Review Article

RAMADAN AND LIVER DISORDERS

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ABSTRACT

The fast of holy month of Ramadan is observed religiously across the globe by Muslims. During some seasons and in some regions of the world, the duration of fast may extend from more than 15 hours over 24 hours, thereby adding to the stress on bodies of people with physical limitations either due to illness or some other obstacle. Same is the case with patients with liver disorders. This review article summarizes the effects of fasting on patients with liver disorders and also sets forward some conclusions from previously conducted studies regarding fasting in patients with acute hepatitis with or without liver failure, Non-Alcoholic Fatty Liver Disease (NAFLD), viral hepatitis B and C, chronic hepatitis, Child grades A, B, and C cirrhosis, liver disorders and concomitant diabetes mellitus, and post-liver transplant. The article concludes that fasting has proven to be beneficial in patients with NAFLD. Patients with chronic stable hepatitis and Child grade A cirrhosis with no past history of variceal bleeds can safely fast while the other categories of cirrhotics should refrain from fasting owing to high associated risks of hepatic decompensation. Patients with stable viral hepatitis can also fast safely, while patients with acute liver failure, concomitant diabetes mellitus and post-liver transplant patients should avoid fasting.

Key Words: Ramadan, Fasting, Liver disorders, Acute Liver Failure, Non-Alcoholic Fatty Liver Disease, Viral Hepatitis, Chronic hepatitis, Child grade A, B, C cirrhosis, Diabetes mellitus, Liver transplant.

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INTRODUCTION

Muslims all over the world fast during the holy month of Ramadan; the fast extending from dawn to sunset. The duration of fast varies from region to region and season to season. Since the Islamic calendar is lunar-based, and 11 days shorter than the Gregorian calendar, each month of the Islamic calendar can fall in any season of the year[1,2]. This means that the duration of fast can vary from 12 hours to 18 hours. And in some parts of the world near the North Pole, it can be as long as 22 hours[3-5]. This also means that Muslims in these parts of the world have only 2 fast-free hours. A month of fasting should not create any physical affects for the normal healthy individuals but people suffering from various diseases may need to consider not fasting in case the long fast or fast of summers poses any threat to their health.

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Islam has offered exemption from fasting for those individuals who are unable to bear the weight; such people include the pregnant and lactating females, who are menstruating, the sick people, the very young and very old and frail people, and those who are travelling[4].

Fasting among individuals with liver disorders is a subject not much touched in literature. Therefore it is important to develop a consensus regarding fasting among patients with various liver diseases. This is the very purpose of our article; to summarize the effects of fasting on patients with liver disorders, and to reach a conclusion regarding advice to be given to such patients regarding the holy fast of Ramadan.

MATERIAL AND METHODS

Over 20 articles published on the effects of fasting on liver disorders were searched and reviewed. Key Words used during the search included: fasting, Ramadan, liver disorders, acute liver failure, Non-Alcoholic Fatty Liver Disease, viral hepatitis, chronic liver disease, cirrhosis, Child grades A, B and C cirrhosis, diabetes mellitus and liver disorders, and liver transplant. A summary was created from these articles and given the shape of the current review article. Literature was searched on Google Scholar, Google search engine, Pub Med and Medline.

LIVER DISORDERS

There is a huge list of liver disorders, but for the purpose of our review article, we mainly focused on the effects of fasting on patients with acute liver failure, Non-Alcoholic Fatty Liver Disease, viral hepatitis B and C, chronic hepatitis, liver cirrhosis Child class A, liver cirrhosis Child class B, and liver cirrhosis Child class C (from any etiology), liver disorders and concomitant diabetes mellitus, and the post-liver transplant population.[6,7]

EFFECTS OF FASTING ON PATIENTS WITH ACUTE HEPATITIS WITH OR WITHOUT LIVER FAILURE:

Patients with acute liver failure have markedly deranged liver functions and a compromised hepatic status. Such patients should refrain from fasting, because prolonged durations of fast can prove deleterious to their health owing to already compromised liver status[3,6,8-10].

EFFECTS OF FASTING ON PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD):

A study conducted in 2015 compared biochemical tests, body composition and anthropometric parameters in Nonalcoholic Fatty Liver Disease (NAFLD) patients before and after Ramadan fasting[5,7] . A remarkable rise in HDL-cholesterol, total plasma cholesterol, triglycerides and fasting blood sugar levels was noticed, whereas the systolic blood pressure, diastolic blood pressure, and ALT showed a declining trend towards the end of and after Ramadan. The study therefore concluded that Ramadan fasting can prove beneficial for patients with NAFLD.

The growing number of obese and overweight patients has been an important issue demanding attention for long. Particularly patients with concomitant diabetes mellitus and other components of the metabolic syndrome are prone to serious health issues as a consequence of their health issues. A reduced intake of calories has long been considered an important health regulator in such patients; however the exact mechanism of the effects of reduced caloric intake, as by intermittent fasting is not exactly known and needs to be worked out. In the quest of this mechanism, one such study was performed, in which scientists looked for liver cell genetic activity differences that were caused by fasting[11]. They were able to determine that the gene for the protein GADD45β was often read differently depending on the diet. The quantity of this molecule produced was directly proportional to the level of hunger.

Subsequent research showed that GADD45β is responsible for controlling the absorption of fatty acids in the liver. Low GADD45β level was accompanied by increased fat accumulation in the liver and an elevated blood sugar level. During fasting, the stress on hepatocytes stimulates production of GADD45β thereby reducing the levels of accumulated fat in the liver by increasing peripheral utilization.

Other studies have also concluded more or less similarly regarding fasting among patients with NAFLD.[12,13] However, more research is needed in this field.

EFFECTS OF FASTING ON PATIENTS WITH VIRAL HEPATITIS B AND C:

Fasting causes hepatic expression of PGC1α which leads to activation of HNF4α activity.[14] The HNF4α then raises the levels of transcription of the gluconeogenic key genes, phosphoenolpyruvate carboxykinase, and G6Pase. This maintains glucose homeostasis during caloric restriction.[14-17] FoxA3 contributes to the process through its effects on GLUT2 expression.[18] The important point to note is that HNF4α and FoxA transcription factors are also major regulators of HBV biosynthesis. The HNF4α nuclear receptor can support viral replication in non-hepatoma cells, whereas FoxA1 and FoxA2 are efficient inhibitors of HBV RNA and DNA synthesis.[19-21] Furthermore, fasting activates PPARα, which can also modulate HBV biosynthesis. Therefore, it is a field of interest to determine the impact of these transcription factors on HBV biosynthesis.

It was noticed initially that serum HBeAg levels rose approximately 40% during fasting.[22] This increase in serum HBeAg was associated with a concomitant increase in viral transcripts. This suggested that the increase in viral transcription was directly responsible for the elevated level of circulating viral antigen. Presumably, this modest increase in transcription was mediated by the activation of HNF4α, and possibly PPARα, by PGC1α, which is induced by fasting.[23] Similarly, the increase in viral transcripts was associated with about a 40% increase in viral replication in experimental mice. As a consequence of the complex metabolic alterations resulting from fasting, additional factors may also contribute to the modulation of HBV transcription and replication in both a positive and negative manner, ultimately producing the observed modest effects on viral biosynthesis.[21-23]

Therefore, it is apparent that the effect of fasting is rather limited in the HBV transgenic mouse model of chronic viral infection. However, this does not mean it is not important. Assuming fasting increases viral biosynthesis approximately 40% in each replication cycle, this would translate into about a 10-fold increase in viral load every seven cycles of synthesis, secretion, and infection of new hepatocytes. Indeed, such findings

linking the levels of viral transcription and replication to the metabolic state of the hepatocyte have led to the suggestion that HBV might be considered a "metabolovirus".[24] Consequently, it may be worth considering metabolic interventions that might limit HBV biosynthesis as an additional therapeutic approach to chronic HBV treatment.

Baseline liver functions have not been seen to deteriorate during Ramadan among otherwise healthy viral hepatitis B and C patients. Nonetheless, liver function tests need to be regularly monitored if these patients intend to fast.[23,25]

EFFECTS OF FASTING ON CHRONIC HEPATITIS AND LIVER CIRRHOSIS:

A few Egyptian studies provide insight into the topic. A study conducted by Elnadry MH et al[2] in Ramadan, 2010 during late summer – early autumn concluded that fasting had no negative impact on patients with chronic hepatitis, while an increased risk of variceal bleeding was observed in fasting cirrhotics due to changes in portal blood flow.[2] The frequency of development of Child C also rose among fasting cirrhotics[2]. Another study conducted by Elfert et al in the same year concluded that values of body mass index (BMI), serum Alanine Transaminase (ALT), Aspartate Transaminase (AST), Gamma Glutamyl trans peptidase (GGT) and Alkaline Phosphatase (ALP) decreased with fasting, while levels of serum bilirubin increased significantly after full Ramadan.[3] The study made two important conclusions: 1. Child A liver cirrhosis with no previous history of gastro-intestinal bleeding may tolerate the Ramadan fast; 2. Child C cirrhotics with previous history of gut bleeding or diabetes should be advised not to fast.[3,28]

Another study conducted by Mohamed et al[26,27] in 2014, when Ramadan had moved to the summer season concluded that cirrhotic patients showed significant short term changes in portal blood flow with the fast. Furthermore, it suggested that patients with Child A or B cirrhosis may fast with good nutritional and medical care, whereas patients with Child C should refrain from fasting owing to the high risk of development of complications.[26,27]

Jafar N et al carried out a study among seminary students in Iran in the month of Ramadan.[29] Adults ranging from 15 to 50 years, with no past history of liver diseases, and no history of use of medications with hepatic side effects were recruited in the study. Fasting serum levels of liver function tests, including ALT, AST, ALP, albumin, and total and direct bilirubin, were measured 4 times: before, during (the second and last weeks), and a month after the holy month of Ramadan. Comparison between the stages was then performed. Results of the study showed that mean AST rose steadily in the second and fourth stages compared to baseline levels, and total serum bilirubin also increased, except for the second week. Mean ALT decreased appreciably in the second week. ALP measurement revealed no remarkable alteration throughout the course of study. Serum albumin only increased considerably 1 month after Ramadan. The study therefore concluded that although fasting has a significant effect on ALT, AST, ALP, and bilirubin levels, these changes were within the normal range and clinically inconsequential. Mild changes in liver function tests may be attributed to alterations in cytokines and in circadian rhythms of hormones during 30 days of fasting.[9,10,30]

EFFECTS OF FASTING ON PATIENTS WITH LIVER DISORDERS AND CONCOMMITANT DIABETES MELLITUS:

During the Ramadan fast, glucose homeostasis is maintained by meals taken between sunset and dawn, and also by hepatic glycogen stores.[31] Serum lipid levels fluctuate and depend on what has been taken in meal and how much of it has been taken. Physical activity, exercise, and changes in body weight also cause fluctuations in lipid levels.[32,33] Well-controlled type 2 diabetics can observe the Ramadan fast, but fasting is not recommended for type 1 diabetics, or diabetics who are non-compliant, poorly controlled or pregnant.[34-36]

In a study conducted on chronic liver disease patients, the non-fasting group showed significant good compliance to therapy (43.4%) compared to the fasting group (27.2%).[37] G.I. bleeding during Ramadan was higher in the fasting group (17.5%) compared to non-fasting (14.1%), but the bleeding due to esophageal varices was significantly higher in the non-fasting group (9.1%) compared to (1%) the fasting group. Fasting chronic hepatitis group showed unremarkable changes in the liver functions during and after Ramadan. However, 13% of fasting cirrhotic patients tripped into Child class C during Ramadan and 32.6% after Ramadan. As gastrointestinal problems tend to be more common and severe in diabetics compared with the non-diabetic population, diabetic fasting patients need to observe extra precautions during fasting which will help them to have an uneventful Ramadan.[38,39]

EFFECTS OF FASTING ON PATIENTS POST-LIVER TRANSPLANT:

Transplant patients carry a high risk of adverse affects from fasting owing to the underlying illness and the immunosuppressive medications they are taking.[40,41] The major issue for concern in this patient population is the accumulation of toxic metabolites in their bodies and

concomitant dehydration, thereby causing irreversible renal deterioration and even transplant rejection from immune system changes.[42] Different studies have come up with different findings in this regard.[43-45] One study concluded no change in circulating immune complexes during fasting among normal healthy people, while another study reported a decrease in complement C3 levels and an increase in C4 levels in renal transplant recipients.[42,46]

Nearly all the studies carried out in the transplant population have been conducted among the renal transplant group. A possible reason could be the increasing number of renal transplants being carried out even in Muslim countries now. Since the patient pool is extensive, researchers also conduct studies on this group of transplant patients. However, most of the findings of these studies can be extrapolated to liver transplant patients to aid in deciding whether they can fast in Ramadan. Many studies have been carried out on renal transplant patients and have not found any significant adverse affects of fasting in these patients. Values of various serum parameters did not change considerably among the fasting transplant recipients in a study conducted by Argani.[43] It was thus concluded by the authors that fasting for duration of 12 hours was not detrimental to the health of these patients. However, it was proposed that patients be evaluated by their physicians before they finally decide to fast.

Einollahi B evaluated kidney transplant recipients who fasted during Ramadan and compared them with 20 transplant recipients who did not fast during Ramadan.[44] All patients had a pre-fasting creatinine level below 1.5 mg/dL. No significant change was observed in the serum creatinine before and after Ramadan fast in both the groups. The authors therefore concluded safety of Ramadan fasting among renal transplant recipients. Another study performed subsequently compared changes in glomerular filteration rate (eGFR) among fasting and non-fasting renal transplant recipients.[45] The mean eGFR did not change significantly over the month of Ramadan (72.8 ± 27.8 and 73.1 ± 29.3 mL/min in the fasting group, and 73.4 ± 18.8 and 73.1 ± 18.5 mL/min in the controls, pre and post 30 days of fasting, respectively). The authors concluded that for patients with GFR higher than 60 mL/min, Ramadan fasting did not cause impairment of allograft function.

Other authors like Abdualla H, Ghalib M, and Said T also concluded that fasting does not pose threat to the health of renal transplant recipients.[46-48] Since all the studies have been conducted on renal transplant patients, we can only presume that liver transplant recipients who are stable with normal pre-fasting baseline liver functions may safely fast during the month of Ramadan but will still need to be monitored for the effects of immunosuppressant therapy during fasting and the overall effect of the disease itself. Many grey zones still need to be answered, like the effects of fasting on liver transplant recipients with concomitant diabetes mellitus.

The authors have tried to include a review of as many articles as available on the topic. But the topic is a naïve one for researchers and despite the fact that it is a very important issue for the growing Muslim population with liver disorders, extensive research is lacking. Therefore, guidelines cannot be set as yet, but a risk to benefit ratio needs to be plotted while considering such patients for fasting.

CONCLUSION

It can therefore be concluded that patients with NAFLD, stable viral hepatitis, chronic hepatitis and child grade A cirrhosis can safely fast in the presence of good supportive care, whereas patients with Child C cirrhosis should refrain from fasting. Patients with Child grade B cirrhosis should be reviewed for liver status and decision about fasting should be made accordingly. Acute liver failure patients should absolutely refrain from fasting. Patients with liver disease and concomitant diabetes should also avoid fasting. Liver transplant recipients need to consult their treating physicians for an insight into fasting during Ramadan.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

Haider I: Main Idea.

Badshah A: Critical Review & finalizing

Humayun M: Supervision and gave final proof reading.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.