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Mexican Journal of Medical Research ICSa

Biannual Publication, Vol. 10, No. 20 (2022) 34-43

ISSN: 2007-5235

Clinical relevance of stress biomarkers as health-disease indicators

Relevancia clínica de los biomarcadores de estrés como indicadores de salud-enfermedad

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Abstract:

Stress is a protective mechanism inherent in living organisms. In humans, it fulfils an adaptive function, capable of generating responses at different levels: physiological, metabolic, endocrine, cognitive, among others. Constant exposure to stressful events or stimuli is capable of exceeding the person's resources, causing discomfort and progressively wearing down health. Recently, a significant increase in stress-associated diseases has been observed. The consequences of this problem are multiple; personal, socioeconomic, and professional difficulties. Current evidence shows that daily stress will tend to increase in the upcoming years, affecting the quality of life and mental health of the population in general. Both environmental and natural factors as well as the economic and social repercussions derived from the current pandemic tend to further aggravate this problem. Given this scenario, developing strategies that promote mental health and the prevention of its associated pathologies is a priority. One way to develop more effective intervention programs is through the use of biomarkers, many of which show high diagnostic sensitivity and specificity, and which represent a wide interest within the clinical area and psychotherapeutic intervention. The objective of this article is to make a general review of the main biomarkers used in clinical practice, as well as potential biomarkers that allow the identification of early signs of health problems related to mental stress in a more efficient and accessible way.

Keywords:

Psychophysiology, psychological stress, autonomic regulation, stress response, physiological markers

Resumen:

El estrés es un mecanismo de protección inherente a los organismos vivos. En el ser humano cumple una función de tipo adaptativa, capaz de generar respuestas a distintos niveles: fisiológico, metabólico, endocrino, cognitivo, entre otros. La exposición constante a eventos o estímulos estresantes, es capaz de sobrepasar los recursos de la persona, provocando malestar y desgastando progresivamente la salud. A fechas recientes se ha observado un aumento significativo de enfermedades asociadas al estrés. Las consecuencias de esta problemática son múltiples; dificultades personales, socioeconómicas, profesionales. La evidencia actual refleja que el estrés cotidiano tenderá a aumentar en los próximos años, afectando la calidad de vida y salud mental de la población en general. Tanto los factores ambientales y naturales como las repercusiones económicas y sociales derivadas de la pandemia actual tienden a agravar aun más este problema. Ante este escenario, resulta prioritario desarrollar estrategias que promuevan la salud mental y la prevención de sus patologías asociadas. Una forma de desarrollar programas de intervención más eficaces es mediante el uso de biomarcadores, muchos de los cuales muestran una alta sensibilidad y especificidad diagnóstica, y que representan un amplio interés dentro del área clínica y de la intervención psicoterapéutica. El objetivo del presente artículo es hacer una revisión general sobre los principales biomarcadores utilizados en la práctica clínica, así como potenciales biomarcadores que permitan identificar de manera más eficaz y accesible señales tempranas de problemas de salud relacionados al estrés mental.

***Palabras Clave**:*

Psicofisiología, estrés psicológico, regulación autonómica, respuesta al estrés, marcadores fisiológicos

INTRODUCTION

The progressive increase in health disorders related to psychological stress constitutes a public health problem of interest, since its consequences can affect different dimensions in the functioning of the person, at a cognitive, social and physiological level.[1] There is multiple evidence on the relationship of stress with various pathologies, especially with

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Received: 22/03/2022, Accepted: 24/04/2022, Published: 05/07/2022

DOI: https://doi.org/10.29057/mjmr.v10i20.8808

cardiovascular diseases,[1–4] as well as with mental disorders.[5] It has been discovered that stressful experiences can favor the appearance of aggressive behaviors and social violence[6] as well as an increase in the consumption of alcohol, tobacco and toxic substances.[7–10] Likewise, bidirectional associations have been observed between stress and addictions,[11] as well as between stress and physiological and mental illnesses.[12,13]

In order to have a broader understanding of this problem, it is necessary to take into account the importance of inter-individual differences, since stress affects each person differently; the level of vulnerability, previous life experiences, type of stressor (social, environmental, academic, economic, family, work, etcetera), intensity, duration, frequency and subjective perception of stress play an important role in the coping capacity of the individual.[14,15] Environmental and social factors, such as socioeconomic level, support networks and ability to access health systems, are also capable of modulating the level of stress affectation.[16]

Stress measurement ranges from paper and pencil tests to the use of different biomarkers, such as salivary cortisol or heart rate variability (HRV).[5] Currently, the implementation of biomarkers allows for a quantitative index of stress in the person, parallel to their subjective perception, which facilitates the development of more accurate diagnoses of stress levels and their negative consequences, facilitating the development of better therapeutic strategies, capable of reducing the levels of morbidity and mortality in the population and the secondary consequences associated.[17] The advantage of biomarkers lies in their objectivity and in the reduced possibility of manipulating or altering the results.[5]

PSYCHOLOGICAL STRESS

Stress is a mechanism of an adaptive nature, which, when it becomes chronic or acute, tends to exceed personal resources, causing emotional discomfort.[1] Chronic stress is capable of causing alterations at the behavioral level that gradually deteriorate the capacity for neuronal plasticity and cognition of the subject.[18] Early detection of psychological stress is not only relevant to improve quality of life, but also constitutes a preventive advantage in reducing diseases.[5]

At the physiological level, stress can aggravate chronic diseases such as asthma, atherosclerosis, hypertension, chronic pain,[1,19] even triggering ischemic stroke, or cause premature death.[1,20] At the psychological level, it is related to post-traumatic stress disorders of mood and sleep disorders.[16,21]

STRESS BIOMARKERS

Initially, biomarkers were defined as biomolecules capable of being measured at the blood level, as well as at the level of tissues or fluids.[22] Currently, this definition has been expanded to include any substance or parameter present in the organism capable of being measured and reflect the functioning of an organ or system,[17,23] such as the electrodermal response, blood pressure, or cholesterol levels.

Biomarkers fulfill three basic functions: *1) predictive, 2) prognostic and 3) monitoring*,[17,22] which is why they are very useful when evaluating the efficacy of a treatment. In the area of psychophysiology, they are considered as objective indices of different mental disorders, such as depressive, anxiety, and sleep-wake disorders, among others.[22] The importance of the use of biomarkers lies in being able to understand safely, objectively and precisely the functioning or the probable alteration caused by a disease in the different physiological, biochemical or molecular systems of the person, as well as its potential repercussions on the mental health of the person.[17]

CLASSIFICATION

There is no single classification of biomarkers. Different authors and research groups propose different categorizations. For example, a systematic review carried out by Condon in 2018,[24] classifies them: 1) based on their physiological system of origin: neuroendocrine function and immune function, also called primary stress mediators, and 2) based on secondary stress responses: neurological, metabolic, musculoskeletal, cardiovascular, respiratory and anthropometric. Arango in 2012 classifies them according to their type: 1) exposure, 2) effect, and 3) susceptibility.[23,25] Dhama and collaborators in 2019[17] classified them based on their characteristics as imaging biomarkers, such as computed tomography (CT), positron emission tomography (PET), magnetic resonance imaging (MRI), and non-imaging biomarkers, such as molecular, biochemical, or physiological. Likewise, they classify them according to their application as diagnostic, prognostic or therapeutic biomarkers.[17]

Despite the different categories proposed, their relevance is essential for the development of clinical research, so the selection of the type of biomarker to use depends on the type of disorder being investigated, the objectives of the research and the existing scientific evidence.[25]

PHYSIOLOGICAL RESPONSE

Stress perception unfolds at the level of the nervous system a complex non-linear network of physiological responses in which different regulatory mechanisms are immersed, seeking the balance of the organism, which prepares it for the *fight-or-flight response*, in contrast to the relaxation response called *rest-and-digest*.[1,6,24] Although in general terms the response to stress is universal, there are differences depending on the type of stress that the person presents. For example, the fight or flight response has immediate and short-lived effects, compared to the response to acute stress and high intensity or chronic stress that can extend itself over months or years, whereby physiological changes vary according to the type of stress.[6]

Broadly speaking, these changes occur mainly in the autonomic nervous system (ANS) and its branches, the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS).[24] The objective of these changes is to maintain the stability of the various physiological systems involved, such as the endocrine, immune and nervous systems. This process is known as homeostasis and is essential for maintaining health.[26]

Homeostatic balance is regulated by allostasis, a process inherent to the organism, of an adaptive and dynamic nature, which facilitates rapid internal changes in response to the demands of the environment.[1,27] In the face of repeated and high-intensity stress events, the allostatic load increases, becoming then maladaptive and overactivating mainly the endocrine and cardiovascular systems (allostatic overload), which can result in physical and psychological illness.[28] Eventually, constant exposure to stress causes the baseline values regulated by homeostasis, known as *set-points*, to be altered by the allostatic load, causing the correct regulation of the organism to be modified. Examples of this dysregulation are higher glucose levels, greater insulin resistance, or higher blood pressure in sick subjects than in healthy subjects.[26]

The physiological response process is presented as a complex cascade of reactions in different systems, and in which both individual variables and multiple environmental factors intervene.[17,24,28] It is important to bear in mind that it is not the stressors themselves that cause disturbances to the person's health, whether of a social, occupational or personal nature, but rather it is the constant exposure to chemicals released by stress that cause the disease.[29]

NEUROENDOCRINE RESPONSE

At the neuroendocrine level, stress causes the hypothalamus, through the SNS, to activate the adrenal glands located in the upper part of the kidneys. Thus, the first response to stress occurs in the neuroendocrine system, which, in turn, activates the response of the cardiovascular system, increasing breathing and heart rate, as well as the immune system. This process favors the release of catecholamines (epinephrine and norepinephrine) in the sympathetic-adrenal-medullary axis (SAM).[28]

In parallel, the hypothalamic-pituitary-adrenal (HPA) axis produces a hormonal response. The hormones secreted by the adrenal cortex have a long-acting response to stress,[28] a process during which mainly glucocorticoids[6,22] are released, capable of crossing the blood-brain barrier (BBB), activating areas such as the amygdala and the hippocampus.[24]

In addition to these axes, there are others that have also been related to stress, such as the hypothalamic-pituitary-thyroid (HPT) axis and the hypothalamic-pituitary-gonadal (HPG) axis, which is responsible for the production of hormones such as testosterone, progesterone and estradiol, although no significant findings related to stress have been reported.[15]

SAM axis activity

This axis is responsible for regulating the secretion of catecholamines.[17] Epinephrine and norepinephrine are the most studied biomarkers of the SAM axis, while salivary alpha-amylase and salivary pH have been measured less frequently.[18,22] Their overactivation can cause cardiovascular changes, increasing heart rate and blood pressure.[21,27]

HPA axis activity

One of the main structures of the HPA axis is the hippocampus, which is capable of inhibiting the high secretion of cortisol, however, chronic exposure to stress causes an overproduction of cortisol that ends up altering the functioning and size of the hippocampus, causing apoptosis of their neurons and preventing correct regulation,[24] this generates, as a consequence, the inability to inhibit the response to stress, even when the stimulus disappears, since the feedback inhibitory mechanism is damaged.[28] It has been observed that the activity of this axis tends to decrease in the elderly, probably due to the reduction in sleep hours, causing the appearance of various neurodegenerative disorders.[30]

Another fundamental structure of the HPA axis is the amygdala, related to emotional processing, specifically to the regulation of fear. Chronic stress causes constant exposure to corticotropin-releasing hormone (CRH), altering the volume and functions of the amygdala.[24] Secretion of both CRH and vasopressin from the hypothalamus stimulates adrenocorticotropic hormone production (ACTH) in the pituitary gland, causing the release of various glucocorticoids, such as cortisol, into the bloodstream.[2]

Cortisol levels are one of the most widely investigated biomarkers of the HPA axis.[14,18,31–33] Due to its low molecular weight, cortisol is capable of migrating out of the cell, into the extracellular space and into the bloodstream, for which is easily detectable in different biofluids.[28] Its levels show circadian fluctuations, being higher during the morning than at nighttime,[27,28,34] for which it is convenient to measure it in time series, for example, in the morning to from the first 30-60 minutes after waking up and during the afternoon.[22]

NEUROLOGICAL RESPONSE

The main cortical regions involved in psychological stress are: 1) *the anterior cingulate cortex*, related to cognitive, affective and visceral control processes, as well as cardiovascular responses, 2) *the insular cortex*, related to cardiac regulation caused by psychological stressors and emotional, and 3), *the amygdala*, whose functions allow the integration, storage and updating of sensory information from other brain areas.[1]

The activity of the parasympathetic nervous system is also regulated by the tenth cranial nerve, the vagus nerve, which is capable of modulating the autonomic cardiac response.[35] Porges' Polyvagal Theory (2007) and Thayer's Neurovisceral Integration Model (2009)[36-38] specify the relationship between states of psychological stress, the neurocardiac response, and the prefrontal cortex, which has been related to affectations at the social and cognitive level of the person.[35,38]

The Central Autonomic Network (CAN) is an internal regulatory system through which the brain is capable of modulating visceromotor, neuroendocrine, and behavioral responses. It comprises multiple cortical structures: anterior cingulate, insular, orbitofrontal, and ventromedial prefrontal cortices. This network collects sensory information from peripheral organs, such as the heart, for which it integrates the functioning between the central nervous system (CNS) and the peripheral nervous system (PNS).[36]

IMMUNE RESPONSE

Like the neuroendocrine function, the immune function also generates responses to psychological stress, which can lead to chronic diseases or aggravate pre-existing diseases, due to the overproduction of pro-inflammatory cytokines capable of altering the immune response (Figure 1-A).[22]

Cytokines

Cytokines are secreted by immune cells and their function is to regulate the immune and inflammatory response. The most commonly used cytokines as biomarkers of stress are interleukins IL-2, IL-6, IL-12 and tumor necrosis factor alpha (TNF-α).[15,22] IL-6 has extensive evidence on its association with chronic and acute psychological stress, since it is more easily detectable than the rest.[29] The use of cytokines as biomarkers of psychological stress has shown discrepant results, for which further research and methodological standardization are recommended.[15]

C-reactive protein (CRP)

This protein is produced in the liver in response to inflammation or infection. It is currently considered as a potential biomarker of immune function.[22] It has been related to chronic stress and burn-out, however, the results are not conclusive and require further investigation.[15]

Natural Killer (NK) cell activity

Inverse correlations have been observed in NK cell activity and high depression scores.[22] Likewise, low NK cell activity has been found in the face of emotional stress, both in humans and animals.[15]

CARDIOVASCULAR AND RESPIRATORY RESPONSE

This response is directly related to changes in the ANS, specifically in the sympathetic branch. The increase in both heart rate and respiratory rate through ASR promotes an immediate response to stress. The production of ACTH and corticosteroids results in an increase in blood pressure and blood volume.[16,28]

Heart rate is determined both by the joint activity of the sympathetic and parasympathetic (vagal) nerves that occur in the sinoatrial node and by intrinsic cardiac mechanisms. There is evidence that cortical activity is capable of modulating cardiac function, both in animals and in humans.[36]

One of the most widely investigated biomarkers to measure changes in cardiac autonomic response is electrocardiography (ECG) and HRV (Figure 1-B), noninvasive methods that are highly associated with psychological stress.[3,14,26,39,40] Currently, HRV is considered one of the most relevant biomarkers for the objective measurement of psychological stress.[5,41]

HRV reflects variations in successive intervals of RR (R wave of the QRS complex) or NN (normal-to-normal) peaks. In situations of stress, the variability of heartbeat intervals tends to be reduced. This decrease in HRV correlates with greater sympathetic activation, as well as poorer health.[5] Low levels of HRV are associated with poor regulation of stress, depression, anxiety,[42–44] poor cognitive and social performance, as well as a general increase of morbidity and mortality in the population,[14,16] for which a low level of HRV is considered a good predictor of disease.[36]

METABOLIC RESPONSE

The secretion of norepinephrine from the adrenal medulla stimulates the production of glucose in the liver, increasing the energy necessary for cellular respiration.[28] Stress is capable of causing metabolic alterations. Overactivity of the HPA axis causes chronic secretion of glucocorticoids and catecholamines, which generates hypersecretion of insulin and hyposecretion of sex and growth hormones, which can result in increased fat from adipose tissue, muscle loss, and obesity.[24]

ANTHROPOMETRIC MEASURES

Alterations in metabolic response can lead to changes in anthropometric measurements. One of the main glucocorticoids, cortisol, is directly related to weight gain and abdominal obesity.[2] In the case of children, it has been observed that chronic stress can affect their growth and development, as well as increase the values of body mass index (BMI) and central adiposity.[24]

MAIN STRESS BIOMARKERS

A compilation of the most investigated biomarkers and their relationship to stress are presented in Table 1. Each biomarker was categorized based on its system of origin.

MAIN MEASUREMENT METHODS

A compilation of the main biomarker measurement methods and their general methodological characteristics is presented in Table 2.

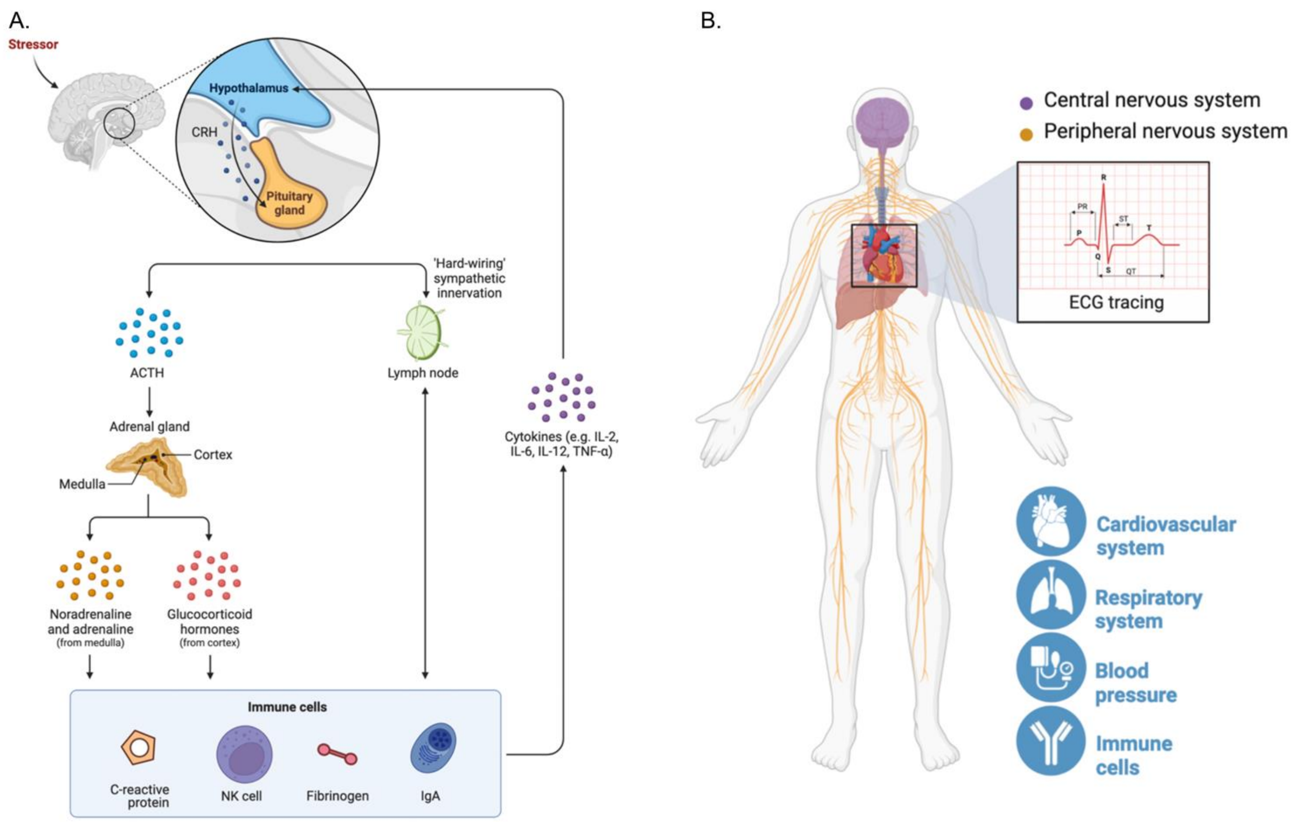

Figure 1. (A) Representation of the immune and neuroendocrine response. The psychological stressor causes a complex cascade response at the central nervous system (CNS) level that affects the immune system and in which it is possible to measure immune cells as biomarkers directly associated with stress. (B) Representation of the peripheral nervous system (PNS) and its sympatho-vagal division, which produces changes in various systems, particularly at the cardiovascular level. These variations are measurable through different methods, especially through ECG. Source: own elaboration based from reviewed literature.[22,24]

Table 1. Biomarkers related to psychological stress.

Biomarker type	Definition and/or function	Measurement	Associated disorders
Anthropometric			
BMI	Body weight in relation to height. Estimation of body fat percentage, according to age and gender	Height and weight	Cardiovascular disease
Growth and height	Measurement of growth/height as a function of age and sex	Height	Cardiovascular disease
Waist circumference	Abdominal adiposity estimate	Waist circumference	Cardiovascular disease
Waist-to-height ratio	Estimation of body fat distribution	Waist circumference and height	Cardiovascular disease

Biomarker type	Definition and/or function	Measurement	Associated disorders
Waist-to-hip ratio	Estimation of central adiposity	Circumference of the waist and hip	Cardiovascular disease
Cardiovascular and respiratory			
Blood pressure	Indicates the level of force of the blood against the walls of the blood vessels during systole and diastole. It is related to the activity of the pituitary and adrenal glands	Blood pressure cuff	Stress, cardiovascular disease
Blood pulse volume	Measurement of blood pulse related to heart rate. It is an index of the activity of the ANS	ECG	Stress
Cardiac output	Amount of blood pumped per minute by each ventricle. It is measured in liters per minute.	Echocardiography	Stress
Heart rate	Number of cardiac contractions during a series of time. Directly related to the activity of the ANS	ECG	Stress
Heart rate variability	Variation in each of the consecutive RR peaks of the ECG during a given time series. Directly related to ANS activity	ECG	Stress
RSA	Coordinated response of the heart rate with the respiratory rate. It is an index of the activity of the vagus nerve. Highly reliable biomarker capable of reflecting mental stress and workload. It includes different mechanisms: central regulation, pulmonary and atrial reflex, local mechanism in the sinus node, among others	ECG	Stress
Immune			
CRP	Plasma protein produced in the liver as a result of inflammation	Serum, blood, plasma, saliva, urine	Cardiovascular disease
Cytokines (IL-2, IL-6, IL-12, TNF-α, etc.)	Proteins that interact with other cells in the immune system, regulate inflammatory responses to stress	Serum, plasma, saliva	Chronic-degenerative diseases, depression, stress
Fibrogen	Glycoprotein produced in the liver, determines plasma viscosity	Serum, urine	Cancer, cardiovascular disease
IgA	Glycoprotein, is one of the body's main antibodies, protects the epithelium from toxins and microorganisms	Serum, saliva, urine	Cancer
Prolactin	Hormone secreted by the anterior pituitary gland. In addition to the promotion of lactation, it is related to the person's immune status. Its increase has been observed in the face of various types of psychosocial stress	Serum, blood, plasma	Stress
NK cells	Lymphocytes of great importance inherent to the immune system	Blood	Cancer, viral infection, autoimmune diseases
Metabolic			
Glucose	Monosaccharide synthesized in the liver and kidney, the body's main source of energy	Serum, saliva, urine	Diabetes, kidney disease
Insulin	Hormone produced in the pancreas, related to glucose metabolism	Serum, saliva, urine	Diabetes, obesity, hypertension
Leptin	Hormone secreted in adipose tissue, regulates energy homeostasis	Serum, saliva, urine	Diabetes, cancer, hypertension, psychiatric diseases, reproductive disorders
Lipids	Lipoproteins and triglycerides responsible for cholesterol and dietary fat transport	Serum, saliva	Neurological and nervous system disorders

Biomarker type	Definition and/or function	Measurement	Associated disorders
Neuroendocrine			
HPA axis activity			
Cortisol	Corticosteroid secreted in the zona fasciculata of the adrenal cortex. Adrenocorticotropic hormone (ACTH) determines its production. Related to inflammation, metabolism, immune system function, appetite, cognitive function, and reproduction	Serum, saliva, urine, hair	Neurodegenerative disorders, cognition, cardiovascular disease, depression
DHEA-S	Steroid hormone produced in the reticular zone of the adrenal cortex. It is produced in response to ACTH. Its values increase in response to acute psychosocial stimuli, since it has neuroprotective, antioxidative, anti-inflammatory and antiglucocorticoid effects	Blood	Neurodegenerative disorders, cognition, cardiovascular disease, depression
Endorphin	Neuropeptide released mainly by the pituitary gland in response to stress stimuli	Urine, blood	Mental health, stress, overexcitement
Galvanic conductance of the skin	Physiological response regulated by the hypothalamus. Adrenergic activity activates the eccrine and apocrine glands. It serves as an index of sympathetic activity. The sweating response related to stress is mainly concentrated in the palms of the hands and soles of the feet, it is not directly associated with environmental temperature, but with stressors. Decreases during sleep and rest	Electrodermal activity sensor	Stress, anxiety
Oxytocin	Neuropeptide produced by the paraventricular nucleus from the hypothalamus, released by the posterior pituitary gland	Saliva, blood	Mental health, stress, social ties
Peripheral temperature	Physiological response whose regulatory center is located in the anterior hypothalamus. It is an index of sympathetic activity	Temperature sensor, infrared thermal image	Stress, anxiety
SAM axis activity			
Catecholamines (epinephrine, norepinephrine, dopamine)	Neurotransmitters released by the adrenal medulla, produced from the activation of the SNS	Serum, urine	Cardiovascular disease, stress
Salivary pH	Level of acidity detected in saliva	Saliva	Cardiovascular disease, stress
Salivary α-Amilasa	Enzyme secreted by the salivary gland in response to adrenergic activity. Norepinephrine production at beta-adrenergic receptors in saliva is stimulated by stress. Under conditions of acute stress, it precedes the release of cortisol by approximately 13 minutes.	Saliva	Cardiovascular disease, stress
Neurological			
Activity/volume of the amygdala	Structure related to emotional processing and fear	MRI, fMRI	Stress
Activity/volume of the hippocampus	Structure involved in learning and memory. Regulates glucocorticoid activity in the HPA axis	MRI, fMRI	Stress

Note. ANS = autonomic nervous system; BMI = body mass index; CRP = c-reactive protein; DHEA-S = dehydroepiandrosterone sulfate; ECG = electrocardiogram; EMG = electromyography; fMRI = functional magnetic resonance imaging; HPA = hypothalamic-pituitary-adrenal; IgA = immunoglobulin-A; IL = interleukin; MRI = magnetic resonance imaging; NK = natural killer; RSA = respiratory sinus arrhythmia; SAM = sympatho-adrenal-medullary; SNS = sympathetic nervous system; TNF-α = tumor necrosis factor alpha.[6,15,22,24,29,34,44,45]

Table 2. Biomarker measurement methods.

Method	Advantages	Disadvantages	Observations
Anthropometric measurement	Non-invasive, easy to measure	Medium precision in the calculation of adiposity	Can be performed with more precise specialized equipment
ECG	No invasive, direct measurement of cardiac activity	Obstructive, requires precise instrumentation, can cause stress	Ambulatory monitoring may be performed. It is recommended to use the 3-R protocol proposed by Laborde and collaborators;[38] 1)Resting, 2)Reactivity and 3)Recovery
EEG	Accessibility and relatively low cost.	Presence of artifacts that can interfere with the results. Requires trained technical personnel	It is recommended to implement it in parallel with neuroimaging studies or with incorporated video
Hair	Non-invasive, indicates the level of stress over time	Reference values are not very clear, longitudinal studies with greater statistical power are required	Cosmetic treatments and cleaning habits can cause variations
Neuroimaging	Direct measurement of brain function	Obstructive, expensive, can cause stress	MRI measures gray or white matter, fMRI measures brain activity and function
Saliva	Noninvasive, easy to obtain, reliable, requires no assistance of medical personnel	Several scans may be needed to assess changes caused by circadian fluctuations. They only measure short-term changes. Possible traces of blood in the sample can bias the results. Sleep disorders can alter daytime cortisol values.	Perform preferably on an empty stomach, or avoid any food 1-2 hours prior to the study. The ingestion of water does not alter the tests. Do not perform previous mouth brushing. It is recommended to measure it at four times throughout the day, during the first hours after waking up and during 7 or 8 at night.
Serum	Reliable and direct measurement of circulation	Invasive method, can cause stress	Some biomarkers can be measured in dried blood
Urine	Noninvasive	Possibility of contamination	Transport and storage depends on sample type and storage time

Note. ECG = electrocardiogram; EEG = electroencephalogram; fMRI = functional magnetic resonance imaging; MRI = magnetic resonance imaging.[2,14,15,24,27,38]

POTENTIAL STRESS BIOMARKERS

In recent years, different cardiovascular biomarkers have been analyzed to study chronic stress, including D-dimer, von Willebrand factor, tissue plasminogen activator, and P-selectin. These biomarkers are predictors of potential cardiac pathology and focus on aspects of blood coagulation. Likewise, serum lipoprotein particles have been evaluated by means of nuclear magnetic resonance (NMR) spectroscopy.[22]

Capillary cortisol is a biomarker of great interest related to cardiovascular disease and chronic stress,[28] its main advantages being the ability to know the levels of cortisol secretion for several weeks and being non-invasive.[2] Regular hair growth is 1 cm per month, so it is possible to have the total production of cortisol in the last 30 days in 1 cm.[28]

It has been observed that chronic stress is capable of affecting various brain structures, especially the prefrontal cortex, which is why it is important to advance in the study of biomarkers of cognitive function, such as brain-derived neurotrophic factor (BDNF), related to synaptic plasticity and neuronal repair.[22]

The study of telomere length is also capable of providing useful information about the person's health status and the repercussions of stress; however, the results of various studies are not very consistent, so further research is required.[22,33] Likewise, thermal markers such as heat shock proteins (HSPs), immune markers and oxidative stress markers are of interest for health research.[17]

The electrochemical components of different biofluids, such as sweat, tears, urine or blood, have recently begun to be studied.[17,28] In the specific case of sweat, interest has arisen in determining the concentration of cortisol.[6] Likewise, different biomarkers have begun to be identified in dermal emissions, called volatile organic components (VCO), related to the intestinal microbiota and anti-stress hormones such as oxytocin.[6] Blood fibrinogen and leptin are two promising biomarkers that require further investigation.[23] Likewise, interleukin 1beta (IL-

1β), interleukin 10 (IL-10), biofluids produced in the stratum corneum of the skin, and the Symmetry of facial expression,[6,34] whose advantages lie in being non-invasive and self-monitoring, are currently being investigated.

FUTURE PERSPECTIVES

The use of biomarkers is a growing need to understand the influence of psychological factors on a person's physical health, particularly in stress-related disorders.[1,5] Research in this area gives rise to more specific interventions in the field of psychotherapy, since assuming that all individuals respond in the same way to stress is reductionist, which is why it is important to advance in the study of this topic and contribute more evidence on the effectiveness of the different psychotherapies used, such as cognitive-behavioral therapy, mindfulness, biofeedback, among others,[2,8,9,40,46,47] as well as recognizing the importance of inter-subject differences when developing interventions based on more effective and personalized evidence.[15] Current health models require integrative perspectives that contemplate both the cognitive, affective and behavioral dimension as well as the physiological one, in order to measure and understand in its complexity the individual differences involved in the health process- disease.[36]

It has been shown that psychological intervention is capable of stabilizing the biochemical levels altered by different diseases,[14] as is the case of cancer (prostate, colon, lung, breast), not only in patients, but also in their primary caregivers,[29,48] strengthening the person's resilience and ability to adapt to adverse conditions.[16]

A much more precise understanding of the relationship between stress and health would involve the analysis of different biomarkers; analyzing a single marker is not enough to understand the complex activity of the autonomic nervous system.[16] Some authors emphasize the importance of combining up to 10 biomarkers belonging to the different systems, such as neuroendocrine, metabolic, cardiovascular and anthropometric measurements in order to diagnose the level of allostatic load of the individual,[22] as well as psychometric tests, questionnaires and clinical interviews.[14,34]

Likewise, the growing development of portable devices plays a fundamental role in the acquisition of new methods for obtaining biomarkers, which implies a highly relevant advance in the field of health, facilitating diagnosis and early warnings, as well as cost reduction and self-monitoring capabilities.[6]

CONCLUSIONS

The main challenges in the use of biomarkers consist of the need to standardize the methodological aspects necessary to obtain them, as well as defining the most optimal set of biomarkers for a specific investigation and which ones may be more appropriate depending on variables such as population, age, disease or specific disorder being studied (anxiety disorders, neurodegenerative disorders, addictions, cardiovascular disease, among others). It is also necessary to explore new non-invasive multisystem biomarkers that are capable of providing more diagnostic and prognostic information.

CONFLICT OF INTEREST STATEMENT

The author declares that the publication of this article was conducted in the absence of any commercial of financial relationship that could be construed as a potential conflict of interest.

REFERENCES

[1] Gianaros PJ, Jennings JR. Host in the machine: A neurobiological perspective on psychological stress and cardiovascular disease. Am. Psychol. 2018;73(8):1031–44.

[2] Iob E, Steptoe A. Cardiovascular disease and hair cortisol: A novel biomarker of chronic stress. Curr. Cardiol. Rep. 2019;21(10):116.

[3] Toohey K, Pumpa K, McKune A, Cooke J, Welvaert M, Northey J, et al. The impact of high-intensity interval training exercise on breast cancer survivors: a pilot study to explore fitness, cardiac regulation and biomarkers of the stress systems. BMC. Cancer. 2020;20(1):787.

[4] Poplawski J, Radmilovic A, Montina TD, Metz GAS. Cardiorenal metabolic biomarkers link early life stress to risk of non-communicable diseases and adverse mental health outcomes. Sci. Rep. 2020;10(1):13295.

[5] The A-F, Reijmerink I, van der Laan M, Cnossen F. Heart rate variability as a measure of mental stress in surgery: a systematic review. Int. Arch. Occup. Environ. Heal. 2020;93(7):805–21.

[6] Zamkah A, Hui T, Andrews S, Dey N, Shi F, Sherratt RS. Identification of suitable biomarkers for stress and emotion detection for future personal affective wearable sensors. Biosens. 2020;10(4):40.

[7] Hagen E, Erga AH, Hagen KP, Nesvåg SM, McKay JR, Lundervold AJ, et al. One-year sobriety improves satisfaction with life, executive functions and psychological distress among patients with polysubstance use disorder. J. Subst. Abus. Treat. 2017;76:81–7.

[8] Soder HE, Wardle MC, Schmitz JM, Lane SD, Green C, Vujanovic AA. Baseline resting heart rate variability predicts post-traumatic stress disorder treatment outcomes in adults with co-occurring substance use disorders and post-traumatic stress. Psychophys. 2019;56(8).

[9] D'Souza MA JM, Wardle M, Green CE, Lane SD, Schmitz JM, Vujanovic AA. Resting heart rate variability: Exploring associations with symptom severity in adults with substance use disorders and posttraumatic stress. J. Dual. Diagn. 2019;15(1):2–7.

[10] Benson S, Ayre E, Garrisson H, Wetherell MA, Verster JC, Scholey A. Alcohol hangover and multitasking: Effects on mood, cognitive performance, stress reactivity, and perceived effort. J. Clin. Med. 2020;9(4):1154.

[11] González E, Arias F, Szerman N, Vega P, Mesias B, Basurte I. Coexistence between personality disorders and substance use disorder. Madrid study about prevalence of dual pathology. Actas. Esp. Psiquiatr. 2019;47(6):218–28.

[12] Daviu N, Bruchas MR, Moghaddam B, Sandi C, Beyeler A. Neurobiological links between stress and anxiety. Neurobiol. Stress. 2019;11(100191):100191.

[13] Bremner JD, Moazzami K, Wittbrodt MT, Nye JA, Lima BB, Gillespie CF, et al. Diet, stress and mental health. Nutrients. 2020;12(8):2428.

[14] Michels N, Matthys D, Thumann B, Marild S, De Henauw S. Children's stress-related reports and stress biomarkers interact in their association with metabolic syndrome risk. Stress. Heal. 2018;34(4):523–33.

[15] Jonsdottir IH, Sjörs Dahlman A. Endocrine and immunological aspects of burnout: a narrative review. Eur. J. Endocrinol. 2019;180(3):147–158.

[16] Pozzato I, Craig A, Gopinath B, Tran Y, Dinh M, Gillett M, et al. Biomarkers of autonomic regulation for predicting psychological distress and functional recovery following road traffic injuries: protocol for a prospective cohort study. BMJ. Open. 2019;9(4):e024391.

[17] Dhama K, Latheef SK, Dadar M, Samad HA, Munjal A, Khandia R, et al. Biomarkers in stress related diseases/disorders: Diagnostic, prognostic, and therapeutic values. Front. Mol. Biosci. 2019;6:91.

[18] Cantus DS, López NS, Ballester MC, Gómez SS, de la Rubia Ortíz JE. El estrés en la enfermedad de Parkinson: Biomarcadores cortisol y amilasa. Revisión sistemática. Rev. Cient. Soc. Esp. Enferm. Neurol. 2019;(50):12–22.

[19] Allen TM, Struemph KL, Toledo-Tamula MA, Wolters PL, Baldwin A, Widemann B, et al. The Relationship Between Heart Rate Variability, Psychological Flexibility, and Pain in Neurofibromatosis Type 1. Pain. Pract. 2018;18(8):969–78.

[20] Lo EWV, Wei YH, Hwang BF. Association between occupational burnout and heart rate variability: A pilot study in a high-tech company in Taiwan. Med. (United States). 2020;99(2):1–11.

[21] Pribék IK, Sz\H ucs KF, Süle M, Grosz G, Ducza E, Vigh D, et al. Detection of acute stress by smooth muscle electromyography: A translational study on rat and human. Life. Sci. 2021;277(119492):119492.

[22] Park J, Ross A, Klagholz SD, Bevans MF. The role of biomarkers in research on caregivers for cancer patients: A scoping review. Biol. Res. Nurs. 2018;20(3):300–11.

[23] Hernández-Ceruelos A, Vázquez-Alvarado P, Pelallo-Martínez N, Muñoz-Juárez S. Bioindicators and Biomarkers. Mex. J. Med. Res. 2013;1(2).

[24] Condon EM. Chronic stress in children and adolescents: A review of biomarkers for use in pediatric research. Biol. Res. Nurs. 2018;20(5):473–96.

[25] Arango V SS. Biomarcadores para la evaluación de riesgo en la salud humana. Rev. Fac. Nac. Sal. Púb. 2012;30(1):75–82.

[26] Fossion R, Rivera AL, Estañol B. A physicist's view of homeostasis: how time series of continuous monitoring reflect the function of physiological variables in regulatory mechanisms. Physiol. Meas. 2018;39(8):84007.

[27] Cozma S, Dima-Cozma LC, Ghiciuc CM, Pasquali V, Saponaro A, Patacchioli FR. Salivary cortisol and α-amylase: subclinical indicators of stress as cardiometabolic risk. Braz. J. Med. Biol. Res. 2017;50(2):e5577.

[28] Lee DY, Kim E, Choi MH. Technical and clinical aspects of cortisol as a biochemical marker of chronic stress. BMB. Rep. 2015;48(4):209–16.

[29] Lengacher CA, Reich RR, Paterson CL, Shelton M, Shivers S, Ramesar S, et al. A large randomized trial: Effects of mindfulness-based stress reduction (MBSR) for breast cancer (BC) survivors on salivary cortisol and IL-6. Biol. Res. Nurs. 2019;21(1):39–49.

[30] Eddington HS, McLeod M, Trickey AW, Barreto N, Maturen K, Morris AM. Patient-reported distress and age-related stress biomarkers among colorectal cancer patients. Canc. Med. 2021;10(11):3604–12.

[31] Rangel Granados ES. Los marcadores psicofisiológicos. Dando certeza al fenómeno psicológico. Bol. Cient. Esc. Super. Ato. Tula. 2017;4(8).

[32] Pulopulos MM, Vanderhasselt MA, De Raedt R. Association between changes in heart rate variability during the anticipation of a stressful situation and the stress-induced cortisol response. Psychoneuroendocri. 2018;94:63–71.

[33] Woody A, Hamilton K, Livitz IE, Figueroa WS, Zoccola PM. Buccal telomere length and its associations with cortisol, heart rate variability, heart rate, and blood pressure responses to an acute social evaluative stressor in college students. Stress. 2017;20(3):249–57.

[34] Egawa M, Haze S, Gozu Y, Hosoi J, Onodera T, Tojo Y, et al. Evaluation of psychological stress in confined environments using salivary, skin, and facial image parameters. Sci. Rep. 2018;8(1):8264.

[35] Hovland A, Pallesen S, Hammar Å, Hansen AL, Thayer JF, Tarvainen MP, et al. The relationships among heart rate variability, executive functions, and clinical variables in patients with panic disorder. Int. J. Psychophysiol. 2012;86(3):269–75.

[36] Thayer JF, Hansen AL, Saus-Rose E, Johnsen BH. Heart rate variability, prefrontal neural function, and cognitive performance: the neurovisceral integration perspective on self-regulation, adaptation, and health. Ann. Behav. Med. 2009;37(2):141–53.

[37] Thayer JF, Lane RD. A model of neurovisceral integration in emotion regulation and dysregulation. J. Affect. Disord. 2000 Dec 2;61(3):201–16.

[38] Laborde S, Mosley E, Thayer JF. Heart Rate Variability and Cardiac Vagal Tone in Psychophysiological Research – Recommendations for Experiment Planning, Data Analysis and Data Reporting. Front. Psychol. 2017;8:213.

[39] Järvelin-Pasanen S, Sinikallio S, Tarvainen MP. Heart rate variability and occupational stress-systematic review. Ind. Heal. 2018;56(6):500–11.

[40] Koerten HR, Watford TS, Dubow EF, O'Brien WH. Cardiovascular effects of brief mindfulness meditation among perfectionists experiencing failure. Psychophys. 2020;57(4):e13517.

[41] Thayer JF, Ahs F, Fredrikson M, Sollers 3rd JJ, Wager TD. A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. Neurosci. Biobehav. Rev. 2012;36(2):747–56.

[42] Mann SL, Selby EA, Bates ME, Contrada RJ. Integrating affective and cognitive correlates of heart rate variability: A structural equation modeling approach. Int. J. Psychophysiol. 2015;98(1):76–86.

[43] Hamilton JL, Alloy LB. Atypical reactivity of heart rate variability to stress and depression across development: Systematic review of the literature and directions for future research. Clin. Psychol. Rev. 2016;50:67–79

[44] Hildebrandt LK, Mccall C, Engen HG, Singer T. Cognitive flexibility, heart rate variability, and resilience predict fine-grained regulation of arousal during prolonged threat. Psychophysiol. 2016;53(6):880–90.

[45] Schaub C, Von Gunten A, Morin D, Wild P, Gomez P, Popp J. The effects of hand massage on stress and agitation among people with dementia in a hospital setting: A pilot study. Appl. Psychophysiol. Biofeedback. 2018;43(4):319–32.

[46] van der Zwan JE, de Vente W, Huizink AC, Bögels SM, de Bruin EI. Physical activity, mindfulness meditation, or heart rate variability biofeedback for stress reduction: a randomized controlled trial. Appl. Psychophysiol. Biofeedback. 2015;40(4):257–68.

[47] Abbing A, de Sonneville L, Baars E, Bourne D, Swaab H. Anxiety reduction through art therapy in women. Exploring stress regulation and executive functioning as underlying neurocognitive mechanisms. PLoS. One. 2019;14(12):e0225200.

[48] Lopes-Júnior LC, Bomfim E, Olson K, Neves ET, Silveira DSC, Nunes MDR, et al. Effectiveness of hospital clowns for symptom management in paediatrics: systematic review of randomised and non-randomised controlled trials. BMJ. 2020;371:m4290.