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Analysis of biomarkers in nursing workers in hospital settings: An integrative review

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RESUMO

Objetivo: Analisar as evidências disponíveis na literatura sobre biomarcadores em trabalhadores de enfermagem no ambiente hospitalar. **Método:** Tratou-se de uma revisão integrativa da literatura. A busca dos estudos primários foi realizada pela *internet* em principais bases de dados. Utilizou-se as expressões de busca por palavras e por descritores relacionados ao tema. **Resultados:** Obteve-se 852 artigos que, após análise inicial, resultaram em 25 artigos que constituíram a revisão. Os autores somaram 197 pesquisadores de variadas universidades e instituições, com publicações que ocorreram entre 2006 e 2021. O total de trabalhadores que tiveram seus marcadores investigados foi de 2.975, de várias nacionalidades. Nestes estudos foram identificados vários biomarcadores, dosados em diferentes amostras como de sangue, saliva, urina e cabelos. As dosagens realizadas foram por meio das amostras de cortisol, 8-OHdG, melatonina, oligoelementos, albumina, número de linfócitos e seus vários tipos, HHV-6, trihalometano, interleucinas, interferon, entre outros. Observou-se que a maior ênfase dos estudos foi na dosagem de cortisol. **Conclusão:** Os trabalhadores investigados apresentaram alterações nestes biomarcadores em todos os países investigados, mostrando a precariedade do trabalho que executam, com riscos ocupacionais e eventuais riscos de adoecimentos.

Descritores: Marcadores biológicos; Enfermeiras e enfermeiros; Pessoal de enfermagem hospitalar; Jornada de trabalho em turnos.

ABSTRACT

Introduction: biomarkers have been widely used to assess and diagnose diseases in workers, including nursing professionals, who work in settings that favor physical and mental illness. **Objective:** to analyze evidence available in literature on biomarkers in nursing workers in hospital settings. **Methods:** this was an integrative literature review. The search for primary studies was carried out on the Internet in major databases. Search expressions were used for words and descriptors related to the topic. Results: 852 articles were obtained, which, after initial analysis, resulted in 25 articles that constituted the review. The authors included 197 researchers from various universities and institutions, with publications that occurred between 2006 and 2021. The total number of workers who had their markers investigated was 2,975, of various nationalities. In these studies, several biomarkers were identified, measured in different samples such as blood, saliva, urine and hair. The dosages performed were through samples of cortisol, 8-OHdG, melatonin, trace elements, albumin, number of lymphocytes and their various types, HHV-6, trihalomethane, interleukins, interferon, among others. It was observed that the greatest emphasis of studies was on the dosage of cortisol. **Conclusions:** the workers investigated presented changes in these biomarkers in all the countries investigated, showing the precariousness of the work they perform, with occupational risks and possible risks of illness.

Descriptors: Biomarkers; Nurses; Nursing Staff, Hospital; Shift Work Schedule.

RESUMEN

Introducción: los biomarcadores han sido ampliamente utilizados para evaluar y diagnosticar enfermedades en trabajadores, incluidos profesionales de enfermería, que trabajan en ambientes que favorecen las enfermedades físicas y mentales. **Objetivo:** analizar la evidencia disponible en la literatura sobre biomarcadores en trabajadores de enfermería del ambiente hospitalario. **Métodos:** se realizó una revisión integradora de la literatura. La búsqueda de estudios primarios se realizó online en las principales bases de datos. Se utilizaron expresiones de búsqueda para palabras y descriptores relacionados con el tema. **Resultados:** se obtuvieron 852 artículos que, luego del análisis inicial, dieron como resultado 25 artículos que constituyeron la revisión. Los autores reunieron a 197 investigadores de diversas universidades e instituciones, con publicaciones ocurridas entre 2006 y 2021. El total de trabajadores cuyos marcadores fueron investigados fue de 2.975, de diversas nacionalidades. En estos estudios se identificaron varios biomarcadores, medidos en diferentes muestras como sangre, saliva, orina y cabello. Las mediciones se realizaron utilizando muestras de cortisol, 8-OHdG, melatonina, oligoelementos, albúmina, número de linfocitos y sus distintos tipos, HHV-6, trihalometano, interleucinas, interferón, entre otros. Se observó que el mayor énfasis de los estudios estuvo en la medición del cortisol. **Conclusiones:** los trabajadores investigados presentaron cambios en estos biomarcadores en todos los países investigados, mostrando la precariedad del trabajo que desempeñan, con riesgos laborales y posibles riesgos de enfermedad.

Descriptores: Biomarcadores; Enfermeras y Enfermeiros; Personal de Enfermería en Hospital; Horario de Trabajo por Turnos.

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Introduction

Biomarkers are used to obtain information about the health status of people or responses to interventions. They are measurable biological parameters capable of indicating a particular state of an organism, and are also characteristics measured as indicators of normal biological processes, pathogenic processes or responses to an exposure or intervention[1]. They participate in numerous chemical reactions in the human body and can be secreted/excreted during the physiological process conducted by the various natural biological fluids. They can be measured experimentally and indicate the occurrence of a certain normal or pathological function of an organism or a response to a pharmacological agent[2-4]. They can be of different types, such as physiological (organ functions), physical (characteristic changes in biological structures), histological (tissue samples obtained by biopsy) and anatomical, and be specific cells, molecules, genes, enzymes or hormones.

Biochemical markers are obtained from urine, saliva, blood, sweat, tears, liquor, feces, hair, skin, among others, and can be measured and indicate health changes in individuals[1]. They therefore include any substance or its biotransformation product, as well as any early biochemical change, the determination of which in biological fluids, tissues or exhaled air, assesses the intensity of exposure and the risk to health[2-3]. Moreover, they can be measured and assessed as indicators of normal or pathogenic biological processes or even be pharmacological responses to certain therapeutic interventions[4].

Research on biomarkers in humans has evolved over the years. There are studies with various of these indicators related to kidney function[5-7], diagnosis of Alzheimer's[8], metabolic syndrome[9], coronary syndrome[10], cardiovascular diseases[11], rheumatoid arthritis[12], cancer[13,14], liver function[15], among others.

In the workplace, biomarkers can help identify diseases in workers. During the work process, workers change their bodies, often with physiologically detectable changes and, at other times, with mental changes that can also be identified. Even if they perform tasks with little physiological expenditure, they need to reason, plan, decide, and think about what they are doing, i.e., there is an energy expenditure at the psychological-neuronal level[16].

The work performed by nursing professionals is often described as exhausting. They work in day and night work settings, exposed to various occupational risk factors that favor illness and accidents at work. These risks can result in physical injuries, such as cuts, scratches, fractures, physical disabilities, skin and mucous membrane punctures, bruises, bleeding, and contamination by infected biological material, including blood, urine, feces and vomit[17-21]. Furthermore, these professionals perform physically and mentally exhausting work, and are subject to occupational risks that can lead to absences from work due to illness and work-related accidents[22]. Workers may experience a variety of illnesses, including excessive sleepiness, physical fatigue, various pains, back pain and

physical sprains. They may also experience changes in mental health, such as stress, depression, anxiety, distress, fear, insecurity, among others[23].

Salivary biomarkers have been widely used in the diagnosis of diseases in different populations, including workers. Screening using these markers can contribute to better prognoses, considering that work activities can negatively impact individuals' health, including nursing professionals. Thus, their use in medical examinations can allow workers to prove their illness, helping to prevent or reduce episodes of presenteeism, absenteeism and decreased productivity in the workplace.

Given the above, it is important to investigate the biological markers that are related to nursing workers, since this may promote a better understanding of the work performed and even favor interventions to mitigate and/or prevent the changes found, according to their biological parameters. In view of this, this study aimed to analyze evidence available in literature on biomarkers in nursing workers in hospital settings.

Methods

The following stages were taken to construct this integrative review (IR): 1. Research question elaboration; 2. Literature search for primary studies; 3. Data extraction; 4. Assessment of studies included in the review; 5. Analysis and synthesis of results; and 6. Review presentation[24].

The question asked was: what evidence is available in literature on biomarkers in nursing workers in hospital settings? To this end, the PICO strategy, an acronym for patient, intervention, comparison and outcomes[25], was used to design the search, with P = nursing workers in the hospital context; I = biomarkers; C = not applicable and O = change in biomarkers.

The search for primary studies was conducted online to access the following databases: Latin American and Caribbean Literature on Health Sciences (LILACS); National Library of Medicine and the National Institutes of Health (PubMed); Cumulative Index to Nursing and Allied Health Literature (CINAHL); and Embase. Scopus and Web of Science were accessed through the CAPES Journal Portal. The controlled descriptors of Medical Subject Headings (MeSH), CINAHL Headings, Embase Indexing and Emtree, and Health Sciences Descriptors (DeCS), defined according to each database, were identified, and then a single search strategy adapted for each database was outlined. Boolean operators AND and OR were used to combine the elements of the PICO strategy in order to obtain a manageable number of studies for conducting the research. The results were exported to the bibliographic reference manager (EndNote), which were organized and duplicate articles were removed[26]. To select the studies, the texts were exported to the Rayyan software, in which labels were created describing the reasons for exclusion/inclusion of each study[27]. Concerning the selection criteria, primary studies that addressed nursing workers working in a hospital setting, on day and/or night shifts among adults and older adults, who presented at least one type of altered biological marker, were included. These articles were published in English, Portuguese and Spanish in the period of fifteen years (2006 to 2021). Moreover, to ensure rigor in conducting the method, part of the Preferred

Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations were used[28].

To locate the studies, search expressions by words and subject descriptors were used. The data obtained from MEDLINE/PubMed are presented below (Chart 1).

Chart 1 - Search in MEDLINE/PubMed and search strategies related to evidence available in literature on nursing workers who showed changes in biomarkers in the different shifts in hospital settings. 2006-2021 (n=238).

Database	Search strategies	Results*
MEDLINE / PubMed	("Biomarkers"[MeSH Terms] OR "Biomarkers"[All Fields] OR "Biomarker"[All Fields] OR "Biological Marker"[All Fields] OR "Biological Markers"[All Fields] OR "Biologic Marker"[All Fields] OR "Biologic Markers"[All Fields] OR "Immune Marker"[All Fields] OR "Immune Markers"[All Fields] OR "Immunologic Marker"[All Fields] OR "Immunologic Markers"[All Fields] OR "Serum Markers"[All Fields] OR "Serum Marker"[All Fields] OR "Surrogate Endpoint"[All Fields] OR "Surrogate Endpoints"[All Fields] OR "Surrogate End Point"[All Fields] OR "Surrogate End Points"[All Fields] OR "Clinical Markers"[All Fields] OR "Clinical Marker"[All Fields] OR "Viral Markers"[All Fields] OR "Viral Marker"[All Fields] OR "Biochemical Marker"[All Fields] OR "Biochemical Markers"[All Fields] OR "Laboratory Markers"[All Fields] OR "Laboratory Marker"[All Fields] OR "Surrogate Markers"[All Fields] OR "Surrogate Marker"[All Fields]) AND ("Nurses"[MeSH Terms] OR "Nurses"[Title/Abstract] OR "Nurse"[Title/Abstract] OR "Nursing Personnel"[All Fields] OR "Nursing Assistants"[MeSH Terms] OR "Nursing Assistants"[All Fields] OR "Nursing Assistant"[All Fields] OR "Nurses Aides"[All Fields] OR "Nurse Aides"[All Fields] OR "Nurse's Aides"[All Fields] OR "nurses aide"[All Fields] OR "Nurses Aides"[All Fields] OR "Nursing Auxiliaries"[All Fields] OR "Nursing Auxiliary"[All Fields]) AND ("Hospitals"[MeSH Terms] OR "Hospitals"[Title/Abstract] OR "Hospital"[Title/Abstract] OR "Shift Work Schedule"[MeSH Terms] OR "Shift Work Schedule"[All Fields] OR "Night Shift Work"[All Fields] OR "Rotating Shift Work"[All Fields] OR "Work Schedule"[All Fields] OR "Scheduling"[All Fields] OR "Staffing"[All Fields] OR "evening shift"[All Fields] OR "rotating shift"[All Fields])	238

* Results: October 25, 2021.

The search strategy was adapted according to the specificities of each database, in such a way that, in MEDLINE/PubMed, 238 articles were obtained, in Scopus, 277, in Web of Science, 238, in CINAHL, 91, and in LILACS, 8, which totaled 852 identified texts.

3. In the extraction stage, a script was used that allowed identifying the study as well as its methodological characteristics and main results.

In study assessment, the methodological approach (quantitative or qualitative) was prioritized, and to identify the methods of each one, the terminology indicated by the authors themselves was used to define the research design; when the method was not identified, the concepts described in literature were consulted[29-30].

In the analysis and synthesis of results, the descriptive form was chosen, considering the characteristics and results of each primary study included in IR. In this stage, a summary table was prepared, demonstrating identification data, objective and main results found in each one.

The results are presented in the format of this scientific article. With the synthesis of the knowledge obtained, we intend to present data on nursing workers who work in a hospital setting and directions for future research on this topic.

Results

The initial search in the databases resulted in 852 articles. After being placed in the EndNote reference manager, they were transported to the Rayyan application. Duplicates were excluded and, in the end, after the analysis of the remaining articles carried out by a pair of evaluators with experience on the subject, in a double-blind stage, 25 remained, presented in Table 2 below. These 25 articles came from Europe (10), the Eastern (8), the Americas (6) and America/Oceania (1), in countries such as Brazil, Colombia, Turkey, Argentina, Italy, Hungary, United States, Japan, Greece, Cyprus, among others.

Chart 2 - Selected articles related to evidence on nursing workers who showed changes in biomarkers during different shifts in hospital settings. 2021 (n=25).

Year/ Country	Objective	Worker involved	Biomarker used	Conclusions
a) 2021 / Brazil and Colombia	Examine molecular/hormonal stress parameters in relation to DNA damage and changes in skills/behaviors that may affect nursing care.	78 nursing team members working in four different hospital units	Salivary cortisol levels	Cortisol levels upon awakening were negatively associated with employee years of employment and positively associated with DNA damage in the comet assay.
b) 2021 / Brazil	Assess the condition of stress in healthcare professionals in southern Brazil, investigating the presence of SARS-CoV-2 in the saliva of individuals.	45 frontline healthcare professionals who worked in Basic Health Units in a municipality in southern Brazil	Hematological, inflammatory and oxidative damage markers in blood	Infected professionals (CoV-2-Prof) showed increased levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), cholesterol, lactic dehydrogenase, lymphocytes and monocytes. The NoCoV-2-Prof group showed elevated plasma cortisol levels.

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c) 2021 / Argentina	Assess stress and burnout in a population of healthcare workers and measure hair cortisol concentration as a current biomarker of stress.	234 healthcare workers from a Buenos Aires hospital	Hair cortisol	40% of the study population presented hair cortisol values outside the healthy reference range. Higher values in hair cortisol levels were found in the group with burnout.
d) 2013 / Italy	Estimate whether occupational exposure to low doses of anesthetic gases can cause changes in hepatic and renal hematochemical parameters in health workers.	154 hospital healthcare workers exposed and 98 controls not exposed to anesthetic gases	Serum albumin, alpha 1, alpha 2, beta and gamma globulins, serum creatinine and gamma-GT	Occupational exposure to low doses of anesthetic gases may influence hepatic and renal hematochemical parameters in exposed healthcare workers.
e) 2006 / Hungary	Assess the clinical, geno and immunotoxicological risk of nurses in oncology units.	500 nurses, with assessment carried out during the last 10 years in Hungarian oncology units	Geno/immunotoxicological biomarkers, iron dosage and serum glucose levels	There was a prevalence of iron deficiency anemia and different thyroid gland diseases among nurses in control groups. The frequency of chromosomal aberrations was increased compared to control groups.
f) 2010 / Italy	Compare the immune status of a group of nurses working shifts with that of nurses working fixed day shifts.	138 nurses at baseline and after one year of follow-up	Number of lymphocytes and subpopulation of CD3+, CD4+, CD8+-CD57+, CD19+ and CD56+, cytotoxic activity and lymphoproliferative response of NK cells, serum concentrations of IL-1beta, IL-6, INFgamma and TNF alpha	No significant changes were found in the parameters studied either at baseline or after one year of follow-up. Biological risks for nurses do not appear to be increased by shift work.
g) 2014 / China	Investigate the relationship between serum levels of trace elements and mental health and the tendency towards depression in shift nurses.	90 shift nurses working in Intensive Care Units (ICUs)	Inflammation markers AST, ALT, CRP, uric acid, plasma ferritin, cortisol, IL-6 and TNF-α were measured; plasma concentrations of calcium, magnesium, phosphate, sodium, zinc, copper and selenium were obtained.	Inflammation markers AST, ALT, CRP, uric acid, plasma ferritin, cortisol, IL-6 and TNF-α were measured; plasma concentrations of calcium, magnesium, phosphate, sodium, zinc, copper and selenium were obtained.

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h) 2020 / Belgium				Assess surgical smoke and its contamination among team members working in operating rooms.	The ambient air was measured, as well as the urine of 15 workers	Analysis of urinary S-phenylmercapturic acid (SPMA), o-cresol, mandelic acid and 1-hydroxypyrene	O-cresol was elevated, but this cannot be clearly related to exposure to toluene from surgical smoke.
i) 2008 / Japan				Assess whether salivary human herpesvirus-6 (HHV) acts as a novel stress-sensitive marker in shift-work nurses.	56 nurses were divided into 3 groups: A (worked only day shifts); B (worked 8-night shifts/month); and C (worked 9-night shifts/month)	Salivary HHV-6, immunoglobulin A (IgA) and mood states	Salivary HHV-6 level was higher in group C than in group A. Salivary IgA and mood levels were not different among the three groups.
j) 2010 / South Korea				Assess the immunosuppressive effects of work stress in nurses at a university hospital.	Four groups of 10 nurses	Serum levels of hydrocortisol, IL-1β, IFN-γ and TNF-α and salivary IgA.	The white blood cell level was lower in the high objective stress group. In terms of immuno-biomarkers, the TNF-α level was moderately lower in the high objective stress group, while the total IgA level was higher among the high objective stress group.
k) 2011 / Canada				Assess the influence of nocturnal exposure to light on melatonin levels.	123 rotating shift nurses	Maximum melatonin levels.	Average light exposure was higher when nurses worked nights, although peak melatonin levels and the daily change in melatonin levels were similar across day/night shifts.
l) 2017 /				Identify the prevalence of exposure to disinfection byproducts, such as trihalomethanes (THM).	179 nurses from two public hospitals	THM measured in urine	Nurses were exposed to almost twice the levels of THM compared to the general population.

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n) 2013 / Brazil	Assess salivary cortisol concentration in nurses on workdays and days off.	57 nurses	Salivary cortisol	The salivary cortisol concentration identified the degree of stress and the difference obtained between a work day and a day off; on the day off, the concentration maintained lower values.
o) 2008 / Japan	Investigate the tuberculosis (TB) infection rate among nurses with a history of working in a hospital's tuberculosis ward.	50 nurses who worked in TB wards	Interferon gamma levels	The infection rate was 6/50 (12.0%) in all nurses. The infection rate in group I was 17.6%, but that in group II was 0%. In other words, TB infection control was effective in reducing the infection rate.
p) 2019 / China	Investigate the role of probiotic intake in preventing DEC205+ dendritic cell (decDC) dysfunction in nurses working day and night shifts.	40 nurses, 20 who ingested probiotics (in yogurt) before the night shift and 20 who ingested only milk	Blood samples	Night shift has a negative impact on the immunotolerogenic functions of decDC, which can be prevented by ingesting yogurt containing probiotics during this type of shift.
q) 2022 / Greece and Cyprus	Compare physical, psychological and physiological adaptations between rotating and morning health workers.	40 nurses - 20 from the morning shift group and 20 from the rotating shift group	Salivary melatonin and blood lipid profiles	Nurses on rotating shifts showed increased body mass and total and abdominal fat, along with decreased sleep quality.
r) 2013 / Turkey	Assess oxidative stress and metabolic activities of nurses on day and night shifts.	Nurses from the ICU and the common service (CS) participated in the study	Oxidative stress parameters and metabolic activities	Oxidative stress parameters increased at the end of all nurses' shifts. Oxidative stress parameters and metabolic activities of CS and ICU nurses were not different and all suffered similar effects of the shifts.

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s) 2020 / United States of America	Examine prospective associations between mean and intra-individual variability in sleep with markers of inflammation in nurses.	392 night shift nurses	Inflammation markers, C-reactive protein, interleukin (IL)-6, tumor necrosis factor α and IL-1β	Greater night-to-night variability in total sleep time as determined by actigraphy and sleep diary was uniquely associated with higher levels of the inflammation biomarkers IL-6 and IL-1β that may increase the risk of inflammation-related diseases.
t) 2017 / Germany	Investigate physical activity, sleep quality, metabolic activity and stress levels in healthcare professionals working regular hours and rotating shifts.	46 volunteer workforce participants from a university medical department	Metabolites	Shift work had no influence on overall physical activity.
u) 2019 / United States of America	Assess the effects of shift work type, chronotype, and their joint effects on 24-hour light exposure and urinary melatonin rhythms in a substudy of practicing nurses participating in the Nurses' Health Study II.	130 active nurses (84 on rotating shifts and 46 on day shifts) from the Nurses' Health Study II	6-sulfatoxymelatonin (aMT6s) dosage	Rotating shift workers on night shifts had greater light exposure and lower melatonin levels during the night. Melatonin rhythms were dependent on both chronotype and type of rotating shift work, and better alignment of rotating shift work and chronotype appeared to produce less disrupted melatonin rhythms.
v) 2021 / Spain	Assess stress response in emergency healthcare professionals by measuring related biomarkers such as cortisol, DHEA and salivary α-amylase throughout the workday.	97 professionals (physicians and nurses)	Salivary measurement of cortisol, dehydroepiandrosterone (DHEA) and salivary α-amylase	Cortisol levels decreased throughout the workday. A similar pattern was observed for DHEA. And α-amylase levels increased throughout the workday, peaking at 3 p.m. and decreasing by 12 a.m., compared with data from the rest of the workday.

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w) 2011 / Japan	Investigate the effects of fatigue on the function of NK (Natural Killer) cells and lymphocyte subpopulations in shift work nurses.	57 nurses engaged in shift work at a Japanese hospital	Blood samples	Shift work has deleterious effects on NK cell function and that the effects depend on the degree of fatigue
y) 2014 / Thailand	Investigate the change in 8-hydroxy-2'-deoxyguanosine (8-OHdG) concentration at different work times among nurses working in shifts.	51 nurses with regulated rotation in medical center or district hospital	Urinary concentrations of 8-OHdG - biomarker of oxidative DNA damage	There was a greater change in 8-OHdG concentration for those who worked the day shift and then the night shift.
z) 2016 / Finland	Examine the association between job strain and cortisol and alpha-amylase markers among female healthcare workers in shifts, laboratory and field workers.	95 participants recruited from hospital and categorized as either high job strain group or low job strain group	Saliva samples	Biomarker results showed no differences between groups. The data showed that the high job strain group had a weak association with decreased heart rate variability.

Source: authors

The authors of these articles totaled 197 researchers from various universities and other institutions. The years of publication were 2021 (5), 2020 (2), 2019 (2), 2017 (2), 2016 (1), 2014 (2), 2013 (3), 2011 (2), 2010 (3), 2008 (2) and 2006 (1). The total number of nurses assessed was 2,322, and the other health workers, in teams containing nurses, were 653. Therefore, 2,975 people were studied and several biomarkers were researched in blood, saliva, urine and hair samples.

Discussion

One of the biomarkers investigated was dehydroepiandrosterone (dehydroepiandrosterone, DHEA), a steroid produced in the adrenal glands and converted into sex hormones, with effects on the body similar to those of testosterone. DHEA supplements are taken to improve mood, energy, feelings of well-being and the ability to function well under stress. It may also reverse aging, improve brain function in people with Alzheimer's and reduce symptoms of systemic lupus erythematosus[31-32]. There appears to be a relationship between depression and dehydroepiandrosterone. Its concentrations are altered in depressed patients and it has already been used in the clinic to improve this problem, although with still contradictory results[33].

In the present study, DHE was measured in the research designated by the letter "v", carried out in Spain, which showed a decrease in DHEA levels and also cortisol levels throughout the working day.

In relation to salivary α-amylase, it is one of the main salivary enzymes in humans, secreted by the salivary glands under sympathetic stimulation[34]. It catalyzes the hydrolysis of the internal α-1,4 bonds of starch, but not the branched α-1,6 bonds. Its action continues until the food in the stomach is mixed with gastric acid, which inactivates the enzyme. Once inactivated by gastric acid, there will be no further processing of carbohydrates in the stomach[32]. Thus, this enzyme has been shown to be a reliable indicator of sympathoadrenal-medullary activity. It can be measured quickly and noninvasively by collecting saliva and has often been used as a surrogate measure of sympathetic arousal. It has a positive relationship with adrenergic blockades and β-blockers, and its activity is measured during stressful situations; therefore, it can be effective in assessing the sympathoadrenal-medullary system[34-36]. In the present study, alpha amylase was used as a biomarker in the Spanish "v" study and in the Finnish "z" study, in which the results of this biomarker showed no significant differences between the morning and night shift groups and on the day off.

In this investigation, the substance trihalomethane (THM), a chemical compound used in industry as a solvent or refrigerant, aids in disinfection in hospital settings and was detected in the urine of the workers studied. The literature establishes a close relationship between exposure to THM, more specifically chronic exposure, and their adverse effects. After their absorption, these elements tend to bioaccumulate in the body, causing cytotoxicity, genotoxicity and mutagenicity, thus resulting in carcinogenic effects. They appear to have a close relationship with bladder cancer and also with colon and rectal cancer[37-38]. In this IR, the Cypriot research designated as "l" showed that nurses were exposed to almost twice the levels of THM compared to the general population, putting their health at great risk.

There are several lymphocytes. Leukocytes/white blood cells are formed elements with the function of defense against foreign organisms and are of the types neutrophils, eosinophils, basophils, T and B lymphocytes and monocytes[39]. The two main types of lymphocytes are B cells (which mature in the bone marrow) and T cells (which mature in the thymus), which can be differentiated by specific surface antigen receptors and other cell surface molecules called clusters of differentiation (CD). Cytotoxic T cells (Ct) are usually CD8 but can be CD4, helping to eliminate intracellular pathogens, especially viruses, and Ct cells play an important role in organ transplant rejection[40]. Leukocytes defend the body against infectious organisms and foreign substances, and the most common cause of leukocytosis is the body's normal reaction to an infection, which may be in response to certain medications, such as corticosteroids, bone marrow cancers, release of immature or abnormal white blood cells from the bone marrow into the blood, among other situations[41]. NK cells or "natural killers" also make up the innate immune system, capable of distinguishing infected or tumor cells and attacking them without the need for stimulation. Their immune response is nonspecific and they can be used as biological markers, which was the case in some studies that appeared in this review.

They are important in immunological surveillance, recognizing cells that are foreign to the organism, those infected by viruses or with some type of alteration that could lead to the emergence of cancer, actively participating in the immune surveillance mechanism[42]. They make up innate immunity and correspond to approximately 10% to 20% of circulating lymphocytes. NK cells are thymus-independent and their absence leads to persistent viral infections, and in this situation, these agents can only be eliminated with the action of antiviral drugs, although they present an adaptive immune response[43].

In this IR, studies assessed these lymphocytes, sometimes some separately, and/or together with others. Some researchers used NK cells as biomarkers: in the article “w”, carried out in Japan in 2011, in which shift work showed its deleterious effects on the function of these cells, effects that depended on the degree of fatigue; in the text “m”, from Italy, in 2010, which, by identifying, over time, whether changes in job satisfaction could affect workers’ immunological-inflammatory state, determining the activity of NK cells, as the authors showed that (dis)satisfaction at work was related to the psychological mechanisms of stress that affected cellular immunological function; in the study “f”, also from Italy, in which 138 nurses were monitored and submitted to tests of perceived stress, daytime sleepiness, number of lymphocytes and lymphoproliferative response of NK cells, among other biological parameters, without significant changes in any of the studied parameters.

Regarding the presence of serum copper, this is an essential trace element for the maintenance of several biological processes[44]. Its plasma concentration is used as an indicator of dietary copper supply; however, this concentration changes with age, exercise and health status and does not increase after a meal nor decrease during short-term fasting[45]. High levels of vitamin A can cause oxidation of vitamin A and decrease in vitamin C, causing muscle and joint pain, learning disorders, depression, and fatigue. Its functional properties can be positive (it aids in the effective absorption of iron, essential for the use of vitamin C, stimulating immunity, aiding in the conversion of tyrosine into melanin, playing a role in the synthesis of elastin and collagen, as well as in hormones T3, T4, anticancer substances, protection against cardiovascular diseases, anti-inflammatory and useful against some forms of arthritis, among others) and negative (removal of vitamin A oxidation; in high doses, it reduces vitamin C, contributing to schizophrenia, altering glucose metabolism in the lens, among others)[46]. In this review, in the Chinese study “g”, nurses who worked at night had mild to moderate levels of depression, higher than those of the control group, and higher levels of plasma copper, ferritin, interleukin (IL)-6 and ALT, compared to the control group.

Herpes is a complex viral condition caused by members of the Herpesviridae family. These viruses share distinct properties that allow them to establish persistent infections in the human body. After the initial infection, the virus can remain latent in specific nerve ganglia, escaping immune control and triggering recurrent episodes; however, viral reactivation can be triggered by a variety of factors, such as stress, intense sun exposure and other environmental stimuli, and the immune response to these reactivations is not always effective, allowing the viruses to replicate and cause varied symptoms.

Emotional stress is recognized as a common trigger for all types of herpes, including zoster[47]. Human herpesvirus 6 (HHV-6) is one of the Betaherpesviruses with high prevalence in the world population, without seasonality, capable of causing latent infection and viral reactivation in its hosts[48]. In the present IR, Japanese researchers ("i" study) investigated 56 nurses who worked different shifts, day and night, and assessed salivary HHV-6, immunoglobulin A (IgA) and mood states among them. They concluded that salivary HHV-6 level can be considered a more sensitive stress marker than salivary IgA or mood to assess chronic fatigue in shift nurses.

Cytokines are also widely used as biomarkers to identify health problems in individuals. This study aimed to determine serum levels of IL (IL-1β, IL-6, IL-8, IL-10), tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), and immunoglobulin levels (IgG, IgA, and IgM) in 30 patients and 30 healthy volunteers, and to examine the relationships between these parameters and lipid parameters. Although total cholesterol, HDL-cholesterol, and IgM levels increased significantly ($p<0.05$) in patients compared with controls, no statistically significant differences were observed with other parameters. IFN-γ was positively correlated with total cholesterol and LDL-cholesterol levels, but other cytokines and immunoglobulins did not correlate with lipid parameters. It was concluded that dysregulation of lipids and the immune system, including the cytokine network, was associated with the etiology and pathophysiology of major depressive disorders[49]. Researching 124 nursing workers, a Brazilian investigation that used IL as biological markers to assess sleep quality identified that although a link was found between sleep deprivation and signs and symptoms of physical, mental and emotional illness among them, IL-6 and TNF-α (pro-inflammatory) and IL-10 – anti-inflammatory showed low serological expression[50]. In the present review, IL were assessed in the North American study "s", in the Chinese "g" study, in the Korean "j" study, in the Chinese "p" study, in the Italian "f" study, among others.

In the 2010 "j" article, the authors aimed to assess the immunosuppressive effects of work stress in 40 nurses from a university hospital and concluded that psychological stress at work appeared to have affected the levels of some immunological biomarkers in these professionals. In the 2019 Chinese "p" study, the authors investigated 40 nurses and identified that the night shift contributed to the alteration in immunotolerogenic functions and IL10 expression, which were impaired after this shift; however, this negative impact on the immunotolerogenic functions of DEC205 + dendritic cells (decDC) can be prevented by the ingestion of yogurt containing probiotics. In the 2021 "s" study, the prospective associations between the mean and intra-individual variability in sleep with markers of inflammation in nurses were examined, and this variability, determined by actigraphy and sleep diary, was not associated with inflammation biomarkers, nor with any mean sleep variable. In 2014, the authors of "g" study intended to investigate the relationship between serum levels of trace elements and mental health and the tendency towards depression in shift nurses, and concluded that those who worked at night had significantly higher levels of depression than those in the control group, in addition to higher levels of plasma copper, ferritin, IL-6 and alanine amino transferase compared to the control group.

Some investigations have assessed salivary melatonin, which is a non-steroidal hormone, synthesized in the pineal gland (N-Acetyl-5-Methoxytryptamine), known for its regulatory action on the circadian rhythm and which can also act on several other important points in the organism physiological regulation[51-52]. Its synthesis involves a sequence of reactions that begin with the conversion of tryptophan into serotonin and the subsequent conversion of serotonin into melatonin. Among its functions, the best known is chronobiological, acting in the synchronization of intrinsic biological rhythms, inducing the nocturnal behavior appropriate for each species. Knowing that the control of the human circadian cycle is fundamental for sleep regulation and that, in turn, sleep is responsible for several physiological processes, including ensuring the proper functioning of the immune system, and melatonin is associated with the indirect control of the same. This hormone does not have its action restricted to the Central Nervous System, but also influences several organs and systems. It attenuates the inflammatory effects of viral infections, increases immune capacity and reduces the harmful effects of oxidizing agents that accelerate pathogenic processes[53]. However, workers who alternate shifts may alter this biomarker.

In São Paulo, Brazil, a study aimed to investigate the possible effects of working fixed night shifts on sleep and selected hormonal and inflammatory biomarkers. The study was conducted in a metal sanitary ware industry in the city, with 17 male night shift workers and 21 male day shift workers. Saliva samples collected at different times during three workdays were analyzed. It was found that night work was associated with a decrease in melatonin secretion and the loss of its secretion rhythm. Night work on fixed shifts may harm workers' health, making it inadvisable. Day shifts with a start time associated with partial sleep deprivation may also cause future harm to these people's health[54]. In the present review, melatonin was researched in the 2011 Canadian study (letter "k"), in the 2021 study by Greek and Cypriot authors ("q") and in the one carried out by North Americans and Australians ("u") in 2019.

8-OHdG is considered a biomarker of oxidative stress associated with high cortisol, high blood pressure, diabetes, cystic fibrosis, atopic dermatitis, rheumatoid arthritis, Parkinson's disease, Alzheimer's disease, Huntington's disease, pancreatitis, chronic hepatitis, breast cancer, and other cancers[55]. It is also used to estimate DNA damage in humans after exposure to cancer-causing agents such as tobacco smoke, asbestos fibers, heavy metals and polycyclic aromatic hydrocarbons (PAHs). The nucleobase most susceptible to oxidative stress is guanine, and its damage results in two main modifications: 8-hydroxy-2'-deoxyguanosine or 8-oxo-7,8-dihydro-2'-deoxyguanosine. Moreover, 8-oxo-dG (8-oxo-2'-deoxyguanosine) is an oxidized derivative of the nucleoside deoxyguanosine, formed by a nitroxenated base derived from 8-oxoguanine linked to 2-deoxyribose sugar, and is one of the main products of DNA oxidation[56]. The 8-OHdG biomarker measures the effect of endogenous factors on oxidative DNA damage, and it is used to estimate risk for several types of cancer and degenerative diseases. Minimizing the presence of 8-OHdG represents an important stage towards health and longevity[55]. In this review, the analysis of this biomarker was shown in the Thai "y" study, from 2014, in which the authors assessed the urinary concentrations of 8-OHdG and showed that there was a greater change in its concentration in nurses working the day shift

and then the night shift, which is considered a health risk factor. Thus, 8-OHdG then helped to identify the workload of these professionals.

Oxidative damage and oxidative stress result from an imbalance between the generation of oxidizing compounds and the action of antioxidant defense systems. The generation of free radicals and/or non-radical reactive species is a result of oxygen metabolism. The antioxidant defense system has the function of inhibiting and/or reducing the damage caused by the deleterious action of free radicals and/or non-radical reactive species. This system is usually divided into enzymatic and non-enzymatic. In the latter case, it is made up of a wide variety of antioxidant substances, with endogenous or dietary origin[57]. In this IR, this topic was worked on in the Turkish "r" study (carried out in 2013) and in the "b" study carried out in Brazil in 2021.

In the Turkish study ("r"), the authors collected blood samples at the beginning and end of shifts to measure oxidative stress parameters, and found that these parameters increased in all nurses at the end of shifts when compared to the beginning of shifts. And in the Brazilian study ("b"), in which oxidative damage was analyzed in nursing professionals and a control group of non-professionals directed at workers in contact with the SARS-CoV-2 virus, infected professionals showed a significant increase in the levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), cholesterol, lactic dehydrogenase, lymphocytes and monocytes. Levels of uric acid, triglycerides, leukocytes, neutrophils, hemoglobin, hematocrit and platelets decreased. Uninfected individuals had a significant increase in HDL levels and percentages of eosinophils and monocytes. Moreover, the levels of uric acid, LDH, triglycerides and cholesterol, and the hematocrit count and mean corpuscular volume were significantly reduced. Both groups showed significant inflammatory activity with changes in the levels of C-reactive protein and mucoprotein.

As for cortisol, it has been widely studied as a biomarker, mainly in relation to the presence of stress in nursing, and in the present review, it was one of the biomarkers that was most used for this purpose. Salivary biomarkers, including cortisol, salivary α-amylase, chromogranin A, brain-derived neurotrophic factor and immunoglobulin A, respond to acute and/or chronic stressors and, therefore, are prerequisite biomarkers in research related to stress[58]. Thus, it was researched in the saliva of nurses[59-60], in the hair of hospital nurses[61-62] in relation to REM and non-REM sleep[63], among others.

In this review, cortisol was measured by Spanish scholars (designation "v") in 2021, who assessed the stress response in emergency healthcare professionals, measuring related biomarkers, including cortisol. It was also assessed in Brazil ("n") in 2008, with the authors studying the concentration of salivary cortisol in 57 nurses on the workday and day off, identifying that, on the day off, the concentration remained lower values, as did the stress score. In South Korea, in 2010, "j" study showed that several immunological biomarkers were investigated in nurses, such as serum levels of hydrocortisol, IL-1β, IFN-γ and TNF-α and salivary IgA, which were measured by enzyme-linked immunosorbent assay. Psychological stress at work appeared to have affected the levels of some of these immunological biomarkers, including those of hydrocortisol.

In Argentina, in 2021, “c” study investigated 234 healthcare workers from a hospital in Buenos Aires in which hair cortisol was measured by a chemiluminescent method. It was found that 40% of the population studied had hair cortisol values outside the healthy reference range. The authors concluded that healthcare professionals are subject to increasing levels of stress and burnout, in addition to high depersonalization, emotional exhaustion and a decreased sense of personal accomplishment. It is the responsibility of health authorities to implement strategies to manage this psychological emergency. Cortisol was also studied in the 2021 “a” study, carried out by Brazilian and Colombian scholars, and was researched in China in 2014 (“g” study), in Korea in 2010 (“j”), and in other investigations, together with other biomarkers.

Limiting factors of this study were the fact that some relevant research was not published in the data sources sought, which could have other information not included in this study. Also noteworthy as limitations are the number of databases consulted as well as some descriptors that are not controlled and that could have been used. However, even with these limiting factors, it is believed that the scientific rigor followed in the development of this review was essential to overcome them. However, it is still necessary to carry out new research, whether through systematic reviews or meta-analysis as well as experimental studies that can analyze these biomarkers in nursing workers and their relationship with the health-disease process.

It is believed that the study presents contributions to the advancement of knowledge in health and nursing, as well as to science, since analyzing the biological markers related to nursing professionals’ work changes can promote a better understanding of the work performed by them, favoring the adoption of interventions to prevent diseases according to the biological parameters that may be modified or in a state of alteration. It may also promote the creation of new public policies that address this issue in protecting workers, especially nursing workers as well as provide reflections for service managers so that they pay attention to the health of their professionals.

Conclusion

We sought to analyze evidence available in literature on changes in biomarkers of hospital nursing workers. Twenty-five primary studies were identified, published between 2006 and 2021, which analyzed 2,975 people, whose biological parameters were investigated by biomarkers. These people were North American, Italian, Brazilian, Argentinean, Turkish, Greek, Chinese, Japanese, South Korean, Canadian, Belgian, Hungarian, Spanish, Colombian, among other nationalities. Levels of cortisol, 8-OHdG, melatonin, trace elements, albumin, number of lymphocytes and their various types, HHV-6, THM, IL, interferon, among others, were measured. Biomarkers were obtained from blood, urine, hair and saliva, and in several studies, the authors investigated multiple biomarkers and, sometimes, only one.

Nursing workers, in most studies, presented alterations in biological markers, evidencing the precariousness of the work they perform, exposed to occupational risks that lead to eventual illnesses. This professional category should be more considered by employers,

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Author Contributions

Robazzi MLCC participated in: study conception and design, data collection, data analysis and interpretation, manuscript writing, and critical revision of the manuscript. Mendes AMOC participated in: manuscript writing. Silva AF participated in: study conception and design, manuscript writing. Terra FS participated in: study conception and design, data analysis and interpretation, manuscript writing, and critical revision of the manuscript. Silva LA participated in: study conception and design, data analysis and interpretation, and critical revision of the manuscript. Gouveia MTO participated in: statistical analysis. Dalri RCMB participated in: study conception and design, data analysis and interpretation, and critical revision. Santos SVM participated in: study conception and design, data collection, data analysis and interpretation, and critical revision. Bardaquim VA participated in: data analysis and interpretation, statistical analysis. Scandiuzzi LAA participated in: study conception and design, data collection, statistical analysis.

Conflict of Interest

The authors certify that no commercial or associative interest presents a conflict of interest regarding the manuscript.

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