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Contents

Monthly Volume 16 Number 8 August 27, 2024

EDITORIAL

MINIREVIEWS

ORIGINAL ARTICLE

Retrospective Cohort Study

Retrospective Study

Observational Study

Clinical and Translational Research

World Journal of Hepatology

Monthly Volume 16 Number 8 August 27, 2024

Contents

World Journal of Hepatology

Monthly Volume 16 Number 8 August 27, 2024

Contents

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EDITORIAL

Intermittent fasting and the liver: Focus on the Ramadan model

Mohamed H Emara, Hanan Soliman, Ebada M Said, Hassan Elbatae, Mostafa Elazab, Shady Elhefnawy, Tarik I Zaher, Ahmed Abdel-Razik, Mohamed Elnadry

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Abstract

Intermittent fasting (IF) is an intervention that involves not only dietary modifications but also behavioral changes with the main core being a period of fasting alternating with a period of controlled feeding. The duration of fasting differs from one regimen to another. Ramadan fasting (RF) is a religious fasting for Muslims, it lasts for only one month every one lunar year. In this model of fasting, observers abstain from food and water for a period that extends from dawn to sunset. The period of daily fasting is variable (12-18 hours) as Ramadan rotates in all seasons of the year. Consequently, longer duration of daily fasting is observed during the summer. In fact, RF is a peculiar type of IF. It is a dry IF as no water is allowed during the fasting hours, also there are no calorie restrictions during feeding hours, and the mealtime is exclusively nighttime. These three variables of the RF model are believed to have a variable impact on different liver diseases. RF was evaluated by different observational and interventional studies among patients with non-alcoholic fatty liver disease and it was associated with improvements in anthropometric measures, metabolic profile, and liver biochemistry

regardless of the calorie restriction among lean and obese patients. The situation is rather different for patients with liver cirrhosis. RF was associated with adverse events among patients with liver cirrhosis irrespective of the underlying etiology of cirrhosis. Cirrhotic patients developed new ascites, ascites were increased, had higher serum bilirubin levels after Ramadan, and frequently developed hepatic encephalopathy and acute upper gastrointestinal bleeding. These complications were higher among patients with Child class B and C cirrhosis, and some fatalities occurred due to fasting. Liver transplant recipients as a special group of patients, are vulnerable to dehydration, fluctuation in blood immunosuppressive levels, likelihood of deterioration and hence observing RF without special precautions could represent a real danger for them. Patients with Gilbert syndrome can safely observe RF despite the minor elevations in serum bilirubin reported during the early days of fasting.

Key Words: Intermittent fasting; Ramadan fasting; Non-alcoholic fatty liver disease; Liver cirrhosis; Peptic ulcer; Liver transplantation; Gilbert syndrome

Core Tip: Intermittent fasting regimens emerged as effective therapeutic strategies not only to improve general health but also as evidence-based treatment for certain diseases. Ramadan fasting, which is a religious fasting for Muslims, is a dry intermittent fasting and was evaluated among patients with different hepatic diseases. It was a promising intervention for patients with non-alcoholic fatty liver disease, however, its deleterious effect on patients with advanced cirrhosis necessitates its prohibition for this category of patients. Liver transplant recipients can observe this type of fasting provided certain modifications and instructions are followed.

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INTRODUCTION

Healthy liver physiology in the fed state

The liver plays a vital role as a metabolic organ in the body. When food is digested in the gastrointestinal (GI) tract, glucose, fatty acids, and amino acids are absorbed into the bloodstream and transported to the liver through the portal vein circulation system. The liver performs various metabolic functions in the postprandial (fed) state. Glucose is converted into glycogen or transformed into fatty acids or amino acids within hepatocytes (Figure 1). Free fatty acids are esterified with glycerol-3-phosphate to generate triacylglycerol (TAG), which can either be stored within lipid droplets inside hepatocytes or secreted into the bloodstream as very low-density lipoprotein particles. Amino acids are metabolized to provide energy or used for protein synthesis, glucose production, or the synthesis of other bioactive molecules[1].

In the fasted state or during exercise, the liver releases fuel substrates such as glucose and TAG into the bloodstream, which are then metabolized by extra-hepatic tissues like muscles and adipose tissue. This metabolic switch between the fed and fasted states in the liver is tightly regulated by hormonal and neuronal systems[1].

Glucose metabolism in the liver is regulated by various enzyme systems and signaling pathways. Glucose is phosphorylated by glucokinase in hepatocytes, generating glucose 6-phosphate (G6P). This process reduces the intracellular glucose concentration and enhances glucose uptake. In the fasted state, G6P is transported into the endoplasmic reticulum and-dephosphorylated by glucose-6-phosphatase, releasing glucose into the bloodstream[1].

Healthy liver physiology in the fasting state

During short-term fasting, the liver primarily produces and releases glucose through glycogenolysis (Figure 1), which involves the breakdown of stored glycogen. In prolonged fasting, when glycogen stores are depleted, the liver synthesizes glucose through gluconeogenesis. Gluconeogenesis involves the synthesis of glucose from non-carbohydrate precursors like lactate, pyruvate, glycerol, and amino acids. These gluconeogenic substrates are either generated within the liver or delivered to the liver through circulation from other tissues[1]. There is an overlap between the two processes, glycogenolysis which is triggered by the declining blood glucose level maintains blood glucose for 12-24 hours, while gluconeogenesis starts after 8 hours in the normal subject and maintains blood glucose beyond the first 24 hours. Also, lipolysis starts in adipose tissue with non-esterified fatty acids release which are converted into ketone bodies in the mitochondria of hepatocytes (ketogenesis). These liver-generated glucose and ketone bodies compose the main fuels for extra-hepatic tissues during starvation and exercise[1,2].

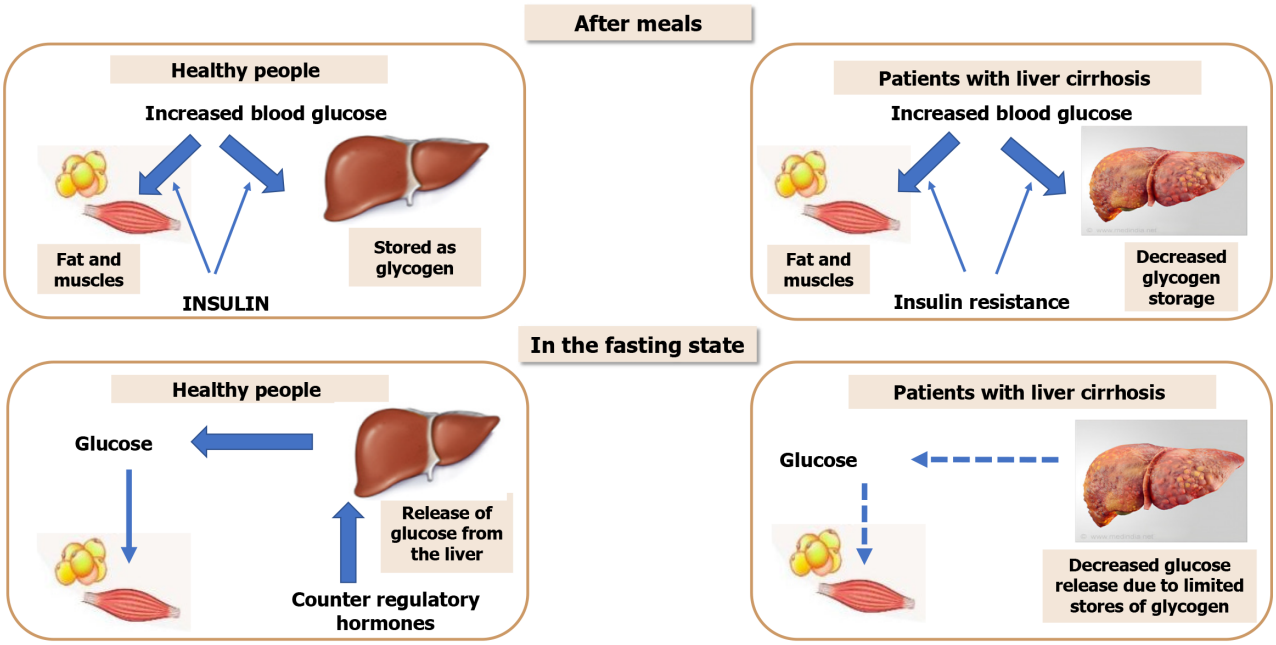

Figure 1 Schematic presentation of glucose homeostasis in the liver during the fed and fasted state.

Energy control within the liver

The process of gluconeogenesis is regulated by multiple factors, including enzymes involved in gluconeogenesis, metabolic states, and the circadian clock. Cytokines, such as interleukin-6 (IL-6), also play a role in regulating hepatic gluconeogenesis. Insulin signaling in the hypothalamus stimulates the production of IL-6 in the liver, which, in turn, suppresses gluconeogenesis. Additionally, GI hormones such as glucagon-like peptide 1 (GLP-1) indirectly regulate hepatic glucose production by stimulating insulin secretion[3,4].

Circulating serotonin levels are lower in the fed state but increase during chronic fasting due to increased secretion from the gut. The presence of chronic liver disease (CLD) significantly affects glucose homeostasis. Glucose intolerance is observed in a significant number of CLD patients, with frank diabetes present in a substantial percentage. Depending on the etiology, CLD has a significant impact on hepatic glucose metabolism[5]. Studies have shown that patients with mild alcoholic liver disease and severe cirrhosis exhibit distorted diurnal patterns of gluconeogenic precursors, with exaggerated postprandial rises in blood lactate concentrations. Patients with severe cirrhosis also experience elevated fasting lactate levels and sustained elevation after meals. The extent of hyperlactatemia in cirrhotic patients correlates with liver function parameters such as serum bilirubin elevation and serum albumin depression (functional decompensation). Impaired hepatic lactate clearance contributes to lactic acidosis in severe liver disease[6,7].

Liver glucose inter-relationship

The relationship between CLD and abnormalities in carbohydrate metabolism, including hyperinsulinemia, hyperglucagonemia, insulin resistance, and down-regulation of insulin receptors, has been extensively studied. The liver, being a central player in metabolic activities, can contribute to glucose intolerance. Oral glucose tolerance tests in patients with cirrhosis showed impaired glucose metabolism, with elevated blood glucose levels after glucose administration. Fasting blood glucose levels may be lower in cirrhosis patients compared to controls, but in cases of cirrhosis with impaired or diabetic glucose tolerance, blood glucose levels are higher than normal[8,9].

Intermittent fasting

Many intermittent fasting (IF) regimens have arisen as a non-pharmaceutical approach to improving health through reduction and control of weight[10]. Generally speaking, IF encompasses various eating patterns and is characterized by alternating periods of eating and fasting that vary in duration from 12 up to 24 hours for two to seven days a week. The most-studied regimens of IF include: (1) Alternate-day fasting; (2) Twice-a-week method; (3) Time-restricted eating (TRE) means calorie intake only during a pre-specified time window (usually for 4-10 hours) with or without calorie restrictions, and may be the oldest form of IF; and (4) Ramadan fasting (RF), when people abstain from food and liquids from sunrise to sunset, with fasting duration ranging from 12 to 18 hours depending on the geographical area[11]. RF, which is our focus, is a model of dry IF; it is a TRE without calorie restriction, which involves abstaining from food and water from dawn to sunset.

Liver function tests in the fed and fasting state

The effect of RF on serum liver biochemistry was studied by Nasiri *et al*[12], and they reported significant reductions in alanine aminotransferase (ALT) and alkaline phosphatase (ALP) contrary to significant increases in aspartate aminotransferase (AST) and bilirubin[12]. These data were re-confirmed by Mohammadian *et al*[13], who reported significant

reductions of ALT levels, and non-significant improvements in AST and ALP among fasting healthy adults[13].

Twenty studies were analyzed by meta-analysis and meta-regression to evaluate the effect of RF on liver function tests (LFTs) among healthy individuals. It was revealed that RF induced significant positive changes in LFTs (bilirubin, AST, ALP, gamma-glutamyl transpeptidase), and the authors[14] inferred that these improvements may provide temporary protection against the development of non-alcoholic fatty liver disease (NAFLD). This conclusion should be interpreted with caution due to some limitations. First, the duration of RF is only one month, a short period to infer this protective effect. Second, the patients included in these studies are heterogeneous and the cut-off for the liver enzymes may differ from one study to another. Third, liver enzymes are used as surrogate markers from the development of steatohepatitis (NASH) rather than the diagnosis of NAFLD limiting the value of liver enzymes in predicting the development of NAFLD.

RAMADAN FASTING AND HEPATITIS

Hepatitis is an inflammatory condition of liver cells; it may be acute or chronic, lasting for > 6 months. The etiologies vary but viral infection by hepatotropic viruses and auto-immune hepatitis remain the most common causes. Acute hepatitis is usually associated with constitutional symptoms including fever, nausea, vomiting, bowel habit changes, abdominal pain, and jaundice while chronic hepatitis has an undulant course with milder rather on-specific symptoms.

Acute hepatitis

There are no studies reporting the outcome of acute hepatitis during RF. However, the typical course of acute hepatitis may extend over several weeks with anorexia, nausea, vomiting, malaise, abnormal LFTs, and jaundice. These patients are primarily treated through supportive parameters[15]. Eating frequent small meals is encouraged because it augments energy levels and the capacity to process and retain food. Furthermore, hospitalization might be justified for patients whose nausea and vomiting expose them to dehydration. Dietary supplementation and intravenous fluids are given to patients with extreme nausea and vomiting who cannot maintain adequate fluid equilibrium[16]. Thus, fasting is not only unfeasible but also strictly prohibited for such patients[15].

Chronic hepatitis

Earlier studies reported an increase in the severity of previously stable CLDs during RF[17]. In addition, it is known that regular food consumption most likely plays a significant role in the maintenance of adequate hepatic circulation.

Focusing on hepatitis B virus (HBV), viral biosynthesis is increased to very high levels during the fasting state and, consequently, there is more risk of infection to new hepatocytes and hence an increased likelihood of infection spread [18]. Whereas several steps in hepatitis C virus replication are affected by the fed and fasting state[19], even though fasting meaningfully affects the activity of hepatitis antiviral prescriptions, it was noted that adherence to therapy was worse during fasting[16].

Moreover, in chronic viral hepatitis B and C patients, baseline LFTs have shown tremendous changes and are not seen to deteriorate pre, during, or post-RF. However, liver biochemistry needs to be regularly monitored if these patients intend to fast[20,21].

RAMADAN FASTING AND NON-ALCOHOLIC FATTY LIVER DISEASE

Non-alcoholic fatty liver is a comprehensive term that describes a condition where more than 5% of hepatocytes exhibit macrovesicular steatosis in individuals with no or minimal alcohol consumption (less than 20 or 30 g/day for women or men, respectively), in the absence of any identifiable alternative causes for steatosis, such as medication use, starvation, or underlying monogenic disorders. Its spectrum comprises different stages, including simple steatosis, nonalcoholic steatohepatitis (NASH) with inflammation and hepatocyte ballooning, ending finally in cirrhosis, with replacement of inflammation by marked fibrosis, and formation of regenerative nodules[22].

The current global prevalence of NAFLD in adults is estimated to be 32%. This burden is substantial and is anticipated to increase parallel to the increased incidence of obesity and metabolic syndrome[23]. We believe that the progression of NAFLD into NASH, cirrhosis, and subsequent liver cancer is a real danger. The emergence of such a huge global health problem necessitates the search for cost-effective ways to prevent and manage metabolic syndrome and NAFLD with its complications.

Many liver disease societies[22,24-26], recommend lifestyle modification as the best management plan for NAFLD. They adopt two essential concepts to treat NAFLD in patients suffering from obesity/overweight: First, a 7%-10% reduction of the current body weight, and second, energy restriction (calorie deficit of 500-1000 kcal/day).

Previously, the American Association for the Study of Liver Diseases (AASLD) clinical practice guidelines for the management of NAFLD did not recommend a particular diet for the management of NAFLD due to uncertainties about histological improvement with dietary modification[27], yet the last update of these guidelines recommended exercise and Mediterranean diet as the best diet for NAFLD, in addition to weight loss which is the mainstay. Weight loss improves hepatic steatosis, fibrosis, and NASH in a dose-dependent manner[22]. For both lean and obese NASH patients, weight reduction induced a significant improvement in histopathology one year after weight reduction[28].

In 2017, Jeffrey C Hall, Michael Rosbash, and Michael W Young won the Nobel Prize for their research which made a breakthrough in chronobiology by discovering the molecular bases for circadian rhythms in fruit flies. However, there is still a long way to understand the same mechanisms in mammals. In man, circadian rhythms in the suprachiasmatic nucleus are assumed to be the master clock for metabolic circadian rhythmicity, which acts synchronously with peripheral circadian rhythms and the 24-hour day/night cycle. The mechanism of this coordination is not yet clear[29].

The timing of our meals, the maintenance of liver functions, and the operation of our internal circadian clock are closely intertwined. Our food consumption acts as a powerful external cue that synchronizes the energy metabolism of our liver with the patterns of eating and fasting, regardless of the natural day-night cycle. As a result, specific dietary habits that diverge from our body's anticipated rhythms, such as skipping breakfast, following irregular meal schedules, or indulging in late-night snacking, are significantly associated with detrimental metabolic and liver outcomes[30]. The timing of energy intake across the day-night cycle affects the natural circadian rhythms. A delay in meal timing, skipping breakfast, chaotic meal patterns and night-time eating were associated with a higher prevalence of obesity[31] and metabolic dysfunctions[32]. Evening chronotype was correlated with increased severity of NAFLD and NASH especially in obese individuals[33,34]. Consuming > 33% of total energy at dinner was associated with a higher likelihood of obesity in a cross-sectional study[35]. Skipping breakfast, chaotic meal patterns, and nighttime eating were all associated with metabolic dysfunction and suggested to be important determinants of individual risk for NAFLD[36].

Clinical practice guidelines of both the American Gastroenterology Association in 2021 and AASLD in 2022 recommend IF and in particular TRE for patients with NAFLD[22,37].

Multiple nutrients, hormones (insulin, glucagon, leptin, ghrelin, and others), and neuronal signals tightly control the process of liver energy metabolism. Dysfunction of liver signaling, and glucose metabolism are proposed to induce NAFLD and/or type 2 diabetes. In the fasted state, the liver stores glucose through glycogenolysis and gluconeogenesis. Also, lipolysis starts in adipose tissue with the release of non-esterified fatty acids which are converted into ketone bodies in the mitochondria of hepatocytes (ketogenesis). These liver-generated glucose and ketone bodies compose the main fuels for extrahepatic tissues during starvation and exercise[2].

In a recent randomized controlled trial, patients with NAFLD obtained a 5:2 IF diet (5 days of normal diet followed by 2 fasting days when patients received a maximum of 25% of the recommended calorie intake between 12:00 to 2:00 p.m. Their calories were divided into 30% from fats, 15% from proteins, and 55% from carbohydrates). Patients who adhered to this regimen were able to obtain weight loss and reduce related parameters of obesity (fat mass and anthropometric measures), as well as triglycerides, hepatic steatosis, liver enzymes, and inflammatory biomarkers, but without change in the levels of fasting blood sugar, insulin, HOMA-IR, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, or total antioxidant capacity[38].

Several epidemiological and clinical trials (Table 1) showed promising data regarding the positive effects of IF models, including RF on various metabolic and inflammatory markers, as well as improvement in lipid profile among both healthy individuals and those who had conditions such as coronary artery disease, cerebrovascular disease, and metabolic syndrome[39-42].

Conversely, shifting energy intake toward the beginning of the day, standardized meal patterns and fasting during Ramadan are all associated with benefits in metabolic and liver health. Moreover, the distribution of total energy intake away from the end of the day may further improve metabolic health[43].

RF is a dry IF, with TRE and no mandated calorie restriction, food intake is exclusively nocturnal. Hence, RF constitutes a sharp shift away from routine eating habits which is expected to have many drawbacks on health and metabolism. However, several meta-analyses have shown numerous metabolic benefits of RF in healthy individuals. RF was generally associated with, a reduction in weight and total fat mass[44,45], improvement in cardiometabolic risk factors including lipid profile[46], and glycemic parameters[14,47].

RF also improves fasting glucose and HOMA-IR in patients with NAFLD in parallel with weight loss and reductions in inflammatory cytokines (*e.g.*, IL-6) and C-reactive protein (CRP)[42].

Interestingly, the exclusive night-time eating pattern in Ramadan is mirrored by the hormones of satiety, including leptin, with blunting of typical nocturnal elevations in leptin and delay in its overnight peak concentrations, in accordance with the shift to later evening meal consumption after sunset[48,49].

RF as a type of TRE can directly influence the rhythmic behavior of metabolically active tissues known to be fundamental to the pathogenesis of NAFLD, like adipose tissue and skeletal muscles. Studies revealed that TRE triggers the oscillation of hundreds of otherwise arrhythmic genes, including genes involved in adipogenesis, adipose browning, and pathways mediating lipogenesis and subsequently the sensitization of adipose tissue to insulin[50,51].

Similarly, the circadian phase of genes controlling amino acid transport in skeletal muscle and circulating serum metabolites are advanced by short-term TRE in overweight men without alterations to muscle clock gene oscillations, suggesting that TRE has direct effects on metabolic function independent of the autonomous clock machinery[52].

Evidence suggests that limiting energy intake and achieving weight loss can lead to improvements in the levels of adipokines and histological hepatic steatosis. Among RF NAFLD patients, notable improvements were observed in mean hip circumference (HC) and body mass index (BMI), accompanied by significant alterations in serum vaspin and omentin-1. Vaspin appears to have the potential to influence the inflammatory process, insulin resistance, and NAFLD. While omentin-1 is linked to the presence of hepatocyte ballooning[53].

RF has revealed notable enhancements in several key health indicators in NAFLD patients including improvements in BMI, insulin resistance, and blood lipid profiles. Interestingly, studies have consistently demonstrated significant weight loss in NAFLD patients who observed RF, even when individuals consumed the same daily calorie intake[54].

One recently published study (London Ramadan Study; LORANS) focusing on patients with many co-morbidities who observed Ramadan, reported improvements in anthropometric measures including waist circumference (WC), HC, and BMI among 146 persons (70% of them were diabetic or hypertensive) after RF. Those effects started to manifest in the

Table 1 Studies focusing on Ramadan fasting and non-alcoholic fatty liver disease

	Aliasghari *et al*[42], 2017	Ebrahimi *et al*[53], 2018	Gad *et al*[56], 2022	Arabi *et al*[58], 2015	Rahimi *et al*[59], 2017	Mari *et al*[63], 2021
Type of study	Prospective observational	Prospective observational	Prospective observational	Prospective observational without a control group	Prospective observational without a control group	Retrospective, case-control study
Number of patients	83	83	40	50	60	155
Anthropometric measures	Improved in fasted NAFLD patients	Improved in fasted NAFLD patients	Improved (no control group)	Non-significant improvement with fasting	Non-significant change	Improved in fasted NAFLD/NASH patients
Hormones and biomarkers evaluated	Plasma insulin, and insulin resistance, reactive protein, and interleukin 6 improved in the fasting group	Vaspin and omentin-1 were reduced in the fasting group	-	-	-	HOMA-IR, CRP improved
Liver biochemical profile		-	Improved	Improved	ALT mean level increased with fasting	
Lipid profile		-	Improved	Improved	-	
Sugar profile	Improved	-	Improved	FBS increased after Ramadan	-	
Imaging profile		-	US calculated liver stiffness and controlled attenuation parameters improved	US used only in the diagnosis of fatty liver	-	-
Others		-	Fibrosis score FIB-4 score improved	Blood pressure significantly improved	-	NFS, BARD scores, and FIB4 scores improved

NAFLD: Non-alcoholic fatty liver disease; FBS: Fasting blood sugar; ALT: Alanine aminotransferase; HOMA-IR: Homeostatic model assessment of β-cell function and insulin resistance; CRP: C-reactive protein; NASH: Steatohepatitis; NFS: Non-alcoholic fatty liver disease fibrosis score; FIB4: Fibrosis-4; BARD scores: The BARD score is composed of only three variables: Aspartate aminotransferase/alanine aminotransferase ratio, presence of diabetes and body mass index; US: Ultrasound.

second week of Ramadan and started to diminish 3 weeks after Ramadan[55]. In the same publication, the authors performed a meta-analysis of 66 related publications focusing on the effect of RF on anthropometric measures and body composition in different populations. The results showed that RF was associated with a reduction in measures of WC, HC, BMI, total body weight, and fat mass, without a significant effect on body lean mass[55]. Nonetheless, the data in this meta-analysis study lacks population homogeneity. Included studies contained healthy, cirrhotic, diabetic, hypertensive, and renal patients besides those with NAFLD and metabolic syndrome.

In a recent cohort study from Egypt, 40 NAFLD patients showed significant improvement in their BMI and hepatic steatosis as quantified by fibroscan controlled attenuation parameters. It is worth mentioning that the authors did not discuss whether the patients were kept on dietary or caloric restrictions during the study[56]. Serum ALT level, which is a critical marker for tracking the progression of NAFLD to NASH, exhibited significant reductions in accordance with the reduction in levels of IL-2, IL-8, and tumor necrosis factor-α compared to their respective values before the onset of Ramadan in 7 patients diagnosed with metabolic syndrome[57]. A larger cohort study revealed similar results in 50 NAFLD patients with decreased ALT levels, serum insulin, systolic and diastolic blood pressure, and an increase in high-density lipoprotein cholesterol after an average of 27 days of RF[58]. In contrast, in another study on 60 NAFLD patients, ALT levels in 36 NAFLD patients who observed fasting were increased compared to their pre-Ramadan levels. This increment was significant when compared to the increase in ALT of 24 NAFLD patients who did not fast and served as controls[59].

Caloric restriction during RF was studied in obese patients and patients with metabolic syndrome and revealed a reduction in leptin levels and body weight in obese patients[60] and a reduction in body weight, fat mass, and visceral fat while retaining lean mass in patients with metabolic syndrome[61]. Even without a restricted diet, RF was associated with a significant decrease in the total cholesterol values, atherogenic index, visceral fat, ultrasound grading of steatosis, and liver enzymes in 83 NAFLD patients who observed RF compared to 40 NAFLD patients who did not fast[62]. RF improved inflammatory markers, HOMA-IR, and noninvasive measures for NASH severity assessment in a retrospective, case control study of 155 NAFLD/NASH patients (74 fasted and 81 did not)[63].

RAMADAN FASTING AND LIVER CIRRHOSIS

Liver cirrhosis is a progressive degenerative disease where the normal liver tissue is replaced by haphazardly arranged tissue with variable degrees of fibrosis which ultimately induces functional impairment of the liver and is associated with portal hypertension (PHTN). It can occur due to multiple etiologies and the most important are viral hepatitis, alcohol, and NAFLD. The global prevalence of cirrhosis is 4.5%-9%. Management of cirrhosis and its complications is associated with a huge budget and is a burden on communities.

The impact of IF including the Ramadan model on liver cirrhosis was studied infrequently in the literature (Table 2). The functional capacity of the diseased liver is evaluated by Child classification. This classification stratifies patients with liver cirrhosis as compensated (represented by Child class A) and decompensated (represented by Child class B and C). The data extrapolated from the few published studies and from clinical experience were given as recommendations[15] in one published article advising patients with Child B and C to avoid RF, while patients with Child A can observe fasting provided certain precautions are followed.

The liver plays a pivotal role in maintaining blood sugar during fasting through breakdown of the glycogen stores and gluconeogenesis[2]; however, both are impaired in the cirrhotic liver and hence cirrhotic patients are hypoglycemia prone during the fasting hours. Consequently, cirrhotic diabetic patients especially if receiving insulin or long-acting secretagogues are not advised to fast[15].

Among cirrhotics, the likelihood of functional decompensation is high particularly with prolonged hours of fasting (> 14 hours), during the summer, and with continuous fasting. This is manifested by deteriorations seen in the LFTs and different aspects of clinical decompensation[17,64,65]. The development of ascites was noted in 25%[66] and 41% of fasting cirrhotics[17] during Ramadan while the amount of ascites increased in 64% of fasting cirrhotics by the end of Ramadan[17]. Clinical jaundice and serum bilirubin also increased with fasting[17,64,66]. Furthermore, hepatic encephalopathy and GI bleeding were reported among 8/300 and 6/300 of patients seen by Elfert *et al*[64], and among 4/40 and 2/40 seen by Mohamed *et al*[66], respectively. Consequently, progression to Child C was reported among 13% and 15% by Elnadry *et al*[17] and Mohamed *et al*[66], respectively. RF was associated with 3/300 case fatalities in the study by Elfert *et al*[64], and this was evident among patients with Child Class B and C cirrhosis who insisted on fasting against medical advice.

PORTAL HYPERTENSION AND RAMADAN FASTING

PHTN and bleeding from gastroesophageal varices are the major causes of morbidity and mortality in patients with cirrhosis. PHTN is induced by increased intrahepatic vascular resistance and a hyperdynamic circulatory state. Patients with PHTN have a high cardiac output, increased total blood volume, and splanchnic vasodilatation, resulting in increased mesenteric blood flow[67]. Ingestion of food is physiologically followed by vasodilatation and increased mesenteric blood flow; a phenomenon known as postprandial hyperemia[68]. In cirrhosis, repeated flares of increased portal pressure and collateral blood flow provoked by postprandial hyperemia may contribute to variceal dilation and rupture[69].

In the study by Albillos *et al*[69], they found that postprandial hyperemia simultaneously increases hepatic venous pressure gradient (HVPG) and collateral flow. The extent of the collateral circulation determines the HVPG response to food intake. Patients with extensive collateralization show less pronounced postprandial increases in HVPG, but are associated with marked flares in collateral flow[69]. These observations explain why cirrhotic patients with PHTN observing RF had an increased risk of bleeding at night after receiving an Iftar meal[15]. Mohamed *et al*[65], found that the congestive index of portal flow during RF showed a statistically significant increase from fasting to postprandial status in Child class A and B with the probability of increased portal flow and consequently a higher risk of bleeding[65].

Peptic ulcer either symptomatic or asymptomatic is prevalent among patients with liver cirrhosis. The risk of bleeding from peptic ulcer in cirrhotic and non-cirrhotic patients is sharply increased during fasting, and the likelihood of perforation is a real threat during fasting especially in females and the elderly. Consequently, all patients with known active peptic ulcer are not allowed to observe RF. Patients with stable CLD are advised to undergo a screening upper endoscopy to detect and treat both varices and ulcers at least 1 month prior to Ramadan[15].

EFFECTS OF FASTING ON PATIENTS POST-LIVER TRANSPLANT

According to Islamic principles, patients who have undergone liver transplant are not required to fast during Ramadan. A study conducted on cirrhotic patients revealed that non-fasting cirrhotic patients exhibited better adherence to therapy and a lower risk of disease progression compared to fasting cirrhotic patients. Consequently, the researchers concluded that fasting during Ramadan is prohibited for cirrhotic patients[17].

Liver transplant recipients face a higher risk of adverse effects from fasting due to their underlying illness and the immunosuppressive medications they receive. The primary concern in this group of patients is the accumulation of toxic metabolites and subsequent dehydration, which can lead to renal deterioration and even rejection of the transplanted liver due to changes in the immune system. Additionally, extended fasting periods during the summer months may hinder patients from taking their medications at the prescribed intervals, particularly if needed to be taken for twelve hours. Inconsistent intake of immunosuppressive medications can result in invariable drug levels and increase the risk of graft loss. Therefore, liver transplant recipients must adhere to the prescribed medication schedule.

Table 2 Publications focusing on liver cirrhosis and Ramadan fasting

Ref.	Type of publication	Patients assessed	Findings
Elnadry *et al*[17], 2011	Observational and comparative	Chronic hepatitis and cirrhotics (child A and B), *n* = 202; Fasting group, 103 patients, 57 chronic hepatitis and 46 cirrhotics. Non-fasting group included 99 patients, 52 with chronic hepatitis, and 47 cirrhotics	Dyspeptic symptoms were higher in the fasting group. GI bleeding during Ramadan was higher in the fasting group compared to the non-fasting, but variceal bleeding was significantly higher in the non-fasting group. The chronic hepatitis fasting group showed non-significant changes pre-, during, and post-Ramadan regarding liver functions. Fasting cirrhotic group patients: The frequency of deterioration to Child class C was high
Elfert *et al* [64], 2011	Observational and non-comparison	Cirrhotics (Child A, B, and C), *n* = 216	Twenty-seven patients discontinued their fast due to fatigue. Variceal bleeding and encephalopathy were reported in 8 and 6 patients, respectively. Ramadan fasting had no significant effect on PV diameter or portal blood flow. Male sex, Child class A, and absence of GI bleeding were independent factors in the reduction of liver enzymes and serum glucose during Ramadan fasting. Older age, DM, and Child class C were independent factors in the elevation of serum bilirubin and creatinine during Ramadan fasting
Mohamed *et al*[65], 2016	Observational and non-comparison	Cirrhotics (Child A, B, and C), *n* = 40	Cirrhotic patients showed significant short-term changes in the portal blood flow (increases CI). Seven patients developed complications including 2 cases of variceal bleeding. Due to deteriorations reported in liver functions Child class C patients should not fast
Mohamed *et al*[66], 2018	Observational and comparative	Cirrhotic (Child A and B) and healthy volunteers; *n* = 72; comprised cirrhotic fasting (*n* = 34), cirrhotic non-fasting (*n* = 8) and healthy volunteers (*n* = 30)	Patients with cirrhosis showed changes in their portal hemodynamics with increased CI. MELD score and serum albumin showed significant changes in comparison to healthy subjects
Emara *et al* [15], 2021	Review and practice recommendations	Cirrhotic patients. Analysis of the evidence for the above-mentioned studies	Cirrhotic patients Child A can observe RF especially if following NAFLD guidelines provided that certain evaluations are done in advance together with close observation during Ramadan. Cirrhotic patients Child B and C should not fast. The risk of decompensation is high
Al-Jafar *et al*[55], 2023	Systematic review and meta-analysis	Healthy individuals and patients with different comorbidities including cirrhosis and NAFLD. Analysis of many studies	RF was associated with reductions in anthropometric measures in all patients including cirrhotics. These changes start to appear in the second week of Ramadan and diminish 3 weeks after Ramadan

NAFLD: Non-alcoholic fatty liver disease; RF: Ramadan fasting; GI: Gastrointestinal; CI: Congestive index; DM: Diabetes mellitus; PV: Portal vein; MELD: Model for end-stage liver disease.

When considering the decision to fast, the risk stratification of the recipient should be assessed. Patients considered to be at very high risk include those who have undergone a transplant within the last 12 months, patients on twice-daily formulations of immunosuppression, pregnant transplant patients, diabetic patients, and patients with unstable graft function. Patients with other organ transplants and reduced graft function, as well as those at risk of dehydration due to fluid restriction requirements, are also considered high risk. Transplant patients not falling into these categories are generally considered to be at moderate or low risk[70].

Despite the increased risk, many liver transplant recipients inquire about the safety of fasting during Ramadan. Derbala *et al*[71] conducted a study to assess the safety of RF and its impact on immunosuppressive levels, as well as biochemical and hematological changes. Interestingly, there was no significant difference in tacrolimus levels (P = 0.96) between those who fasted and those who did not. The authors concluded that patients with stable graft function, in the absence of cirrhosis, can safely observe fasting during Ramadan[71].

Another study conducted by Montasser *et al*[72], aimed to evaluate the effect of RF on renal and liver functions among liver transplant recipients and propose a protocol for adapting immunosuppression regimens and follow-up schedules for patients interested in fasting after liver transplantation. The study reported positive outcomes for RF when accompanied by an adapted immunosuppression protocol and regular follow-up of recipients who wish to fast. It was suggested that fasting during Ramadan in post-liver transplant patients should be individualized based on each patient's baseline estimated glomerular filtration rate and their specific immunosuppressive regimen[72].

GILBERT SYNDROME AND RAMADAN FASTING

Gilbert syndrome is an autosomal recessive disorder of bilirubin metabolism within the liver with a prevalence rate of 3%-7% in the general population. Reduced glucuronidation of bilirubin leads to unconjugated hyperbilirubinemia and recurrent episodes of jaundice, but does not affect the patient's life expectancy. There are triggers that induce rises in serum bilirubin levels among patients with Gilbert syndrome including fasting, dehydration, fever, and certain drugs. It is thus expected that this category of patients will have high serum bilirubin levels during RF. One case series shed light on the rise in serum bilirubin[73]. Initially, during Ramadan, patients had a rise in their serum bilirubin level; however,

they attained stable bilirubin levels thereafter, and did not report any serious sequels.

INTERMITTENT FASTING AND HEPATOCELLULAR CARCINOMA

Present-day lifestyles are characterized by increased sedentary behavior and easy access to and increased intake of high-calorie food. These lifestyles have led to the worrying prevalence of obesity, diabetes, and NAFLD, which are risk factors for hepatic and extra-hepatic cancer. However, increased calorie intake is not the only determining factor for deteriorating metabolic health, as the timing of food intake is also a key player in maintaining the body's metabolic flexibility. IF, in which the timing of food intake is more important than the quantity, may therefore have a range of potential benefits. Indeed, pre-clinical and clinical studies have outlined the beneficial effects of IF in establishing weight loss, improving cardio-metabolic health, preventing neurodegenerative diseases, and reducing the risk of cancer development and prolonging lifespan[74-76].

Importantly, the presence of obesity results in an approximately two-fold increased risk of hepatocellular carcinoma (HCC) development, a four-fold increased HCC-related risk of mortality, and a two-fold increased risk of life-threatening complications[77]. Apart from patients with NAFLD, obesity is also frequently encountered in patients with other etiologies such as chronic hepatitis B or Cand alcohol-related liver disease[78].

Obesity may favor the development of HCC through the increased hepatic oxidative stress and inflammation secondary to altered microbiome composition and altered white adipose tissue adipokine production, namely increased levels of leptin and decreased levels of adiponectin[79]. Moreover, the increase in substrate availability that characterizes obesity favors the chronic activation of insulin and insulin-like growth factor receptors, which results in increased cell glucose uptake, cell proliferation, and angiogenesis, creating a pro-malignant microenvironment[80].

In obese cirrhotic patients without features of sarcopenic obesity, dietary interventions such as IF can reduce hepatic and systemic inflammation and insulin resistance, re-balance the levels of adipokines, and reduce the risk of liver decompensation, finally decreasing the risk of HCC development[81].

The potential anti-carcinogenic effect of fasting can also be derived from studies which outlined that drug actions can mimic fasting effects, fasting can inhibit hypoxia-induced metastasis, angiogenesis, and metabolic reprogramming in HCC, as is the case with SGLT2 inhibitors, which have the potential to modulate molecular pathways that affect hallmarks of HCC, including inflammatory responses, cell proliferation, and oxidative stress[82].

To date, numerous signaling pathways involved in HCC carcinogenesis that have been identified can be grouped into five main categories, with emerging pathways still under research: (1) Tyrosine kinase-dependent growth factor receptors and their downstream mediators; (2) Pathways involved in differentiation and cell-cell-signaling; (3) Inflammation pathways; (4) Epigenetic pathways; and (5) Angiogenesis[83], which are potential targets for fasting effects. The fasting state stimulates multiple pathways that ultimately increase autophagy, reducing protein synthesis and cell growth by suppressing the activity of the mTOR pathway which is involved in HCC carcinogenesis. Also, by re-synchronizing the circadian clock (more evident with RF) and re-setting key metabolic pathways involved in cell proliferation, growth, defense, and function, IF can prevent the evolution of CLD towards HCC[81].

The low glucose levels during fasting stimulate pancreatic glucagon secretion and favor glucose synthesis through glycogenolysis and gluconeogenesis. After liver glycogen depletion, there is a switch from glucose to lipid metabolism, with a preferential utilization of fatty acid-derived ketones[2,84]. Apart from being an energy source, ketone bodies such as β-hydroxybutyrate can act as an endogenous histone deacetylase inhibitor, thus protecting against oxidative stress and slowing tumor development[85].

Patients with HCC usually have a variable degree of hepatic functional decompensation, and hence observing any kind of IF model including RF should not be recommended as the likelihood of deterioration is high[15,16].

SHORT-TERM FASTING AND ITS RELATION TO HEPATOBILIARY SURGERY

Preoperative fasting was introduced in the 19th century to reduce the risk of aspiration pneumonia while patients were under general anesthesia[86].

The temporary occlusion of the hepatic inflow (Pringle maneuver) or the hepatic inflow and outflow (total hepatic vascular occlusion) is a common method used during liver resection or liver transplantation. The prolonged interruption results in liver ischemia/reperfusion injury (IRI) caused by progressive hepatocellular injury and death after reperfusion, which is considered to be a risk factor for recent and distant damage to residual liver or transplant liver[87].

The development of a protective strategy against IRI is warranted to alleviate the consequences of hepatic IRI. Calorie restriction and fasting have displayed some beneficial effects on the prolongation of life and increased resistance to stress. Preoperative short-term fasting attenuates mouse IRI, which greatly piqued our interest in verifying whether fasting produces similar protective effects in patients undergoing hepatectomy[88].

According to Zhan *et al*[89], preoperative short-term fasting effectively improves clinical outcomes and markedly attenuates inflammatory responses and oxidative stress in patients undergoing hepatectomy, and the Nrf2 signaling pathway may play a key role in fasting against inflammatory responses and oxidative stress.

OVERVIEW OF INTERMITTENT FASTING AND THE LIVER

The act of eating is a powerful external cue that effectively synchronizes the liver's energy metabolism with the alternating cycles of feeding and fasting, independent of the natural day-night rhythm. Hence, the timing of food intake should be chronologically consistent to avoid chaotic eating behavior. This situation holds great promise for potential therapeutic interventions in the context of obesity and NAFLD by simply adjusting the timing of calorie intake.

Exploring RF as a specific form of IF and TRE reveals numerous favorable effects for both healthy individuals and patients with NAFLD. By resetting circadian rhythms in various metabolically active tissues intricately connected to NAFLD development, RF may reduce the risk of NAFLD in healthy individuals and ameliorate the severity of NAFLD/NASH in affected patients. Collectively, there is a compelling rationale supported by human observational studies and clinical trials to warrant further in-depth investigation of RF as a potential dietary strategy which may indeed emerge as a promising therapeutic option for individuals afflicted by NAFLD and NASH.

One open question that needs further research to answer is, does RF achieve the desirable weight loss, dietary modifications and calorie restriction recommended by the current practice guidelines for the treatment of NAFLD? The evidence described above including multi-ethnicity, considerable number of patients recruited, and the heterogeneous groups of patients with multiple co-morbidities recruited (*e.g.*, LORANS) demonstrates the potential impact of RF in the management of NAFLD especially if combined with dietary advice and calorie restriction. However, RF is conducted over a short period and the durability of the effects has not been studied and these benefits may be temporary. Future studies for longer duration may shed light on these controversial issues.

RF was associated with clinical decompensation and biochemical deteriorations among patients with advanced cirrhosis and hence patients with Child class B and C should avoid RF, while patients with Child A especially if due to NAFLD can observe fasting. The long-term effects of fasting on the natural progress of cirrhosis have not been fully evaluated as most of the studies followed patients during Ramadan month and for one month after Ramadan. Probably, the frequency of decompensation will increase if cirrhotic patients who observed fasting were followed for a longer period. Moreover, many diseases, patient and environmental parameters were not evaluated among fasting cirrhotic patients *e.g.*, age, work conditions, underlying cause of cirrhosis *etc.*, and that is why we proposed a risk assessment tool to evaluate cirrhotic patients case by case before observing fasting[90]. This assessment includes clinical assessment, laboratory evaluation, imaging studies, dietary modifications, medication revision, and endoscopic assessment in a selected population[15,90]. This would reduce the risk of decompensation reported in the earlier studies[17,64-66] among cirrhotic individuals observing RF.

Cirrhotic patients are vulnerable to variceal and non-variceal GI bleeding during RF due to the state of PHTN with collateral circulation and the increased frequency of peptic ulcers. Hence, patients with active variceal bleeding and those with active peptic ulcer disease (PUD) should avoid fasting, while patients with non-risky varices in compensated patients and patients with inactive PUD should be treated before and during RF to avoid complications.

Liver transplantation offers improved survival and quality of life (QOL) for eligible patients. Fulfilling religious obligations may be an important aspect of QOL for Muslim patients. Many transplant recipients ask their clinicians about fasting during Ramadan, and the answer provided is that patients at moderate or low risk can fast while following medical advice. It is important to educate patients about the risks of fluid imbalance, electrolyte abnormalities, nutritional requirements, and fluid intake. Changes to the immunosuppression regimen should ideally be made one month before Ramadan, and exploring once-daily alternatives may be beneficial. Monitoring graft function, electrolytes, and levels of immunosuppressive agents during Ramadan is advised, and patients should discontinue fasting if they become unwell.

CONCLUSION

RF was evaluated by different observational and interventional studies among patients with NAFLD and it was associated with improvements in anthropometric measures, metabolic profile, and liver biochemistry regardless of the calorie restriction among lean and obese patients. The situation is rather different for patients with liver cirrhosis. RF was associated with adverse events among patients with liver cirrhosis irrespective of the underlying etiology of cirrhosis. Cirrhotic patients developed new ascites, ascites were increased, had higher serum bilirubin levels after Ramadan, and frequently developed hepatic encephalopathy and acute upper gastrointestinal bleeding. These complications were higher among patients with Child class B and C cirrhosis and some fatalities occurred due to fasting. Liver transplant recipients as a special group of patients, are vulnerable to dehydration, fluctuation of blood immunosuppressive levels, likelihood of deterioration and hence observing RF without special precautions would represent a real danger for them. Patients with Gilbert syndrome can safely observe RF despite the minor elevations in serum bilirubin reported during the early days of fasting.

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