CIRCADIAN CHANGES IN ANTIOXIDANT ENZYMES, CIRCULATING LIPID PEROXIDES, OTHER MOLECULES IN GYNECOLOGICAL MALIGNANCIES AND ITS MANAGEMENT: A REVIEW

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ABSTRACT

In this paper we explore the Circadian Changes in Antioxidant Enzymes, Circulating Lipid Peroxides, Other Molecules in Gynecological Malignancies and its Management. Carcinogenesis is considered to be a multi-stage process. A physical, chemical, or biological agent induces a permanent change in the molecular structure of the cell's DNA during the initiation period. Following this, a promotion period exists, during which the expression of genes that govern cell division and development is changed. There have been several studies on the function of free radicals and oxidative defense mechanisms in various forms of cancers. In gynecological malignancies, however, the circadian variance of the pathophysiological load of cancer on lipid peroxide concentrations and oxidative protection mechanisms must be periodically mapped by inferential statistical parameter calculation until a reproducible chart can be validated.

***Key Words**: Circadian Changes, Antioxidant Enzymes, Lipid Peroxides, Molecules, Gynecological, Malignancies, Management.*

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I. INTRODUCTION

Recently, with more than 800,000 new cases each year, cancer has become a major public health concern in India and one of the top ten leading causes of death. It is estimated that the world has nearly 2.5 million cancer patients at any given time and nearly 400,000 cancer-related deaths. India's cancer prevalence is projected to be about 70-90 per 100,000 residents. The age-adjusted incidence rates for males range from 44 to 122 per 100,000 populations in India's population-based registries, which include 28-30 million people from various sections of the world. For females, the age-adjusted incidence rates range from 52 to 128 per 100,000 populations in India's population-based registries (Uma Devi, 2009). According to cancer registries, more than 80% of cancer in females occurs between the ages of 35 and 64, with 3.5 percent to 4.5 percent occurring in infancy. At any given moment, approximately 1,500,000 patients need services for care, recovery, and follow-up.

Chemicals (polycyclic aromatic hydrocarbons, nitroamines, polychlorinated biphenyls, and so on), physical (radiation), and biological (leukaemia and retrovirus) agents can all cause cancer. These causative factors, individually or in combination, may cause cancer. The primary and secondary preventive approaches to cancer care are most common. Any of them could potentially be prevented if the root cause of cancer and preventive factors were understood. (Borek, 1989).

Many articles have been conducted on the status of free radicals and antioxidant protection mechanisms in various cancers (Palan et al. 1994; Halliwell et al.1889 and Singh et al. 2001, 2003, 1998, 1987). However, until a reproducible map of the circadian variation of the pathophysiological load of cancer on lipid peroxide concentrations and ant oxidative protection mechanisms in gynecological malignancies can be validated, the circadian variation of the pathophysiological load of cancer on lipid peroxide concentrations and ant oxidative defence mechanisms must be repeatedly mapped through inferential statistical parameter estimation (Singh et al. 2003). This study aims to help establish reference values for circadian variations in the circulation of lipid peroxides, antioxidant enzymes, and other molecules in an attempt to find new and less expensive putative markers for early detection and treatment of gynaecological malignancies.

II. CIRCADIAN CHANGES IN ANTIOXIDANT ENZYMES, CIRCULATING LIPID PEROXIDES, OTHER MOLECULES IN GYNECOLOGICAL MALIGNANCIES: A REVIEW

Uterine cancer is responsible for 13% of all cancers in women. It often affects individuals between the ages of 55 and 79. Cervical cancer is more prevalent in younger people. The third most prevalent cancer in women is endometrial cancer. Women above the age of 50 are more likely to acquire ovarian cancer. Vulvar cancer is an unusual cancer that often affects elderly people. Women of all of these tumours have a higher probability of survival if they are detected and treated early. Ovarian cancer is the most common gynaecological malignancy that leads to death in women. The severity of oxidative stress caused by free radicals may be exacerbated by the inefficiency of antioxidant systems. The aim of this research was to see how much oxidative stress there was and how much antioxidants were in the blood of genital cancer patients (Senthil K et al. 2004)

Ovarian cancer is a form of cancer that affects the ovaries, which are female reproductive organs close to men's testes. Ovarian carcinoma is a common cancer in women, responsible for 5% of all cancer deaths in women in the United States (American Cancer Society Statistics for 2003). Ovarian carcinoma mostly affects middle and upper class women in developed countries, despite the fact that the precise cause remains unknown (Travis et al., 2004). This year, it is expected that 30,000 additional cases of ovarian cancer will be identified, with 15,000 people dying as a result of the condition. It more often affects people over the age of 60 (about half of patients are over 65), but it may also affect younger women with a family history of the disorder.

Cervical cancer is a form of cancer that involves the cervix, which is the lower part of the uterus. Cervical intraepithelial neoplasia (CIN), a precancerous syndrome that can or may not progress to cancer, precedes this disorder. According to studies, 15 percent to 70% of CIN cases will progress to invasive cervical cancer if left untreated. The most prevalent gynecologic disease is uterine cancer (i.e., cancer that originates in female reproductive system). It grows in the uterus, or womb, which is a hollow organ in the lower abdomen. An inner lining (called the endometrium) and an exterior layer of muscular tissue make up the uterus's wall (called myometrium). Cervical cancer is the most prevalent form of uterine, cervical, and ovarian cancer in women from low socioeconomic backgrounds. Organic carcinogens, radiation and viral diseases, and oxidative stress are also possible triggers of these cancers. In a healthy aerobic cell, there is a balance between oxidative damage and antioxidant defence (Sun, 1990). Oxidative stress is a disorder induced by a loss of antioxidant defence or an accumulation of reactive oxygen species (ROS), and is believed to play a part in diseases such as cancer (Chiou et al., 1999).

Superoxide dismutase, glutathione peroxidase, catalase, and reduced glutathione, as well as a number of dietary antioxidants including tocopherol and ascorbic acid, play a key role in the cell's protection against oxidative harm (Halliwell et al., 1989). The lack of these enzymes can cause structural and functional disorganisation of the polyunsaturated fatty acid-rich cell membrane. Malondialdehyde is generated by the non-enzymatic auto oxidation of polyunsaturated fatty acids. The function of these enzymes is limited in a number of female genital cancers (Sen, 1995). Increased free radical development (due to a depleted antioxidant system) leads to lipid peroxidation, which is one of the fundamental reactions involved in oxygen free radical-induced cellular harm (Halliwell et al., 1992). The strong connection between free radical action and cancer has been well established (Dormandy, 1983). The basic theory tends to be that free radical disruption to cellular materials causes nonmalignant cells to activate or turn into malignant cells. Carcinogenesis is a multistage operation, as we all know. It can be broken down into three stages: initiation, promotion, and progression (Friedewald et al. 1944; Pilot et al. 1981).

Endometrial cancer, which begins in the uterus' inner lining, accounts for about 90% of all uterine cancers. Uterine sarcoma is an uncommon cancer that begins in the myometrium and affects fewer than 10% of people. Only the vagina may be impaired by vaginal malignancy. The tumour is known as a primary cancer originating from the cervix or vulva whether the cervix or vulva is concerned (Peters WA et al., 1985).

A cell's initiation is a long-lasting and heritable transition. Promotion and development will lead to malignant transformation of initiated cells. It just takes a short period of time and a single dose of carcinogen to start the process. This happens to be an inevitable step and can be caused by a mutation, translocation, or amplification in a target cell. Free radicals have been implicated in the enzymatic activation of organic carcinogens in recent years. Three of the five pathways proposed by Pryor for the chemical initiation of tumours include free radicals (Pryor, 1986; 1987). There is mounting evidence that highly reactive oxygen product known as ‘free radicals’ play a role in neoplastic cell conversion, especially during tumour promotion. ‘Molecular species capable of autonomous existence and containing one or more unpaired electrons’ are free radicals. They are paramagnetic and relatively reactive due to the unpaired electron.

III. ROLE AND IMPACT OF ANTIOXIDANT ENZYMES, CIRCULATING LIPID PEROXIDES, OTHER MOLECULES IN MALIGNANCIES

Recent years have shown that highly reactive oxygen products known as free radicals and other reactive oxygen metabolites can play a role in a variety of pathophysiological conditions, including reperfusion damage, inflammation, Parkinson's disease, shock, ageing, cancer, and the development of degenerative diseases and other conditions.(Sies, 1986 and Cross,1987). As a byproduct of normal cell metabolism, free radicals or reactive oxygen species (ROS) are formed. They can be made inside the cell and then released into the extracellular space, or they can be made inside the cell and then released into the extracellular space (Frei B, 1994). Furthermore, ROS is developed as part of the pathophysiology of cancer and chronic inflammatory disorder. Increased and/or incomplete elimination of reactive oxygen species (ROS) is known as oxidative stress (Halliwell B et al. 1999 and Irshad et al. 2002). Aerobic species rely on defences such as enzymes (SOD, CAT) and small molecular weight endogenous antioxidants such as reduced glutathione (GSH) and complete thiols (T-SH) to fight ROS-induced oxidative stress (Halliwell et al., 1999). Malondialdehyde (MDA) and complete lipid hydroperoxides are used to measure lipid oxidation (LOOH) (Dalledorne et al. 2006; Ray et al. 2000). Both acute and chronic illnesses, as well as cancer and leukemias, now include oxidative stress as a prominent characteristic (Suzuki VJ et al. 1997 and Singh V et al. 2001). Furthermore, the body's defensive system, in the form of antioxidants, will play a crucial role in attempting to reduce harm by responding to the above traumatic circumstances. Antioxidants are compounds that dispose of, scavenge, suppress, or oppose the development of reactive oxygen species (ROS), suggesting that cellular antioxidants can play a significant role in a variety of diseases, including cancer 9 and its clinical manifestations (Sie et al. 1991; Manoharan et al. 2005; Czeczand their clinical manifestations (Sie et al. 1991; Manoharan et al. 2005; Czeczot et al. 2006; Navarro J et al. 1999; UzuN et al.2007 and Singh et al. 2009).

Preventive antioxidants serve as a first line of protection by quenching superoxide decomposition of H2O2 and sequestering metal ions. The key role of superoxide dismutase (SOD) is to quench superoxides. Human cells include many varieties of SOD, namely MnSOD, Cu-SOD, and Mn-Cu-SOD. At the start, promotion, and transition stages of carcinogenesis, SOD acts as an antiproliferative factor, anticarcinogenesis, and inhibitor. Catalase (CAT) is a tetrameric enzyme that catalyses the decomposition of H2O2 into water and oxygen in most cells. Glutathione peroxidase (GPx) is a selenium-containing enzyme that uses reduced glutathione as a substrate to catalyse the reduction of H2O2 and lipid peroxide (LO2H) produced during lipid peroxidation to water. Many environmental

mutagens include the inactivation of GPx and CAT. Se, Mn, Cu, and Zn are antioxidant minerals that mainly act in metalloenzymes.

Glutathione (GSH), Vitamins A, C, E, Uric acid, bilirubin, albumin, and ubiquinol are antioxidants that belong to the second line of protection. It scavenges free radicals and reactive oxygen species (ROS). They can prevent genetic changes by preventing free radical-induced DNA disruption. Third-line antioxidants are a diverse category of enzymes that aid in the repair of degraded DNA, proteins, oxidised lipids, and peroxides, as well as the prevention of peroxyl lipid radical chain propagation. Lipase, protease, DNA, repair enzymes, transferase, and methionine sulphosidereductase are examples of enzymes that repair biomolecules and reassemble weakened cell membranes. Free radicals play a role in carcinogenesis' initiation, promotion, and development, as well as signal transduction and apoptosis. Their enhanced development has the potential to trigger cellular and molecular harm, including lipid peroxidation and mutations in tumour suppressor genes and antioxidant enzyme genes. Malondialdehyde (MDA) is a byproduct of lipid peroxidation and a predictor of cellular free radical development. MDA is a mutagenic and genotonic substance that has been linked to the growth of cancer in humans. As a result, increased MDA output in cancer can be a sign of increased free radical production.

Mammalian cells release a limited amount of reactive oxygen species (ROS) under physiological conditions, which affect biological processes. ROS is the mediator of lipid, protein, and nucleic acid damage at elevated concentrations. Organisms have developed a set of defensive mechanisms to defend themselves against oxidative stress as a result of their exposure to free radicals. Non-enzymatic antioxidants and enzymatic antioxidants, mostly superoxide dismutases (SOD), catalase (CAT), and glutathione peroxidases (GPx), glutathione reductase, are part of the protection system (GR) (Galecka et al., 2008).

Many of these reactive species are free radicals, with more than one or more free-floating electrons than paired groups, making them unstable and reactive. The hydroxyl radical (OH.), the superoxide radical (O 2), the nitric oxide radical (NO.), and the lipid peroxyl radical (LOO.) are examples of free radicals (Bagchi et al., 1998). ROS (reactive oxygen species) and antioxidants are in equilibrium in a stable organism. Oxidative stress (OS) happens as the equilibrium is broken, resulting in an accumulation of ROS. OS has an effect on a woman's reproductive lifetime and well beyond that (i.e. menopause). OS is induced by a conflict between prooxidants (free radical species) and the body's capacity to scavenge them (antioxidants). ROS are a two-edged sword: they are essential signalling molecules in biochemical processes, but they often play a part in pathological processes affecting the female reproductive tract. From oocyte maturation to fertilization, embryo formation, and conception, ROS have an effect on a variety of physiological processes. OS is thought to play a role in the age-related reduction in fertility. It is involved in breastfeeding, natural parturition, and the onset of preterm labour. The majority of ovarian cancers start in the surface epithelium, and it's been suggested that repeated ovulation is a contributing factor. Antioxidants can protect the ovarian epithelium from oxidative base damage and DNA damage caused by ovulation. OS has been implicated in the pathophysiology of preeclampsia, hydatidiform mole, free radical-induced birth defects, and other circumstances such as abortions, according to a growing body of literature. OS has been involved in the pathophysiology of infertility and aided reproduction in various reports. Endometriosis, tubal and peritoneal factor infertility, and unexplained infertility have also been connected to it. may aid in determining the cause of certain female reproductive disorders, such as preeclampsia.

Superoxide dismutase, Cu-Zn superoxide dismutase, and Mn superoxide dismutase, glutathione peroxidase, glutamylsynthetase, and lipid peroxides have all been studied (these markers were calculated using immunohistochemical localization, m-RNA expression, and the thiobarbituric acid process, respectively). In regular cycling human ovaries, the presence of multiple oxidative stress biomarkers has been shown. The expression of SOD was studied in all follicular phases, including primordial, middle, preantral, nondominantantral, dominant follicles, and atretic follicles in the follicular process (Suzuki et al., 1999). In the ovarian tissues, there is a fragile equilibrium of reactive oxygen species and antioxidant enzymes. Antioxidant enzymes prevent oxidative oocyte and embryo stress by neutralizing ROS production. High levels of free radicals are thought to lead to genetic changes that contribute to tumor formation.

IV. DIOGNOSIS AND TRETMENT OF MALIGNENCIES

The analysis of body biorhythms is useful not just for diagnosis, but also for optimising care times, safe control, and family planning to specific levels of circadian rhythmic variables, as defined by chronotherapeutics or other marker rhythms (Halberg, 1977). Biological rhythms, according to Halberg et al. (1990), will now redefine evaluation, prognosis, rehabilitation, and recovery. Since the biological mechanism changes in a rhythmic pattern, the cells biochemically vary at various times of the day. As a consequence, it responds to the same stimuli in various forms

at different periods. For a number of stimuli, this variation in responsiveness to similar stimuli at various phases of the circadian system has been repeatedly reported. Drugs, Poisons, Chemicals, and other similar substances are among them. Noise X-ray radiation, for example, is a physical agent. Endotoxins, for example, are biochemical agents. Chronobiologic theories admit at least the probability of achieving drastic variations in the magnitude of an effect at various predictable times, and also admit exposure to the same stimuli and dosage at different predictable times. As a result, if chronobiologic anomalies are neglected, the testing of a specified theory can be muddled. As used in drug development, chronobiology data seems to be especially helpful. It's now been shown that the same drug's role on cancerous growth shifts from stimulation to suppression as a result of timing on two scales: circadian and circaseptan. Chronobiology is the analysis of how different processes tend to align or coordinate in time. Of course, the topic is complicated, but it is critical for maintaining good health.

The relevance of chronobiology in reality is better shown by citing several cases. The blood levels of corticosteroid are an illustration of how a single test of any component may be deceptive. Per day, the concentration of adrenocorticosteroid in human blood is transiently poor enough to be associated with the diagnosis of Addison's disease of adrenal in-sufficiency; however it is likely to be compliant with Cushing's syndrome of adrenal hyper function around 12 hours later. At one point, a person's blood pressure might be regular, however at another time on the same day, it may be elevated enough to be labelled as hypertension.

Changes in natural circadian patterns may even be used to diagnose certain illnesses. Many emotional illnesses, for example, are accompanied by insomnia, which is described as a significant disturbance of the sleep-activity period. Patients with depression often report of anxiety and all of them suffer from fragmented and reduced sleep periods. Antidepressant medicines that boost their disposition often lengthen their sleep period. Dust-sensitive housewives or hay fever sufferers have been found to have their highest histamine reaction at night, right before going to bed, so antihistamine medications can have their most visible impact at night (Rein berg, 1980). Infection immunity is often rhythmic; mice, for example, have been found to be more susceptible to pneumonia infection at the end of the dark activity cycle. Immunity or resistance includes circadian cycles, which may suggest that pacing vaccines may boost their efficacy. Healthy participants who were immunized against Venezuelan equine encephalomyelitis seemed to be more protected if the injection was provided at 8 a.m. rather than 8 p.m. Since protein bonds differently depending on the moment tissue and other biological samples are extracted from the body, biological periods are often crucial for correct biopsy and laboratory testing. Also the histologist uses time of day knowledge while producing plates. Cell division happens at various stages of the cycle in different tissues and organs, so understanding the step of the cycle from which the tissue was taken is often essential in biopsy. Similarly, the reactions to penicillin, antihistamine, and aspirin are different at different times of the cycle (Rein berg and Ghata, 1964).

Every part of a child's growth may be thought of as the product of two distinct influences: The accumulation of knowledge and a natural maturation phase The human baby is unexpectedly introduced to a wide range of different sensory experiences as it emerges from the uterus, and this sensory perception is characterised by a strong nyctothemeral rhythm. The alternation of light and illumination is probably the most noticeable outward rhythm; nevertheless, similar alternations of noise and quiet, as well as the attention given to the child by adults, can also be important. The rhythmic fluctuations of many frequency ranges encountered in most endocrine and metabolic processes are of considerable physiological and pathological significance, and the proposed work on biorhythms of lipid peroxides and antioxidant variables would advance a greater understanding and avoidance of oxidative stress through oxidative stress.

Diagnosis

The likelihood of contracting a disease is determined by the following factors: diagnosis, personal records, and physical examination: - A variety of tests can be performed, including: A physician's gloved finger is used to look for lumps or changes of size or appearance in the uterus, vagina, ovaries, fallopian tubes, bowel, and rectum during a pelvic exam. Imaging scans (ultrasound, CT scan, and MRI scan) - tests that provide images of the ovaries and surrounding tissues in order to determine whether or not a tumour exist. Lower Gastrointestinal Sequence or since receiving a barium enema, a sequence of x-rays of the colon and rectum are taken. CA-125 is an abbreviated version of CA- Assay - A blood examination that measures the amount of CA-125 in the blood, a compound that may be increased if ovarian cancer is present.

Treatment

The standard treatment for ovarian cancer patients is to get as extensive a surgical operation as possible first. A trained gynecologic oncologist must conduct this operation. When ovarian cancer is discovered after the first

surgery, staging procedures are conducted to determine if the cancer has advanced and, if so, to what degree. Treatment for ovarian cancer is determined by the cancer's stage and the patient's overall wellbeing. Patients are typically offered chemotherapy after that, depending on the results. Abdominal radiation treatment is also recommended. The most effective treatment is determined by the practising doctors' expertise and the potential side effects. The below are some of the treatments: Surgery involves the surgical removal of a cancerous tumour, as well as all nearby tissues and lymph nodes. Chemotherapy is the application of medications to cancer cells in order to suppress them. Chemotherapy may be administered in a variety of ways, including pills, injections, and catheters. The medications reach the bloodstream and circulate across the body, destroying cancer cells as well as certain healthy cells. The application of radiation to destroy cancer cells and reduce tumours is known as radiation therapy (radiotherapy). Radiation can take the following forms: External Radiation Therapy (ERT) is a form of radiation therapy that uses a source outside the body to provide radiation to the abdomen, Preventative steps.

V. CONCLUSION

The human body has a number of processes in place to protect itself against the effects of free radicals and other reactive oxygen species. These have differing effects on various oxidants and in separate cellular compartments. A system of enzymes, including glutathione peroxidases, superoxide dismutases, and catalase, which reduce the concentrations of the most dangerous oxidants in the tissues, is one significant line of protection. The production or action of these enzymes includes many important minerals, including selenium, copper, manganese, and zinc. As a result, if certain minerals are in short supply in the diet, enzymatic defences against free radicals may be compromised. An antioxidant is a molecule that is stable enough to donate an electron to a rogue free radical, neutralising it and reducing the free radical's ability to cause harm. Some antioxidants, such as glutathione, ubiquinol, and uric acid, are formed by the body's natural metabolism. Dietary sources of lighter antioxidants may also be used. While over 4000 antioxidants have been reported, vitamin E, vitamin C, and carotenoids are the most well-known. Many other non-nutrient food substances, phenolic or polyphenolic compounds in particular, have antioxidant effects and can therefore be helpful to one's wellbeing. This article aims to contribute to the task of providing reference values for circadian variations in the circulation of lipid peroxides, antioxidant enzymes and other molecules to identify new and less expensive putative markers for early detection and treatment of different cancers.

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