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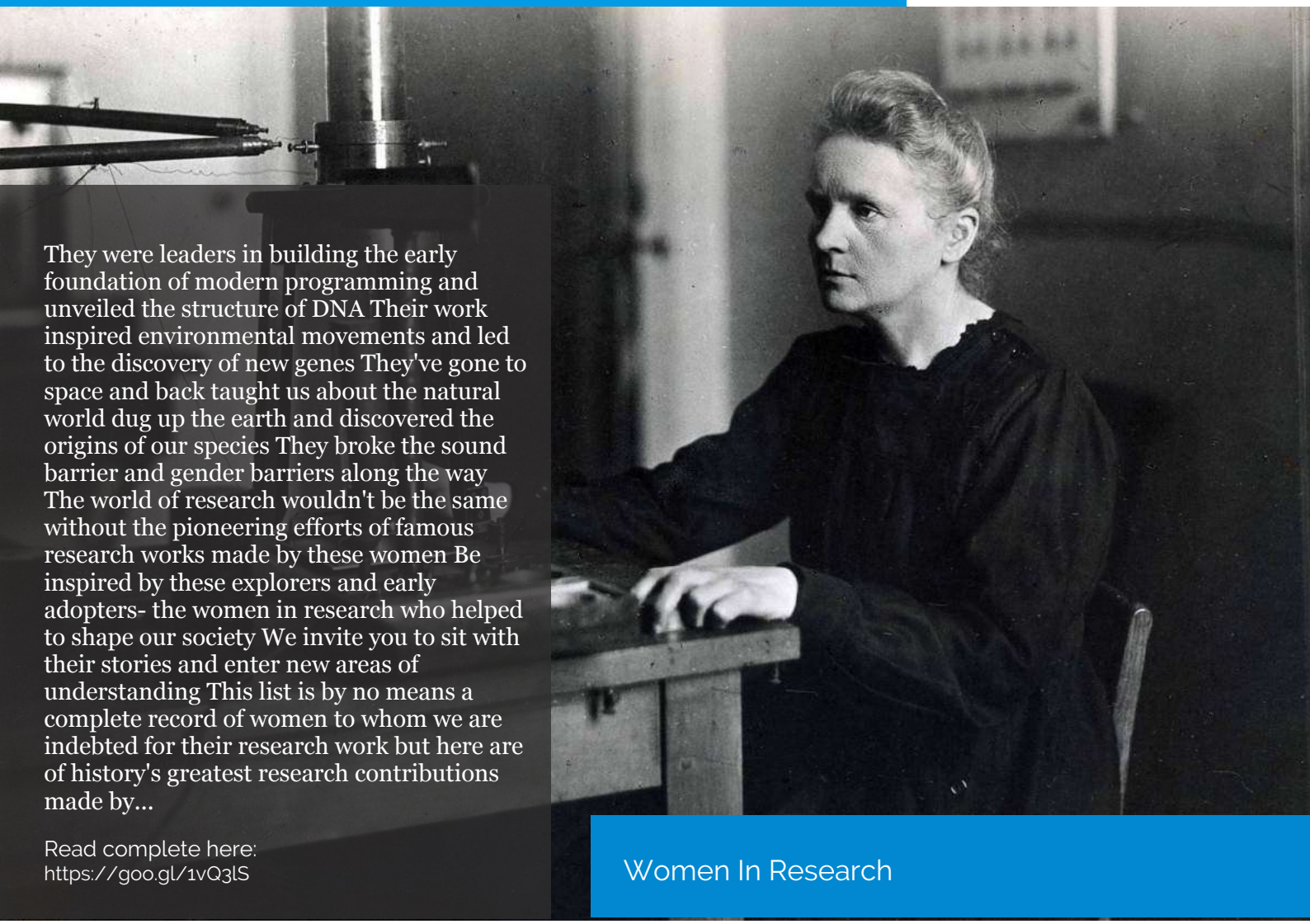

They were leaders in building the early foundation of modern programming and unveiled the structure of DNA Their work inspired environmental movements and led to the discovery of new genes They've gone to space and back taught us about the natural world dug up the earth and discovered the origins of our species They broke the sound barrier and gender barriers along the way The world of research wouldn't be the same without the pioneering efforts of famous research works made by these women Be inspired by these explorers and early adopters- the women in research who helped to shape our society We invite you to sit with their stories and enter new areas of understanding This list is by no means a complete record of women to whom we are indebted for their research work but here are of history's greatest research contributions made by...

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Disordered Breath-Brain Lateralization: At the Core of Schizophrenia Pathogenesis

Ashok Kumar Dudi

ABSTRACT

The nasal cycle's rhythmic lateralization is connected to hemisphere dominance in the brain, resulting in parasympathetic and sympathetic autonomic nervous system states. These rhythms regulate homeostasis and catecholamine levels by controlling the ergotrophic and trophotrophic BRAC phases of the body. The parasympathetic nervous system is linked to the oligotrophic phase, which is characterised by decreased heart rate, blood pressure, and respiration while increasing digestive activity and immune function. The sympathetic state is associated with the trophotropic phase, which is distinguished by increased heart rate, blood pressure, and respiration, while the ergotrophic state is distinguished by activity and alertness. The nasal cycle is regulated by the autonomic nervous system, with sympathetic dominance causing vasoconstriction and decongestion in one nostril and parasympathetic dominance causing vasodilation and congestion in the other.

Keywords: autonomic nervous system, neuro degeneration, neurotransmitter deregulation, schizophrenia, ultradian rhythms, homeostasis, catecholamines.

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The nasal cycle's rhythmic lateralization is connected to hemisphere dominance in the brain, resulting in parasympathetic and sympathetic autonomic nervous system states. These rhythms regulate homeostasis and catecholamine levels by controlling the ergotrophic and trophotrophic BRAC phases of the body. The parasympathetic nervous system is linked to the oligotrophic phase, which is characterised by decreased heart rate, blood pressure, and respiration while increasing digestive activity and immune function. The sympathetic state is associated with the trophotropic phase, which is distinguished by increased heart rate, blood pressure, and respiration, while the ergotrophic state is distinguished by activity and alertness. The nasal cycle is regulated by the autonomic nervous system, with sympathetic dominance causing vasoconstriction and decongestion in one nostril and parasympathetic dominance causing vasodilation and congestion in the other. The nasal cycle rhythm pattern is regulated by the hypothalamus central regulator, which causes bilateral vasoconstriction. Schizophrenia causes anomalous rhythmic brain and body lateralization, which may be generated by the SCN creating rhythms in asymmetrically lateralized organs. Disrupted nasal cycle variation may result in uneven functioning between the hemispheres, which can lead to neurodegeneration and neurotransmitter dysregulation, which can contribute to psychopathology. The primary cause of all of this is brain hypoxia.

Keywords: autonomic nervous system, neuro-degeneration, neurotransmitter deregulation, schizophrenia, ultradian rhythms, homeostasis, catecholamines.

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I. INTRODUCTION

The modern age is characterised by development, innovation, and technology, which make life full of ease, comfort, and miracles. Nevertheless, it also brings new peculiarities and complications.

Increasing rates of chronic stress, anxiety, and schizophrenia are products of overcompetition. Last century witnessed an unprecedented increase in cases of schizophrenia, and this decade of the COVID-19 pandemic has accelerated it further. However, scientists are still struggling with the core aspect: why does schizophrenia occur?

Schizophrenia affects 0.3-0.7% of the global population, with a 2016 global age-standardised point prevalence of 0.28%. The median incidence is 15.2/100,000 people, with the middle 80% of estimates fluctuating by a factor of five. The 12-month prevalence is 0.33%, while the lifetime prevalence is 0.48%. However, there has been an increase in the number of cases of schizophrenia in certain areas, such as London, UK, where a doubling in the prevalence between 1965 and 1997 has been attributed to migration.

Research Domain Criteria (RDoC) is a new tool for investigation in clinical psychology (Kang 2017, Cuthbert 2022). In this self-analysis report, using empirical (introspective) findings and a review of the literature, an attempt is made to bridge the knowledge gap between three prominent theories on schizophrenia, namely neuro-degeneration theory, mitochondrial dysfunction theory, and neurotransmitter deregulation theory. By using the concepts of nasal cycle rhythmic dominance, cerebral brain hemispheric lateralization, and the autonomic

nervous system's (ANS) sympathetic and parasympathetic states, the aetiology of psychopathology that leads to disordered brain hemispheric function is elaborated.

II. METHODS AND TOOLS

This narrative review summarises the onset of the psychopathology of schizophrenia using biological as well as behavioural constructs through the self-analysis (introspection) method. The author is a 20-year-old introspective psychologist. Google Scholar and extensive snowball searching on relevant insight points summarised the research findings. Transparent and impartial review quality is sought. Non-English articles are excluded, and only high-quality systematic reviews that address the research question are included. Schizophrenia research and knowledge are the main objectives. The objective is theoretical integration.

The author followed defined methodologies and guidelines to ensure credibility and reliability in the self-analysis approach. Among them were maintaining a clear head, being honest and straightforward, avoiding preconceptions, taking a systematic approach, and critically scrutinising information. The method proved reliable since it relied on high-quality systematic reviews and summaries from Google Scholar.

2.1 Oxygen Requirement for Brain Functioning

Mental and emotional states have a direct impact on the respiratory, cardiac, and digestive systems via the ANS. The ANS is divided into three parts: sympathetic, parasympathetic, and enteric.

The respiratory system has an immediate and long-lasting effect on the body's physiological and mental well-being. ANS has direct involuntary control over the mind, regulated by breath (Kang S. W., 2017).

Emotional stress is correlated with respiratory oxygen intake by the body. Stress increases brain oxygen needs, which may go unmet. Stress is correlated with an increased respiratory rate (Widjaja, Orini, et al. 2013). Increased anxiety scores and heart rates are symptoms of stress manipulation (Suess, Alexander, et al., 1980).

Mammals have only 2% brain weight in comparison to total body mass but consume about 20% of the total oxygen requirement (Sokoloff 1989). Oxygen homeostasis perturbations cause reduced oxygen availability, called hypoxia (Widjaja, Orini et al. 2013). Non-stressful attention decreases total respiratory variability, while mental load increases it (Widjaja, Orini, et al. 2013). Stress can bring about a hyperventilation reaction in the action-oriented reaction mode towards fight or flight, while feelings of defeat, depression, and being overwhelmed may produce a hypoventilation response (Suess, Alexander et al. 1980). Hypoxia impacts physiological systems through altered neuronal functions by adversely influencing neurotransmitter synthesis. Molecular oxygen is needed by rate-limiting enzymes in the fusion of many neurotransmitters for their activity (Widjaja, Orini, et al. 2013).

Neurotrophin signalling is disregulated in the pathogenesis of schizophrenia, involving obstetric complications along with psychopathology. In persons with genetic susceptibility to schizophrenia, prenatal hypoxia is associated with an increased risk of developing schizophrenia later in life (Cannon, Yolken et al. 2008). In the following section, we will investigate how stress can impact the human body and mind through altered patterns of breathing and oxygen intake. In addition, genetic vulnerability can increase the probability of this psychopathology.

2.2 Asymmetrically Lateralized Rhythms

Biological systems are functionally lateralized in the body. These bilateral organ systems have complex functions that work through activation in a simultaneous pattern. Bilateral organs distribute workload and enhance survivability with enhanced awareness and improved movement.

Bilateral organ systems are groups of organs that work together to execute specialised tasks on one side of the body. The cerebral hemispheres are responsible for language, logical reasoning, creativity, and spatial awareness, as do the lungs for breathing and the kidneys for waste filtration.

The central nervous system (CNS) and autonomic nervous system (ANS) are asymmetrically

organised in a lateralized body, with rhythmic lateralization to independently complement each other's activities. These periodic patterns are essential components of the basic rest-activity cycle (BRAC), which also contains ultradian and circadian rhythms. This brain rhythm is linked to the nasal cycle. These regular patterns meet physical needs through ultradian and circadian rhythms, which govern human homeostasis and catecholamine levels. The lateralized neuronal functions of the CNS and ANS collaborate to maintain bodily homeostasis, and the BRAC is essential to this process. The nasal cycle, an ultradian oscillation characterised by a periodic variation in left and right nasal airflow, is also important in regulating the body's autonomic, cerebral, and functional states. The paired Central Nervous System (CNS)-ANS is asymmetrically organised in a lateralized body, possessing asymmetrical activity in the form of rhythmic lateralization to complement each other's functions independently. Lateralized neural activities of the CNS and ANS fulfil bodily necessities through ultradian rhythms (exercise, rest, feeding, etc.) and circadian rhythms (light-dark habituation cycle), known as BRAC (basic rest activity cycle) (Kleitman 1967).

2.3 Nasal Cycle Dominance

Shannonhoff-Khalsa (1991) worked extensively on the nasal cycle study. The nasal cycle is the most important rhythmic lateralization of the ANS.

Differential nasal congestion influences the half-sided response to the lungs. The dominant nostril involves the homolateral lung to generate sympathetic tone (Shannahoff-Khalsa 1991).

Alternating congestion and decongestion of the nostrils is called the nasal cycle (Shannahoff-Khalsa, Boyle et al. 1991). The concept of "nasal cycle" referred to the interchanges in nostril breathing efficiency. Erectile tissue causes transient blockage in the nasal passage, producing an asymmetry of higher airflow in one nostril over the other, with the mechanism of physical blockage in the air by asymmetrically increased tissue. The anterior nasal septum with the inferior turbine of the nostril achieves engorgement of erectile tissue alternatively because of asymmetrical blood flow. A rhythmic shift of nasal dominance delivers engorgement of nasal mucosa for 25–200 minutes in each nostril (Schiff and Rump 1995).

Vasoconstriction (and decongestion) in one nasal passage is connected to unilateral sympathetic dominance, while simultaneous vasodilation (and congestion) in another is connected to parasympathetic dominance. In this way, the ANS is connected to the nasal cycle, and ANS asymmetry is due to nasal asymmetry.

The nose and hypothalamus are linked through autonomic nerve fibres, and nasal airflow affects brain activity. Rhythmic nasal cycles are produced by hypothalamic regulation. Brain stem oscillators, collections of sympathetic neurons, function as central regulators of sympathetic tone.

Reciprocal changes in the nasal airflow take place through left and right oscillators in the brain-stem region to produce an asymmetric sympathetic tone along the brain activity. Autonomic nervous fibres, through vasoconstrictor sympathetic nerves embodying large veins in turbines, supply peripheral regulation (Price and Eccles 2016).

2.4 Breath and Brain Inter-Relationship

Breath is interlinked with both body and mind (Werntz, Bickford, et al., 1983). Fluctuations in cerebral hemispheric activity remain associated with rhythmic variations in nasal airflow. Nostril dominance is associated with cerebral dominance.

Hence, there is a link between brain asymmetry and nasal airflow (Price and Eccles, 2016). The nasal cycle is coupled with cerebral hemispheric lateralization. Homo-lateral body-half provocation of sympathetic dominance can be accomplished through nasal airflow. Metabolism and mental states may be affected by the self-regulation of breathing (Werntz, Bickford, et al., 1983).

The nasal cycle is connected with the arousal of cerebral hemispheric lateralized rhythms (Werntz, Bickford, et al. 1983). Contra-lateral nostril dominance is linked with the peak of arousal in each brain hemisphere. Contra-lateral hemisphere arousal generates unilateral

contraction effects. Contraction pathways of sensory as well as motor parts are crossed to work with contralateral hemisphere cortices. Laterality of contraction produces emotions (Schiff and Rump 1995).

The sympathetic nervous system (SNS) has a correlation with cerebral hemispheric action and nasal airflow. The brain-stem area reticular formation involved in arousal and consciousness enhances arousal by air insufflations. The sensation of nasal airflow entering the trigeminal nerve stimulates the nasal mucosa's intense cold receptors. Nasal airflow stimulation increases arousal, activates reticular formation, and improves cognitive performance. Unilateral nasal airflow stimulation generates contralateral and ipsilateral effects on the hemispheres, with greater effects on the contralateral side. Lower cortical stimulation (with nasal airflow) is effective in the ipsilateral hemisphere (Price and Eccles 2016).

The dominant nostril leads to the arousal of the contralateral brain hemisphere through relative nostril effectiveness (Schiff and Rump 1995). The cerebral hemisphere gets vasoconstricted because of ipsilateral vasoconstriction in the nasal vessels (with unilateral forced nostril breathing), inducing ipsilaterally diminished cerebral blood flow with a contralateral increase. This enhances blood flow contralaterally and improves cognitive performance. Nasal airflow stimulation creates arousal of the cerebral cortex using the medium of reticular formation (Price and Eccles 2016).

The dominant nostril with the contralateral hemisphere has increased blood flow due to cerebral parasympathetic dominance. The ipsilateral hemisphere has decreased blood flow due to cerebral sympathetic activity. Increased sympathetic activity reduces cerebral circulation.

The hemisphere contralateral to the dominant nostril has increased mental activity and metabolic rates. Due to dilated cortical arteries and increased parasympathetic tone, cognitive performance efficiency is increased in the contralateral cerebral hemisphere of the dominant (greater airflow) nostril (Shannahoff-Khalsa, Boyle et al., 1991; Shannahoff-Khalsa, Kennedy et al., 1996; Shannahoff-Khalsa, Shannahoff-Khalsa 2007). Vasoconstriction and decongestion of the nostril are caused by unilateral sympathetic dominance, while concurrent vasodilation and congestion of the opposite nostril are caused by parasympathetic dominance.

2.5 Basic Rest and Activity Cycle

Each hemisphere functions independently. The ANS regulates cognition. Cerebral and ultradian rhythms (nasal cycle) are tightly coupled and controlled by the ANS (Shannahoff-Khalsa, Boyle et al. 1991). Werntz, Bickford, et al. (1983) supported the idea that the ultradian rhythms of the nasal cycle are tightly coupled to the alternating lateralization of cerebral activity.

Increased parasympathetic tone is a generalised resting position as left nostril/right brain dominance enhances parasympathetic activity and peaks healing, regeneration, and immune function (Werntz, Bickford, et al. 1983). To uphold proper homeostasis, the lateralization rhythms of ANS-CNS activity are produced for coupling mind and metabolism. Nature uses this alteration process to maximise economic efficiency.

ANS functions endure as "ergotrophic" (energy expenditure) and "trophotrophic" (protection and restitution of energy) functions. The active phase of BRAC correlates with the dominant status of left-brain right-nostril, while the resting phase of BRAC correlates with dominant right-brain left-nostril. Greater sympathetic activity in the right side of the physique produces the active phase of BRAC (Werntz, Bickford, et al. 1983).

BRAC's active phase, right nostril or left-brain dominance, generates increased corticotrophin-releasing hormone (CRH), favouring the fight-or-flight response, called the ultradian rhythm of the CRH. The Active phase" of BRAC increases sympathetic tone via right nostril breathing (Werntz, Bickford et al. 1983). Left nostril-right brain dominant status is associated with the resting phase of the basic rest activity cycle. Moreover, right nostril-left hemisphere dominance correlates to the active phase (Shannahoff-Khalsa, Boyle et al. 1991). The

fight-or-flight state prevails as the left-sided (right brain hemisphere) sympathetic dominant mode (Selye 1946). Higher vertebrates adapt to change by means of shifting ANS and CNS lateralized rhythms. Lateralized neural rhythms of the ANS and CNS are behind all ultradian rhythms.

Ultradian rhythms possess lateralized autonomic dominance. (Kleitman 1967; Kleitman 1982) The ultradian BRAC hypothesis, in its extended form, explains the lateralized ultradian ANS-CNS coupling alteration. To maintain homeostasis, together with adaptation in the structural and temporal elements, these rhythms must persist and be organised economically.

2.6 Catecholamine Regulation through Ultradian Rhythms

The CNS and body periphery possess ANS fibres located in an uncrossed manner. The nasal cycle is coupled to the lateralized ultradian ANS-CNS rhythm in the body for plasma catecholamine level regulation (Kennedy, Ziegler et al. 1986).

Connections between cortex and hypothalamus and between periphery and hypothalamus are linked with uncrossed fibre systems of the ANS (Netter 1969; Saper, Loewy et al. 1976; Saper 1985; Saper 2000). Circulation has a more direct effect on right adrenal action by way of quick metabolism. Adrenals may have unbalanced hormone (pro-phlogistic and anti-phlogistic) secretion as a result of excessive corticoids and catecholamines. Elevated levels of plasma norepinephrine are correlated with nasal vasoconstriction in sympathetic predominance on one side (Shannahoff-Khalsa, Boyle et al. 1991).

Werntz (1983) demonstrated plasma catecholamine (norepinephrine, epinephrine, and dopamine) levels. These rhythms produce coupling between the CNS and ANS. BRAC has coupling with the hypothalamic-pituitary-adrenal axis (HPA), a psychological phenomenon. CRH in the hypothalamus, considered a stress peptide, co-varies with locomotor movement. Ultradian rhythms are connected to pituitary hormone secretions such as cortisol and adreno-corticotropin (ACTH).

2.7 Onset of Schizophrenia

With psychological conditions shifting in ANS, lateralization episodes switch instantaneously. Immune functions are affected by states of CNS-ANS action, with distinct stressors playing an important role. Cerebral states and personality profiles can be impacted by overstimulation of one-half of the body's periphery, consisting of the CNS and ANS. Stress or overactivity combines the right sympathetic mode with excessive left-brain activity, depending on how long and how frequently a particular status is maintained. A prolonged shift towards one status is easy to imagine in the form of extended shifts and acute swings. Immune functions may be over- or under-activated with the atypical over-stimulation endeavour of one hemisphere.

In humans, when there is no alternative to fight or flight or no control of circumstances, they are forced towards a passive state for an extremely long time, which makes them inclined to depression, a right cerebral disorder. This is a determinant disease condition due to un-equalised lateralization action in the form of uneven metabolic shifts with a negative psychological and physiological impact. This occurs because of the environmental condition that is responsible for excessive use of the cerebral state (Selye 1946). Stress or overactivity contributes to right sympathetic dominance as a result of too much brain activity (Werntz, Bickford et al. 1983). These produce diseases of adaptation or stress-induced mental disorders.

Prolonged stress may induce a condition of hypoactivity in the brain, which, if not restored to its normal resting phase within its normal rhythmic cycle time, may continue for a prolonged period. This over-work of one hemisphere may exhaust the brain's (impulse) energy resources and disturb homeostatic adaptation between brain hemisphere and nostril dominance; both may start working in a contrary to normal (opposite) dominant position.

In the extended continuance attributed to the "active phase" of BRAC, sudden neuro-degeneration into one (right) brain hemisphere's

prefrontal cortex (PFC) may occur because of acute or prolonged imbalance comprising lateralized autonomic arousal in the brain. Deep into the right nasal path, the inferior turbine nasal septum is engorged with erectile tissue obstruction due to greater blood flow into the ipsilateral hemisphere. A higher sympathetic state of arousal (Ergotrophic state) is correlated with a higher right-sided sympathetic tone. Greater sympathetic activity is produced in the right side of the physique (Selye 1946) during this arousal phase, and it may activate right adrenal action through quick metabolic change. Plasma catecholamine levels, such as norepinephrine, epinephrine, and dopamine, may become disordered and imbalanced, and immune functions may get disturbed (with over- or under-aactivation) due to overstimulation generated in one single hemisphere.

A choked right nostril produces a lack of oxygen supply to the active hemisphere, creating hypoxia in the neuro-cells and impacting cortical stimulation. Literally speaking, the right brain stops breathing, which may create neuro-degeneration and hypo-frontality in a particular (right) hemisphere, leading to the psycho-pathological disorder of schizophrenia.

This creates lateralized cerebral dysfunction. Hence, schizophrenia and similar lateralization diseases may occur due to the cortical connection of nasal airflow asymmetry (Price and Eccles 2016).

Physiological malfunctions are connected with nasal cycle dysfunctions such as schizophrenia, autism, Kallmann's syndrome, Parkinson's disease, etc.

2.8 Mitochondrial Dysfunction

Dysfunction in the mitochondria leading to cell death (due to apoptotic cell death or neurosis) is caused by the formation of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Lack of oxygen, or hypoxia, produces oxidative stress (OxS). Moreover, a high influx of sodium and calcium in the glutamate-dependent N-methyl-D-aspartate (NMDA) channels also causes overproduction of free radicals, which finally leads to OxS. This OxS may decrease the respiratory complex's activities, which in turn cause defective mitochondrial respiratory chain complexes. Due to excessive oxidants or reduced antioxidants, an imbalance in oxidants and antioxidants is created, causing oxidative damage to the cell. This increases free iron levels or generates free radicals, causing ROS. Neural membranes rich in polyunsaturated fatty acids are particularly susceptible to the formation of ROS.

Nicotinamide adenine dinucleotide phosphate (NADPH) oxydase, which oxidises NADPH by donating electrons to an oxygen molecule (O_2) to produce superoxide (O2), may also lead to reactive oxygen species (ROS) formation.

Inefficient oxidative phosphorylation (OXPHOS) in cells may also lead to ROS, which in turn leads to impaired energy metabolism due to a low adenosine triphosphate (ATP) supply. Energy metabolism is responsible for the oxidation of mitochondrial proteins, lipids, and DNA (Curtis, Seeds, et al., 2022).

Defective energy metabolism leads to compromised viability of mitochondria and, hence, mitochondrial dysfunction. Necrosis, or apoptotic cell death, is caused by mitochondrial dysfunction, leading to neurodegeneration and neuroinflammation.

2.9 Right Prefrontal-Cortex Neurodegeneration

Murray (1987) advocated hypo-frontality and said that negative symptoms and attention-cognitive deficits in schizophrenia are due to dysfunctional frontal lobes. Neuro-degeneration is found to occur in the dorso-lateral prefrontal cortex (DLPFC) of the right hemisphere through apoptosis, which leads to slow activation of frontal and prefrontal lobe regions and is called "hypo -frontality" of prefrontal areas. According to Murray, schizophrenia is a disorder of connectivity. Default Mode Network (DNM), which is a baseline for neuron activity, is severely altered in schizophrenia; this alteration may occur due to varied causes. Neural injury occurring to cells is called "brain gliosis and may occur due to apoptosis in the brain. There are two types of brain gliosis due to apoptosis: astroistosis and microgliosis. Oligodendrocytes perform the

myelination process. It strengthens and maintains the axon connection through altered mechanisms.

Myelination leads to the loss of white matter in the prefrontal cortex. This white matter works to join the frontal and temporal lobes. The imbalance in the inhabitation and excitation processes in the prefrontal cortex leads to reduced formation and excessive shortening of this inhibitory and excitatory process, which may cause loss of grey matter in the brain. Diminished neuroplasticity leads to loss of neuropil due to small apoptosis in dendrites and individual synapses. Due to loss of neuropil by apoptosis, excess neuropil excretion, retention, and degeneration, without causing cell death, leads to synaptic degeneration (disappearance of synapses) and a reduction in neuron size (Murray and Foerster 1987). Hence, neurodegeneration is the cause of negative symptoms and hypo-frontality.

2.10 Hypo-Active Right Brain Hemisphere

Gur (1978) showed that people with schizophrenia overactivate their left hemisphere, which gets dysfunctional to a greater degree than typical humans. Chaotic use of the left (dysfunctional) hemisphere creates malfunctioning logic and a lack of affect (Gur 1978). Right dorsolateral prefrontal cortex hypometabolism influences emotion expression, with social affiliation leading to abnormal emotional behaviour. Hypo-frontality enjoys a positive correlation with chronic schizophrenia, which in turn is associated with negative symptoms.

2.11 Hyper-Active Left Brain Hemisphere

The left brain hemisphere gets hyper-active due to right hemispheric hypo-frontality. Gur (Feb. 1987a) showed this in patients with the left as compared to the right sub-cortex. Due to hypo-frontality in schizophrenia, frontal regions, as compared to posterior ones, have reduced metabolic rates in addition to glucose metabolism.

Also, the left temporal lobe shows higher activity, and the left basal ganglia receives reduced metabolism. They possess left hemispheric over-activation (Gur, Resnick et al. 1987).

More severely disturbed patients showed greater left-hemispheric metabolism. Gur (Feb. 1987b) showed that hemispheric arousal is atypical in the right cerebral hemispheric cortex as compared to the left one. The dopaminergic system in schizophrenia contains greater left-hemispheric involvement (Gur, Resnick et al. 1987).

Unilateral forced nostril breathing yields clinical effects for the treatment of a variety of disorders. Differential stimulation of cognitive efficiency can be produced by altering cerebral activity through breathing, which is used as a remedy for psychopathologies connected with lateralized cerebral dysfunctions (Shannahoff-Khalsa, Boyle et al. 1991).

Kucharska-Pietura (2006) has noted similarities between right-sided brain-damaged people and people with schizophrenia. There is right-hemisphere impairment in schizophrenia (Kucharska-Pietura 2006). Right hemisphere damage patients (due to an accident) and schizophrenia patients share a number of characteristics, according to Rotenberg (1994), including apathy, indifference, an inability to express emotions, a poor assessment of negative emotions, impaired perception of fear and anger, deficits in the affective process, and general cognitive deficits (Rotenberg 1994). Schizophrenia patients who take the chirmic faces test exhibit left-hemisphere bias (Levy, Heller et al. 1983).

2.12 Hypo - to Hyper-Brain Activation: A Compensatory Effort

Rotenberg (1984) stated that the right hemisphere performs imagination and information processing, while the left one performs arithmetic tasks and numerical counting. The right hemisphere is "entropic" of image thinking (polysemantic context). To limit the interconnections of things and phenomena and for probability forecasting, the left hemisphere requires additional activation.

Brain "hypo-activation" is due to the right hemisphere's thinking manner leading to functional inadequacy during task resolution, which activates "hyper-arousal" of the left

hemisphere during difficult tasks (Rotenberg 1994).

In schizophrenia, right-hemisphere functioning is disordered (David and Cutting 1990). Kucharska-Pietura (2006) stated that there is a functional deficiency and inadequacy or an anatomical abnormality of subtle brain impairment in the right cerebral cortex in schizophrenia.

Rotenberg (1994) explained that the left hemisphere undertakes additional compensatory physiological and psychological activation because of right hemisphere functional insufficiency. The left hemisphere makes effort as compensatory hyper-activation (due to the weakness of right hemisphere skills) in the realms of logical thinking and decision-making in non-verbal tasks that are accomplished by right hemisphere competence. Although unsuccessful and inefficient, the brain attempts to transfer all its resources to perform at its best. Search activity, in addition to brain catecholamines, upholds the appositive feedback loop mechanism, which is entirely performed by hyperbolic left hemisphere functions. Dopamine pathways support higher action in the left hemisphere over the right one.

The left sub-cortical structure has an additional number of dopamine receptors as compared to the right one (Rotenberg 1994).

2.13 Neurotransmitter Deregulation

With respect to schizophrenia, Weinberger (1987) described that defects in the DLPFC myelination process may cause dysfunction in the mesolimbic dopamine system by making it functionally overactive. Degenerative changes in the prefrontal cortex affect dopamine neurons by diminishing activity at their terminals. The mesocortical system stretches from the prefrontal cortex to the midbrain up to the amygdale, nucleus accumbens, and other areas such as the hypothalamus and hippocampus. To enhance physiological activity in the prefrontal cortex, dopamine function attempts an up-regulation of post-synaptic receptors, and increased dopamine turnover, such as homovanillic acid concentration and chronic dopamine hyperactivity, develops. Hallucinations, delusions, and other positive symptoms are caused as a result of enhanced dopamine (Weinberger 1987).

Oxygen supply can limit the synthesis of a few neurotransmitters in the brain. Under limited oxygen supply, catecholamine and serotonin synthesis get restricted, and "transmission failure" occurs because of decreased biosynthesis of neurotransmitters under hypoxic conditions (Feinsilver, Wong et al. 1987).

Molecular oxygen is needed by rate-limiting enzymes for the synthesis of many neuro-transmitters and their activity. Hypoxia impacts neuronal functions by adversely influencing neurotransmitter synthesis. Biogenic amines, amino acids, acetylcholine, and bio-active peptides, together with gas transmitter synthesis, are impacted by hypoxia (Kumar 2011).

This study has some limitations that must be considered. The author's humanities background as a self-analysis (introspecting) reporting psychologist may be limiting in his descriptions of biological concepts. References may be less recent because they come from their original sources. Introspection can be biassed, even with care. Additionally, this method is unrepeatable.

III. CONCLUSION

Disturbed nasal cycle rhythms may be considered reasons behind the onset of schizophrenia. A chronically chocked right nostril creates hypoxia in the ipsilateral right hemisphere, causing neurodegeneration in the right PFC, making it hypofrontal. As a compensatory mechanism, the left brain attempts hyper-activation, producing neurotransmitter dysregulation. Hence, cerebral hemispheric lateralization and ANS functioning get disordered, leading to abnormal behaviour. Future research should aim to regenerate neural cells that have died.

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Prevalence and Coping Strategies of Work-Related Musculoskeletal Disorders among Healthcare Workers in Douala, Cameroon: A Cross-Sectional Study

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ABSTRACT

Background: Work-related musculoskeletal disorders (WRMSDs) poses a major problem among Nurses and Laboratory technicians (LTs) today, affecting the quality of services offered, and may lead to long term disability and job abandonment. Although there is evidence that many Nurses and LTs suffer from WRMSDs, there is no sufficient data on its prevalence, possible risk factors and the coping strategies at the LDHD, NDH and NDHD, 4th category hospitals in the city of Douala, Cameroon.

Objective: To determine the prevalence, occurrence of associated risk factors and the coping strategies of WRMSDs among Nurses and LTs at the LDHD, NDH and NDHD.

Methods: This was a cross-sectional study conducted in three 4th category hospitals in Douala from February to April 2023. A total of 250 questionnaires were distributed to LTs and Nurses who gave their consents to participate in the study, 133 returned the questionnaires, giving a response rate of 53%. A total of 84 nurses and 49 LTs participated in the study. Data on demographic characteristics, and associated factors were collected using a structured questionnaire while the Nordic questionnaire was used to obtain the prevalence of WRMSDs.

Keywords: work-related musculoskeletal dis-orders, prevalence, risk factors, coping strategies, Cameroon, nurses, laboratory technicians, 4th category hospitals, musculoskeletal pain intensity, cross-sectional study.

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Musculoskeletal pain intensity was assessed using the visual analog scale (VAS) where 0 = no pain, 1-4 = mild pain, 4-6 = moderate pain, and 7-10 = severe pain. The data collected was entered into Microsoft Excel, verified for consistency then analyzed using SPSS version 23.0. Descriptive statistics was used to present the results on tables and figures, while statistical analysis was set at $p < 0.05$.

Results: The overall prevalence of WRMSDs among nurses and LTs was 69.9% (93/133). The prevalence of WRMSDS among Nurses and LTs was at 67.9% and 73.5% respectively. The lower back (48.1%), neck (41.4%) and upper back (32.3 %) were the most affected body regions reported in this study.

With respect to the intensity of pain, the majority (42.9%; 57/133) reported having severe pain within the past 7 days. Sitting for long on the same position ($\chi^2 = 4.894$; $p = 0.027$) and doing repetitive tasks (3.871; 0.049) were significantly associated with WRMSDs, while working one shift (74.4%), standing for long (72.2%), and working above eight hours (70.0%) were common among nurses and LTs, but not significantly associated with WRMSDs in the study. Praying and believing in God (51%), regular exercises (51.9%), seeking for professional help from colleagues (60.2%), taking some days off from work (88.0%), going for physiotherapy (84.2%) and applying ergonomic techniques (85.0%) were the best coping strategies used by nurses and laboratory technicians in this study.

Conclusion: The prevalence of WRMSDs was high among Nurses and LTs practicing in LDHD, NDH and NDHD, and LTs were the most affected. The lower back, neck and upper back, were more affected than other body regions.

Sitting for long in the same position and doing repetitive tasks were significantly associated risk factors of WRMSDs. Praying and believing in God, regular exercises, seeking professional help

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from colleagues, taking some days off from work, going for physiotherapy and applying ergonomic techniques were the major coping strategies applied.

Keywords: work-related musculoskeletal disorders, prevalence, risk factors, coping strategies, Cameroon, nurses, laboratory technicians, 4th category hospitals, musculoskeletal pain intensity, cross-sectional study.

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I. BACKGROUND

Work-related musculoskeletal disorders (WRMSDs) are conditions in which the work environment and performance of work contribute significantly which may persist longer due to work conditions [1, 2, 3]. They cause an alteration in the quality of life, a drop-in productivity at work, early withdrawal from the workplace represent a high cost for the health system [5].

Musculoskeletal disorders (MSDs) are among the largest contributors of disabilities among health workers [6]. In Europe, out of every five workers, three complain of MSDs [2]. Moreover, they are ranked first among the conditions that lead to prolonged absenteeism from work [5]. The United States estimates that approximately $45 billion is the annual expenditure related to these conditions [5, 7]. Approximately 1.71 billion people globally live with WRMSDS [8, 9]. WRMSDs are also the biggest contributor to years lived with disability (YLDs) worldwide with approximately 149 million YLDs, accounting for 17% of all YLDs worldwide [8, 6]. In developed countries, WRMSDs have been controlled thanks to a better assessment of the nature of work-related risk factors and of protective factors, which has led to good preventive measures, which is not the case with most of Africa, especially Sub-Saharan Africa (SSA) [5]. Sub Saharan African countries are characterized by lack of resources, the little resources these countries have is mainly channeled to fight deathly diseases like malaria and cholera. Therefore, little is done to manage or prevent work-related musculoskeletal disorders among health workers. Furthermore, lack of resources in SSA can be reflected by poor infrastructure and non-respect of work-space ergonomic principles which could predispose nurses and LTs to WRMSDs. Given the challenges related to economic growth, African countries are facing increasingly important prevalence and deleterious effects of WRMSDs among healthcare workers especially in nurses and laboratory technicians. Health professionals are exposed to these disorders which are often manifested with varying intensity of pain or discomfort. Cezar-Vaz *et al.* [11] reported intense low back pain ((≥8 points) on the visual analogue scale in 30.5% of nurses.

According to Jacquier-Bret and Gorce, [10] Africa and Europe have prevalence rates of MSDs three times higher than Asia and America for lower back. In Ghana, the prevalence of WRMSDs among nurses reported was 94% with a significantly higher (p=0.031) prevalence in females (97%) than males (87%) [12]. Similarly, a Ugandan study reported a 12-month period-prevalence of MSD at anybody site of 80.8% among nursing professionals with the most common site of MSD being the lower back (61.9%) [14]. Furthermore, Alwahaibi *et al.,* [13] in Nigeria observed a lower prevalence of 71.1% at anybody parts and most affected body regions were the neck (50.6%) shoulder (49.4%) and lower back 43.4%. In Cameroon, a study among nurses in the Fako division of the Southwest Region reported a prevalence rate of WRMSDs at any given body region of 76.6% and occurred mostly in the lower back (68.2%), neck (54.5%) and the upper back (47.4%). Working in the emergency/accident wards and surgical ward, working for less than five days but more hours in week and not taking enough rest breaks during working shift were seen to be associated with WMSDs [15]. Furthermore, Buh *et al.,* [16] reported a prevalence of WRMSDs among Nurses and physiotherapists of 77.89% and 78.26% respectively with repetitive task (88%) as major risk factors for Nurses and

manual therapy (96%) for physiotherapists. Most recently, Meh *et al.*, [17] observed a prevalence of 80.8% and 88.8% among nurses and laboratory technicians respectively, in Douala, Cameroon and working on the same position (90.6%), stressful job (89.6%) and repetitive tasks (85.9%) were the major risk factors.

Despite the fact that several studies have reported coping mechanisms of WRMSDs among nurses (help in handling a heavy patient, modification of nursing procedures and patient/nurse position etc.) [18, 19, 20, 21], most of the studies conducted in Cameroon were limited as they focused on the prevalence and risk factors of MSDs and did not address coping strategies.

Therefore, this study will help identify priority areas for interventions in WRMSDs and will also serve as a baseline for the decision-making processes of musculoskeletal health promotion, work safety measures imple- mentations, and prevention programs at the workplace.

II. MATERIALS AND METHODS

2.1 Study Design, Period, Research Setting and Participants

A cross-sectional study was conducted within a 3-months period from February to April 2023 to assess the prevalence, associated risk factors and coping strategies of WRMSDs among nurses and LTs in three 4th category hospitals in Douala, Cameroon.

This design was chosen because it permits the collection of data on particular subjects in a specific period of time, which is suitable for this study. Participants of the study were nurses and LTs in active service who have been working for at least one year at the LDHD, NDH and NDHD.

These are 4th category hospitals that receive several patients from more than five different neighborhoods, including internally displaced persons from the northwest and southwest regions of Cameroon due to the ongoing crisis.

Due to this, nurses and LTs at the LDHD, NDH and NDHD receive hundreds of patients per day with one or two shifts, and increase workload that may pre-expose them to WRMSDs. These hospitals have the following departments; theater, intensive care, emergency, hospitalizations, medical laboratory, pharmacy, and outpatient departments.

Was included in the study all full-time working nurses and LTs of both sexes at the LDHD, NDH and NDHD with at least 18 years of age and who consented to take part in the study and have been working for at least 12 months. Participants who had not worked for up to 12 months and who did not sign the informed consent forms, students, part-time workers, visiting healthcare workers from other countries or hospitals, having a MSDs before their commitment in to the healthcare profession or recent trauma, injury, surgery, motor vehicle accident, sport related injury in the past two weeks were excluded from this study.

Judgmental sampling was used to select these 4th category hospitals, as they receive many patients and also have a higher number of health workers.

Lorenz's formula was used to estimate the sample size needed, and a prevalence of 88.8% obtained from the study of Meh *et al.*, [17] was used.

$N = P(1-P)\ 2^2/d^2$ Where: n = same size, d = 0.05, z = 1.96; Statistical Corresponding level of confidence. After calculations the estimated sample size was n = 152. Finally, a total of 133 participants returned the questionnaires, giving a response rate of 53 %.

A semi-structured questionnaire was employed as the study instrument which was designed to collect socio-demographic data (age, gender, specialty, work experience, academic qualification and marital status) as well as factors associated with WRMSDs and coping strategies. The standardized Nordic questionnaire [22] was used to obtain the prevalence of WRMSDs and consisted of questions referring to nine body areas. These are 03 upper limb segments (Shoulders, elbows, wrists/hands/thumb), 03 lower limb segments (Hips/thighs, knees, ankles/ feet), and 3 trunk segments (Neck, upper back and lower back). Musculoskeletal pain intensity was assessed using the visual analog scale (VAS) where 0 = no pain, 1-4 = mild pain, 4-6 = moderate pain, and 7-10 = severe pain.

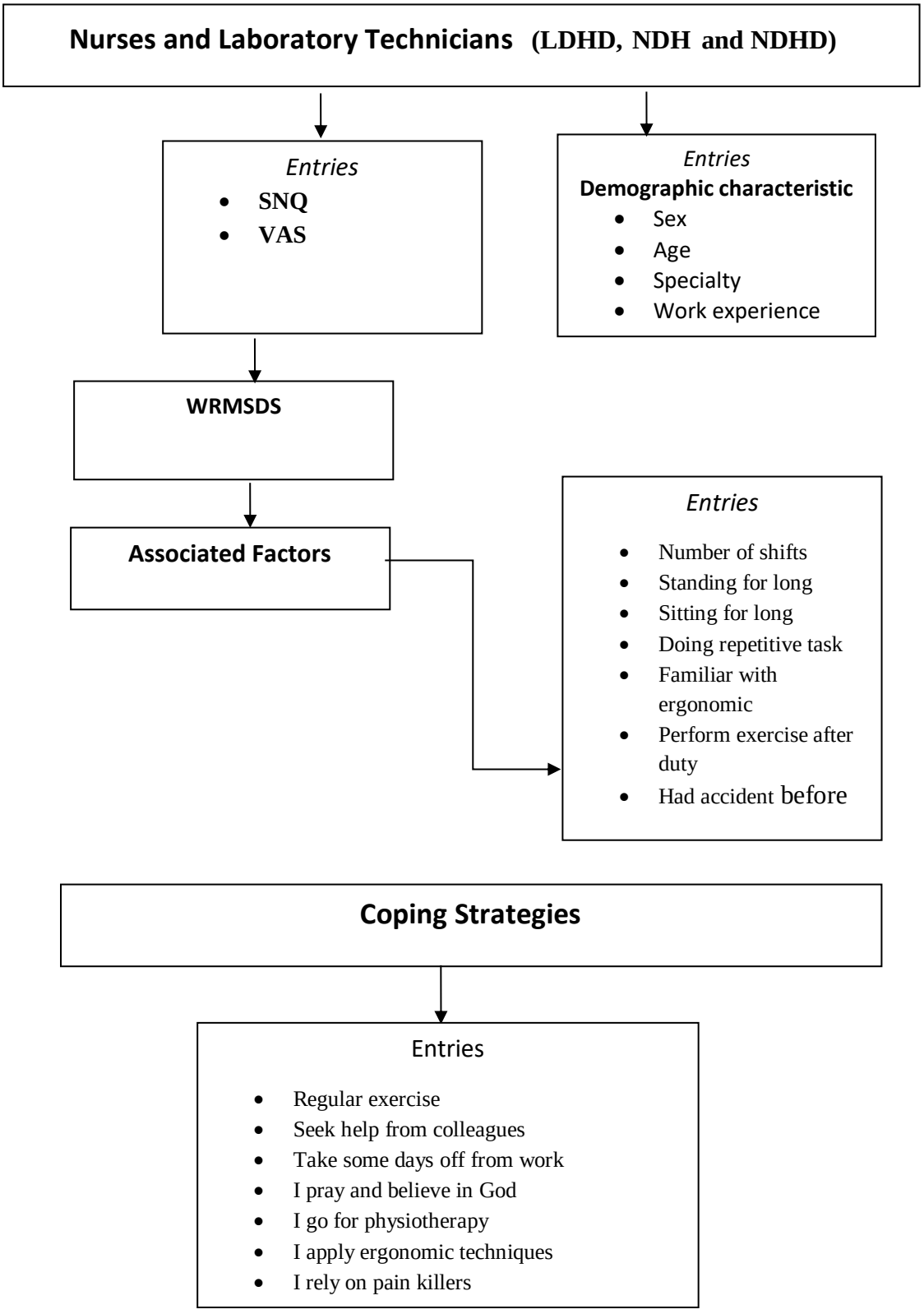

Figure 1: Flow Diagram Showing Data Collection and Instruments

A total of 250 questionnaires were distributed to all the nurses and LTs of the study hospital, but 133 questionnaires were returned yielding a 53 % response rate. All the 133 returned answered questionnaires were used for data analysis.

III. DATA ANALYZES

The data collected was entered into Microsoft Excel, verified for consistency and analyzed using SPSS version 23.0. Descriptive statistics was used to present the results on tables and figures, while the Pearson's chi square test was used to determine associations within groups. Statistical significance was set at $p < 0.05$.

Ethical Consideration

Research authorization (0265/AAR/MINSANTE/DRSPL/BCASS) was obtained from the Douala Regional Delegation of Public Health and from the hospital's administration. All the participants gave their signed consent. The fundamental principles of medical research according to Helsinki's Declaration were strictly respected and the names of the hospitals were coded for ethical reasons.

IV. RESULTS

4.1 Socio-Demographic Characteristics of Study Population

Table 1 presents the socio-demographic characteristics of the study population. A total of 250 questionnaires were distributed to all the nurses and LTs of the study hospital, but 133 questionnaires were returned yielding a 53% response rate. Out of the 133 participants recruited into the study, the majority was from the age group of 29-38 years (43.6%), females (76.7%), nurses (63.2%), single (53.4%) and had between 1-5 years (65.4%) of working experience.

Table 1: Socio-Demographic Characteristics of Study Population

Factor	Variable	Frequency)	Percentage (%)
Age range (years)	19-28	30	22.6
	29-38	58	43.6
	39-48	37	27.8
	49 and above	8	6.0
Sex	Male	31	23.3
	Female	102	76.7
Specialty	Nursing	84	63.2
	Laboratory scientist	49	36.8
Marital status	Single	71	53.4
	Married	62	46.6
Work experience	1-5 years	87	65.4
	6-10 years	28	21.1

4.2 Prevalence of WRMSDs and Pain Intensity

The overall prevalence of WRMSDs among nurses and LTs observed in the study was 69.9 % (93/133) (figure 2). Although the prevalence of WRMSDs was not significantly associated (χ^2 = 0.464; p = 0.496) with specialty, more laboratory technicians (73.5%; 36/49) experienced WRMSDs in one or more body part compared to nurses (67.9%; 57/84) (Figure 3).

WRMSDs was not significantly associated with sex but more females (70.6%; 70/102) experienced WRMSDs than males (67.7%; 21/31) (figure 4). Also, there was a significant association (χ^2 = 11.365; p = 0.0.010) of WRMSDs with age group in which, majority of healthcare workers in the age group of 39-48 years (83.8%; 31/37) experienced WRMSDs in one more body parts (figure 5). Findings from the study showed that, within the past 7 days, most of the participants had experienced one or more musculoskeletal disorder at the level of the lower back (48.1%) followed by neck (41.4%) and upper back (32.3%),

while the least was at the level hips (9.8%) (Figure 6).

It was revealed that a minority (11.3%; 15/133) of the total population felt mild pain while the majority (42.9%; 57/133) felt severe pain (Figure 7). Furthermore, the intensity of pain was not significantly associated with specialty but LTs (46.9%; 23/49) experienced severe pain more than nurses (40.5%; 34/84) (figure 8).

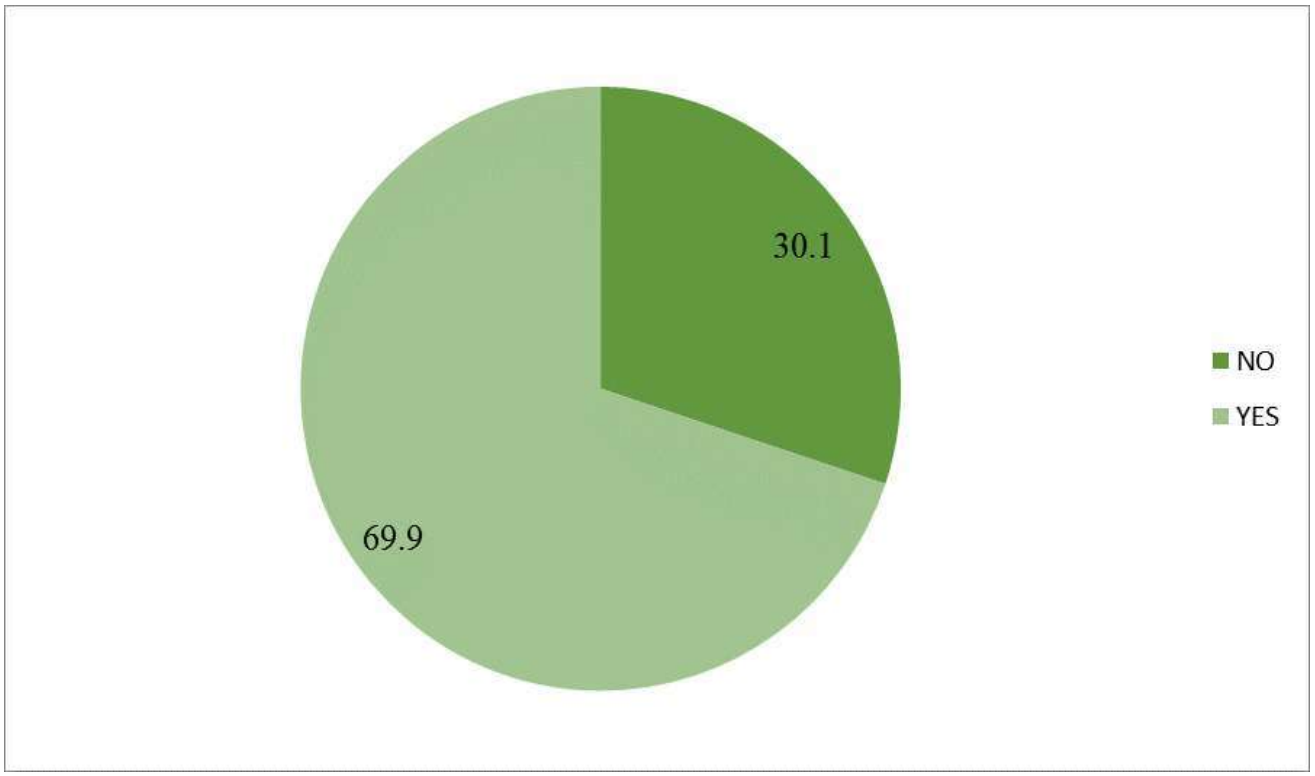

Figure 2: Overall Prevalence of WRMSDs

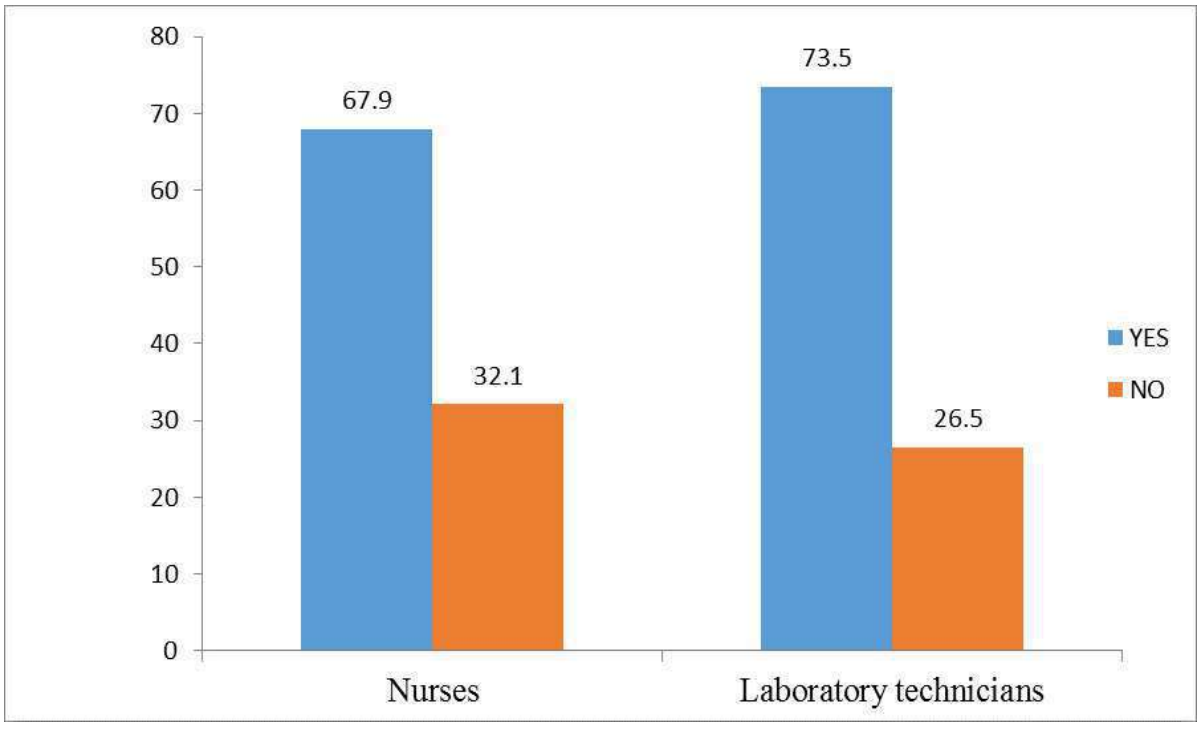

Figure 3: WRMSDs was not significantly associated with specialty (p = 0.496)

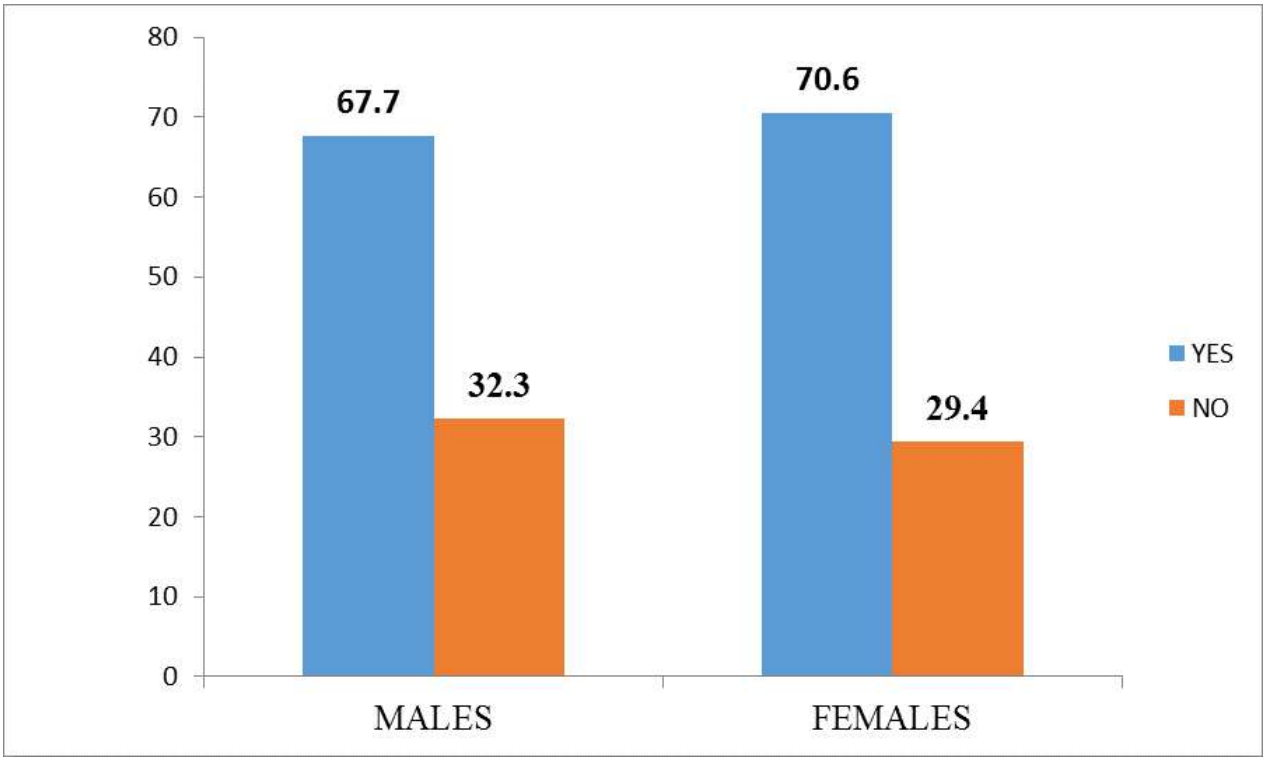

Figure 4: Prevalence of WRMSDs with respect to sex (p = 0.762)

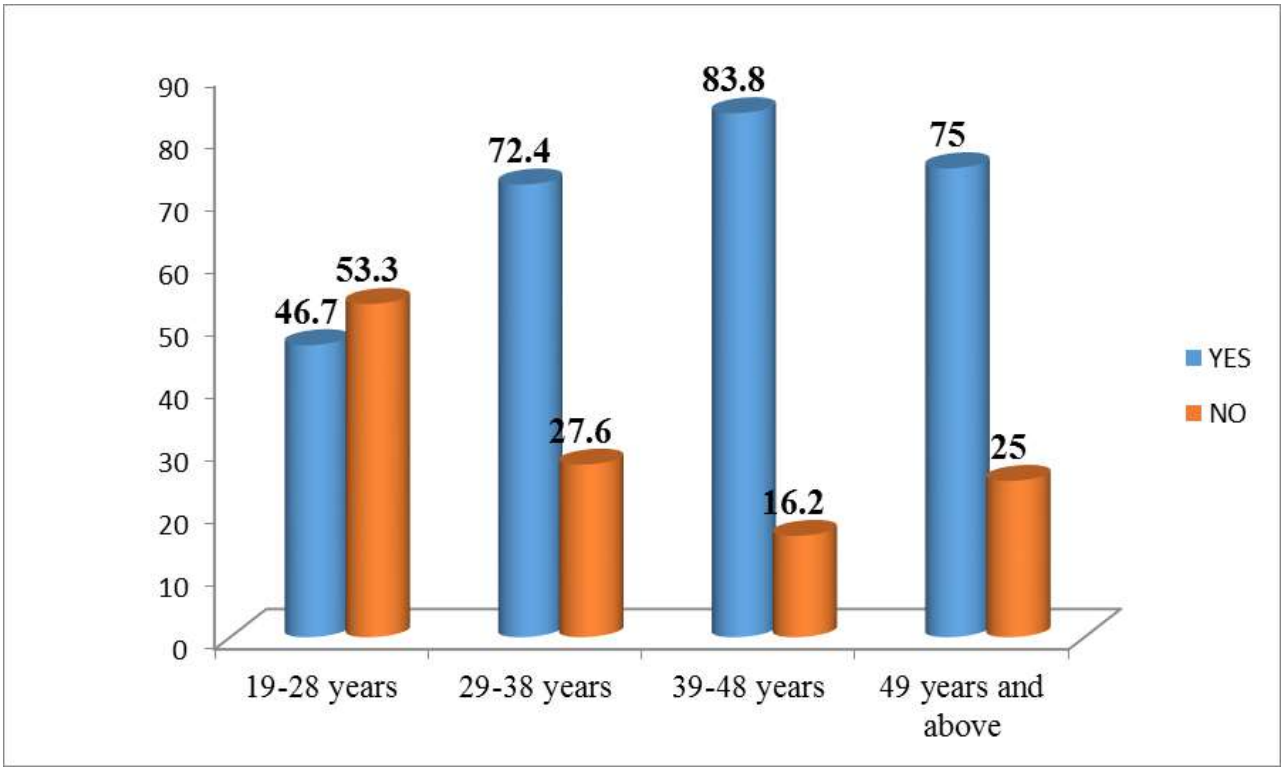

Figure 5: Prevalence of WRMSDs with respect to age group (p = 0.010)

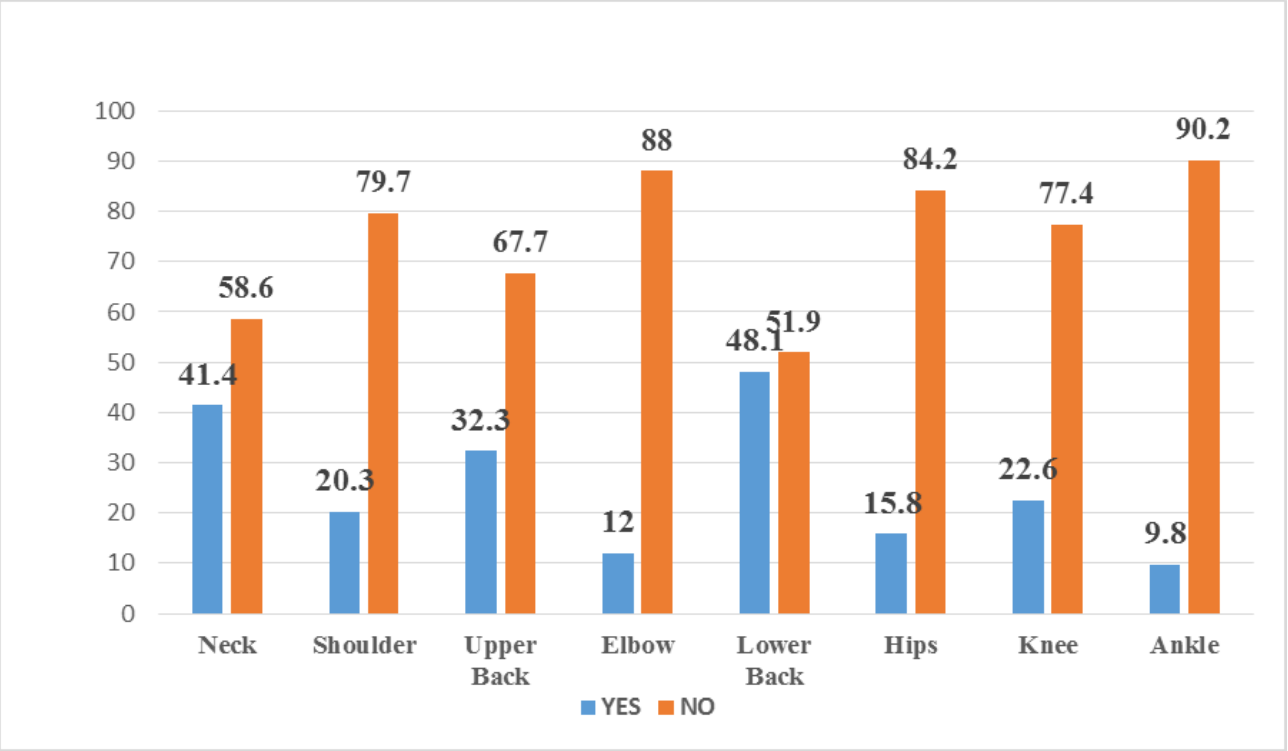

Figure 6: Prevalence with Respect to Different Body Regions

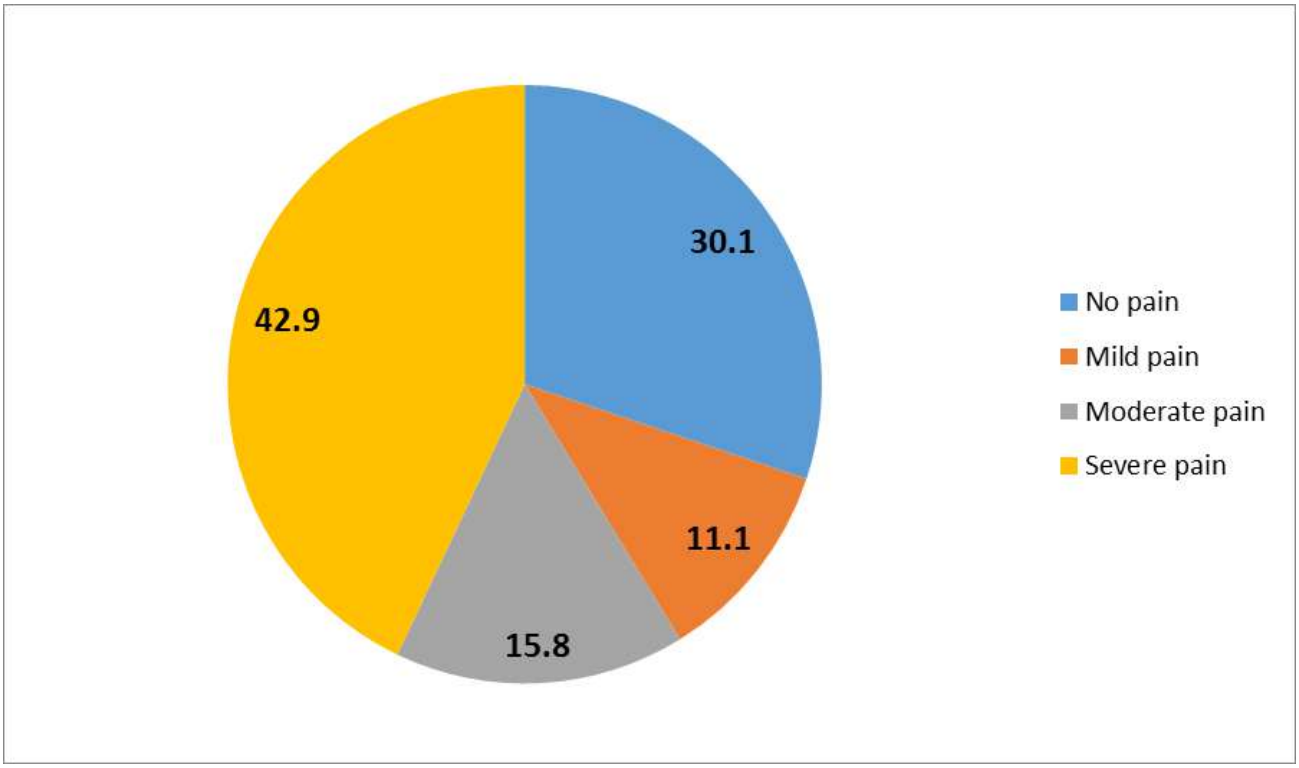

Figure 7: Intensity of Musculoskeletal Pain within the Past 7 Days

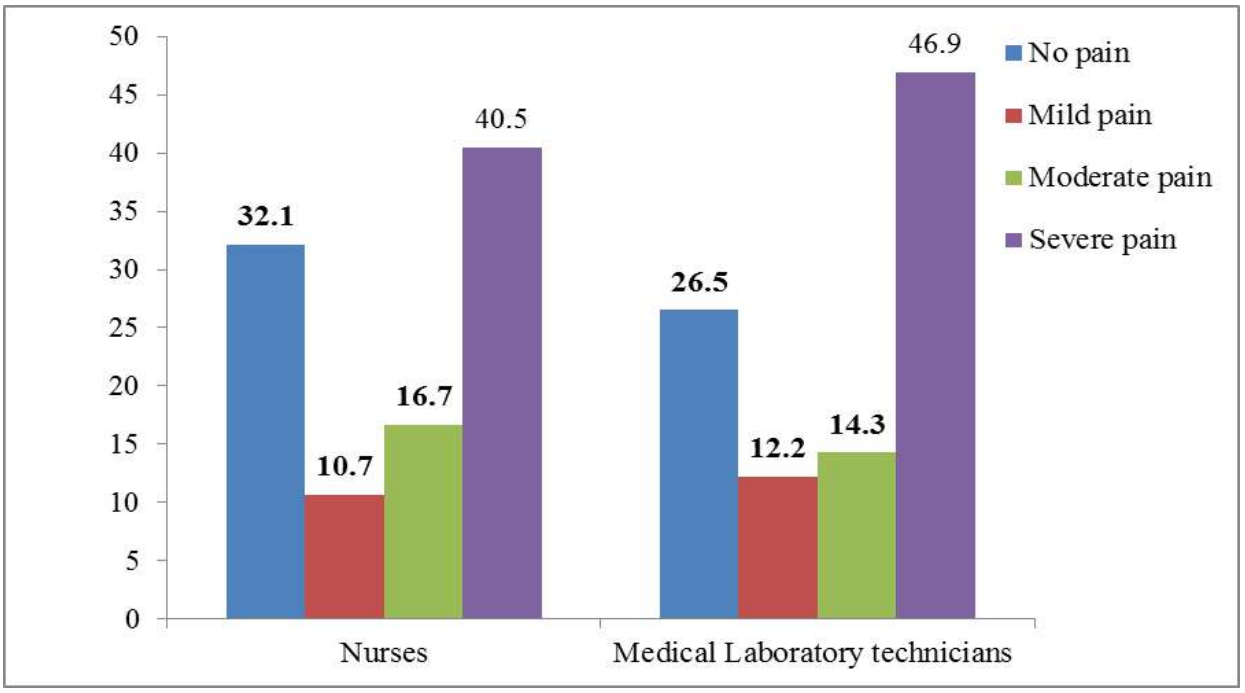

Figure 8: Intensity of Musculoskeletal Pain within the Past 7 Days With Respect to Specialty

4.3 Possible Factors Associated with WRMSDs

The study further evaluated the possible risk factors of WRMSDs and it was revealed that, Sitting for long in the same position ($\chi^2 = 4.894$; p = 0.027) and doing repetitive tasks (3.871; 0.049) were significantly associated with WRMSDs. Number of shifts per day (3.148; 0.207), standing for long (0.459; 0.498),, s, using vibrating objects (0.011; 0.918) and Stressfulness of job (0.984; 0.787) were not significant risk factors of WRMSDs (Table 2).

Table 2: Possible Risk Factors of WRMSDs

Factor	Variable	Prevalence of work related musculoskeletal disorders % (n)		Chi-square; p-value
		Positive	Negative	
Number of shifts	One	74.4 (61)	52.5 (21)	3.148; 0.207
	Two	59.0 (23)	41.0 (16)	
	Three	75.0 (9)	25.0 (3)	
Hours per day	Below 8 hours	69.7 (23)	30.3 (10)	0.001; 0.974
	Above 8 hours	70.0 (70)	30.0 (30)	
	NO	66.7 (36)	33.3 (18)	
Standing for long	YES	71.1 (59)	28.9 (24)	0.141; 0.707
	NO	68.0 (34)	32.0 (16)	
Sitting for long	YES	78.8 (52)	21.2 (14)	4.894; 0.027
	NO	61.2 (41)	38.8 (26)	
Doing repetitive task	YES	72.5 (87)	27.5 (33)	3.871; 0.049
	NO	46.2 (6)	53.8 (7)	
Using vibrating objects	YES	69.4 (34)	30.6 (15)	0.011; 0.918
	NO	70.2 (59)	29.8 (25)	
Stressfulness of job	YES	69.8 (44)	30.2 (19)	0.984; 0.787
	NO	70.0 (49)	30.0 (21)	

4.4 Coping Strategies of WRMSDs

The study further assessed the coping strategies used by nurses and laboratory technicians in coping with WRMSDs, and it was revealed that, regular exercises (51.9%), praying and believing in God for divine healing (51.1%), seek for professional help from colleagues (60.2%), taking some days off from work (88.0%), going for physiotherapy (84.2%) and applying ergonomic techniques (85.0%) were the major strategies used to cope with WRMSDs. Majority (52.6%) of the nurses and laboratory technicians did not rely on pain medications as a means to cope with WRMSDs. (Table 3).

Table 3: Coping Strategies of WRMSDs

Factor	Variable	Frequency (n)	Percentage (%)
Regular exercise	YES	69	51.9
	NO	64	48.1
Seek professional help from colleagues	YES	80	60.2
	NO	53	39.8
Take some days off from work	YES	117	88.0
	NO	16	12.0
Pray and believing in God	YES	68	51.1
	NO	65	48.9
Going for physiotherapy	YES	112	84.2
	NO	21	15.8
I apply ergonomic techniques	YES	113	85.0
	NO	20	15.0
I rely on painkillers	YES	63	47.4
	NO	70	52.6

V. DISCUSSION

The objective of this study was to determine the prevalence of work-related musculoskeletal disorders, pain intensity, associated factors and coping strategies among nurses and laboratory technicians working in three 4th category hospitals in the city of Douala, Cameroon.

This study revealed that the overall prevalence of WRMSDs for the past 12 months among nurses and LTs at the LDHD, NDH and NDHD was 69.9 %, with LTs having a higher prevalence rate (73.5%) compared to nurses (67.9%). With respect to the various body parts, the prevalence was highest at the lower back (48.1%), followed by the neck (41.4%) and upper back (32.3%). These findings are in line with the study carried out by Buh *et al.,* [16], who reported a 12 month prevalence of 77.89% of WRMSDs among nurses working in a 4th category hospital in the city of Douala. Most recently, similar results were also observed in a study by Meh *et al.,* [17], in which nurses and LTs had a prevalence rate of WRMSDs of 80.0% and 88.8% respectively. Furthermore, our findings corroborate with that of Ngunde *et al.,* [15] who revealed a 76.6% prevalence of WRMSDs among nurses in the Fako division of Cameroon, with the lower back (84.4%), neck (54.5%) and upper back (47.4%) being the most affected body parts. The prevalence of WRMSDs was not significantly different with respect to specialty, with LTs (73.5%) experiencing a higher prevalence compared to LTs (67.9%). This finding is in line with that by Meh *et al.,* (17), where the prevalence of WRMSDs in nurses and LTs was 82% and 89% respectively.

This high prevalence among nurses and LTs can be explained by the fact that these professionals often adopt prolonged positions either in standing or sitting, which has been identified as a key risk factor to WRMSDs [17]. WRMSDs was not significantly associated with sex, but more females (70.6%; 70/102) experienced WRMSDs than males (67.7%; 21/31). This corroborates

reports in literature, where the female sex is more likely to have musculoskeletal disorders [30].

Also, there was a significant association ($\chi 2$ = 11. 365; p = 0.0.010) of WRMSDs with age group in which, majority of healthcare workers in the age group of 39-48 years (83.8%; 31/37) experienced WRMSDs in one or more body parts compared to the other age groups. This is in line with the recent findings reported by Abla *et al.*, [12] and Meh *et al.,* [17].

Findings from this study show that about 42.9% of the participants had severe pain within the previous 7 days. This is not in line with the result obtained by Bryndal *et al.,* [29] in Poland, where most of the nurses had moderate pain. This higher pain intensity observed in our study may be due to the fact that our study was conducted in a low income setting where little or no preventive measures of WRMSDs and their impact exist, compared to high income countries like Poland where work space exercises and risk identification and management are instituted, thus reducing WRMSDs and its effects among their healthcare workers.

With regards to the factors associated with WRMSDs among nurses and LTs, findings from the study revealed that; sitting for long in the same position was significantly associated (χ^2 = 4.894; p = 0.027) to WRMSDs. Also, doing repetitive tasks was significantly associated (3.871; 0.049) with WRMSDs. Also, it was shown that; standing for long (72.2%), having only one shift (74.4 %), working above eight hours (70.0%) were common among nurses and LTs, but not significantly associated with WRMSDs. This is partly inline to the study carried out by Meh *et al.,* [17] among healthcare workers in the City of Douala Cameroon, who reported that; having only one shift (91.2%), standing for long (87.3%), sitting for long (86.3%), and doing repetitive task (85.9%) were the main non-demographic factors associated with WRMSDs. The slight difference might be due the sample size differences in both studies. The results from this study partially agrees with that of Tinubu *et al.,* [18] in Ibadan, South-west Nigeria who found out that 95% of nurses complained that working on the same positions for long periods and treating an excessive number of patients in one day as the most perceived associated factors of WRMSDs among nurses. The sample size and the slight difference of the risk factors assessed in both studies could explain this difference. Our findings are not in line with those of Agrawal *et al.,* [23] among laboratory professionals in Udupi district of Karnataka who reported young age, female professionals, paramedical staff and duration at work as the factors associated with WRMSDs. This difference could be explained by differences in the risk factors assessed and difference of sample size in both studies.

It can therefore be observed that the type of WRMSDs risk factors assessed vary greatly among studies. Therefore, further research taking into consideration both demographics and non-demographics factors, physiological and anthropometric variables using longitudinal study type needs to be implemented to give a more generalized conclusion as concerns the factors associated with WRMSDs among nurses and LTs including other health professionals.

Concerning the coping strategies of WRMSDs used by the study population; Praying and believing in God (51%), regular exercises (51.9%), seeking for professional help from colleagues (60.2%), taking some days off from work (88.0%), going for physiotherapy (84.2%) and application ergonomic techniques (85.0%) were the best coping strategies used by nurses and laboratory scientist in this study.

This study is not consistent with the study of Olutende *et al.,* [25] in Kakamega Kenya where all the nurses (100%) who experience one or more WRMSDs took analgesics drugs during and after work as a means of coping with WRMSDs. The observed differences could be attributed to the difference in the coping strategies evaluated in both studies, including differences in socio-cultural and religious beliefs among the studies populations.

The practice of regular exercise reported in this study as a coping strategy is supported by the study by Kovacevic and Avdic, [26] who reported most physiotherapists performed regular exercises as a means of coping with WRMSDs.

Furthermore, cognitive and behavioral strategies to cope with musculoskeletal disorders at work have been reported [27]. Cognitive strategies included techniques such as; distraction, visualization, self-talk, and blocking thoughts [27]. Seeking-social support, exercise/stretching, exposure management, self or accompanied treatment, eating/drinking were categorized as behavioral coping strategies [27]. This slightly differs with our findings because most of these factors were not assessed. Also, results from this study were in harmony with those of other studies where nurses used ergonomic techniques and modification of the nursing procedures as a coping strategy of WRMSDs [27, 28].

VI. LIMITATIONS OF THE STUDY

There were a few limitations to the study: the smaller sample size which may not be representative of the general population of nurses and LTs. Also, the different units of work of the nurses were not considered in the analysis. This may be essential as the work structure and work space in all the units are not the same. In future studies, we seek to evaluate these risk factors into categories such as; environmental, work, and personal risk factors; this will permit us to consider almost all factors susceptible to be associated with WRMSDs among nurses and laboratory technicians.

VII. CONCLUSION

The overall prevalence of WRMSDs was high among nurses and laboratory technicians. Laboratory technicians had the highest prevalence of WRMSDS than nurses, and the most affected body parts were the lower back, neck, and upper back. Sitting for long and doing repetitive tasks were significantly associated with WRMSDs, meanwhile maintaining prolonged standing postures, doing repetitive tasks, working only one shift were high in occurrence among the study population who had WRMSDs. In other to cope and manage these WRMSDs, the participants mostly relied on praying and believing in God, regular exercises, seeking professional help from colleagues, taking some days off from work, going for physiotherapy and applying ergonomic techniques. These findings will help to inform National and local healthcare providers on the high prevalence of WRMSDs among nurses and LTs and also on the predisposing factors. Also, the results obtained would help in risk management which will in turn reduce the occurrence of WRMSDs among nurses and LTs. Thus, productivity of these healthcare workers would be improved in Douala, and Cameroon as a whole.

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Declarations

Ethical consideration

Research authorization and clearance (0265/AAR /MINSANTE/DRSPL/BCASS) was obtained from the Douala regional delegation of public health which is in charge of reviewing public health research protocols. Also, administrative authorization was obtained from the different hospital administrators. The names of the study hospital were coded for ethical reasons, and all the participants gave their signed consent. This study respected the ethical principles of the European Union. The fundamental principles of medical research according to Helsinki's Declaration were strictly respected.

Consent for publication

All the authors consented and accepted for this article to be submitted for publication.

Availability of data and materials

Most data generated or analyzed during this study are included in this article. Also, all findings that support the result of this study are included.

Conflict of Interest

The authors certify there is no conflict of interest.

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This research did not receive any grant from funding agencies.

Abbreviations

LT:	Laboratory Technician,
MSDs:	Musculoskeletal Disorders,
WRMSDs:	Work - related Musculoskeletal Disorders,
VAS:	Visual Analog Scale,
SNQ:	Standardized Nordic Questionnaire

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Transformation of Antibody Status in HIV/AIDS Patients Treated with Medicinal Synthetic Aluminum-Magnesium Silicate {$Al_4(SiO_4)_3 + 3Mg_2SiO_4 \rightarrow 2Al_2Mg_3(SiO_4)_3$}

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ABSTRACT

Since viruses and abnormal cells are electrically charged, we postulated opposite charges electrostatic-mopping as treatment-mechanism for viral diseases and tumors. Molecules of Aluminum-magnesium silicate (AMS), WHO-approved medicine/adjuvant, consist of Nano-particles with positive and negative ends. Their ultra-small size (0.96 nm) enables them to get to all organs to mop viruses and abnormal cells. As an adjuvant and a silicate, AMS improves antimicrobials` efficacies and enhances patients` immunity. Mopping viruses and abnormal cells, clearing secondary infections and enhancing immunity cure viral diseases (including HIV/AIDS) and tumors. AMS- deposits may not exist in some countries and the medicine is un-absorbable. So, Aluminum silicate and Magnesium silicate (approved medicines) were used to formulate AMS-brand, named Medicinal synthetic *AMS* {*MSAMS:* $Al_4(SiO_4)_3 + 3Mg_2SiO_4 \rightarrow 2Al_2Mg_3(SiO_4)_3$}. Dextrose monohydrate was incorporated to transport it into blood- circulation.

Keywords: mopping pathogens; enhancing immunity; clearing secondary infections; ams-nanoparticles; electrostatic attraction.

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Transformation of Antibody Status in HIV/AIDS Patients Treated with Medicinal Synthetic Aluminum-Magnesium Silicate $\{Al_4(SiO_4)_3 + 3Mg_2SiO_4 \rightarrow 2Al_2Mg_3(SiO_4)_3\}$

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ABSTRACT

Since viruses and abnormal cells are electrically charged, we postulated opposite charges electrostatic-mopping as treatment-mechanism for viral diseases and tumors. Molecules of Aluminum-magnesium silicate (AMS), WHO-approved medicine/adjuvant, consist of Nano-particles with positive and negative ends. Their ultra-small size (0.96 nm) enables them to get to all organs to mop viruses and abnormal cells. As an adjuvant and a silicate, AMS improves antimicrobials ` efficacies and enhances patients ` immunity. Mopping viruses and abnormal cells, clearing secondary infections and enhancing immunity cure viral diseases (including HIV/AIDS) and tumors. AMS- deposits may not exist in some countries and the medicine is un-absorbable. So, Aluminum silicate and Magnesium silicate (approved medicines) were used to formulate AMS-brand, named Medicinal synthetic AMS {MSAMS: $Al_4(SiO_4)_3 + 3Mg_2SiO_4 \rightarrow 2Al_2Mg_3(SiO_4)_3$}. Dextrose monohydrate was incorporated to transport it into blood-circulation. That MSAMS-treated patient remained HIV-negative, 10 months post treatment has already been reported. Another patient monitored for 34 months also remained negative.

Keywords: mopping pathogens; enhancing immunity; clearing secondary infections; ams-*nanoparticles*; electrostatic attraction.

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I. INTRODUCTION

Any medicine that bonds to viruses will inhibit their attachment to cells of their hosts and so, terminate their infections (1) leading to cure for their diseases. Aluminum-magnesium silicate (AMS), a WHO-approved medicine, is made of molecules whose units are only 0.96 nm thick (*Nanoparticles*). The AMS-*Nanoparticles* have positive charges on their edges and negative charges on their surfaces (2, 3). Viruses are also electrically charged. RNA viruses including HIV are positively charged while DNA viruses and abnormal (tumor and infected) cells are negatively charged (4). So, we propounded the hypothesis of opposite charges electrostatic attraction for curing viral and abnormal cell diseases including HIV/AIDS. Since the AMS-*Nanoparticles* are much smaller than HIV (≥ 110 nm) they would get to all infected cells in all organs to mop both the virus and cells it infects, including the "sanctuary cells" ("HIV-reservoirs").

Though AMS is an existing medicine (5) its natural deposits do not occur in every country. Also, before now, its use as a medicine was restricted to treating localized ailments such as gastroenteritis and as topical applications because it is not absorbable. To make use of the two electrical charges on its *Nanoparticles* for systemic treatment of viral diseases and tumors, there was a need to get it into blood for circulation to all organs and tissues. So, we had to use two other medicinal minerals that are abundant in Nigeria (Aluminum silicate and Magnesium silicate) to formulate a brand of AMS which we

named *Medicinal synthetic Aluminum-magnesium silicate* (MSAMS) and developed a reaction-equation $\{Al_4(SiO_4)_3 + 3Mg_2SiO_4 \rightarrow 2Al_2Mg_3(SiO_4)_3\}$ as formula for the *MSAMS*. To get the *MSAMS-Nanoparticles* (with charges, opposite those on any virus) into blood for circulation to all organs, we employed the principle of active transport (6). By that principle, Dextrose monohydrate (a simple sugar) is incorporated in *MSAMS* formulations to convey the *Nanoparticles* across mucous membranes into blood.

Electrostatic mopping of HIV and HIV-infected cells which is antiviral-mechanism of the *MSAMS* is a physical effect. So, the medicine is safe for the long treatment-durations often needed to terminate HIV-infections. Medicines that act physically are better than medicines that inhibit viral biochemistry in treatment of HIV/AIDS because similarity of viral biochemistry and biochemistry of animal cells makes medicines that inhibit viral biochemistry to exhibit intolerable side effects when treatments are prolonged.

For its small size (≥ 110 nm: 7) HIV, reaches and infects some cells in the brain, bone marrow and testes which big molecules cannot reach. Those inaccessible cells are called "sanctuary cells" or "HIV-reservoirs" because infections in them cannot be terminated by existing antiretroviral medicines (ARVs). It therefore means that size is vital in developing medicines that can achieve permanent cure for HIV/AIDS. Since the AMS *Nanoparticles* are much smaller (3) than even the smallest HIV, the medicine gets to and terminates HIV-infections in every cell and in every organ or tissue, including the "sanctuary cells". The positive charges on HIV (8) and the negative charges on abnormal cells (9, 10) are biomedical markers by which the *MSAMS-Nanoparticles* mop HIV with their surfaces and destroy HIV-infected cells with their edges (3).

As a silicate, MSAMS also stimulates immunity (11) while as an adjuvant it improves efficacy of antimicrobials (12). Improving efficacy of drugs makes it possible to use lower doses for desired effects. Use of lower doses for treatments leads to further improvement of immunity. High immunity in patients compliments effects of drugs in terminating both secondary infections and viral infections.

To be sure that the HIV/AIDS cure which we have been reporting is permanent, we started monitoring patients who become HIV-negative for antibodies, after they stop taking any ARV. A patient was monitored every month, for 10 months (13). This second patient being reported was monitored 34 months after he recovered and has been without any anti-retroviral medicine.

II. CASE-HISTORY

A patient who recovered from HIV/AIDS was monitored for HIV-antibodies after 34 months, post treatment to extend the monitoring period beyond that of a recovered patient who was monitored for 10 months (13). Both patients were treated with a formulation of the *MSAMS* and Ampicillin trihydrate (Antivirt® A) and Immunace extra protection® (antioxidants) for one month.

Then, their treatment was changed to a formulation of *MSAMS* alone (Antivirt® B) and the antioxidants, till they tested HIV-negative (antibody and antigen). From the month they became antigen-negative, treatment with any ARV was stopped while they were tested for HIV antibodies.

III. RESULTS

It took 19 months of daily treatment with the *MSAMS* before the patient became HIV-negative (antibody and antigen). He has remained HIV-antibody negative for 34 months. He also remained in good health within the period.

IV. DISCUSSION

HIV/AIDS was said to be incurable. The opposite charges electrostatic attraction we introduced as a mechanism for curing viral diseases is an old scientific principle. It is also in literature that Aluminum-magnesium silicate which we are using for the treatment is an approved medicine.

Molecules of the medicine consist of *Nano-particles* which have both positive and negative

electrically charged ends while viruses have either positive or negative electrical charges. Again, size of the AMS-*Nanoparticles* is less than any known virus (≥ 5 nm). Even with these facts, some people still hold the belief that HIV/AIDS has no cure. They fear that those patients we reported to have recovered could test HIV-positive again, because HIV-infections in the "sanctuary cells" may not have been terminated.That HIV/AIDS was without cure till now, is not a mystery. Lymphocytes which the virus destroys are responsible for immunity (14) and immunity is vital in terminating viral infections because viruses are so small that they get to and infect cells which are inaccessible to most medicines.

In addition to the severe immune deficiency which HIV causes, it is very invasive and so, its infections take a long treatment-time to terminate. Use of medicines made to inhibit biochemistry of viruses is not good when treatments are to be for a long time, because, similarity of viral biochemistry and biochemistry of animal-cells makes such medicines exhibit intolerable side effects. Medicines that act physically have their own limitation which is that they need to get to every viral particle and every infected cell before terminating infections. When it is not possible for physical-effect medicines to reach all infected cells, immunity must be adequate for infections to be terminated. With the severe immune-deficiency caused by HIV, nothing is left to terminate its infections if physical-effect medicines (mild side effects) that cannot reach all infected cells are used in treating patients.

Sizes of active principles are therefore vital for antiviral medicines if they are to act physically. The discovery that every virus has either positive electrical charges or negative electrical charges and that abnormal (infected/tumor) cells are negatively charged while normal cells remain neutral (without charges) means that electrical charges are biomedical markers to exploit in developing medicines to act physically in order to terminate viral infections including HIV-infections.

The negative charges on surfaces of AMS-*Nanoparticles* enable them to displace HIV from cells. That means inhibition of the first stage in viral replication (1). Since the *Nanoparticles* have positive charges on their edges, they also bond to HIV-infected cells to mop and/or destroy them (3), thereby unmasking "hidden infections". Their ultra-small size (0.96 nm) makes it possible for them to get to HIV in every organ and in every cell, including the "sanctuary cells". Since the medicine acts by a physical effect (mopping), it is safe for prolonged treatment required to terminate infections of the very invasive virus.

Transformation of HIV-status from positive to negative observed with this patient suggests that he has been cured. No HIV-infected person can remain HIV-negative for more than six months (window period), without ARV. So, for persons who were confirmed HIV-positive to remain HIV-negative for 10 months and 34 months, respectively, without being on any ARV means that the *MSAMS* terminates the HIV infections and leads to cure for HIV/AIDS. If treated patients do not get exposed again they could remain HIV-negative for life.

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Prevalence of Pressure Ulcer and Associated Factors among Home Health Care Patients at King Abdullah Medical City, Makkah Al-Mukarramah, Saudi Arabia, a 2022-Cross-Sectional Study

Dr. Fatima B Al-Nahdi, Dr. Rami Faraj, Dr. Mohammed Andijany, Dr. Omar Alahdal, Dr. Areej Qadah, Abrar Albukhari, Nada ALghamdi, Sami Magrabi & Yasir Ahmed Alemam

ABSTRACT

Introduction: Pressure ulcers (PU), are the degradation of skin and underlying tissue in localized areas, most often the sacrum.

Aim: To determine the prevalence of PU in home health care patients and associated risk factors to improve the related care processes.

Methods: Cross-sectional study was conducted for one month. doctors and nurses trained and visited HHC patientsThe team inspected the patients' skin from head to toe. The PU site was identified on the data collection sheet using NPUAP classification system and Braden Scale Score.

Results: 175 patients from Home Health Care patients at King Abdullah Medical City in Makkah, with a mean of age 69.55±14.9, were included. 20 patients (11.4%) had PU. The most common site of PU was Buttocks and sacral (50%), least were Left posterior leg and ankle (1%). According to The Braden Scale risk, the majority of patients were at Minimal risk (37.1%) or Mild risk (33.7%) of PU, while 9.7% of patients were at high risk of PU, and 4.6% were at Very high risk of PU.

Keywords: prevalence, pressure ulcer, factors, bed sores, skin, injuries.

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Prevalence of Pressure Ulcer and Associated Factors among Home Health Care Patients at King Abdullah Medical City, Makkah Al-Mukarramah, Saudi Arabia, a 2022-Cross-Sectional Study

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Conclusion: we demonstrated a low prevalence of pressure ulcers among studied patients. Buttocks and sacrum were the most prevalent PU locations. Age, gender, mobility, and Braden risk significantly influence PU prevalence.

Keywords: prevalence, pressure ulcer, factors, bed sores, skin, injuries.

I. INTRODUCTION

Pressure ulcers (PU) are the destruction of skin and underlying tissue of localized areas usually present in a bony prominence.[1] Pressure ulcer locations differ; The most common site of ulcers is acquired while the patient is lying in bed; sacrum, trochanters, heels, and feet; [2, 3] The leading cause of PU is applying pressure externally for an extended period. The main risk factor for PU is immobility. [4]

Patients with comorbidities are associated with high-risk for developing PU. [2]

Studies showed that old age, morbid obese, dehydration, are risk for getting PU. [5]

II. AIM OF WORK

This study sought to determine the prevalence of PU in home healthcare patients and associated risk factors to improve the related care processes.

III. METHODS

Study design

A Cross-sectional study

Study area

The study was conducted in Makkah at King Abdullah Medical City (KAMC). This tertiary and quaternary healthcare facility provides the highest

quality of care, excellence, and integration of patient care, education, and research.

Study Population

Inclusion criteria

- All home health care Patients at KAMC
- Adult Males and females
- All nationalities

Exclusion Criteria

- Pediatric patients
- Patient with medical device-related pressure injuries

Sample size

The total number of HHC patients at KAMC is 315 patients.

Using an online sample size calculator from www.roasoft.com.The sample size was 174, setting a confidence level (Cl) of 95% and a sampling error of 5%.

Sample technique

By reviewing the patients' data recorded in Home Health Care (HHC) department at KAMC, each patient was coded by number starting from the number (1, 2, 3) and so on. Then, using a stratified sampling technique, patients were divided according to their living areas West, East, North, and South. Randomly forty-four patients were chosen from each area using the online website Research Randomizer®.

Data collection tools

The data collection sheet was designed in English with a cover letter coded by number to ensure confidentiality, and the consent paper signed by patients or their caregivers. These were linked to the patient's name and MRN in a separate identification log sheet which will be kept in a safe, locked place.

Based on the literature review, the authors developed a data collection sheet that contains three major parts; the first one is about patient demographic data, the Second part describes possible factors associated with bed sores, and the third part is validating instruments, including Braden scale and Pressure ulcer staging scale.

Study procedure

A cross-sectional study was conducted over one month after obtaining KAMC Intuitional Review Board approval. Every patient was chosen randomly to be visited within one month of the scheduled visit to HHC patients. Patients or their caregivers signed the consent form during the HHC visit.

The data collection team included doctors and nurses that visit HHC patients, trained to use the data collection tool. Before conducting the study, an educational session on the NPUAP classification system and Braden Scale score was given to the team that visit home health care patients. The team inspected the patients' skin from head to toe when visiting. The PU site was identified on the data collection sheet by drawing a circle over the relevant area in the body figure.

At the end of the visiting day, the primary investigator collected the data collection sheets and kept them secure.

Statistical Analysis Plan

SPSS software was used for statistical analysis. In addition, a statistician was recruited for the statistical analysis of this study.

Ethical part & confidentiality

- Ethical approval was sought from KAMC IRB.
- The patients were included in the study after signing the informed consent form.
- If vulnerable groups could not decide, consent was taken from the next of kin.
- All information remains confidential and not be accessed except for scientific research.
- Acknowledgments for the team, helpers, and facilitators indicating their role in the research process.

Conflict of Interest, Incentive, and Payment

The research participants did not receive any payments, reimbursement of expenses, or any other benefits or incentives for participating in this research.

The individual researchers did not receive any personal payment over and above normal salary or any other benefits or incentives for participating in this research.

The Chief Investigator or any other investigator/ collaborator did not have any possible conflict of interest (e.g., financial, shareholding, personal relationship, etc.) as the study is neither sponsored nor funded.

IV. RESULTS

One hundred seventy-five patients from Home Health Care at King Abdullah Medical City in Makkah Al-Mukarramah, in different age categories with a mean of 69.55±14.9, were included in the study. Most patients were older than 60 years old (81.1%). 55.4% of patients were females. 33.7% of included patients had normal weight, while 23.4% of patients were obese and 23.4% of them were overweight. Most of the patients had average social status (90.3%). 18.9% of patients were bedbound, 19.4% were Bedridden, 24.6% were Chair bound, 28% were moved with assistance, and 9.1% moved without assistance.

Table 1: Presence of Bed Sores among the Studied Patients

		Frequency	Percent
	No	155	88.6
	Yes	20	11.4
	Total	175	100.0

Out of 175 patients, 20 patients (11.4%) had bed sores (pressure ulcers).
Out of 20 patients who had PU, 45% had 1 PU, 20% had 4 PU, 15% had 2 PU, 10% had 3 PU and 5% had 5 PU.

Table 2: Description of Pressure Ulcer Cases

		N=20	%
Complication	infection	4	20%
	Infection& osteomyelitis	1	5%
Location	Buttocks	10	50.0
	left trochanter	5	25.0
	Right trochanter	3	15.0
	heel	4	20.0
	sacral	10	50.0
	posterior upper thigh	1	5.0
	Shoulder	1	5.0
	Left posterior leg	1	5.0
	ankle	1	5.0
Stage	First	5	
	Second	10	
	Third	6	
	fourth	2	
	Un stageable	12	

Out of 20 patients who had PU, 4 (20%) had an infection, and 1 (5%) had an Infection& osteomyelitis. The most common site of PU was Buttocks and sacral (50%), followed by left trochanter (25%), Right trochanter (15%), and heel (20%), then posterior upper thigh, shoulder, Left posterior leg and ankle (1%). The majority of patients had Un-stageable PU (12), and 10 patients had the second stage PU, 6 patients had a third stage, 5 patients had first-stage PU.

Table 3: Braden Scale Risk of PU among the Studied Patients

Frequency	Number	Percent
Minimal risk	65	37.1
Mild	59	33.7
Moderate	26	14.9
High risk	17	9.7
Very high risk	8	4.6

The majority of patients were at Minimal risk (37.1%) or Mild risk (33.7%) of PU, 14.9% of patients were at Moderate risk of PU, while 9.7% of patients were at high risk of PU, and 4.6% were at Very high risk of PU.

Table 4: Prevalence of Pressure Ulcers According to Demographic Characters

			Presence of PU		P Value
			No	Yes	
age	< 40	n	5	3	0.015
		%	62.5%	37.5%	
	40-60	n	20	5	
		%	80.0%	20.0%	
	>60	n	130	12	
		%	91.5%	8.5%	
gender	Female	n	81	16	0.019
		%	52.3%	80.0%	
	Male	n	74	4	
		%	47.7%	20.0%	
Social status	Accepted	n	141	17	0.396
		%	91.0%	85.0%	
	Poor	n	14	3	
		%	9.0%	15.0%	
Living area	East	n	41	3	0.151
		%	26.5%	15.0%	
	North	n	40	3	
		%	25.8%	15.0%	
	South	n	39	5	
		%	25.2%	25.0%	
	West	n	35	9	
		%	22.6%	45.0%	
weight	thin	n	26	8	0.093
		%	16.8%	40.0%	
	Normal	n	55	4	
		%	35.5%	20.0%	
	Over weight	n	37	4	
		%	23.9%	20.0%	
	Obese	n	37	4	
		%	23.9%	20.0%	

The factors associated with PU prevalence were age (P=0.015) and gender (P= 0.019). However, living area and weight did not significantly affect PU prevalence (P>0.05)

Table 5: The Factors Associated with Pressure Ulcer among Studied Patients

			Presence of Bed sores		P value
			No	Yes	
Urinary catheters	Yes	N	22	4	0.492
		%	14.2%	20.0%	
	No	N	133	16	
		%	85.8%	80.0%	
Mobility	Bed bound	N	26	7	0.009
		%	16.8%	35.0%	
	Bedridden	N	26	8	
		%	16.8%	40.0%	
	Chair bound	N	41	2	
		%	26.5%	10.0%	
	Mobile with assistance	N	46	3	
		%	29.7%	15.0%	
	Mobile without assistance	N	16	0	
		%	10.3%	.0%	
Braden risk	'Minimal risk		64	1	0.002
			41.3%	5.0%	
	mild	N	52	7	
		%	33.5%	35.0%	
	Moderate	N	22	4	
		%	14.2%	20.0%	
	high	N	12	5	
		%	7.7%	25.0%	
	Very high	N	5	3	
		%	3.2%	15.0%	

Table 6 shows that mobility (P= 0.009) and Braden risk (P=0.002) were significant factors associated with PU among the studied patients

Table 6: Percent of Pressure Ulcer in Relation to Co-Morbidity

	Presence of Bed sores		P value
	No	Yes	
Peripheral Neuropathy	22	3	0.923
	88.0%	12.0%	
DM	92	9	0.221
	91.1%	8.9%	

Table 6 shows that the presence of co-morbidities such as peripheral neuropathy or DM did not significantly (P> 0.05) associate with PU prevalence among the included patients.

V. DISCUSSION

Bedsores, also called ulcers, are areas of localized pressure injury to the skin and surrounding tissue. [6] PU causes ischemia, necrobiosis, and tissue necrosis; This approach leads to painful and sluggish pressure ulcer healing. [7] Pressure ulcers are a major issue in hospitals, homes, and communities. The development of a pressure ulcer is complex and multidimensional. Pressure ulcers provide an additional co-morbid risk in critically sick physiologically challenged patients.

Indeed, one of the most overlooked medical complications in critical care patients is pressure ulcers. Despite medical technological advancements and the implementation of clinical

practice guidelines-based the prevalence of pressure ulcers during hospitalization remains high (80%). [8] The frequency of acquired pressure ulcers was highest in patients in the intensive care unit (ICU), ranging from 14% to 42% of all hospitalized patients. Pressure ulcers are also linked to fatality. Several studies found that elderly people with pressure ulcers died at a rate of up to 60% within a year of being discharged from the hospital. [9] This study sought to evaluate the prevalence of PU in home healthcare patients and associated risk factors to improve the related care processes. One hundred seventy-five patients from Home Health Care patients at King Abdullah Medical City in Makkah Al-Mukarramah, with a mean of age 69.55±14.9, were included in this study. The majority of patients were older than 60 years old. 55.4% of patients were females. Out of 175 patients, 20 (11.4%) had bed sores (pressure ulcers). Out of 20 patients who had PU, 4 (20%) had an infection, and 1 (5%) had an Infection& osteomyelitis. The most common site of PU was Buttocks and sacral (50%), followed by left trochanter (25%), Right trochanter (15%), and heel (20%), then posterior upper thigh, shoulder, Left posterior leg and ankle (1%). The majority of patients had Un-stageable PU (12), 10 patients had the second stage of PU, 6 patients had the third stage, and 5 patients had first-stage PU.

Similarly, Sifir et al. (2022) investigated the prevalence of bed sores and the variables that contribute to them in rehabilitated patients in medical and surgical wards at Yekatit 12 Hospital Medical College. A total of 7 bedsores were found in 226 patients, with a frequency rate of 3.0, suggesting a low prevalence. [10] In addition, a systematic review by Borojeny et al. (2020) showed that the incidence rate of pressure ulcers was 12% [11]. In our study, the most common site of PU was Buttocks and sacral (50%), followed by the left trochanter (25%), Right trochanter (15%), and heel (20%), then the posterior upper thigh, shoulder, Left posterior leg and ankle (1%). The majority of patients had Un-stageable PU (12), 10 patients had the second stage of PU, 6 patients had the third stage, and 5 patients had first-stage PU. Borojeny et al. (2020) reported that the sacrum was the most often afflicted location, accounting for 44% of all cases, followed by the buttocks (15%), the heel (15%), and the trochanter (4%). Moreover, the prevalence rate of first, second, third, and fourth-stage pressure ulcers was 45%, 4%, and 4%, respectively. [11] The majority of patients were at Minimal risk (37.1%) or Mild risk (33.7%) of PU, 14.9% of patients were at Moderate risk of PU, while 9.7% of patients were at high risk of PU, and 4.6% were at Very high risk of PU. Sprigle et al. (2020) investigated the risk of pressure ulcers (PU) in people with mobility disabilities. They discovered that while the vast majority of people were at high risk of PU, roughly 25% were at moderate or low risk. [12]

Our findings indicated that the factors associated with PU prevalence were age (P=0.015) and gender (P= 0.019). However, living area and weight had not a significant effect on PU prevalence (P>0.05), mobility (P= 0.009), and Braden risk (P=0.002). However, our results showed that co-morbidities such as peripheral neuropathy or DM did not significantly (P> 0.05) associate with PU prevalence among the included patients. In a similar study, Akram et al. (2022) showed that bed sores were associated with age, socioeconomic status, educational status, length, immobility, chronic kidney disease, obesity, diabetes mellitus, and history of hypertension, stroke, or heart disease. [13] Arba et al. (2020) discovered that patients older than fifty-three years, residing in rural areas, and being bedridden were variables related to bedsore development in Southern Ethiopia. [14] In addition, Liao et al. (2019) reported that pressure sores in acute ischemic stroke patients were associated with advanced age, immobility, being unmarried, low hemoglobin, significant neurological and a history of diabetes mellitus, and peripheral vascular disease. [15]

VI. CONCLUSION

The present study demonstrated a low prevalence of pressure sores among Home Health Care patients at King Abdullah Medical City, Makkah Al-Mukarramah, Saudi Arabia. Buttocks and sacrum were the most prevalent PU locations. The majority of patients had a low or moderate Braden risk of PU. Age, gender, mobility, and Braden risk were the significant factors associated with PU prevalence. However, place of residence, weight,

and the presence of co-morbidities such as peripheral neuropathy or diabetes did not have a significant influence on PU prevalence.

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Vitamin -Medication and Post Vaccination Rabies Antibody Titres in Nigerian Dogs

Maduike Chiehiura Onwubiko Ezeibe, Kingsley John Jaja, Ijeoma Favour Ezeibe, Ijeoma Joy Ogbonna & Clara Amaka Akpan

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ABSTRACT

Rabies antibody titres in dogs (aged ≥ 3 months) which had been vaccinated with the Ptovac® Anti-rabies vaccine brand and administered B-vitamins, post vaccination, in Nigeria, were assessed by passive haemagglutination (PHA) test. The groups were named: Treated with B-vitamins (Vetzyme®) for one day post vaccination; Treated with B-vitamins for two days post vaccination; Treated with B-vitamins for three days post vaccination and Control. Two weeks post vaccination, serum from each dog was tested for rabies antibodies by PHA. Antibody titres in the groups differed, significantly (P≥ 0.05), from 24.74±0.08 in the control to 64.08±0.03 in Treated with B-vitamins for one day post vaccination, 89. 29±0.17 in Treated with B-vitamins for two days post vaccination and 140.73±0.14 in Treated with B-vitamins for three days post vaccination. Adopting post vaccination B-Vitamins` treatment and routine assessment of immune response of dogs to anti-rabies vaccinations could improve success of rabies control-efforts in the country.

Keywords: PHA; rabies; post vaccination; vitamins.

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Vitamin-Medication and Post Vaccination Rabies Antibody Titres in Nigerian Dogs

Post Vaccination Vitamins` Treatments and PHA Antibody Testing

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ABSTRACT

Rabies antibody titres in dogs (aged ≥ 3 months) which had been vaccinated with the Ptovac® Anti-rabies vaccine brand and administered B-vitamins, post vaccination, in Nigeria, were assessed by passive haemagglutination (PHA) test. The groups were named: Treated with B-vitamins (Vetzyme®) for one day post vaccination; Treated with B-vitamins for two days post vaccination; Treated with B-vitamins for three days post vaccination and Control. Two weeks post vaccination, serum from each dog was tested for rabies antibodies by PHA. Antibody titres in the groups differed, significantly (P≥ 0.05), from 24.74±0.08 in the control to 64.08±0.03 in Treated with B-vitamins for one day post vaccination, 89. 29±0.17 in Treated with B-vitamins for two days post vaccination and 140.73±0.14 in Treated with B-vitamins for three days post vaccination. Adopting post vaccination B-Vitamins` treatment and routine assessment of immune response of dogs to anti-rabies vaccinations could improve the success of rabies control-efforts in the country.

Keywords: PHA; rabies; post vaccination; vitamins.

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I. INTRODUCTION

Rabies is fatal encephalitis, caused by *Rabies virus* (Nandi and Kumar, 2011). It is a zoonosis that occurs in all parts of the world, accounting for more than 59,000 deaths per year (WHO, 2013). Of human deaths caused by rabies, 56 % occur in Asia while 44% is in Africa (Bourhy *et al.*, 2010, WHO, 2013; OIE, 2016). The disease affects all warm blooded animals (Ogunkoya *et al.*, 2003), both wild and domestic including man. This wide host range makes its control difficult.

Main method of rabies control in most countries is annual vaccination of dogs and cats. Such vaccinated animals need to be tested to ensure they have high levels of rabies antibodies but presently, the method of assessing effectiveness of anti-rabies vaccination processes is by challenging vaccinated laboratory animals with the virus (WHO, 2013).

Virus-neutralization tests to assess immune response in vaccinated animals also involves challenging laboratory animals with the live virus. By such methods antibody titre of 0.5 IU/ml has been suggested as protective (WHO, 2013) but it has also been reported that vaccinated animals with lower antibody levels survived RABV challenge. Other reports also have it that some animals with neutralizing antibody titres at time of challenge came down with the disease (Aubert, 1992) though such animals were better protected against RABV than those without detectable virus neutralizing antibodies (Aubert, 1992).

The type of vaccine used, number of vaccinations, intervals between vaccinations and blood sampling, age at vaccination, sex, reproductive status, size and breed can influence antibody response of animals to anti-rabies vaccines (Mansfield *et al.*, 2004). Also, it has been reported that in post-vaccination serological studies, the percentage of animals with inadequate titres range between 3.10 to 8.10 % for dogs (Minke *et al.*, 2008) and 2.85 % for cats (Mansfield *et al.*, 2004).

According to WHO recommendations, titre of 0.5 IU/ml or its equivalent is adequate vaccination-response and a booster vaccination is recommended once the level goes lower. Despite annual vaccination of Nigerian dogs, records still show that dog bites are still responsible for a very high percentage of cases of human rabies in Nigeria (Ogunkoya, 2008). Yet the immune status of Nigerian dogs (even when vaccinated) is not known.

There is therefore a need to adopt a simpler, cheaper and more rapid test so that anti-rabies vaccinations can be verified to ensure that vaccinated animals have protective antibody titres. Also, post vaccination Vitamins-treatment is known to enhance immune response in poultry.

It may also enhance rabies antibody titres in vaccinated dogs and so prolong the time vaccinated dogs would remain protected.

II. MATERIALS AND METHODS

Twenty Nigerian mongrel dogs, aged 3 months and above were randomly assigned to 4 groups (A, B, C and D) of 5 dogs each. They were vaccinated with a foreign anti-rabies vaccine (Provac®). Group A was given post vaccination vitamins` treatment (Vetzyme®) for one day.

Group B was given the post vaccination vitamin-treatment for 2 days, group C was treated for 3 days while group D served as control (no post vaccination vitamin- medication). Two weeks post vaccination, blood samples were collected from each dog for passive haemagglutination (PHA) test, to determine titres of antibodies against rabies.

Chicken RBCs were sensitized with *Rabies virus* (Gough and Dierks, 1971). To 30 ul of 0.25 % chicken RBC, equal volumes (30 ul) of *Rabies virus* and of 0.1% chromium chloride in 0.86 % NaCl were added. The mixture was kept at room temperature for 5 minutes. Then the RBC was washed again, 3 times with 0.86 % NaCl. To obtain a highly concentrated RBC, the entire washing fluid was decanted, leaving just sufficient for homogenization of the RBCs. Haematocrit concentration of the RBC was determined by inserting a capillary tube into the container and allowing the tube to fill up to one quarter. Then its other end was sealed before it was centrifuged in a microcentrifuge at 1176xg (3000rpm) for 5 minutes. The haematocrit value was read on a PCV reader.

For the PHA test, to a clean "V" bottomed microtiter plate, 0.05ml of 0.86 % NaCl was put in each well in a row. Equal volume of the dog-serum (after inactivation) was added to the first well in the row and serially double-diluted till the last well. Then, equal volume of the sensitized chicken RBCs was added to each well and the setup was incubated at 4 °C for 1 hour. Reciprocal of highest dilution of each dog-serum sample which gave complete agglutination of the *Rabies virus*- sensitized chicken RBCs was read as titre of Rabies antibody in it. Means of antibody titres of the 4 groups of dog sera were compared by one way analysis of variance (ANOVA).

III. RESULTS

Rabies antibody titres in sera of Nigerian dogs vaccinated with anti-rabies vaccine and given post vaccination Vitamin-B treatment increased from 24.74±0.08 in the controls to 64.08±0.03 in those treated with the vitamins for 1 day, 89.29 ± 0.17 in those treated with the vitamins for 2 days and 140.73±0.14 in those treated with the vitamins for 3 days (Table 1)

Table 1: Passive Haemagglutination Antibody Titres in Nigerian Mongrel Dogs Vaccinated With Anti-Rabies Vaccine and Given Different Courses (0-3 Days) of Post Vaccination Vitamin-B Treatment

Days	Control	A(1 day)	B (2 days)	C (3 days)
	32	64	64	64
	8	32	128	128
	16	32	128	0
	4	64	64	256
	64	128	0	128
Mean	24.74±0.08	64.08±0.03	89.29±0.17	140.73±0.14

IV. DISCUSSION

Rabies is the most fatal infectious disease that is known worldwide (WHO, 2018). Although it has been neglected for some time, international health organizations (WHO, OIE and FAO) are now working together to eradicate the disease by the year 2030. They have adopted different strategies to achieve this goal, mainly through intensive vaccination of domestic and wild carnivores. New generation anti-rabies vaccines that are more economical and more efficient than conventional vaccines are now being used. There are even oral vaccines against rabies (plant based) that are showing promising results (Lucka *et al.*, 2015; Laere *et al.*, 2016).

Existence of these prophylactic measures against rabies does not diminish the fact that rabies is still a significant cause of human and animal mortality (WHO, 2018). Success of post-exposure prophylaxis against rabies infection in endemic countries is usually hindered by obstacles such as cost of vaccine, availability of post infection care and lack of awareness about the disease in rural areas. Critical prophylactic regulations such as massive vaccination of dogs often fail to achieve their aims in rabies-endemic countries due to lack of awareness and vaccine-related issues such as inadequate transportation and storage facilities for vaccines (Ullas *et al.*, 2012).

Rabies and canine distemper are the most endemic viral diseases of dogs in Nigeria to which vaccination is usually applied as a control measure (Ezeibe *et al.*, 2008; Nwoha, 2015). In Nigeria, though rabies has been responsible for many human deaths and suffering, vaccination has been poorly implemented. Shortcomings in anti- rabies vaccination in Nigeria include low coverage and poor compliance rates as in most other developing countries (Fagbami *et al.*, 1981).

Challenges to use of vaccine in rabies control include, high cost of materials, lack of reagents, lack of biologics, lack of chemicals, lack of consumables and other supplies, lack of constant electric power and failure of governments to enforce legislations on annual vaccination of dogs and cats (Foggin and Swanepoel, 1985). Also, there are problems of lowered vaccine potency due to improper cold chain, failure to achieve sufficient herd immunity after vaccination and antigenic variations (Foggin and Swanepoel, 1985).

In this study, post vaccination treatment of the Nigerian dogs with Vitamins improved their antibody responses to the vaccine. Prolonging the post vaccination Vitamins` treatment for three days increased the antibody titres from 24.80±10.91 to 140.80±31.35. Stantic-Pavlinic *et al.* (2004) reported that vitamin C enhances interferon production in humans and could therefore be used for stimulation of interferon response to rabies vaccines. So, these results agree with their suggestion. It is also in agreement with Igado *et al* (2010) who reported that vitamin C has immune-potentiating effects.

Vetzyme is a tablet dosage form of Vitamins and antioxidants. Its use in this study was for convenience. With the tablet-vitamin medication, dog owners do not need to come back to the clinic for days after anti-rabies vaccination. This makes adoption of post vaccination Vitamins-treatment for control of rabies, convenient.

Failure to monitor antibody responses of vaccinated dogs is another hindrance for efforts

to control rabies in Nigeria. For Nigerian veterinarians to start post vaccination assessment of dogs for rabies antibodies, there is a need to adopt a simple, inexpensive and yet reliable diagnostic test.

Previous clinical studies have found that *Rabies virus* neutralizing antibody titres of between 8-16 IU/ml is protective (CDC, 2016) but the neutralization test is complex, such that most field veterinarians cannot run it. Results of Rabies passive haemagglutination (RPHA) gave correlation coefficient of 0.81 with results of Mouse Serum Neutralization test (Gough and Dierks, 1971) and RPHA test requires less sophisticated and less rigorous protocols, compared to other serological techniques including the Mouse neutralization test (MNT), ELISA test and rabies fluorescent antibody test (RFAT). RPHA is easy to use and affordable.

Its adoption would reduce limitations veterinarians in most African countries have in carrying out post vaccination assessment of antibody titres against rabies. It may be easier to convince field veterinarians to adopt post vaccination antibody tests with the RPHA test than with the other tests which are more difficult to perform.

Currently, most veterinarians in Nigeria do not practice post vaccination Vitamins medication for rabies control. Though dogs in the control group in this study had titres up to the protective titre, such titres may not remain at protective level for a long time. So, it would be good to ensure higher antibody levels in vaccinated dogs so that the titres may not fall below the protective level before the dogs are revaccinated. Administering multivitamins to dogs for three days post anti-rabies vaccination would ensure high levels of antibodies that would remain at protective level till next annual revaccination.

V. CONCLUSION

Post vaccination Vitamins treatment of dogs under the Nigerian environmental conditions is necessary to improve their antibody responses against rabies. Also, post vaccination assessment of dogs for rabies antibody titres can be adopted if veterinarians are taught to use the rapid and inexpensive passive haemagglutination test which does not require sophisticated equipment and results are got within 3 hours. These two strategies could enhance the success of rabies control efforts in Nigeria.

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Is the C-Reactive Protein (CRP) Test a Worthy Indicator of Inflammation?

Dr. Shalini Singh & Dr. E. Maruthi Prasad

ABSTRACT

C-reactive protein (CRP) functions as an acute inflammatory protein, serving as an indicator of systemic inflammation. CRP originates from sites of inflammation or infection and can experience an increase of up to 1,000-fold in such regions. CRP exists in two forms: native CRP (nCRP), which is a homopentameric protein, and monomeric CRP (mCRP). mCRP is the result of the irreversible dissolution of nCRP into five separate monomers at sites of inflammation and infection. Although the liver's hepatocytes are the primary producers of the CRP protein, it is also produced by a range of cells, including smooth muscle cells, macrophages, endothelial cells, lymphocytes, and adipocytes. This article discusses the role of CRP in measuring inflammation for diagnostic purposes is unparalleled, solidifying its status as the 'gold standard' of inflammation markers.

Keywords: C-reactive protein, risk factors, marker of inflammation.

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C-reactive protein (CRP) functions as an acute inflammatory protein, serving as an indicator of systemic inflammation. CRP originates from sites of inflammation or infection and can experience an increase of up to 1,000-fold in such regions. CRP exists in two forms: native CRP (nCRP), which is a homopentameric protein, and monomeric CRP (mCRP). mCRP is the result of the irreversible dissolution of nCRP into five separate monomers at sites of inflammation and infection. Although the liver's hepatocytes are the primary producers of the CRP protein, it is also produced by a range of cells, including smooth muscle cells, macrophages, endothelial cells, lymphocytes, and adipocytes. This article discusses the role of CRP in measuring inflammation for diagnostic purposes is unparalleled, solidifying its status as the 'gold standard' of inflammation markers.

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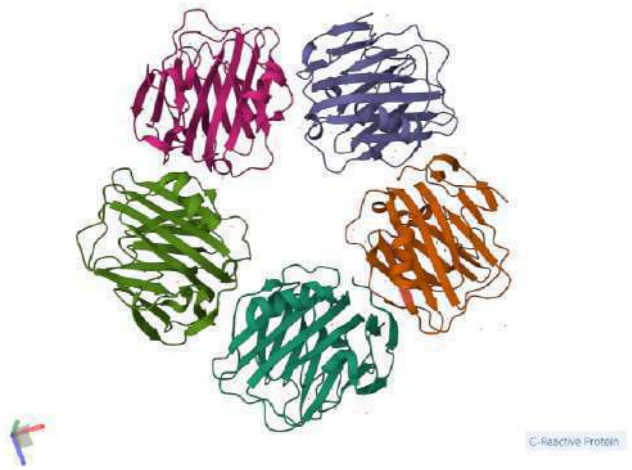
I. INTRODUCTION

C-reactive protein (CRP) is a homopentameric acute-phase protein (115-kDa) that is produced by the liver and binds exclusively to phosphorylcholine in a Ca^{2+} dependent manner under the management of interleukin-6 [1] (Figure 1). When the body undergoes inflammation, CRP levels rise sharply. Typically, CRP levels are less than 0.9 mg/dL [2]. Several things can influence the CRP level in the body. A CRP test result between 1.0 and 10.0 mg/dL is often considered to be a moderate level [3].



Source: PDB DOI: 10.2210/pdb3PVO/pdb

Figure 1: PDB Structure of Human C-Reactive Protein (3PVO)

CRP is considered an inflammatory marker and is a part of the body's defense against illness or injury. The CRP test is used to detect an infection if you have symptoms of inflammation like fever, chills, redness or flushing, nausea, vomiting, rapid breathing, and/or a rapid heart rate (Figure 2).

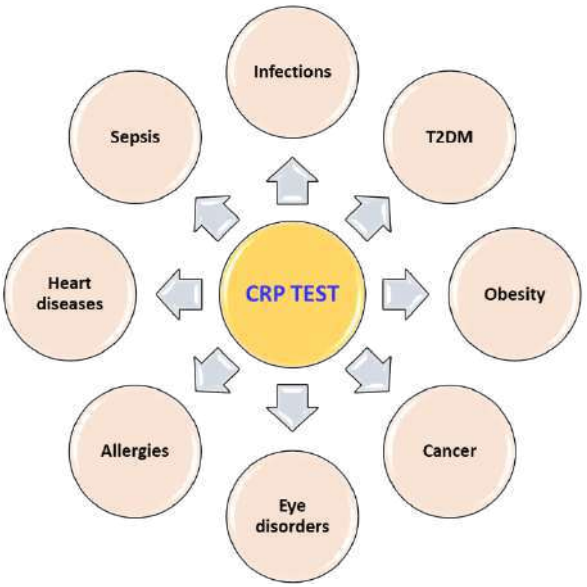


Figure 2: Indications of CRP test for Diagnosing Different Clinical Conditions

II. RISK FACTORS

An elevated CRP level exceeding 10 mg/dL is typically considered significantly high, indicating a range of pathophysiological conditions such as acute bacterial infections, viral illnesses, systemic vasculitis, tumors, or trauma [1]. Although a modest rise has also been associated with several non-inflammatory illnesses related to cellular distress or injury, an increase in CRP is commonly regarded as a critical indicator of inflammation. [4]. Aging significantly contributes to elevated CRP levels in both males and females. Males often experience more heart attacks, however, the mortality rate is higher in females. In terms of inheritance, children whose parents have high CRP levels are more likely to develop heart disease [5]. Furthermore, a higher risk of elevated CRP may exist for specific ethnic groups, including African-Americans, Mexican Americans, Native Americans, Native Hawaiians, and some Asian Americans [6].

Other factors that contribute include diet, smoking, blood pressure, cholesterol, physical activity, diabetes, and obesity [7]. Generally, medical professionals recommend this test if there is a moderate chance of you suffering a heart attack in the forthcoming 10 years [8].

III. CONDITIONS LINKED WITH HIGH CRP: MARKER OF INFLAMMATION?

High CRP is typically linked to the illnesses listed below. However, this does not mean that the CRP is elevated, it may show any of these conditions.

3.1 Heart Disease

Cardiovascular diseases, such as atherosclerosis, are the leading cause of death globally [9]. If inflammation is indeed the cause of heart attacks, the value of CRP testing would hinge on its proven capacity to precisely predict such incidents.

Studies have found a strong correlation between raised levels of CRP and the odds of experiencing a heart attack. This correlation has indeed been shown in previous studies published in respected journals. For instance, Ridker et al. (2002), concluded that CRP exceeds LDL cholesterol in its ability to forecast cardiovascular risk [10].

Furthermore, the researchers discovered that these two tests identify distinct high-risk groups, indicating that employing both methods is superior to relying on either one individually [11].

The formation of atherosclerosis involves a critical role of inflammatory mediators in the initial recruitment of cells and throughout the process until the plaque ruptures [12]. The development of cardiac stress initially presents as

inflammation, resulting in enhanced production and release of inflammatory chemokines and cytokines in the affected heart tissues. CRP aggravates inflammation in blood vessels and plays a part in the stiffening of the arteries, which can ultimately result in heart disease [13].

Additionally, it can activate cells that line the interior of blood vessels, causing them to malfunction. Nitric oxide is good for the cardiovascular system because it relaxes blood vessels, increases oxygen, and improves blood flow throughout the body [14]. Furthermore, CRP decreases the release of nitric oxide from arteries and veins, depriving tissues of adequate blood flow [15]. Innate immunity serves as the immediate defense mechanism against cardiac tissue damage in cardiac injury. More specifically, coronary atherosclerosis, the prime contributor to myocardial infarction, leads to the loss of cardiac tissue [16]. In this scenario, when the cardiac cells die and become necrotic, the inflammatory cells swiftly move to remove the dead cells and debris from the site of the necrotic tissue. This initiates acute inflammation, which is triggered by the inducer of cell death that releases internal signals recognized as danger signals [17]. Then, toll-like receptors (TLRs)- mediated pathways activate the NF-kB pathway to activate inflammatory responses [18].

Subsequently, chemokines recruit the leukocytes to the infarcted areas, while cytokines facilitate adhesion between leukocytes and endothelial cells. Cardiac repair is stimulated by transforming growth factor (TGF)-β and interleukin (IL)-10 by suppressing inflammation [19].

3.2 High CRP and High LDL

Increased levels of LDL cholesterol in at-risk patients cause blood vessels to produce more CRP, which subsequently aids in the entry of more LDL cholesterol into blood vessel cells. The level of CRP in healthy individuals can partially predict the risk of death from heart disease or a heart attack [20]. The CRP is more effective than LDL cholesterol in predicting the risk of all study endpoints. This benefit continued in multivariable analyses that were used for all traditional cardiovascular risk factors. It was also apparent among both users and non-users of hormone replacement therapy at the baseline [10].

However, C-reactive protein and LDL cholesterol levels were minimally correlated, thus the combined evaluation of both C-reactive protein and LDL cholesterol proved to be superior as a method of risk detection to the measurement of either biological marker alone. The study by Ridker et al. in 2002 showed that CRP is a stronger predictor of future cardiac events compared to LDL cholesterol [10]. Finally, at all levels of estimated 10-year risk for events according to the Framingham risk score and at all levels of LDL cholesterol, C-reactive protein remained a strong predictor of future cardiovascular risk.

3.3 High Blood Pressure (hypertension)

CRP is a marker that indicates systemic inflammation and has been suggested to raise the risk of developing hypertension. Multiple studies have found that higher levels of CRP in the bloodstream are associated with increased blood pressure. CRP shows a positive correlation with systolic blood pressure, pulse pressure, and hypertension [21]. These associations have sparked the idea of creating and testing pharmaceutical agents that can lower CRP levels, with the goal of potentially preventing and treating vascular disease. However, CRP is linked to various factors that could complicate its relationship with systolic blood pressure and hypertension [22]. When adjusting for a variety of potential confounding factors, the connection with hypertension was eliminated. Additionally, the link between systolic blood pressure and pulse pressure was significantly diminished [21].

However, it is important to note that these connections may not be causative. Various factors, such as obesity, smoking, adverse socioeconomic circumstances, and different disease states, can elevate CRP levels and also affect blood pressure levels. CRP levels are used to predict cardiovascular events and guide treatment decisions for individuals at intermediate risk [11].

Research suggests that CRP may activate a pro-inflammatory switch in blood vessels, which

can cause them to become narrower and stiffer, resulting in high blood pressure. Those with the highest CRP levels had twice the risk of high blood pressure compared to those with the lowest CRP levels.

3.4 Metabolic Syndrome

Metabolic syndrome is a collection of metabolic abnormalities that collectively heighten the risk of diabetes and heart disease [23]. These features encompass upper-body obesity, hypertriglyceri demia, low HDL cholesterol, hypertension, and unusual glucose levels. It's crucial to understand that all these traits have a connection to elevated CRP levels [24]. These traits include high blood pressure, high blood sugar levels, excessive abdominal fat, high LDL/low HDL cholesterol, and high triglycerides levels. Notably, individuals suffering from metabolic syndrome exhibit more inflammation and higher CRP levels [25]. Thus, the more characteristics of metabolic syndrome a person exhibits, the more their CRP levels tend to rise. The consistency of CRP levels with various aspects of the metabolic system aligns with other research findings and supports the suggested role of inflammation in the development of diabetes and atherothrombosis [26]. Moreover, CRP levels serve as a potent predictor not only of heart attack and strokes but also of the onset of type 2 diabetes [27].

Recent studies have shown that CRP, besides being an indicator of innate immunity, also has a direct impact on the vascular system [1]. The inflammation mechanisms underlying diabetes and vascular dysfunction have provided evidence of a shared inflammatory basis for insulin resistance and atherosclerosis [28]. Furthermore, CRP has been found to be associated with several aspects of metabolic syndrome that are not easily identifiable through routine clinical practice, such as fasting insulin, impaired fibrinolysis, and microalbuminuria [29].

3.5 Obesity

CRP is widely recognized as an indicator of inflammation and has the ability to stimulate the innate immune system actively [1]. CRP, a member of the Pentraxin family, is part of a highly conserved protein family that significantly impacts the regulation of the innate immune system [30]. Obesity is defined by a state of constant low-level inflammation. CRP, which is an acute-phase responder to infection and inflammation, has been identified as the most significant factor related to obesity [31]. Increased levels of CRP are associated with obesity and abnormal fat metabolism in both adults and children. This increased CRP is closely related to higher BMI and total calorie intake. Studies have shown that overweight or obese school children have higher levels of CRP and IL-6, while those with more belly fat and total body fat only exhibited higher levels of CRP [32]. The long-term elevation of CRP levels regulates the amount of complement components in the traditional pathway, affects the blood count of various kinds of white blood cells, and significantly changes the structure of the spleen, which acts as the largest lymphoid organ [33]. Notably, the number of T-lymphocytes and B-lymphocytes in the spleen multiplies by approximately 2.5 times [30]. This possibly acts a role in the detection of pathogens, the activation of the complement system, and interaction with Fc-gamma receptors. Recent findings suggest that chronic inflammation goes hand in hand with the continuous nature of obesity [34]. Even a minor increase has been linked to the activation of inflammation and obesity caused by a Western diet is marked by an enhanced natural immune system [35]. The continuous, low-grade elevation in CRP levels might convey a warning of non-contagious inflammation to the body, which then overreacts, leading to the onset of obesity.

3.6 Obstructive Sleep Apnea

Obstructive sleep apnea is a common condition, characterized by repeated obstructions of the airway during sleep, often accompanied by inflammation. CRP levels also tend to increase in patients with obstructive sleep apnea, which is characterized by periods of cessation of breathing during sleep [36]. Both CRP and high-sensitivity CRP serve as indicators of systemic inflammation and have potential utility as biomarkers for diagnosing obstructive sleep apnea. The frequency of hypoxic episodes can range from five times per

hour in those with mild obstructive sleep apnea to over thirty times per hour in those with severe condition [37]. The apnea-hypopnea index is a useful tool for assessing the severity of obstructive sleep apnea in patients. There is a significant correlation between obstructive sleep apnea and cardiovascular disease [38]. Obstructive sleep apnea can notably increase the risk of cardiovascular disease via elevated sympathetic activity, systemic inflammation, oxidative stress, and impaired endothelial function [39]. Repeated episodes of low oxygen levels and the associated inflammatory responses can lead to the development of atherosclerosis and an increased incidence of cardiovascular or cerebrovascular diseases.

3.7 Rheumatoid Arthritis

High levels of CRP in the bloodstream indicate the presence of infection or significant tissue damage [40]. The levels of CRP in the blood rise due to inflammation. When the root cause is treated, high CRP levels will decrease. Rheumatoid Arthritis (RA), a type of autoimmune disorder, results in significant inflammation and symptoms such as joint swelling and pain. [41].

CRP can bind to white blood cells and other inflammatory cells within the joint cavity of patients with Rheumatoid Arthritis. The inflammation seen in Rheumatoid Arthritis is closely linked to the production of CRP and pro-inflammatory cytokines. High CRP levels are directly related to worsening symptoms in patients with this condition. CRP levels that exceed 100 mg/L are considered elevated and pose a potential risk, depending on various factors such as medical history and the underlying cause of the high levels [42]. Elevated CRP levels are associated with several conditions, including rheumatologic diseases. Notably, infection was the most common diagnosis. CRP levels exceeding 350 mg/L were linked to bacterial infections in 90% of cases [42]. In the event that CRP levels are elevated, it is recommended to promptly seek medical attention for diagnosis and to determine the subsequent course of action [1]. However, addressing increased CRP levels is crucial for identifying the source of inflammation and treating the underlying condition.

3.8 Gum Disease

Recent studies have shown an association between CRP and periodontal disease. Periodontal disease is a chronic infection of the gums that's characterized by a gap between the tooth and bone, accompanied by bone loss. The increase in CRP levels is a response to both acute and chronic inflammation [43]. Elevated levels of CRP have been observed in periodontal disease, as it is a liver-produced acute-phase reactant that responds to various inflammatory stimuli [44].

This condition arises as a result of a primarily gram-negative bacterial infection that originates from dental plaque [45]. However, the illness usually does not show any symptoms for many years and can only be identified through a clinical examination using a periodontal probe or intra-oral radiographs. Recent discoveries have revealed the local and systemic inflammatory processes that promote an abnormal response to the initial commensal microflora. Higher levels of acute-phase proteins have been observed in cases of gingival inflammation and periodontitis, indicating a locally strained environment [46].

Several studies on the population have indicated that patients with chronic periodontitis have increased levels of CRP in the blood [40]. CRP levels can rise to hundreds of µg/mL within hours of infection [47]. Though, CRP levels are higher in people with gum disease, and CRP tends to increase with gum destruction [48]. People with aggressive periodontitis typically exhibit significantly higher CRP levels, compared to those suffering from localized aggressive periodontitis and healthy individuals [40]. Previously, CRP values exceeding 10 mg/L were primarily associated with bacterial infections, while values below 10 mg/L were generally disregarded [49].

This discrepancy could potentially be attributed to the limited accuracy and sensitivity of CRP assays during that period, which made them less capable of detecting CRP levels under 10 mg/L. However, with the widespread introduction of high-sensitivity CRP (hs-CRP) assays, laboratories are

now capable of measuring CRP levels within the serum as low as 0.15 mg/L.

3.9 Inflammatory Bowel Disease

CRP serves as a commonly used serum marker for inflammation in cases of Inflammatory Bowel Disease (IBD) [50]. Increased CRP levels assist in differentiating active disease affecting the mucosa from IBD in remission. A CRP level below 10 mg/L suggests the IBD is in remission [51].

There's a considerable variation in the CRP response between Crohn's Disease (CD) and Ulcerative Colitis (UC), even though CRP is elevated in most inflammatory diseases, including IBD [52]. The CD is associated with a significant CRP response, while UC generally shows a weak or non-existent CRP response. When using CRP in clinical practice, it's important to bear this in mind. Additionally, the elevation of IL-6, IL-1β, or TNF-α has also been observed in UC [51]. However, no definitive explanation for this variation has been found.

Higher CRP before diagnosis was associated with a greater risk of Crohn's disease and ulcerative colitis [53]. Serum IL-6 levels are increased in patients with Crohn's disease (CD) compared to those with Ulcerative Colitis (UC) and healthy controls [54]. Another possible explanation is that while inflammation in CD affects all layers of the bowel wall, it is confined to the mucosa in UC [55]. Recent research has revealed that variations in human baseline CRP production among individuals are caused by polymorphisms in the CRP gene, which is located on the long arm of chromosome 1 (1q23–24) [56]. People with inflammatory bowel disease may have high CRP levels, but this is not always the case. Moreover, there is no definitive correlation between blood CRP levels and CRP polymorphisms in patients with IBD [53].

3.10 Conditions Linked with Low CRP

3.10.1 Systemic Lupus Erythematosus

Systemic Lupus Erythematosus (SLE), often just referred to as lupus, is a chronic inflammatory disease that can affect various parts of the body, especially the skin, joints, blood cells, kidneys, heart, and lungs [57]. It is characterized by periods of illness (flares) and remissions, SLE can be mild or life-threatening. The relationship between CRP levels and SLE is intriguing. In many inflammatory conditions, CRP levels rise. However, people with SLE often have normal or even low levels of CRP, even during flares [58].

3.10.2 The CRP and SLE Connection

Generally, low CRP levels are beneficial. The contribution of such levels to the development of lupus has been observed [59]. The underlying reason might be the potential protective role of CRP against autoimmunity. CRP might reduce the risk by binding to cellular waste and autoantigens, facilitating the clearance of dying cells [60]. If damaged and dying cells aren't cleared away by macrophages, their waste products accumulate in various tissues. However, high CRP levels in a lupus patient may indicate a bacterial infection [61]. While there is much still to be understood about the relationship between CRP and SLE, the insights it offers into the disease process and patient care are invaluable.

IV. CRP IN INFLAMMATION

Inflammation can present in either acute (from injury or infection) or chronic forms. An elevated hs-CRP level can be influenced by a variety of factors, thus, it is not a very precise prognostic indicator. However, it has been found that a CRP level of 3 mg/L, compared to levels below 1 mg/L, is associated with twice the risk of coronary events [62].

Neurodegeneration of the complex between the photoreceptor and retinal pigment epithelium leads to a condition called age-related macular degeneration, also known as a progressive visual impairment acquired disease of the macula [63].

The abnormal functioning related to age-related macular degeneration is predominantly influenced by chronic inflammation [64]. In the advanced, or exudative, stage of age-related macular degeneration, increased CRP levels have been found in comparison to early stages [65].

The risk of the advanced form of this condition strongly correlates with higher CRP levels.

Additionally, high CRP levels may trigger the complement system at the border of the retina and choroid, resulting in ongoing inflammation and subsequent tissue degradation [65]. Clinical observations suggest that CRP plays a crucial role in the pathogenesis of age-related macular degeneration. It can also be used to measure the severity of the degeneration [66]. While plasma levels of CRP are independently associated with the risk of age-related macular degeneration, it's unclear whether these connections are causal or if CRP simply acts as an indicator of age-related macular degeneration. CRP's increase is due to a heightened plasma concentration of IL-6, primarily produced by macrophages and adipocytes. During the acute phase response, CRP levels rise rapidly within 2 hours of acute injury exceeding normal limits within 6 hours, and peaking at 48 hours [67]. As the acute phase response is resolved, CRP levels decrease with a half-life of 18–20 hours [1]. In acute inflammation, such as during an infection, CRP can surge up to 50,000-fold. Its level is primarily determined by its production rate due to its constant half-life. A notable exception is in cases of renal failure, where elevations in CRP levels can occur even in the absence of clinically significant inflammation.

In the early stages of a hemorrhagic stroke, experts believe that mechanical damage to the underlying and surrounding tissues is followed by ischemia, cytotoxicity, and inflammatory changes [68]. There has been increased interest among researchers in recent years in the different inflammatory biomarkers and growth factors released after an intracerebral hemorrhage.

Bernstein et al. (2018) examined biomarkers such as CRP, Tumor necrosis factor-α (TNF-alpha), homocysteine, and vascular endothelial growth factor in estimating the immediate intensity result of internal brain hemorrhage. In incidents of cerebral hemorrhage, elevated CRP levels are associated with a 30-day mortality rate and an 8% increase in the accuracy of a cerebral hemorrhage score [69].

V. DO CONDITIONS AFFECT CRP AND ERYTHROCYTE SEDIMENTATION RATE?

The Erythrocyte Sedimentation Rate (ESR) and CRP tests are among the oldest laboratory tests that are still used to identify inflammation [70]. A multitude of cells contribute to the release of inflammatory mediators, which collectively can induce pain in the joints, muscles, discs, ligaments, tendons, and fascia [71]. These two tests can serve dual purposes; they can determine both the presence of pain and inflammation, as well as the effectiveness of treatment since pain and inflammation are often correlated.

CRP cannot be used to diagnose a specific disease such as rheumatoid arthritis because many different disorders, such as obesity, can also increase CRP production [49]. Obesity, renal disease, aging, and being female are all factors that can impact ESR rates [72].

Today, a hs-CRP test utilizes laser nephelometry to evaluate low levels of CRP [40]. Arterial injury is caused by white blood cell incursion and inflammation within the walls of the coronary arteries, and this injury is used to predict an increased hs-CRP. As such, a high hs-CRP is a general indicator of cardiovascular risk. The widespread use and media coverage of the association between hs-CRP and heart disease may have obscured its diagnostic value in treating pain and other non-cardiac illnesses. If a pain patient has an elevated hs-CRP, any active inflammation, whether in the heart, the central nervous system, or elsewhere in the body, must be addressed [73].

Following several recent studies, there is now a lot of interest in CRP in the field of diagnosis for infection/inflammation. The CRP test is often performed with another blood test called the ESR.

Both are non-specific markers for inflammation but, together, can offer important clues as to what is going on in the body [4]. Compared to ESR, CRP is more responsive and specific to inflammation. Although an increase in CRP indicates inflammation or infection in the

appropriate clinical context, it can also occur in cases of obesity and kidney dysfunction [40].

The key difference between the two tests is that changes happen more quickly with CRP values.

For example, CRP may revert back to normal levels swiftly after an infection has been treated, while ESR tends to stay increased [74]. In such cases, the ESR offers a detected "trace" of a disease, even when the symptoms are no longer present.

VI. LIMITATIONS OF CRP TEST

Medications, like nonsteroidal anti-inflammatory drugs, can inaccurately decrease CRP levels [75]. Statins can also inaccurately decrease CRP levels [76]. Recent injuries or illnesses can falsely raise levels, especially when the test is used to stratify heart risk. Additionally, magnesium supplementation can decrease CRP levels [3]. However, individuals suffering from hepatic failure or flare-ups of conditions such as systemic lupus erythematosus may not show an elevation in CRP levels despite the presence of inflammation [40].

As previously mentioned, a slight increase in CRP can be seen even in the absence of a systemic or inflammatory disease. Women and elderly patients have higher CRP levels. Being obese, having insomnia, depression, smoking habits, and diabetes can all contribute to a slight elevation in CRP, these results should be interpreted with caution in individuals with these coexisting conditions [3].

Lipemic or contaminated sera can cause false positive reactions in CRP tests [77]. Only serum should be used in this test. A quantitative titration procedure is necessary for positive specimens to observe increasing or decreasing levels. Patients with high levels of rheumatoid factors may also yield positive results. Furthermore, consumption of trans-fats is associated with high CRP blood levels. This can partly depend on individual factors, including age, gender, number of risk factors, and metabolic disorders.

VII. DISCUSSION

A simple blood draw is all that's required for the CRP test. This test can identify potential inflammation causes, but it cannot pinpoint the reason or location of the inflammation. The so-called acute phase response is caused by increased levels of IL-6. These are produced by adipocytes and macrophages in reaction to a variety of acute and chronic inflammatory conditions such as bacterial, viral, or fungal infections; rheumatic and other inflammatory diseases; malignancy; and tissue injury and necrosis. It triggers opsonin-mediated phagocytosis by macrophages, which are known to have CRP receptors [78]. This acts as a preliminary defense against pathogens in innate immunity [79].

CRP has long been used as an indicator of cardiovascular and infectious issues. This test, which is used to determine the risk of a heart attack or stroke, has a variation known as the hs-CRP. Occasionally, it can be distressing to discover that a test result is abnormal. The external blood clotting cascade, the system that breaks down blood clots (fibrinolytic system), and the functionality of blood platelets all seem to be significantly regulated by CRP. CRP amplifies the clot-forming response to vascular damage. CRP seems to demonstrate a crucial mechanistic relationship between inflammation and clotting, as inflammation increases CRP production. The structure and biological activity of CRP are regulated by the initiation of the blood clotting system, specifically platelet activation. Consequently, there is a two-way interaction between inflammation and clotting, which is dependent on CRP [3]. Even patients without symptoms but with elevated CRP levels may be indicative of cardiovascular disease, according to several cross-sectional and case-control studies.

The Multiple Risk Factor Intervention Trial (MRFIT) was the first prospective study to emphasize the relationship between CRP and coronary disease in symptomless, yet high-risk, men. This study of 17 years directly correlated high CRP levels with increased mortality [80].

CRP levels and the risk of MI and stroke in healthy men were linked in the Physicians' Health Study, a randomized, double-blind trial of aspirin and beta carotene therapy for the prevention of cardiovascular disease. It's interesting to note that risk reduction is correlated with CRP levels when smoldering endovascular inflammation is controlled with aspirin therapy. These circumstances lead to the release of interleukin-6 and other pro-inflammatory cytokines, which set off the liver's production of CRP and fibrinogen [78].

There is increasing evidence that CRP plays a crucial role in several host responses to infection and inflammatory processes, such as the complement pathway, apoptosis, phagocytosis, nitric oxide (NO) production, and thrombosis, among others [81]. Although, the CRP test is employed both to detect inflammation and to monitor it in acute as well as chronic illnesses, including viral and bacterial infections, and IBDs such as Crohn's disease and ulcerative colitis.

High CRP levels do not necessarily indicate a need for medical treatment. In fact, it's worth noting that 5% of completely healthy individuals might exhibit results outside the normal range [82].

Each body is unique and these numbers may simply represent your normal condition [3]. Moreover, low-grade inflammation, which can result in fatigue, is associated with higher CRP levels, both in healthy people and in survivors of breast cancer who have no disease. In a similar vein, low-grade inflammation has also been linked to depression, with a significant correlation between elevated CRP levels and depressive symptoms. Individuals with depression were more likely to have high CRP levels, particularly if they were overweight and had poor HDL cholesterol [83]. High CRP levels have also been linked to dementia, particularly in women.

There is an increased risk of developing cancer associated with high CRP levels. Apart from the CRP test, additional tests are required to identify the cause of the abnormal levels [84].

There are other methods to gauge inflammation, but the data overwhelmingly implies that C-reactive protein is a superior predictor of cardiovascular events such as heart attacks, strokes, bypass surgeries, or angioplasty, compared to other inflammation markers, and become a crucial predictor of other inflammation measures. If CRP levels are high, it is recommended to seek immediate consultation with a healthcare professional for diagnosis and to determine the subsequent steps.

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