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ESTABLISH A RELATIONSHIP BETWEEN CIRCADIAN VARIATION (OF OXIDATIVE STRESS MARKERS & ANTIOXIDANT STATUS) AND DISEASE PROCESS.

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Abstract

The circadian periodicity of plasma lipid peroxide levels and activities of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx), glutathione reductase (GSH), total antioxidant status were studied in 30 clinically, alcoholic hepatitis proven fresh cases (age: 18-70 years) and 30 age matched healthy volunteers with diurnal activity from 06:00 to about 22:00 and nocturnal rest. A marked circadian variation in plasma lipid peroxide level was recorded in healthy subjects and alcoholic patients with significant amplitude and acrophase around 16:21 and 17:12 respectively. The acrophase tended to be delayed in alcoholic patients. Furthermore, a statistically significant circadian rhythm was found in SOD, CAT and GPx, GSH, TAS, MDA activities in normal volunteers and alcoholic hepatitis patients. SOD and CAT enzyme activity was noted to be maximum at 06:00 and minimum at 00:00 in alcoholic hepatitis patients. The circadian acrophase for GPx activity was recorded at 16:15 in normals and around 22:45 in patients. Moreover, the activity was found to be decreased at all sampling hours during 24-hours sleep-awake period in patients in comparison to healthy counterparts. The MESOR and circadian amplitude also decreased markedly. The decreased activity of measured antioxidant enzymes in Alcoholic hepatitis patients could probably be associated with oxidative stress and/or decreased anti-oxidant defensive mechanism in such patients.

Keywords: Circadian Variation, Oxidative Stress Markers, Alcoholic Hepatitis

Introduction

Numerous metabolic, chemical, microbial, circulatory, and malignant insults may affect the liver. Sometimes the liver is the first organ to experience the effects of the illness. Hepatic involvement occurs as a subsequent complication in various cases; they include alcoholic liver disease, extrahepatic infections, cardiac decompensation, cancer that has spread, and alcoholism. Early liver damage might be somewhat concealed by the liver's functional reserve. The effects of abnormal liver function may be fatal in the early stages of a disease or when bile flow is deliberately disrupted.

In both industrialized and developing nations, alcoholic hepatitis is a leading cause of liver disease and a major contributor to both mortality and morbidity. One of the leading killers in the West is alcoholic hepatitis. Although alcoholism is the main cause, chronic hepatitis, biliary illness, and iron overload are all important factors. On anatomical evaluation, it is characterized by the development of nodules and fibrosis throughout the body.

Cirrhosis is a stage in the progression of many chronic liver disorders that is thought to be permanent. While stabilizing or slowing the advancement of cirrhosis may be

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achieved by removal or management of the fundamental disease process, the existence of this process suggests effects that are unrelated to the cirrhosis's aetiology. Impaired parenchymal function impacts hormone metabolism and protein synthesis, while vascular disruptions such intrahepatic blood shunting and blocked portal venous blood flow cause portal venous hypertension.

literature review

Gyurászová (2018) Plasma is a common medium for measuring oxidative stress indicators because it is a stable habitat for biomarkers. Although there are alternate biofluids, their usage is restricted owing to their high variability, and blood collection is intrusive. The purpose of this research was to determine the variability in oxidative stress indicators and to set reference values for these markers in the plasma, urine, and saliva of healthy adult mice. Adult, healthy CD-1 mice (ranging in age from 95 to 480 days and weighing 21 to 55 grams) were used to collect samples, with 41 females and 37 males participating. Utilizing conventional spectrophotometric and fluorometric techniques, the following parameters were assessed in plasma and urine: TBARS, AOPP, fructosamine, GSH/GSSG, TAC, and FRAP. In saliva, the parameters TBARS, GSH/GSSG ratio, TAC, and FRAP were monitored. Women had greater levels of GSH/GSSG in their saliva and AOPP in their urine. There was an increase in urinary fructosamine, GSH/GSSG, and FRAP in men. There was a positive correlation between weight and urine GSH/GSSG, and a negative correlation between age and urinary TAC and FRAP. We found that mice can have enough of their own saliva and urine collected non-invasively to reliably measure their oxidative state. To determine whether these biofluids represent the oxidative state of the system in illnesses, more research is required.

Jomova (2023) In oxidative eustress, also called "good stress," there is a normal amount of oxygen/nitrogen free radicals and non-radical reactive species (ROS/RNS). These oxidants play a role in regulating biochemical transformations like carboxylation, hydroxylation, peroxidation, and signal transduction pathways like NF-κB, the MPK cascade, phosphoinositide-3-kinase, Nrf2, and others. Oxidative stress, sometimes known as "bad stress," occurs when both internal (mitochondria, NADPH oxidases) and external (radiation, certain medications, foods, cigarette smoke, pollution) sources of reactive oxygen species (ROS) and reactive nitrogen species (RNS) are elevated. Even while many long-term health problems have several causes, oxidative stress is a common thread among them. We take a look back at oxidative stress and how it causes disease by reviewing its significance and the ways it does so. The oxidative damage of DNA, proteins, and membrane lipids is mostly addressed by studying the chemistry of reactive oxygen species (ROS) and reactive nitrogen species (RNS), such as superoxide radical, hydrogen peroxide, hydroxyl radicals, peroxyl radicals, nitric oxide, and peroxynitrite. Also included are methods for quantitative and qualitative evaluation of biomarkers for oxidative stress. Cancer, heart disease, diabetes, neurological disorders (such as Down syndrome, Alzheimer's disease, and Parkinson's disease), mental disorders (such as depression, schizophrenia, and bipolar

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disorder), kidney disease, lung disease (such as chronic pulmonary obstruction and lung cancer), and the aging process are all impacted by oxidative stress. Enzymes that neutralize free radicals (superoxide dismutases, catalase, glutathione peroxidase, etc.) and small molecular weight compounds (vitamins C and E, flavonoids, carotenoids, melatonin, ergothioneine, etc.) work together to reduce the negative effects of oxidative stress. As a first line of defense against lipid peroxidation, vitamin E is among the most potent low molecular weight antioxidants. An intriguing strategy might be the use of certain antioxidants, like as flavonoids, which possess modest antioxidant capabilities and could potentially enhance cellular antioxidant systems, making them effective anticancer preventative agents. Possible pharmacological interventions based on redox metal-based enzyme mimetic drugs and sirtuins as prospective therapeutic targets for age-related disorders and anti-aging methods are covered.

Miyata (2016) Possible contributors to the severe neurological impairments seen in Xeroderma pigmentosum group A (XPA) include oxidative stress and abnormalities in melatonin metabolism, as well as a hereditary defect in DNA nucleotide excision repair (NER). In this study, we used enzyme-linked immunosorbent assay (ELISA) to establish that melatonin metabolites, oxidative stress indicators, and antioxidant capacity in the urine of XPA patients and age-matched controls varied throughout the day. The 6-sulfatoxymelatonin peak, a melatonin metabolite, was seen around 6:00 in both the control group and the XPA patients, with the former showing a lower peak value, especially in the younger XPA patient age group. A sign of oxidative DNA damage, 8-hydroxy-2′-deoxyguanosine, and a marker of lipid peroxidation, hexanoyl-lysine, both showed a rise in urine levels in older XPA patients. The former had a strong peak at 6:00 and the latter around 18:00. Older XPA patients also had lower levels of total antioxidant power in their urine. The circadian cycle is likely to impact the NER, and there has been recent speculation that antioxidant qualities and oxidative stress may vary during the day. Our research suggests that melatonin, by influencing circadian rhythm and melatonin metabolism, may help reduce the increased oxidative stress associated with neurodegeneration, particularly in older XPA patients.

Kıran (2023) Oxidative stress, which damages cells in metabolism, results from an imbalance between pro-oxidants and antioxidants, which in turn produces an increase in the creation of reactive oxygen and nitrogen species, whether these species originate internally or outside. An increase in cellular inflammation, cell death, necrosis, DNA damage, protein cross-links, peroxidation of lipid membranes, and mitochondrial dysfunction may result from this. Antioxidants are part of a defensive mechanism that helps keep biomolecules and the body safe from free radicals; they neutralize or fix damage that reactive oxygen species (ROS) cause to the target molecule. It is well-established that oxidative stress elevates reactive oxygen species (ROS), which in turn contributes to the pathophysiology of several illnesses. These include cancer, metabolic syndrome, atherosclerosis, malaria, Alzheimer's disease, rheumatoid arthritis, neurological disorders, preeclampsia, and many more.

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Wilking M (2013) From blood pressure and sleep/wake cycles to cellular signaling pathways that are important in health and illness, oxygen and circadian rhythmicity are vital in a plethora of physiological activities that maintain homeostasis. Internal system regulation, such as redox levels and circadian rhythms, may be compromised when the human body or cells undergo substantial stress. Disruptions in redox regulation and circadian rhythms may have far-reaching consequences, impacting both cells and organisms. These disruptions can pave the way for the development of several illnesses, including cardiovascular disease, neurological disorders, and cancer. New Developments: The significance of the many species of oxidative stress components and the fundamentals of the circadian rhythm mechanism have been clarified by researchers. There has been a lot of research on the impacts of oxidative stress and dysregulated circadian rhythms ever since they were found. More recently, researchers have begun to shed light on the molecular pathways that connect the two. Important Points: Although a lot is understood about the inner workings and significance of circadian rhythms and oxidative stress systems, the area where these two interact has received surprisingly little attention from researchers. This review delves into the concept that these two systems work hand in hand, both in a healthy body and when illness strikes. Our research leads us to assume that addressing oxidative stress and circadian rhythm together would provide better results in the treatment of illnesses that share both pathways.

Materials and Methods

This research comprised two groups of participants: one group consisted of thirty newly diagnosed cases of alcoholic hepatitis (group A; age: 21–45 years), while the other group consisted of thirty healthy volunteers (age: 17–40 years) of either sex. In this investigation, only individuals with mild or moderately advanced alcoholic hepatitis were considered (13). Over the course of a week, everyone was in sync, working from around 6:00 in the morning until approximately 22:00 in the evening, with sleep in between. Without altering their regular fluid consumption, all individuals continued with their regular (albeit not exact) eating schedule: breakfast at 8:30 a.m., lunch at 13:30 p.m., and supper at 7:30 p.m. Everybody had to deal with the effects of the weather and whatever pollution that was there. Participants are asked to abstain from any medication or preparation that might influence oxidative stress, its protective mechanism, level, or rhythm before blood samples are collected. At 06:00, 12:00, 18:00, and 00:00 hrs., during a full 24-hour cycle, six millilitres of blood were drawn from each patient in simple, sterile vials containing heparin as an anticoagulant. Lipid peroxides were measured in terms of malondialdehyde (MDA) in the plasma after separation (14). In order to assess the activity of the enzymes glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase, the haemolysate was produced from the red cells (15,16,17). The results were assessed using standard statistical methods, including the one- and population-mean cosinor procedures (18,19). As a result, we estimated the following: the MESOR, which is a rhythm-adjusted mean that is typically more accurate and precise than the arithmetic mean; the circadian amplitude, which is

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half of the extent of change within a 24-hour cycle; the double amplitude, which is the total extent of change within a day predicted by the fitted curve; and the circadian acrophase, which is the timing of overall high values of the fitted 24-hour cosine function. At the 5% confidence level, the zero amplitude (no rhythm) test was used to evaluate rhythm detection.

Results and Discussion

Mean plasma MDA concentration found to be 2.90 nmol/ml plasma at 18:00hrs., declined significantly for the remainder of the time, peaking at 06:00 in the healthy volunteer group. With an acrophase at around 16:21, these differences at various collection hours during the 24-hour cycle were statistically significant ($p<0.001$). Patients with alcoholic hepatitis had the lowest SOD activity at 00.00 and the highest at 06.00. In healthy participants, catalase activity peaked at 14.55 U/ml RBCs at 06:00 and then dropped steadily to a minimum at 18:00. Catalase activity in alcoholic hepatitis patients peaked at 11.18 U/ml RBCs at 6:00 AM and steadily decreased during the day, reaching a low of 10.47 U/ml RBCs at 0:00 AM. The average GPx activity peaked at 18.00 and dropped to 00.00 in the control group of healthy individuals. The circadian rhythm of individuals with alcoholic hepatitis was shown to be disrupted, peaking at 12.00.

Table.1 Distribution of Patients of Alcoholc Hepatitis According to Groups

Group	Number of Patients
A	30
B	30
total	60

Table.2 Serum Superoxide Dismutase (SOD), Malondialdehyde (MDA), Glutathione Peroxidase (GPx), Glutathione Reductase (G-SH), Catalase and Total Antioxidant Status (TAS) Levels amongst Normal Healthy Individuals and Patients of Alcoholic Hepatitis

Parameters	Control (n=30)	Patients (n=30)
SOD	19.95±0.05	16.05±0.09
MDA	2.28±0.03	2.90±0.03
GPx	4.14±0.03	2.88±0.03
G-SH	5.15±0.02	2.93±0.03
TAS	2.80±0.03	2.10±0.02
Catalase	14.55±0.04	11.18±0.08

*P<0.001]

Both healthy Indians and patients with alcoholic hepatitis showed a significant diurnal fluctuation in plasma MDA level, with a peak at 16:21 and a trough at 17:12, respectively. Although patients' circadian acrophase of plasma MDA levels occurred around half an hour later than healthy controls', there was no discernible difference in the MESORS between the two groups.

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Patients with alcoholic hepatitis had a higher circadian amplitude compared to healthy volunteers. Even while there was a change in circadian acrophase that showed oxidative stress was involved, plasma lipid peroxide levels in terms of MDA concentrations were normal in this investigation. Additionally, this research only included individuals in the minimum and moderately progressed groups. Consistent with previous studies (20–22), the current findings show that plasma MDA levels in healthy participants fluctuate throughout the day. Circulating lipid peroxide changes in tropical alcoholic hepatitis patients have not been reported.

In both healthy individuals and those with alcoholic hepatitis, a statistically significant circadian rhythm was seen in the concentrations of SOD, CAT, and GPx. A patient's superoxide dismutase (SOD) activity peaked around 6:00 in the morning and crashed at midnight. Patients' activity levels were also lower than healthy controls' across the board throughout a 24-hour sleep-awake interval. Alcoholic hepatitis patients exhibited a significant decline in both the MESOR and circadian amplitude, indicating a drop in SOD concentrations. Thirty minutes after healthy subjects experienced the circadian acrophase, patients did as well. Patients with lower levels of MESOR and circadian amplitude also exhibited lower levels of CAT activity throughout the whole data collecting period. About one hour and thirty minutes after that, patients experienced the circadian acrophase. Patients with alcoholic hepatitis showed considerably reduced GPx activity across all collection hours, peaking at 00:00 and falling to a bare minimum at 12:00. There was a significant drop in the circadian amplitude and MESOR. In addition, the activity of this crucial antioxidant enzyme showed a maximum swing and changed rhythm, with the circadian amplitude occurring around 6 hours and 30 minutes later in patients compared to healthy participants.

The reduced amounts of identified antioxidant enzymes in people with alcoholic hepatitis are likely linked to oxidative stress and/or a weakened antioxidant defense system. A considerable disparity between the body's antioxidant and oxidant defense systems becomes apparent in pathological circumstances, as GPx activity remains persistently lower in patients compared to healthy individuals over all sampling hours. So that known antiherpetic regimens may be enhanced with micronutrients, antioxidant vitamins, and transition metals, more proof that this is a possible critical component in the etiopathogenesis of the disease is required.

conclusion

It is also recommended that, in accordance with the biological clock, antioxidant vitamins and nutrients be added to the current cocktail of hepatic medications at the correct dosage and for the correct duration to improve therapeutic utilization and efficiency.

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