The comparison of means for each factor in the Physiotherapy and Medicine academic programs is described in Figure 1; it was found that the “academic overload” is a prevalent factor with greater response to stress in the Medicine students than in the Physiotherapy students, another factor affected through the academic semester is the one corresponding to “exams”, being higher the frequency of stressors in Medicine students. Figure 1 shows the perception of the different stressors in the students by academic program, where it is evident that the Medicine students exhibit greater perception in the SAS academic stressors. The “activity overload”, “exams”, “beliefs about performance” and “methodological deficiencies” means values are the three factors with the highest stress load perceived by Medicine students with a “fairly often” value above 3, while the factor perceived as the most stressful in the Physiotherapy program was “exams”.

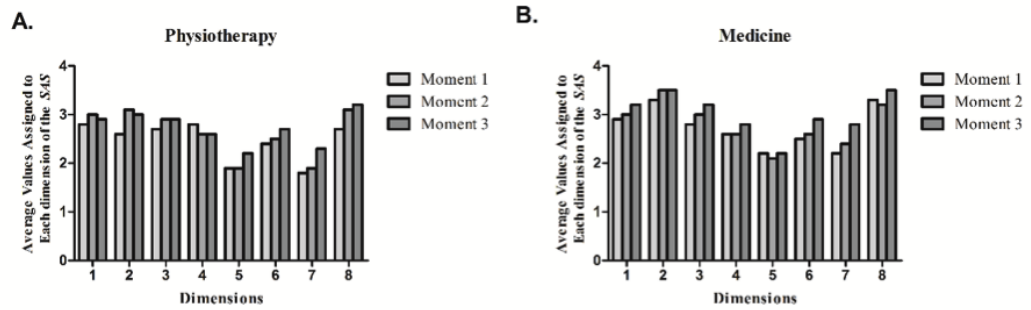


Figure 1. Averages comparison for each SAS factor by academic program.

The data represent the means by factors relating to: 1. Methodological deficiencies; 2. Student Overload; 3. Beliefs About Performance; 4. Public Interventions; 5. Negative Social Climate; 6. Lack of Content Value; 7. Participation; 8. Exams. The values were represented as 0-0.9 = never; 1.0-1.9 = Sometimes; 2.0-2.9 = Fairly often; 3.0-3.9 = Many times; 4.0-5 = Always.

Levels of IL-6 in serum in physiotherapy and medicine students

When performing the descriptive analysis of the IL-6 concentration behavior in the serum of students, it was observed that the data median increased progressively at each moment (Table 3).

	1st Moment	2nd Moment	3rd Moment
Sample size	51	51	51
Minimum value	0.0	0.05	1.9
Percentile 25	1.15	2.15	5.25
Median	3.8	5.1	10
Percentile 75	6.9	9.9	14.6
Maximum value	37.05	44.9	54.4

Table 3. Descriptive values of the IL-6 quantification in Medicine and Physiotherapy students during the academic semester

When the ANOVA test for repeated samples and the Dunn's multiple comparison test were performed, a significant difference was shown in the IL-6 production between the 1st moment and the 3rd moment. Likewise, a significant difference was shown between the 2nd moment and the 3rd moment (Figure 2). The above shows that, at a general level, the students of the Physiotherapy and Medicine programs suffered an increase of this pro-inflammatory cytokine during the academic semester.

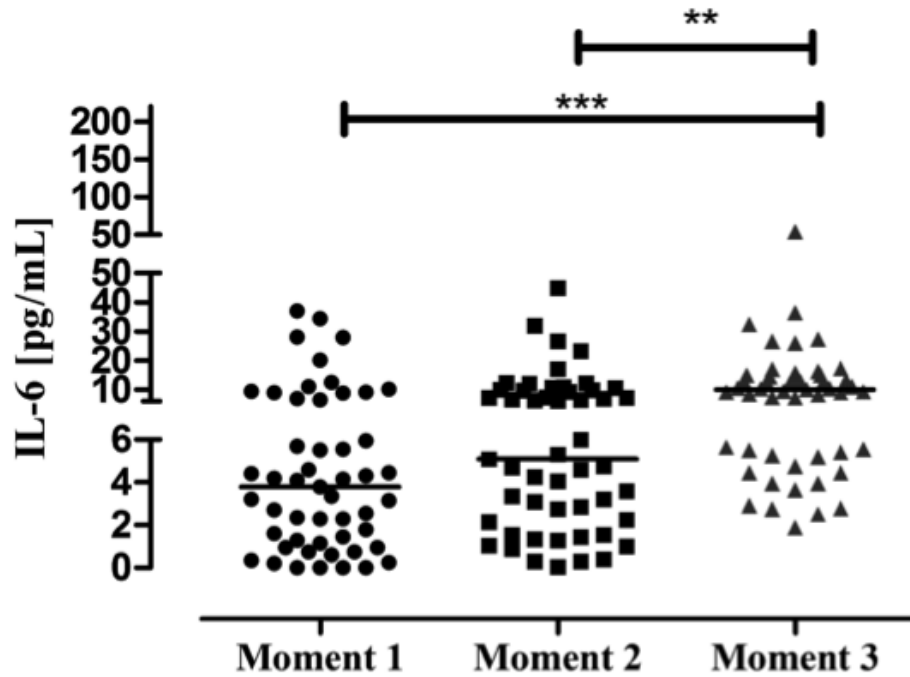


Figure 2. IL-6 quantification (pg / mL) in serum of Physiotherapy and Medicine students throughout the academic semester.

The figure shows the pooled values of the cytokine IL-6 quantification during three moments of the academic semester. The 1st Moment (black circles) corresponding to the beginning of the semester; The 2nd Moment (black squares) corresponding to the 70% grading period of the academic semester; The 3rd Moment (black triangles) corresponding to the end of the semester. The data represent each individual in the study and the horizontal line represents the data median, which were analyzed by the ANOVA test for repeated samples and the Dunn's multiple comparison test, $p < 0.001$ (***) and $p < 0.01$ (**).

When analyzing the IL-6 production in each program, it was observed that the Physiotherapy program students do not show significant changes in the IL-6 production between the first and the second moment, even though the values show a relative increase. However, between the 1st moment and the 3rd moment a significant increase is shown (Figure 3.A). Regarding the Medicine program students, a significant increase was observed between the 1st moment and the 3rd moment (Figure 3.B). These results reflect that the IL-6 values increase progressively throughout the semester, both in the Physiotherapy program and in the Medicine program, according to the behavior of the grouped data.

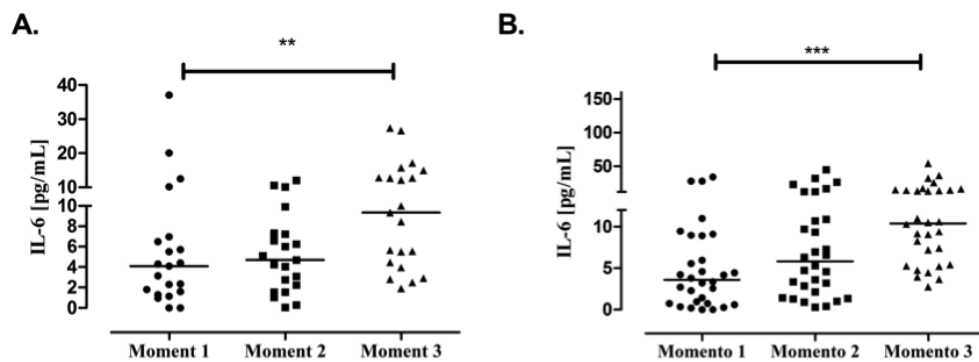


Figure 3A-3B. IL-6 levels (pg / mL) in serum of Physiotherapy and Medicine students throughout the academic semester.

The figure shows the quantification of the Cytokine IL-6 in students of the Physiotherapy program (A) and the Medicine program (B) during three moments of the academic semester. The 1st Moment (black circles) corresponding to the beginning of the semester; the 2nd Moment (black squares) corresponding to the 70% grading period of the academic semester; the 3rd Moment (black triangles) corresponding to the end of the semester. The data represent each individual in the study and the horizontal line represents the data median, which were analyzed by the ANOVA test for repeated samples and the Dunn's multiple comparison test, $p < 0.001$ (***) and $p < 0.01$ (**).

Correlation between the SAS survey results and the IL-6 production

When analyzing the overall correlation between SAS factors and the IL-6 quantification for each moment, an association was found in the Methodological Deficiencies factor with a 0.78 value at the 1st moment, in the other factors there was no correlation among the variables (Table IV). The situational stimuli that the students rated as more threatening for each of the 3 moments were correlated with the IL-6 production and no significant

relationship was found (data not shown).

IV. DISCUSSION

The students who participated in the study share similar sociodemographic characteristics and are enrolled in the semester with the highest number of academic credits of each program. When investigating the level of perceived stress in the population, it was observed that as academic semester progresses, the level of perceived stress by the students was higher, characterized by an anxiety and distress feeling; however, a scale was not applied to determine such levels of anxiety (Castillo, Chacón, Díaz, 2016).

Regarding the SAS survey factors, it was found that in studied population (6 out of 8), factors such as: “methodological deficiencies”, “student overload”, “beliefs about performance”, “lack of content value”, “participation” and “exams”, presented variability in the three moments of the survey administration. Though, Medicine students showed greater stressors in the “Academic overload”, “Methodological deficiencies” and “Exams” factors; similar to what was found in the study by Taboada & Cabanach (2015) who found that university students are “fairly often” stressed by situations related to the factors corresponding to “methodological deficiencies”, “academic overload” and “exams”, which, corresponds to the results obtained by this investigation. Meanwhile, in Physiotherapy students the factors with the most frequent stressors were: “Academic overload” and “exams”. The results presented in this study agree upon the results obtained by Toribio et al. (2016), who studied a population of undergraduate nursing students at the University of Papaloapan (Mexico), where he found that the most affecting stressors in this population were: “exams”, “academic overload”, “short delivery period” and “teacher’s personality / character”.

Regarding the “exams” factor, which is perceived as an important stressor and is related both, to its preparation and its proximity or administration of the exam, it has been determined that is the one that produces greater anxiety and tension, for this reason it is assigned an important role as a trigger for a state of emotional stress associated with the action of taking exam. The result of this study, just like that of Hernández et al. (2011), show that anxiety about exams not only affects academic performance, but is also related to the emotional state and students’ health. The obtained results were corroborated with the results of other investigations (Cardona-Arias, Pérez-Restrepo, Rivera-Ocampo, Gómez-Martínez, Reyes, 2015; García, Arrieta, Montagut, 2014) and are coherent with the related studies in the corresponding subject. That is, “exams” and “academic overload” are among the most frequent academic stressors in the life of a university student.

Regarding the “participation” factor, this study shows that what affects students the most is giving an oral presentation about their work, or expressing themselves to others during

a certain period of time, as well as answering questions, expressing opinions or explaining their point of view to the audience. These stress situations may have their origin in the quality of the academic preparation to be presented, or in a personal insecurity. Thus, it can be concluded that students perceive as stressful, any situation in which they are evaluated through participation, these findings are similar to those reported by [García et al. \(2014\)](#). In our study, the “participation” factor is classified as a stressor that can have a negative impact on the health of university students. The participation situations that affect students the most are giving an oral presentation about their work or expressing themselves to others. In the “negative social climate” factor, students perceive an uncomfortable environment within their respective classrooms, which hinders peer support and collaboration. This factor can be explained related to the natural grouping constituted by the classroom and the interactions taking place in it through cooperation, competition or leadership, and which configure what we know as social climate, which can be explained with the time students spend throughout their academic training in both, theoretical, and practical activities; these academic stressors were assessed with a “many times” occurrence, but in spite of this, no significant differences were found, similar to what was found in the study by [García et al. \(2014\)](#), where the least stressful factor was “the negative social climate” perceived by students in Health programs.

Cytokine profiles are immune-biochemical markers frequently used in stress situations. Studies have shown relationship between problems associated with stress with pro-inflammatory cytokines increase in patients, for example in the meta-analysis conducted by [Segerstrom & Miller \(2004\)](#), it was found that in patients with psychological stress, there is a high concentration of cytokines such as IFN- γ and IL-6. This increase in pro-inflammatory cytokines has also been documented in studies where circumstances of academic stress were evaluated in students of Health Sciences programs ([Assaf, Al-Abbassi, Al-Binni, 2017](#)). Our results show an increase of the cytokine IL-6 when analyzing the grouped data of the students of the Physiotherapy and Medicine programs; this increase appears when comparing three moments of the academic semester, being significant the difference between the first and the third moment, and between the second and the third moment. These data correlate with the ones reported by different authors ([Kang & Fox, 2001](#)). Likewise, Marshall et al., 1998 analyzed the IFN- γ and IL-10 levels, four weeks before and 48 hours after a partial exam in 16 Medicine students at the University of Texas; results showed higher IFN- γ values before the test, which decreased after 48 hours, while the IL-10 values increased. These data suggest that “exams” situation is psychologically stressful, and changes the balance of Th1/Th2 type cytokines, causing the Th2 type content to increase, which produces an immunological dysregulation ([Marshall, Agarwal, Lloyd, Cohen, Henninger, Morris, 1998](#)). Similarly, [Lester et al.\(2010\)](#), analyzed the concentrations of various cytokines, including IL-6, in saliva samples from 36 Anatomy students from different programs in the health area one day before the 3 evaluations of the semester, the results showed that IL-6 concentrations

as well as other pro-inflammatory cytokines increased gradually from the first evaluation to the third one.

Increase of the IL-6 in Physiotherapy and Medicine students should be taken into account as a starting point to conduct new studies to evaluate the immune status of students, since it has been suggested that the changes evidenced in the balance between Th1/Th2 responses, could lead to a decrease in cell-mediated immunity, which would increase the risk of susceptibility to viral, mycotic and bacterial infections (Elenkov & Chrousos, 1999); at the same time, chronic increase of the cytokine IL-6 could be related to short, medium or long term development of diseases of inflammatory etiology, such as cardiovascular diseases, diabetes, obesity, periodontal diseases, even cancer (Godbout & Glaser, 2005; Wellen & Hotamisligil, 2005).

In addition, the chronic inflammatory condition, not only would be related to the physical health of students, but also to their mental health, since the inflammation affects several neurotransmitter systems in the brain, including the serotonin, dopamine and glutamate pathways, as well as to the kynurenine pathway, which generates quinolinic acid, a neurotoxic metabolite. Neuroimaging studies have shown that disruption of neurotransmitter pathways is associated with inflammation-induced alterations in brain circuits that mediate motivation and motor activity, as well as anxiety, activation and alarm (Miller & Raison, 2016), so that eventually this chronic inflammatory process caused by academic stress could converge in depression (Loftis, Huckans, Morasco, 2010).

Regarding the correlation between SAS factors and the cytokine IL-6, it was only found correlation in the "1st Moment", specifically in the "methodological deficiencies" factor (0.78) In this regard, authors such as Taboada et al. (2015), express a relationship between academic performance and stress expressed by students, with the disparity between what the teacher teaches and how he/she evaluates. Several studies have addressed the teaching-learning process itself as one of the most significant stressors, mainly related to teacher-student relationships, so it is striking how this strong relationship appears at the beginning of the academic semester before formally starting classes. Undeniably, the difficulties derived from this poor teacher-student interaction are sources of instability, imbalance and academic tensions (Toribio et al., 2016; García et al., 2014). Nevertheless, no significant correlations were found between SAS factors and IL-6; this concurs with the study by Koh et al., 2012 (Koh, Lee, Beyn, Chu, Kim, Seo, 2012) who analyzed effects of psychological stress and pro-inflammatory and anti-inflammatory (IL-6, TNF- α) cytokines in Medicine students. In this case, they did not find a significant relationship between the results of survey and those of the cytokines; still, independently, significant data related to academic stress circumstances were found.

Despite having a measurement scale of academic stressors such as SAS, an instrument that allowed to evaluate specific factors to qualify the perception of students' academic stressors, when correlating them with the biological IL-6 measurements, it was observed

an absence of equivalence between scale and biological measure as expressed by Tangarife-Lujan and Cardona Arias (Tangarife & Arias, 2015).

V. CONCLUSIONS

This study revealed that the greatest stressors perceived with the SAS survey administration in the Medicine and Physiotherapy students were (6 out of 8): “methodological deficiencies”, “student overload”, “beliefs about performance”, “lack of content value”, “participation” and “exams”, these presented a rising stress variation, in the three moments of the study, going from presenting stress manifestations “Sometimes” to “Fairly often”.

The study revealed an association between IL-6 values and methodological deficiencies in the evaluation of academic stress level. There was no correlation between the other SAS factors and the IL-6 quantification in students of the Faculty of Health Sciences of the University of Cauca, probably due to the absence of equivalence between the scale and the biological measure. However, the obtained results show that, independently, there is an increase in the cytokine IL-6 over time during the academic semester and that the SAS scale serves to identify the main stressors of students.

This study showed the importance of academic stressors identification to mark a roadmap for the close support of students who experience stress, at same time as it calls for strategies to reduce stressors in University context.

In addition, this study shows the progressive increase of interleukin-6 during a state of chronic academic stress, which correlates with the evidence of the relationship between inflammation and psychiatric illness. Because there is also a relationship between inflammation and progression of different diseases, knowing the inflammatory state of people who experience stress is an interesting topic to explore and prevent diseases linked to chronic inflammatory processes.

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REFERENCIAS

- Abdulghani HM, AlKanhal AA, Mahmoud ES, Ponnampereuma GG, Alfaris EA.** Stress and its effects on medical students: a cross-sectional study at a college of medicine in Saudi Arabia. *Journal of health, population, and nutrition*. 2011;29(5):516.
DOI: [10.3329/jhpn.v29i5.8906](https://doi.org/10.3329/jhpn.v29i5.8906)
- Assaf AM, Al-Abbassi R, Al-Binni M.** Academic stress-induced changes in Th1-and Th2-cytokine response. *Saudi pharmaceutical journal*. 2017;25(8):1237-1247.
DOI: [10.1016/j.jsps.2017.09.009](https://doi.org/10.1016/j.jsps.2017.09.009)
- Cabanach RG, Souto-Gestal A, Franco V.** Escala de Estresores Académicos para la evaluación de los estresores académicos en estudiantes universitarios. *Revista iberoamericana de psicología y salud*. 2016;7(2):41-50.
DOI: [10.1016/j.rips.2016.05.001](https://doi.org/10.1016/j.rips.2016.05.001)
- Cardona-Arias JA, Pérez-Restrepo D, Rivera-Ocampo S, Gómez-Martínez J, Reyes Á.** Prevalence of anxiety in university students. *Diversitas: Perspectivas en Psicología*. 2015;11(1):79-89.
<http://www.scielo.org.co/pdf/dpp/v11n1/v11n1a06.pdf>
- Castillo Pimienta C, Chacón de la Cruz T, Díaz-Véliz G.** Ansiedad y fuentes de estrés académico en estudiantes de carreras de la salud. *Investigación en Educación Médica*. 2016;5(20):230-237.
DOI: [10.1016/j.riem.2016.03.001](https://doi.org/10.1016/j.riem.2016.03.001)
- Compton MT, Carrera J, Frank E.** Stress and depressive symptoms/dysphoria among US medical students: results from a large, nationally representative survey. *The Journal of nervous and mental disease*. 2008;196(12):891-897.
DOI: [10.1097/NMD.0b013e3181924d03](https://doi.org/10.1097/NMD.0b013e3181924d03)
- Dahlin M, Joneborg N, Runeson B.** Stress and depression among medical students: A cross-sectional study. *Medical education*. 2005;39(6):594-604.
DOI: [10.1111/j.1365-2929.2005.02176.x](https://doi.org/10.1111/j.1365-2929.2005.02176.x)
- Deinzer R, Hilpert D, Bach K, Schawacht M, Herforth A.** Effects of academic stress on oral hygiene—a potential link between stress and plaque-associated disease?. *Journal of clinical periodontology*. 2001;28(5):459-464.
DOI: [10.1034/j.1600-051x.2001.028005459.x](https://doi.org/10.1034/j.1600-051x.2001.028005459.x)
- Dube SR, Fairweather D, Pearson WS, Felitti VJ, Anda RF, Croft JB.** Cumulative

childhood stress and autoimmune diseases in adults. *Psychosomatic medicine*. 2009;71(2):243.

DOI: [10.1097/PSY.0b013e3181907888](https://doi.org/10.1097/PSY.0b013e3181907888)

Dyrbye LN, Thomas MR, Massie FS, Power DV, Eacker A, Harper W, et al. Burnout and suicidal ideation among US medical students. *Annals of internal medicine* . 2008;149(5):334-341. DOI: [10.7326/0003-4819-149-5-200809020-00008](https://doi.org/10.7326/0003-4819-149-5-200809020-00008)

Dyrbye LN, Thomas MR, Shanafelt TD. Systematic review of depression, anxiety, and other indicators of psychological distress among US and Canadian medical students. *Academic medicine*. 2006;81(4):354-373.

DOI: [10.1097/00001888-200604000-00009](https://doi.org/10.1097/00001888-200604000-00009)

Dyrbye LN, West CP, Satele D, Boone S, Tan L, Sloan J, et al. Burnout among US medical students, residents, and early career physicians relative to the general US population. *Academic medicine*. 2014;89(3):443-451.

DOI: [10.1097/ACM.0000000000000134](https://doi.org/10.1097/ACM.0000000000000134)

Ekpenyong CE, Daniel NE, Aribo E. Associations between academic stressors, reaction to stress, coping strategies and musculoskeletal disorders among college students. *Ethiopian journal of health sciences*. 2013;23(2):98-112. [PubMed](#)

Elenkov IJ, Chrousos GP. Stress hormones, Th1/Th2 patterns, pro/anti-inflammatory cytokines and susceptibility to disease. *Trends in Endocrinology & Metabolism*. 1999;10(9):359-368.

DOI: [10.1016/s1043-2760\(99\)00188-5](https://doi.org/10.1016/s1043-2760(99)00188-5)

García BR, Arrieta MdPG, Montagut ALEB. Estresores académicos percibidos por estudiantes pertenecientes a la escuela de enfermería de Ávila, centro adscrito a la Universidad de Salamanca. *Revista Enfermería CyL*. 2014;6(2):98-105
<http://www.revistaenfermeriacyl.com/index.php/revi>

Glaser R, Pearl DK, Kiecolt-Glaser J, Malarkey WB. Plasma cortisol levels and reactivation of latent Epstein-Barr virus in response to examination stress. *Psychoneuroendocrinology*. 1994;19(8):765-772.

DOI: [10.1016/0306-4530\(94\)90023-x](https://doi.org/10.1016/0306-4530(94)90023-x)

Godbout JP, Glaser R. Stress-induced immune dysregulation: implications for wound healing, infectious disease and cancer. *Journal of Neuroimmune Pharmacology*. 2006;1(4):421-427.

DOI: [10.1007/s11481-006-9036-0](https://doi.org/10.1007/s11481-006-9036-0)

Gomathi KG, Ahmed S, Sreedharan J. Causes of stress and coping strategies adopted by

undergraduate health professions students in a university in the United Arab Emirates. Sultan Qaboos University Medical Journal. 2013;13(3):437.

[PubMed](#)

Hernández JÁ, Parra JMA, Campoy JMF, García DS, Pérez-Gallardo ER. El estrés ante los exámenes en los estudiantes universitarios. propuesta de intervención. International Journal of Developmental and Educational Psychology. 2013;2(1):179-187.
<https://www.redalyc.org/articulo.oa?id=34985217300>

Hojat M, Vergare M, Isenberg G, Cohen M, Spandorfer J. Underlying construct of empathy, optimism, and burnout in medical students. International journal of medical education. 2015;6:12.

[DOI: 10.5116/ijme.54c3.60cd](https://doi.org/10.5116/ijme.54c3.60cd)

Jalilian F, Karami Matin B, Ahmadpanah M, Ataee M, Ahmadi Jouybari T, Eslami AA, et al. Socio-demographic characteristics associated with cigarettes smoking, drug abuse and alcohol drinking among male medical university students in Iran. Journal of research in health sciences. 2015; 15(1):42-46 [PubMed](#)

Kang DH, Fox C. Th1 and Th2 cytokine responses to academic stress. Research in nursing & health. 2001;24(4):245-257. [DOI: 10.1002/nur.1027](https://doi.org/10.1002/nur.1027)

Koelsch S, Boehlig A, Hohenadel M, Nitsche I, Bauer K, Sack U. The impact of acute stress on hormones and cytokines, and how their recovery is affected by music-evoked positive mood. Scientific reports. 2016;6:23008.
[/doi.org/10.1038/srep23008](https://doi.org/10.1038/srep23008)

Koh KB, Lee YJ, Beyn KM, Chu SH, Kim DM, Seo WY. Effects of high and low stress on proinflammatory and antiinflammatory cytokines. Psychophysiology. 2012;49(9):1290-1297.
[DOI: 10.1111/j.1469-8986.2012.01409.x](https://doi.org/10.1111/j.1469-8986.2012.01409.x)

La Fratta I, Tatangelo R, Campagna G, Rizzuto A, Franceschelli S, Ferrone A, et al. The plasmatic and salivary levels of IL-1?, IL-18 and IL-6 are associated to emotional difference during stress in young male. Scientific reports. 2018;8(1):3031.
[DOI: 10.1038/s41598-018-21474-y](https://doi.org/10.1038/s41598-018-21474-y)

Lester SR, Brown JR, Aycock JE, Grubbs SL, Johnson RB. Use of saliva for assessment of stress and its effect on the immune system prior to gross anatomy practical examinations. Anatomical sciences education. 2010;3(4):160-167.
[DOI: 10.1002/ase.161](https://doi.org/10.1002/ase.161)

Loftis JM, Huckans M, Morasco BJ. Neuroimmune mechanisms of cytokine-induced

depression: current theories and novel treatment strategies. *Neurobiology of disease*. 2010;37(3):519-533.

DOI: [10.1016/j.nbd.2009.11.015](https://doi.org/10.1016/j.nbd.2009.11.015)

Marshall Jr GD, Agarwal SK, Lloyd C, Cohen L, Henninger EM, Morris GJ.

Cytokine dysregulation associated with exam stress in healthy medical students. *Brain, behavior, and immunity*. 1998;12(4):297-307.

DOI: [10.1006/brbi.1998.0537](https://doi.org/10.1006/brbi.1998.0537)

Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to

modern treatment target. *Nature reviews immunology*. 2016;16(1):22. DOI:

[10.1038/nri.2015.5](https://doi.org/10.1038/nri.2015.5)

Murali R, Hanson MD, Chen E. Murali R, Hanson MD, Chen E. Psychological stress and its

relationship to cytokines and inflammatory diseases. *Cytokines: Stress and Immunity*. 2nd Edition ed. Boca Raton, FL: Taylor & Francis Group. 2007.

<https://www.scholars.northwestern.edu/en/publicati>

Sarid O, Anson O, Yaari A, Margalith M. Academic stress, immunological reaction, and

academic performance among students of nursing and physiotherapy. *Research in nursing & health*. 2004;27(5):370-387. DOI: [10.1002/nur.20028](https://doi.org/10.1002/nur.20028)

Segerstrom SC, Miller GE. Psychological stress and the human immune system: a meta-

analytic study of 30 years of inquiry. *Psychological bulletin*. 2004;130(4):601.

DOI: [10.1037/0033-2909.130.4.601](https://doi.org/10.1037/0033-2909.130.4.601)

Taboada MVF, Cabanach RG. La medición del estrés en contextos académicos en

estudiantes universitarios: Universidade da Coruña; 2015.

<https://ruc.udc.es/dspace/handle/2183/15705>

Tangarife JL, Arias JAC. Construcción y validación de escalas de medición en salud:

revisión de propiedades psicométricas. *Archivos de medicina*. 2015;11(3):1.

<http://www.archivosdemedicina.com/medicina-de-fami>

Tian R, Hou G, Li D, Yuan T-F. A possible change process of inflammatory cytokines in the

prolonged chronic stress and its ultimate implications for health. *The Scientific World Journal* .2014.

DOI: [10.1155/2014/780616](https://doi.org/10.1155/2014/780616)

Toribio-Ferrer C, Franco-Bárceñas S. Estrés académico: el enemigo silencioso del

estudiante. *Revista Salud y Administración*. 2016;3(7):11-18

http://www.unsis.edu.mx/revista/doc/vol3num7/A2_Es

Trueba A, Ryan MW, Vogel PD, Ritz T. Effects of academic exam stress on nasal leukotriene B4 and vascular endothelial growth factor in asthma and health. *Biological psychology*. 2016;118:44-51.

DOI: [10.1016/j.biopsycho.2016.04.009](https://doi.org/10.1016/j.biopsycho.2016.04.009)

Tseng T, Iosif AM, Seritan AL. Stress effects: A study of salivary cortisol levels in third-year medical students. *Stress and health*. 2011;27(5):436-440. DOI: [10.1002/smi.1377](https://doi.org/10.1002/smi.1377)

Walsh J, Feeney C, Hussey J, Donnellan C. Sources of stress and psychological morbidity among undergraduate physiotherapy students. *Physiotherapy*. 2010;96(3):206-212.

DOI: [10.1016/j.physio.2010.01.005](https://doi.org/10.1016/j.physio.2010.01.005)

Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. *The Journal of clinical investigation*. 2005;115(5):1111-1119.

DOI: [10.1172/JCI25102](https://doi.org/10.1172/JCI25102)