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Effect of Life Stress on Incidence of Fatty Liver Disease

***Lect. Dr. Saleh Salman Omairi, **Asst. Prof. Hussein Adnan Mohammed**

*Dept of Anatomy and Biology, College of Medicine, Wasit University, Iraq
**Dept of Internal Medicine, College of Medicine, Wasit University, Iraq

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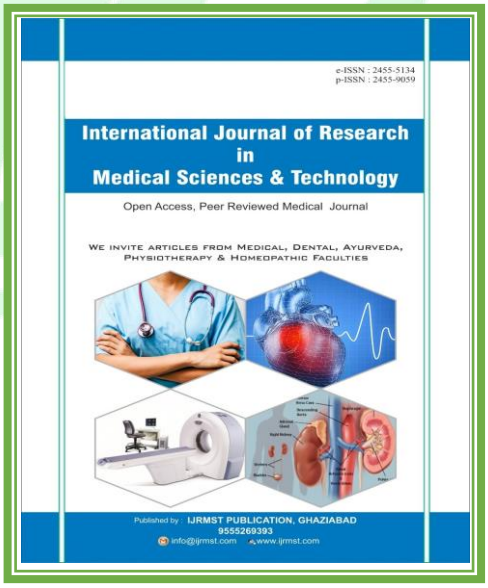

ABSTRACT

We hear about fatty liver more and more often: at least one European adult in five suffers from it and pediatric cases are also on the rise, a consequence of childhood obesity of epidemic proportions in recent years. The cause is metabolic : liver cells normally combine free fatty acids in the blood - introduced with the diet and produced by metabolism - with sugars, giving rise to complex lipids such as triglycerides, which can be accumulated in the liver for storage and energy reserve and to be exploited if necessary. Overweight, dyslipidemia, diabetes, bowel disease or abuse of certain medications (like cortisones) can increase the workload on the liver which is thus storing more fat than necessary. Feeling nervous when stressed is completely natural. This is a short-term stress sign. Chronic stress, on the other hand, is characterized by prolonged symptoms, including breathing difficulties, dizziness, decreased desire, chest pains and fatigue. Many of these symptoms are immediately identifiable by the sufferer. However, the impact of stress is not only visible externally. Inside, our bodies desperately struggle to restore a natural balance. This chemical disruption caused by chronic stress affects many other biological features. This article highlights the effect of stress on fatty liver.

Keywords: life stress, incidence, fatty liver, disease.

INTRODUCTION

There is an important difference between positive stress and negative stress. Stress is a complex subject. It affects each individual in different ways, while its duration and severity depend on dozens of internal (biological) and external (environmental) factors. However, short periods of stress can be beneficial for our health. It may seem strange and, to clarify, we need to analyze in detail our "fight-or-flight" reaction. Faced with a saber-toothed tiger, our prehistoric ancestors would have two options: stay and fight, or run away. Each of us knows how we would react, but perhaps we are unaware that both possibilities trigger physiological changes in our organism. **(Yoichi, 2009).** The body receives a surge of epinephrine, norepinephrine and cortisol. As a result, adrenaline levels, concentration, heart rate and blood pressure increase. Millions of years have passed, and the threat of predatory animals no longer exists, but modern society presents us with new challenges to test our response to stress. **(Regina, 2013)**. Deadlines at work, busy conversations, public speaking or meeting partner's parents are activities that can activate our natural "fight or flight" stress

response. Running away from future in-laws is not advisable, but the increased level of concentration produced by stress will help deal with even the most awkward moments of the conversation. If acute periods of stress are positive, what does negative stress consist of? Periods of prolonged stress do not allow the build-up of chemicals released during the fight-or-flight reaction to be disposed of. They stay inside the body, promoting the development of anxiety and other health problems. Staying stressed over a long period of time has a major impact on the body. **(Devi, 2019)**.

LITERATURE REVIEW

1. General Framework of Fatty liver

Hepatic steatosis is, in short, the expression of many metabolic diseases and usually of overweight. In particular, non-alcoholic fatty liver disease (NAFLD - Non-Alcoholic Fatty Liver Disease) consists of an accumulation of fats (triglycerides) in the liver cells. Normally fat represents less than 5% of the weight of the liver, when this percentage is higher it is called steatosis. It is considered one of the most common diseases of the liver in the most developed countries while alcohol-related fatty liver disease is dependent on the excessive consumption of alcohol and is also characterized by the accumulation in the liver cells of fat in the form of droplets. This injury is reversible if the person refrains from drinking. **(Brunt, 2015).** In fact, we hear about fatty liver more and more often: at least one European adult in five suffers from it and pediatric cases are also on the rise, a consequence of childhood obesity of epidemic proportions in recent years. The cause is metabolic: liver cells normally combine free fatty acids in the blood - introduced with the diet and produced by metabolism - with sugars, giving rise to complex lipids such as triglycerides, which can be accumulated in the liver for storage and energy reserve and to be exploited if necessary. Overweight, dyslipidemia, diabetes, bowel disease or abuse of certain medications (like cortisones) can increase the workload on the liver which is thus storing more fat than necessary. **(Eslam, 2020)**.

- **Causes of Fatty liver**

Non-alcoholic fatty liver disease is present in 10-25% of the general population, especially if overweight; these percentages increase significantly in obese patients, up to values of 50-90%. The extent of this problem should not be underestimated, not only because the percentage of obese people in our country is significant (approx. 20%), but above all because in recent years there has been a trend of

significant increase. **(Neuschwander, 2003)**. The formation of steatosis is linked to the role that the liver has in the metabolism of fats and in particular of triglycerides. Steatosis occurs when the liver cell accumulates triglycerides as a result of an increased uptake of fatty acids as occurs in the course of diabetes or in the presence of obesity, or due to an increase in the endogenous synthesis of fatty acids as occurs during insulin resistance. **(Ravisankar, 2014).** A third mechanism underlying the development of steatosis is represented by a reduced elimination of lipids by the liver as occurs during malnutrition, jejuno-ileal bypass and diabetes. Excluding the alcoholic origin in non-drinkers, hepatic steatosis is more frequently caused by: in addition to overweight and obesity, high cholesterol and especially triglycerides in the blood, diabetes and other metabolic diseases, viral diseases (in particular hepatitis C) and numerous drugs (e.g., estrogen, corticosteroids). However, many cases of steatosis observed in daily clinical practice recognize a wrong diet as a cause or co-factor. **(Pravallika, 2015)**. The liver, in fact, is one of the first victims of incorrect nutrition, facing steatosis due to too much fat that the body produces or that are introduced with an unbalanced diet; the liver, therefore, unable to dispose of them and transform them into energy, is forced to accumulate them. The high prevalence in the population of the risk factors mentioned above explains how hepatic steatosis is an increasing disease or in any case of increasingly frequent clinical finding: nutrition, in fact, increasingly tends to not be adequately balanced, as it is reduced. Healthy foods such as vegetables, legumes and fruit are more favorable than those rich in fat, processed and super-seasoned. Eating habits, however, often are aggravated by a sedentary lifestyle (**Gramlich, 2004)**. In the suspicion that there is also inflammation and / or fibrosis " non-alcoholic steatohepatitis", in the absence of other causes of liver disease that could justify it (e.g., chronic C virus hepatitis or alcohol abuse, perhaps underestimated), for the aforementioned reasons of risk of progression, it could, at times, resort to liver biopsy. This will serve both for the diagnostic confirmation and for the prognostic evaluation (degree of inflammation and fibrosis) of the liver disease. Furthermore, hepatic steatosis, in a variable percentage from 8 to 20%, can evolve towards inflammatory and / or necrotic processes "non-alcoholic steatohepatitis" or NASH from “nonalcoholic steatohepatitis”) with eventual progressive fibrosis (in 10-50% of cases) of the liver. The two pathologies, in particular, must therefore be distinguished, as "non-inflammatory"

steatosis is reversible with the correction of the factors that induced it, while steatohepatitis, by definition, is complicated by an inflammatory, cytonecrotic and sometimes fibrotic similar state as a clinical and anatomical and pathological picture to that of alcoholic liver disease and can sometimes progress towards cirrhosis (in about 10% of patients in ten years). The mechanisms at the origin of liver damage in this condition would be the alteration of the metabolism of fatty acids induced by insulin, the oxidation of fats or the abnormal production of cytokines, known molecules mediating inflammation **(William, 2013).**

- **Diagnosis of Fatty liver**

Hepatic steatosis has no symptoms or, in any case, is not associated with specific disorders, if not with a vague sense of pain, "discomfort" or heaviness below the right costal arch or with the upper right side of the abdomen, halitosis and generic post-prandial heaviness. Very frequently, the finding of hepatic steatosis is random, following routine blood tests or for other clinical reasons. Hepatic steatosis is sometimes characterized by a modest rise in transaminases (ALT and AST), a biochemical expression of liver damage, often associated with a concomitant increase in gamma GT **(Kumar, 2017)**. The liver may appear enlarged on palpation; ultrasound hepatic examination, a simple and immediate examination, shows a "bright" liver, thus facilitating a rapid diagnosis. In the case of hepatic steatosis, these data, associated with predisposing factors, are already sufficient for the diagnosis and the consequent therapeutic approach (for example, in the case of steatosis secondary to overweight or obesity, the gradual weight loss will tend to favor the resolution of the steatosis and normalization of transaminase levels) **(Tan, 2020).**

- **Cures and Treatments of Fatty liver**

As stated above, there is no specific therapy to treat fatty liver. In fact, since this is the expression of numerous diseases and, often of overweight, the therapy must be aimed at the primary cause. In particular, the measures to be taken are the elimination of alcohol, a correct diet (mixed, not focused only on fats and carbohydrates but rich in fruit and vegetables) which leads to a reduction in body weight, integrated with physical activity or sports, where possible. In the case of steatosis secondary to diabetes or other pathologies, the therapy will be that of the diabetes itself or of the primary pathologies. Recent study highlights how weight loss, based on a diet of 25 kcal/kg of ideal body weight/day for 6 months, results in a significant reduction in fatty

liver **(Tolman, 2008).** Practical tips to keep the "fatty liver" under control are: avoid alcohol and animal fats (butter and meat fat); reduce the calorie intake in the diet, until any overweight is eliminated; prevent any risk of hepatitis virus: vaccination against hepatitis B and avoid contagion from sick cohabitants or healthy hepatitis-C carriers, eliminating the mixed use of razors and other toilet items; pay attention to drugs, whose tolerance can never be predicted in these subjects: it is better to limit oneself to the usual drugs, which are known to be harmless and in a minimum effective dose, especially for antibiotics and statins; exercise every day (e.g. 5 km at a brisk pace); treat associated metabolic diseases, especially diabetes and dyslipidemias **(Monjur, 2018).**

2. Ways by which chronic stress damages the body

Feeling nervous when stressed is completely natural. This is a short-term stress sign. Chronic stress, on the other hand, is characterized by prolonged symptoms, including breathing difficulties, dizziness, decreased desire, chest pains and fatigue. Many of these symptoms are immediately identifiable by the sufferer. However, the impact of stress is not only visible externally. Inside, our bodies desperately struggle to restore a natural balance. This chemical disruption caused by chronic stress affects many other biological features **(Yaribeygi, 2017).**

Stress causes digestive problems: Feeling an uncomfortable in the stomach before facing a stressful situation, happens because the digestive system is replicating the fight-or-flight stimulus. The digestive system is much more complex than one might imagine. It houses millions of nerve cells, so a stressful situation can trigger an intense reaction in the gastrointestinal tract as evidenced by gastro-esophageal reflux, nausea, diarrhea or constipation, and even abdominal cramps or spasms. All of these symptoms can be caused by chronic stress — stress that doesn't go away. In the worst case, if a disorder such as irritable bowel syndrome or an ulcer is already present, stress can aggravate the condition **(Huerta, 2013)**.

Stress leads to obesity: After a tiring day at work, the last desired thing is cooking a full meal. We usually look for foods high in fat and sugar instead. Ready in minutes, they offer instant fulfillment and stress relief, at least apparently and in the short term. The craving for fatty foods does not stem from laziness or a lack of self-control. Instead it is related to the gratification system present in our brain. When eating foods that are pleasant for (most of the time it is junk food), the body

releases dopamine, to fight the accumulation of stress-related toxins. It is quite easy to predict the consequences of this habit. Once stressed, one eats comfort food to feel better, and ends up gaining weight. Weight gain causes emotional distress, and the cycle begins again. Stress can lead to obesity, a condition that involves symptoms of varying severity **(Koch, 2008).**

Stress weakens the immune system: The immune system is in charge of managing stress. When we get sick, our body is subjected to additional stress and has to work harder. It is a perfectly natural reaction, because it allows eradication of infections and diseases when necessary. Sickness stress is usually more intense at first, and gets better as the days go by. Within a week or two, the body returns to normal, and the body restores a state of homeostasis. The immune system acts just as when an urgent deadline approaches. The commitment to complete the project increases progressively, and then decreases once completed. Now, if one replaces the stressed version with his immune system. It is designed to increase blood flow and trigger an inflammatory response when one is under stress, but only for a short time. Chronic stress weakens the immune system, compromising its functionality. An article published by the NCBI concluded that "*research on the effects of stress on inflammation has shown that exposure to stress can increase the risk of disease*." **(Pruett, 2003).**

Nervous system problems: The consequences of an amplified inflammatory response extend far beyond the immune system. Our nervous system is also involved. The Department of Psychiatry in Korea found that stress can "*raise the level of pro-inflammatory cytokines*". Cytokines are molecules that act as messengers, telling cells what to do in case of disease or infection. The inflammatory response is necessary in certain situations, but the increase in pro-inflammatory cytokines is also related to the onset of heart disease, diabetes and some types of cancer **(Borikar, 2016)**.

Cardiovascular Disorders: Besides the brain, the heart is probably the second most important organ in the human body. Keeping it in top condition is essential for a long and healthy life. Unfortunately, chronic stress greatly affects the proper functioning of the heart. Using scientific data from various sources, an article in the Nature International Journal of Science set out to explore the direct link between psychological stress and cardiovascular disease. The key points of the study indicate that "*psychological stress contributes to the development of*

cardiovascular disorders of various kinds", and also "*chronic stress at work and in private life is associated with an increase in coronary and heart disease of about 40-50 %*". Chronic stress at work and in private life is associated with an increase in coronary and heart disease by approximately 40-50% **(Esch, 2002)**.

- **Managing chronic stress**

Chronic stress generates deleterious effects on a large scale. It affects the functioning of major organs, causes weight gain and impairs our ability to fight disease. Therefore, managing stress correctly is very important. Many methods are designed to reduce stress in a few simple steps. **(Onyebuchukwu, 2015)** Science suggests that by focusing on the body, awareness, mind and art, it is possible to reduce stress. Fortunately, despite the heavy repercussions, much can be done to reduce stress. By engaging in physical or creative activities, natural and healthy food, or social activities, one can prevent chronic stress from affecting life. The key is to understand how fight-or-flight reaction works, and use it to make advantage **(Dadkhah, 2004)**.

3. **Psychological Stress and Liver Disease: Possible Correlations**

Researchers have hypothesized that symptoms of anxiety and depression may be associated - directly or indirectly - with the development of liver disease. Meta-analysis studies investigate whether psychological stress can be a predictor of liver disease, and then identify potentially modifiable risk factors. One meta-analysis of data relating to a representative group of the population, drawn from 16 different prospective cohort studies conducted since 1994 in the United Kingdom. The sample examined consisted of 166,631 people. To "measure" the level of psychological stress, the General Health Questionnaire (GHQ) was used, a 12-item scale that does not provide a clinical diagnosis of anxiety or depression, but is a valid screening tool for identifying symptoms, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) **(Vere, 2009).**

The GHQ-12 test detects the symptoms of anxiety, depression, social dysfunction and loss of confidence. For each item, people can choose an answer on a 4-point Likert scale: " the symptom is not present at all ", " ... is present as usual ", " ... is present more than usual " , " ... much more than usual ". A score higher than 4, indicates that the person is suffering from psychological stress. Based on the results obtained, the people were assigned to four groups:

- *asymptomatic condition - with zero score*
- *sub-clinical condition - scoring 1 to 3*
- *slightly symptomatic - with a score of 4 to 6*
- *highly symptomatic - with a score of 7 to 12* **(Russ, 2015)**.

People with a score of 0 - considered asymptomatic - were taken as a reference group to be compared with the other three. The researchers also looked at data on: health-related habits (amount of alcohol consumed per week, amount of cigarettes smoked per day); socio-economic status (level of education, social class, employment situation); body mass index (BMI); presence of diabetes mellitus (**Russ, 2015**). Where available, variables such as the habit of physical activity, the use of antihypertensive drugs and other parameters such as: systolic (maximum) and diastolic (minimum) blood pressure, blood tests detected through a nurse visit were also considered and analyzed at the National Health Service Hospital. The first outcome of the research was the level of mortality, verified in relation to national data. In the observation period (mean follow-up of 9 and a half years), 17,368 deaths occurred, of which 457 were caused by liver disease **(Sulla, 2015).**

The causes of death, reported in the death certificates, have been classified according to ICD-9 and ICD-10 and two main categories of fatal diseases have been identified: Alcoholic Liver Disease and Non-Alcoholic Fatty Liver Disease or NAFLD. For these two groups, there were stronger correlations with psychological distress than the remaining deaths due to liver-related diseases'. In the follow-up, the researchers used the Cox proportional hazards model - with a 95% confidence interval - to compare the survival / mortality rate between the groups studied and calculate the specific relative risk (hazard ratio) for the association between hepatic mortality levels and the GHQ-12 test score **(Bianchi, 2005).** While specifying that further analyzes will be needed, they therefore concluded that: "Higher levels of psychological stress have been associated with a 26% higher mortality risk from liver disease". While they failed to determine with certainty the causal relationship between psychological distress and liver disease, they added further evidence on the impact the psychological condition has on physical health, however revealing a new relationship. "The next step could be an etiological study to investigate the effects of psychological stress treatments - through psychotherapy or drugs - on liver functions", as has already been done for

cardiovascular disorders **(Ogino, 2021).** The research is very interesting in the next step concerning the investigation of the effects of psychological stress on liver functions but not only, through psychotherapy, psychopharmacology, but also with the use of food supplements with fatty acids and antioxidants (which improve the functionality cell membranes), with relaxation techniques **(Amany, 2020)**.

CONCLUSION

Following a balanced diet and physical exercise is the winning combination to treat non-alcoholic steatosis for which there is currently no effective drug therapy. In summary, it is the preventive strategy for many other diseases, including cardiovascular ones. And, in fact, heart and liver hand in hand, also confirmed by some results, non-alcoholic steatosis was an independent cardiovascular risk factor, demonstrating an impact on the progression of atherosclerotic plaques. Those at risk for cardiac troubles are the same who may own risk for hepatic steatosis. This is why it took us a long time to understand that there was a primary liver cancer caused by non-alcoholic steatosis: many cases, obese or with metabolic syndrome, die from cardiovascular disease before manifesting cancer. It must be borne in mind that a patient with pathology liver disease due to insulin resistance will have the same increased risk of developing liver cancer and a cerebrovascular problem related to metabolic disease».

The frustration of the needs of the human being, including the state of discomfort characterized by social and emotional isolation (man is by nature a social entity), represents a condition, if prolonged over time, of distress (noxious stress). Numerous researches have shown how stress, in its neurophysiological manifestations, can cause organic diseases, organ dysfunctions and pathologies (target organs), psychopathologies, death. The human being needs stimuli (sensory, affective, social, etc.).

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