OPINION ARTICLE

Received: 02/18/2018
Accepted: 08/27/2018
Funding: none

Biomarkers as innovative trend for aid in the diagnosis of mental diseases among workers

Os biomarcadores como tendência inovadora para auxiliar no diagnóstico de doenças mentais em trabalhadores

Sérgio Valverde Marques dos Santos[1], Rita de Cássia de Marchi Barcellos Dalri[1], Vanessa Augusto Bardaquim[1], Maria Lucia do Carmo Cruz Robazzi[1]

ABSTRACT | Given the weaknesses of technological advances, and the transformations in the world of work occurred in the 21st century, the demands on workers are increasing, with consequent elevation of their physical and psychological load. Such higher load might increase the frequency of stress-related diseases, anxiety and depression disorders, which might be seen as a consequence of the interaction between other psychosocial variables and the organization of work. An approach to the diagnosis of these diseases involves the use of specific biomarkers, which have been used for diagnosis of diseases in several populations, including workers, resulting in better prognosis. Chromogranin A might be a useful biomarker for investigation of mental diseases such as anxiety. The salivary cortisol has been used to assess the functioning of the hypothalamic-pituitary-adrenal axis in cases of cognitive dysfunction, stress, anxiety and depression. Hair cortisol is considered a useful biomarker for assessment of chronic stress associated with depression and depressive episodes. Prevention of psychosocial hazards and early diagnosis with the help of biomarkers in combination with the clinical interview and examination might reduce presenteeism and absenteeism, and promote improvement of the mental health of workers. More thorough knowledge on anxiety, stress and depression, and diagnosis with the help of biomarkers might contribute to improve the working and health conditions of workers, with reflection on the quality of the work they perform.

Keywords | biomarkers; occupational health; anxiety; psychological stress; depression.

RESUMO | Com as fragilidades dos avanços tecnológicos e as transformações ocorridas no mundo do trabalho no século XXI, os trabalhadores passaram a ser mais exigidos no ambiente laboral, aumentando a sua carga física e psíquica. Tais cargas podem levar ao aumento de doenças relacionadas ao estresse, a quadros ansiosos e depressivos, que podem ser vistas como consequência da interação entre outras variáveis psicossociais e a organização laboral. Uma possibilidade de diagnosticar tais enfermidades é a utilização de biomarcadores específicos, que têm sido utilizados para o diagnóstico de doenças em diversas populações, entre elas a de trabalhadores, resultando em melhores prognósticos. A Cromogranina A pode ser um biomarcador útil para investigar doenças mentais como a ansiedade. Além desse, o cortisol salivar tem sido utilizado para avaliar o funcionamento do eixo hipotálamo-hipófise-adrenal em alterações da função cognitiva, em situações de estresse, ansiedade e depressão. O cortisol presente nos fios de cabelos também é considerado um biomarcador útil para avaliar o estresse crônico relacionado à depressão e aos episódios depressivos. A prevenção em relação aos riscos psicossociais e o diagnóstico precoce por meio do auxílio dos biomarcadores, junto ao exame clínico e anamnese, podem diminuir o presenteísmo e absenteísmo e promover melhorias na saúde mental dos trabalhadores. O aprofundamento do conhecimento sobre ansiedade, estresse e depressão e o diagnostico com o auxílio os biomarcadores pode contribuir para a melhoria das condições laborais e de saúde dos trabalhadores e, sobretudo, reverter-se na qualidade do trabalho executado por eles.

Palavras-chave | biomarcadores; saúde do trabalhador; ansiedade; estresse psicológico; depressão.

[1]Nursing School of Ribeirão Preto, Universidade de São Paulo – Ribeirão Preto (SP), Brazil.
DOI: 10.5327/Z1679443520180234

INTRODUCTION

The Brazilian society has sought advances in workers' health in the past decades by means of public policies ranging from healthcare and health promotion actions to prevention and surveillance of work-related health problems. However, such advances are still too weak to improve indicators, due to several hindrances to a sound development of programs and actions centered on workers' health[1].

Given the weaknesses of the aforementioned advances, and the transformations in the world of work which occurred in the 21st century, the demands on workers are increasing, with consequent elevation of their physical and psychological load[2]. Psychosocial factors and the organization of work have significant impact on the health, well-being and quality of life of workers[3].

Psychosocial hazards are all the risk factors or agents present in the work environment which might harm the mental health of workers. They are associated with daily life tensions, including the ones originated in work[4], which are related to how work is conceived of, organized and performed. These factors might eventually impair the mental and/or physical health of workers[5], and contribute to increase their levels of stress.

Among the psychosocial factors more frequently reported by workers, stress, anxiety and depression stand out. These conditions might be seen as a consequence of the interaction between other psychosocial variables and the organization of work, in addition of being a cause of work disability[6].

These conditions might be diagnosed on the basis of the symptoms exhibited by individuals, as well as by means of measurement with scales or inventories, which are most often responded on Likert scales, and ae frequently used in studies to evaluate populations[7]. Alternatively, these conditions might be diagnosed through the use of specific biomarkers.

Biomarkers are substances or their biologically transformed products (blood, saliva, hair, urine, stools) as well as any early biochemical change in biological fluids, tissues or the exhaled air which measurement allows establishing the intensity of exposure and risk to health[8]. Biomarkers thus consist in predictive tests for some diseases, as e.g., intestinal and liver cancer and mental diseases. Application of such tests might be seen as a search and health surveillance strategy[9].

Biomarkers have been used to diagnose diseases in different populations, including workers. This approach to screening might result in better prognosis, given that work might make workers ill[10]. Biomarkers might provide proof of mental illness in medical legal examinations, and thus contribute to prevent/reduce presenteeism, absenteeism and loss of productivity.

In this regard, we should observe that the use of biomarkers does not replace the clinical interview and evaluation, which in the opposite are crucial for diagnosis. Biomarkers might be used as auxiliary methods to confirm diagnosis, and contribute to the establishment of the prognosis of a case of mental disease through their correlation with the factors investigated in the clinical evaluation. Such evaluations should be highly detailed, and seek to identify mental, social and occupational stress to reach a precise diagnosis based on the List of Work-Related Diseases, given that mental disorders correspond to the International Classification of Diseases (ICD-10) chapter V. In recent years, the use of biomarkers as research method for mental diseases consolidated as an innovative indicator with high potential for detection and diagnosis worldwide[11]. Recent studies pointed to the effectiveness of biomarkers for assessment of psychosocial hazards related to occupational health[12-14]. As a result, the use of biomarkers represents an innovative, safe and efficacious trend for diagnosis of mental diseases among workers and other populations. They favor faster diagnostic and better prognosis for workers affected by mental disorders, and thus contribute to improve their working and living conditions.

The aim of the present article is to discuss some of the mental diseases most often diagnosed among workers, such as anxiety, stress and depression, and some biomarkers used for their diagnosis. In addition, we describe some of the scientific evidence which demonstrates the efficacy of biomarkers.

METHODS

The present is a theoretical and opinion essay on the use of biomarkers to contribute to the diagnosis of mental diseases among workers. It is based on a logical and reflexive discussion, with careful argumentation, in addition to substantial

interpretation and personal criticism[15]. The present study was developed based on our critical and careful assessment and perception of the subject of interest, with support on the national and international literature on the use of biomarkers for diagnosis of mental diseases.

For being a theoretical and opinion essay, there was no need of clearance by a research ethics committee.

We formulated guiding points to describe the analyzed biomarkers. For this purpose, we surveyed and reflected on the main biomarkers discussed in the literature, as well as on the main mental diseases among workers, based on the significance of results and correlations among the considered determinants (chromogranin A and anxiety, salivary cortisol and stress, hair cortisol and depression). The resulting guiding points were: chromogranin A (CgA) as biomarker of anxiety, salivary cortisol as biomarker of stress, and hair cortisol as biomarker of depression.

RESULTS AND DISCUSSION

CHROMOGRANIN A AS BIOMARKER OF ANXIETY

Pathological anxiety is seen as a psychiatric problem, which might be defined as a state of vague and unpleasant apprehension, attended by symptoms such as nervous stomach, chest tightness, palpitations, faster heart rate, trembling, symptoms derived from the activation of the sympathetic system, or a feeling of insecurity originated the perception of uncertain danger of unknown origin[16].

Anxiety disorders affect people all across the world. At the global level, anxiety is the sixth cause of impairment of the state of health. About 264 million people worldwide lived with anxiety disorders in 2015, being the Americas the third in number of cases, and the global prevalence 21%[17]. Anxiety is one of the most prevalent mental diseases among workers. It is defined as a mental-emotional state able to cause physiological, emotional and social disorders, and eventually also disability when in high level. This condition might derive from pressure and stressors in the work environment[18].

Anxiety might be characterized as a feeling of apprehension, with effects on the consciousness and the autonomous nervous system. Therefore, high levels of anxiety might impair the learning and professional performance[19]. It might be diagnosed based on its symptoms by means of scales and inventories[7]. Another diagnostic approach has resource to salivary biomarkers. The saliva is seen as a favorable source for diagnosis, because collection is noninvasive and does not pose any risk[20].

About 98% of the saliva is water, and the other components include electrolytes, mucopolysaccharides, glycoproteins, antiseptic substances and enzymes. CgA is one of the salivary glycoproteins, which is stored in secretory vesicles in the adrenal medulla and sympathetic nerves, being released by exocytosis together with catecholamines[21,22].

CgA, also known as secretogranin I, is a part of a group of proteins present in several neuroendocrine tissues. It is abundant in endocrine cells which secrete peptide hormones from storage vesicles, and acts in the neuroendocrine secretion through binding to the intravesicular calcium[23]. CgA has called considerable attention as a salivary biomarker in healthy individuals and patients with chronic diseases. Its main advantage is its durability. The interval between a mental stimulus and the peak salivary concentration is short, and remains elevated for up to 60 minutes following a stimulus, i.e., during the stage of recovery. Therefore, salivary CgA might represent a useful biomarker for mental diseases[24].

A study conducted with nursing students in Japan found that the CgA levels increased in stressful situations, mainly in the presence of anxiety symptoms associated with examination stress[25]. In another study, the salivary CgA increased during stress load tasks, pointing to its possible candidacy as a biomarker for mental workload, stress and anxiety[26]. A study on the elevation of the anxiety levels upon driving vehicles found positive correlation with higher CgA levels[27].

Therefore, CgA might be used as aid in the diagnosis of mental diseases or symptoms, including anxiety. However, we should observe that the clinical interview and examination are crucial, and their correlation with changes in the CgA levels is relevant to establish a precise diagnosis. In this regard, we stress the need for more studies on mental illness among workers and its relationship with CgA.

SALIVARY CORTISOL AS BIOMARKER OF STRESS

Stress is an occupational hazard for workers, whence the relevance of early detection.

Stress is the term used to designate the body response to any stimulus, no matter whether favorable, unfavorable or imaginary, which interferes with the body balance. For this reason, it is directly related to homeostasis, as it disrupts the mutual balance of the body systems, and the balance between the body and the outer environment. Stress is further considered a biopsychosocial process, because its occurrence depends on personal and environmental aspects[28]. The body response is the same for either positive or negative events.

Stress management programs need to be formulated, in addition to interventions to eliminate or minimize environmental stressors, and actions centered on individuals to reduce the impact of existing hazards through the development of an adequate repertory of individual coping strategies[29].

The main mediators of stress are steroids produced in the adrenal glands, catecholamines (epinephrine and norepinephrine) and other hormones, such as dehydroepiandrosterone (DHEA), prolactin and growth hormone (GH), and cytokines with immune activity[30].

The reaction to stressors is often considered as a fight–or–flight response, because in extreme conditions it prepares the body for these two alternatives. The response involves elevation of the respiratory and heart rates to increase the oxygen flow to the main muscles; skin vasoconstriction to reduce bleeding in case of wounds; mobilization of the liver and muscle carbohydrates to increase the blood sugar and thus provide fuel to reactions; and reinforcement of the immune system for defense[31].

Occupational stress is a phenomenon that develops in the body of workers, and might affect their health. The main causes of stress in the work environment are related to the work organization, management and system, and the quality of human relationships[32].

When discussing stress, one should consider two fundamental aspects: the situation likely to cause stress (stressor) and the individual's reaction to a stressor (stress response or process). When the response is negative, and triggers an inadequate adaptive process eventually causing disease, it is designated distress. Contrariwise, when the response is positive, it is named eustress[33].

Stress activates the hypothalamic-pituitary-adrenal (HPA) axis, resulting in elevation of the circulating glucocorticoids. Exposure to stressors activates the neurons of the paraventricular nucleus of thalamus, which secrete releasing hormones, such as corticotropin-releasing hormone (CRH). CRH is secreted by neuron terminals close to the hypophyseal portal system at the median eminence of the hypophysis, but might also have effects on other areas, such as the amygdala, hippocampus and locus coeruleus. CRH acts on the anterior pituitary, where it promotes the release of adrenocorticotropic hormone (ACTH), which in turn acts on the adrenal cortex, where it triggers the synthesis and release of glucocorticoids, such as cortisol in humans. The plasma peak glucocorticoid concentration occurs some dozens of minutes after the onset of stress[34,35].

Cortisol is a primary glucocorticoid synthesized from cholesterol in the adrenal cortex under the action of ACTH. Also known as hydrocortisone, its chemical designation is 11-ß, 17a, 21-Trihydroxypregn-4-ene-3,20-dione, chemical formula $C_{21}H_{30}O_5$, and molar mass 362.466 g/mol. It is essential to life, as it regulates the carbohydrate, protein and lipid metabolism. In addition, it maintains the blood pressure within the normal range, and inhibits allergic and inflammatory reactions[36].

There are four methods to measure the cortisol levels (blood, saliva, urine and chair). Saliva sample collection for cortisol measurement is noninvasive, has low cost, and is easy to perform[37].

Measurement of the salivary cortisol allows assessing the HPA axis function in cases of cognitive dysfunction, stress, anxiety, depression, panic syndrome, sleep deprivation among workers allocated to the night shift, and individuals with chronic fatigue[38].

A study performed with hospital nurses in Singapore investigated and compared self-perceived occupational stress and the salivary cortisol. The results showed that the nurses allocated to the emergency department exhibited higher levels of occupational stress, and that the morning salivary cortisol was correlated with occupational stress[39]. Another study which analyzed the cortisol levels as a function of emotions triggered by exposure to stressors found correlation between the cortisol response and stress[40]. A study conducted in Japan analyzed the effects of psychosocial strain at work on the excretion of neuroendocrine stress hormones (epinephrine, norepinephrine and cortisol). The results showed significantly lower cortisol concentration in the high-strain group.

The lower cortisol concentration in the high-strain group might indicate circadian rhythm disturbance induced by job strain[41].

As a result, the study of cortisol as an aid in stress research is calling the attention of investigators interested in further developing studies aiming at the control of the effects of stress not only on the quality of life of individuals, but also on the performance and efficiency of workers in general.

HAIR CORTISOL AS BIOMARKER OF DEPRESSION

Depression affects more than 350 million people, and is one of the main causes of disability worldwide[42]. It might be triggered by several factors, such as loss of a beloved person, end of a relationship, financial problems, long working hours, pressure, competitiveness and stress[43].

However, the biological aspects of depression are the same in all cases, and independent from sex. Depression includes periods of melancholy, anxiety, weight loss, low-self-esteem, self-blame, neurotransmitter release, and consequent reduction of the function of anatomical structures[44].

Within the field occupational health, the fact that long working hours are associated with depression, anxiety, insomnia and heart disease is well known[45]. The working conditions are a significant determinant of psychological well-being and mental disorders, depression in particular[46]. In Brazil, almost 30% of intensive care unit nursing professionals exhibited depression, and the associated factors were: allocation to the night shift, double shifts, and being separated or divorced[47].

The HPA axis plays a crucial role in the response to external and internal stimuli, including psychological stressors. Hyperactivity of the HPA axis is a constant finding in major depression. Patients with major depression exhibit increased cortisol concentration in the plasma, urine and cerebrospinal fluid (CSF), exaggerated cortisol response to ACTH stimulation, and increase of the pituitary and adrenal glands[48].

In regard to long-term biomarkers, the activity of the HPA axis might be abnormal; hair cortisol (hair CORT) is considered a biomarker of chronic stress[49]. According to some authors, hair CORT might be the best biomarker for assessment of chronic stress, because it does not require repeated measures, and thus reduces the cost with biochemical agents[50].

Recent studies on stress evidenced an increasing interest in the measurement of hair CORT[13]. However, different groups use different methods for analysis, which hinders the comparison and standardization of results[51].

The work environment might be considered a relevant psychosocial stressor, and has been associated with excessive cortisol release, reduced immune function, and increased susceptibility to infections and neoplasms[52]. A study performed with nursing professionals found atypical patterns of cortisol secretion and work-related chronic stress[53].

Some studies showed that hair CORT exhibits relevant properties for large-scale evaluation (3,507 participants) which confirms that the mental and physical state of health is related to this biomarker. The hair CORT levels were found increase in major depression[13,14]. This finding might indicate new opportunities for prevention and treatment of depression based on diagnosis by means of hair CORT.

FINAL CONSIDERATIONS

Prevention of psychosocial hazards and early diagnosis with the help of biomarkers might reduce presenteeism and absenteeism, and promote improvement of the mental health of workers.

More thorough knowledge on anxiety, stress and depression might contribute to improve the working and health conditions of workers, with reflection on the quality of the work they perform. Several studies showed that various biomarkers might be used in the assessment of these diseases among workers in different areas.

Identification of hazards and mental illness factors in the workplace might be considered a means for change. Such identification might be performed with the help of biomarkers, together with the clinical interview and examination. Once these factors are identified, workers and managers might discuss them, and suggest possible solutions to minimize their effects. As a result, the daily routine of workers might become more productive and less exhausting, and their human and professional aspects attributed their proper value.

REFERENCES

1. Lacaz FAC. Política Nacional de Saúde do Trabalhador: desafios e dificuldades. In: Lourenço E, Navarro V, Silva J, Sant'ana R (Eds.). O avesso do trabalho II: trabalho, precarização e saúde do trabalhador. São Paulo: Expressão Popular; 2010. p.199-230.
2. Kamimura QP, Tavares RSCR. Acidentes do Trabalho Relacionados a Transtornos Psicológicos Ocupacionais. Rev Gestão Sist Saúde. 2012;1(2):140-56. http://doi.org/10.5585/rgss.v1i2.27
3. Theme Filha MM, Costa MAS, Guilam MCR. Estresse ocupacional e autoavaliação de saúde entre profissionais de enfermagem. Rev Latino-Am Enf. 2013;21(2):1-9.
4. Caran VCS. Riscos psicossociais e assédio moral no contexto acadêmico [MA dissertation]. Ribeirão Preto: Universidade de São Paulo; 2007.
5. Matos SS. Riscos Psicossociais em Trabalhadores na Arábia Saudita [MA dissertation]. Setúbal: Escola Superior de Ciências Empresariais; 2014.
6. Serafim AC, Campos ICM, Cruz RM, Rabuske MM. Riscos psicossociais e incapacidade do servidor público: um estudo de caso. Psicol Ciênc Prof. 2012;32(3):686-705. http://dx.doi.org/10.1590/S1414-98932012000300013
7. Cunha JA. Manual da versão em português das Escalas de Beck. São Paulo: Casa do Psicólogo; 2001.
8. World Health Organization. Biological Monitoring of Chemical Exposure in the Workplace. Geneva: World Health Organization; 1996.
9. Soreide K, Watson MM, Lea D, Nordgard O, Soreide JA, Hagland HR. Assessment of clinically related outcomes and biomarker analysis for translational integration in colorectal cancer (ACROBATICC): study protocol for a population-based, consecutive cohort of surgically treated colorectal cancers and resected colorectal liver metastasis. J Transl Medic. 2016;14(1):192. https://doi.org/10.1186/s12967-016-0951-4
10. Maschirow L, Khalaf K, Al-Aubaidy HA, Jelinek HF. Inflammation, coagulation, endothelial dysfunction and oxidative stress in prediabetes - Biomarkers as a possible tool for early disease detection for rural screening. Clin Biochem. 2015;48(9):581-5. https://doi.org/10.1016/j.clinbiochem.2015.02.015
11. Wang H, Zhang H, Deng P, Liu C, Li D, Jie H, et al. Tissue metabolic profiling of human gastric cancer assessed by 1H NMR. BMC Cancer. 2016;16(371):2-12. https://doi.org/10.1186/s12885-016-2356-4
12. Noto Y, Kudo M, Hirota K. Back massage therapy promotes psychological relaxation and an increase in salivary chromogranin A release. J Anesth. 2010;24:955-8. https://doi.org/10.1007/s00540-010-1001-7
13. Abell JG, Stalder T, Ferrie JE, Shipley MJ, Kirschbaum C, Kivimäki M, et al. Assessing cortisol from hair samples in a large observational cohort: The Whitehall II study. Psychoneuroendocrinology. 2016;73:148-56. https://doi.org/10.1016/j.psyneuen.2016.07.214
14. Staufenbiel SM, Penninx BW, Spijker AT, Elzinga BM, Van Rossum EF. Hair cortisol, stress exposure, and mental health in humans: A systematic review. Psychoneuroendocrinology. 2013;38(8):1220-35. https://doi.org/10.1016/j.psyneuen.2012.11.015
15. Severino AJ. Metodologia do trabalho científico. 22nd ed. São Paulo: Cortez; 2002.
16. Graeff FG, Brandão ML. Neurobiologia das doenças mentais. 5th ed. São Paulo: Lemos; 1999.
17. World Health Organization. Depression and Other Common Mental Disorders: Global Health Estimates. Geneva: World Health Organization; 2017.
18. Vieira TG, Beck CLC, Dissen CM, Camponogara S, Gobatto M, Coelho APF. Adoecimento e uso de medicamentos psicoativos entre trabalhadores de enfermagem de unidades de terapia intensiva. Rev Enf UFSM. 2013;3(2):205-14. http://dx.doi.org/10.5902/217976927538
19. Carvalho R, Farah OGD, Galdeano LE. Níveis de ansiedade de alunos de graduação em enfermagem frente à primeira instrumentação cirúrgica. Rev Latino-Am Enferm. 2004;12(6):918-23. http://dx.doi.org/10.1590/S0104-11692004000600011
20. Yeh CK, Christodoulides NJ, Floriano PN, Miller CS, Ebersole JL, Weigum SE, et al. Current development of saliva/oral fluid-based diagnostics. Text Dent J. 2010;127(7):651-61.
21. Pink R, Simek J, Vondrakova J, Faber E, Michl P, Pazdera J, et al. Saliva as a diagnostic medium. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2009;153(2):103-10.
22. McVicar AJ, Greenwood CR, Fewell F, D'Arcy V, Chandrasekharan S, Alldridge LC. Evaluation of anxiety, salivary cortisol and melatonin secretion following reflexology treatment: A pilot study in healthy individuals. Complement Ther Clin Pract. 2007;13:137-45. https://doi.org/10.1016/j.ctcp.2006.11.001
23. Almeida JRC. Farmacêuticos em oncologia: uma nova realidade. São Paulo: Atheneu; 2004.
24. Obayashi K. Salivary mental stress proteins. Clin Chimica Acta. 2013;425:96-201. https://doi.org/10.1016/j.cca.2013.07.028
25. Takatsuji K, Sugimoto Y, Ishizaki S, Ozaki Y, Matsuyama E, Yamaguchi Y. The effects of examination stress on salivary cortisol, immunoglobulin A, chromogranin A nursing students. Biomed Res. 2008;29(4):221-4.
26. Yoto A, Murao S, Nakamura Y, Yokogoshi H. Intake of green tea inhibited increase of salivary chromogranin A after mental task stress loads. J Phys Ant. 2014;33:20. https://doi.org/10.1186/1880-6805-33-20
27. Wagner J, Cik M, Marth E, Santner BI, Gallasch E, Lackner A, et al. Feasibility of testing three salivary stress biomarkers in relation to naturalistic traffic noise exposure. Int J Hyg Environ Health. 2010;213(2):153-5. https://doi.org/10.1016/j.ijheh.2009.08.004
28. Selye H. The stress of life. New York: McGraw-Hill; 1956.
29. Dalri RCMB. Carga horária de trabalho dos enfermeiros de emergência e sua relação com estresse e cortisol salivar [doctoral thesis]. Ribeirão Preto: Universidade de São Paulo; 2013.
30. Mcewen BS, Lasley EN. O fim do estresse como nós o conhecemos. Rio de Janeiro: Nova Fronteira; 2003.
31. Cannon WB. The wisdom of the body. New York: W.W. Norton; 1932.
32. Organização Internacional do Trabalho. Factores psicosociales en el trabajo. Geneva: Oficina Internacional del Trabajo; 1986.
33. França ACL, Rodrigues AV. Stress e trabalho: uma abordagem psicossomática. 4th ed. São Paulo: Atlas; 2012.
34. Johnson EO, Kamilaris TC, Chrousos GP, Gold PW. Mechanisms of stress: a dynamic overview of hormonal and behavioral homeostasis. Neurosci Biobehav Rev. 1992;16(2):115-30.

35. Ulrich-Lai YM, Herman J. Neural regulation of endocrine and autonomic stress response. Nat Rev Neurosci. 2009;10:307-409. https://doi.org/10.1038/nrn2647
36. Araújo MR. A influência do treinamento de força e do treinamento aeróbio sobre as concentrações hormonais de testosterona e cortisol. Motri. 2008;4(2):67-75.
37. Schmidt NA. Salivary cortisol testing in children. Issues Compr Pediatr Nurs. 1997;20(3):183-90.
38. Castro M, Moreira AC. Análise crítica do cortisol salivar na avaliação do eixo hipotálamo-hipófise-adrenal. Arq Bras Endocrinol Metab. 2003;47(4):358-67. http://dx.doi.org/10.1590/S0004-27302003000400008
39. Yang Y, Koh D, Ng V, Lee FC, Chan G, Dong F, et al. Salivary Cortisol Levels and Work-Related Stress Among Emergency Department Nurses. J Occup Environ Med. 2001;43:1011-8.
40. Nejtek VA. High and low emotion events influence emotional stress perceptions and are associated with salivary cortisol response changes in a consecutive stress paradigm. Psychoneuroendocrinology. 2002;27(3):337-52.
41. Fujiwara K, Tsukishima E, Kasai S, Masuchi A, Tsutsumi A, Kawakami N, et al. Urinary catecholamines and salivary cortisol on workdays and days off in relation to job strain among female health care providers. Scand J Work Environ Health. 2004;30(2):129-38.
42. World Health Organization. Depression. Nº 369. Geneva: World Health Organization; 2012.
43. Cruz Junior AJ. Questões/problemas em perícias médicas nos casos de depressão. Rev Hosp Univ Pedro Ernesto. 2011;10(2).
44. Coutinho MEM, Giovanini M, Pavini LS, Ventura MT, Elias RM, Silva LM. Aspectos biológicos e psicossociais da depressão relacionado ao gênero feminino. Rev Bras Neurol Psiquiatr. 2015;19(1):49-57.
45. Bannai A, Tamakoshi A. The association between long working hours and health: A systematic review of epidemiological evidence. Scand J Work Environ Health. 2014;40(1):5-18. https://doi.org/10.5271/sjweh.3388
46. Muntaner C, Li Y, Xue X, Thompson T, O'Campo P, Chung H, et al. County level socioeconomic position, work organization and depression disorder: A repeated measures cross-classified multilevel analysis of low-income nursing home workers. Health Place. 2006;12:688-700. https://doi.org/10.1016/j.healthplace.2005.09.004
47. Vargas D, Dias APV. Prevalência de depressão nos cuidados intensivos trabalhadores de enfermagem da unidade: um estudo em hospitais em uma cidade do noroeste do Estado de São Paulo. Rev Lat-Am Enf. 2011;19(5):1-9.
48. Juruena MF, Cleare AJE, Pariante CM. O eixo hipotálamo-pituitária-adrenal, a função dos receptores de glicocorticóides e sua importância na depressão. Rev Bras Pisquiatr. 2004;26(3):189-201. http://dx.doi.org/10.1590/S1516-44462004000300009
49. O'Brien KM, Tronick EZ, Moore CL. Relationship between Hair Cortisol and Perceived Chronic Stress in a Diverse Sample. Stress Health. 2013;29(4):337-44. https://doi.org/10.1002/smi.2475
50. Russell E, Koren G, Rieder M, Van Uum S. Hair cortisol as a biological marker of chronic stress: current status, future directions and unanswered questions. Psychoneuroendocrinology. 2012;37(5):589-601. https://doi.org/10.1016/j.psyneuen.2011.09.009
51. Albar WF, Russell EW, Koren G, Rieder MJ, Van Umm SH. Human hair cortisol analysis: comparison of the internationally-reported ELISA methods. Clin Invest Med. 2013;36(6):E312-6.
52. Amorim MAP, Siqueira KZ. Relação entre vivência de fatores estressantes e surgimento de câncer de mama. Psicol Argum. 2014;32(79):143-53. http://dx.doi.org/10.7213/psicol.argum.32.079.AO09
53. Yamaguti STF, Mendonça ARB, Coelho D, Machado AL, Souza-Talarico JN. Padrão atípico de secreção de cortisol em profissionais de Enfermagem. Rev Esc Enferm USP. 2015;49(n. Esp.):109-16. http://dx.doi.org/10.1590/S0080-623420150000700016

Correspondence address: Sérgio Valverde Marques dos Santos – Avenida São José, 133, apto. 101, Centro – CEP: 37002-130 – Varginha (MG), Brazil – E-mail: sergiovalverdemarques@hotmail.com