

Safety and Deleterious Effect of Fasting Ramadan in Liver Transplant Recipients

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Abstract

Ramadan fasting is a unique model of prolonged intermittent fasting, in which Muslims all over the world abstain from food and water from dawn to sunset. Few clinical trials have addressed the effect of fasting in cirrhotic patients, but to date, has been conducted to study the effect of fasting in liver transplant patients.

Aim: To Study the safety of fasting, the effect on immunosuppressive level and biochemical and hematological changes.

Results: There was no significant difference in tacrolimus levels ($P=.96$) between those who observed fasting and those who did not observe fasting during Ramadan. Significantly higher albumin ($P<.0001$), total proteins ($P<.0001$), cholesterol ($P<.0001$), creatinine ($P=.04$), hemoglobin ($P<.001$), and platelet count ($P<.0001$) before Ramadan, and after Ramadan compared to during Ramadan. We detected no significant difference fast in any of the biochemical, and hematological indices between patients who fasted and patients who did not.

Conclusion: The patients with stable graft function, in the absence of cirrhosis, can fast safely.

Keywords: Fasting; Liver Transplant; Liver Function; Imunosuppressive

Background

Fasting during the lunar month of Ramadan is a ritual followed by Muslims throughout the world. During fasting, Muslims are required to refrain from all intakes of food, water, beverages, smoking from sunrise to sunset for a period of a month. Although non-healthy as well as weak people are allowed not to fast in this month, some transplant recipient patients are willing to fast, but are concerned about adverse effects on their health. Among healthy adults, there are no reported adverse effects of Ramadan fasting on the brain, heart, lung, liver, kidney, hematologic, endocrine profile and cognitive functions [1]. No significant changes pre, during and post-Ramadan regarding liver function was reported in the chronic hepatitis patients [2]. Good adherence to therapy and less risk of progression, was reported in non-fasting cirrhotic patients compared to fasting-cirrhotic, and the investigators concluded that fasting Ramadan is prohibited in Cirrhotic patients [2]. Weight loss in patients with chronic hepatitis during fasting Ramadan, has been documented to be associated with a decline in hepatic transaminases [3,4].

Liver transplant program in Qatar, was activated in December 2011 and the first liver transplant was performed in on December 6, 2011 [5]. Patients with organ transplants represent a special group of patients owing to their special nutritional needs and medication interactions. Although few studies have addressed this issue in patients with renal transplant, no studies to our knowledge have been done among liver transplant recipients. Currently, no established guidelines exist from any major liver societies regarding the safety of fasting or the lack of it among patients with Liver Transplant.

Few clinical trials have addressed the effect of fasting in cirrhotic patients, but to date, has been conducted to study the effect of fasting in liver transplant patients [6]. Few studies have shown that fasting, in patients with Renal transplant, is safe in stable renal transplant patients, but in others, Cyclosporine toxicity, acute rejection episodes, urinary tract infection, was reported in fasting Kidney transplant patients [7].

We aim to study such effect retrospectively in a cohort of liver transplant recipients, who insisted to fast Ramadan compared to non fasting recipient followed in the same study period. We studied the safety of fasting for them, the effect on immunosuppressive level and the more specific question regarding what would be the precautions and outcome if these patients continue the month long fasting.

Patients and Methods

The Hamad liver Transplant Hepatitis Database, Qatar, was analyzed, after approval of local research and The Ethical Committee of Hamad Medical Corporation, Qatar. A retrospective, controlled, observational study, including 96 liver transplant patients, who are followed in Transplant clinic from August 2008 to August 2017, who were at least 18 years of age. Basic, clinical, ultrasound scanning laboratory data, in addition to liver biopsies (when available), pre-during and post Ramadan, were collected. The date was collected within 4 weeks before and After Ramadan and every two weeks during Ramadan. The patients were classified into fasting and non-fasting (control), groups. The effect of fasting were studied by comparing and intragroup analysis of the patient data. We studied the safety of fasting for them, the effect on immunosuppressive level and the more specific question regarding what would be the precautions and outcome if these patients continue the month long fasting.

Statistical methods

The data were described using means (SD) and frequency (percentages) for continuous and categorical variables respectively. To account for the multiple observations per patients, we used mixed linear models for continuous outcomes and generalized estimated equations for categorical outcomes.

The study carried out in accordance with the Declaration of Helsinki in 1979, and the ethics research committee of the Hamad Medical Corporation provided ethical approval.

Results

The study included 96 patients, received a liver transplant in the period of 1986-2014, and followed up in transplant clinic, Hamad Hospital. The patients were mostly men 58 (60.4%), with an average age of $49.71 \pm (SD 14.11)$. All the patients had baseline normal synthetic liver function, and none showed decompensated features. No cirrhotic changes were reported liver pathology, for those underwent liver biopsy prior to fasting Ramadan.

The minimum fasting hours was 12 hours and 2 minutes, while the maximum fasting hours was 15 hours and 16 minutes, in June 2017.

BMI

Weight loss was seen more than 1Kg was seen 49 patients (51.04%) with a decrease in BMI, while 10.4% showed an increase in weight . There was an insignificant reduction in BMI among the fasting group, compared to their BMI before Ramadan ($30,71 \pm 3.96$ and $30,35 \pm 3.96$, respectively)

Biochemical and hematological indices

| | All | | | Not fasting | | | Fasting | | | p value |
|-----------------|--------|-----------------|--------|-------------|-----------------|--------|---------|-----------------|--------|---------|
| | Mean | 95% CL for Mean | | Mean | 95% CL for Mean | | Mean | 95% CL for Mean | | |
| Albumin | 34.21 | 26.54 | 41.88 | 36.14 | 28.74 | 43.53 | 30.21 | 12.32 | 48.11 | 0.609 |
| Total bilirubin | 17.81 | 5.09 | 30.54 | 20.21 | 0.50 | 39.93 | 13.33 | 5.63 | 21.04 | 0.630 |
| Total protein | 58.43 | 43.55 | 73.32 | 62.42 | 47.80 | 77.03 | 51.08 | 20.01 | 82.14 | 0.822 |
| ALP | 145.34 | 85.34 | 205.35 | 172.52 | 86.35 | 258.69 | 93.45 | 70.66 | 116.25 | 0.115 |
| AST | 44.95 | 25.05 | 64.86 | 42.26 | 20.89 | 63.62 | 49.80 | 2.94 | 96.66 | 0.808 |
| ALT | 63.21 | 20.66 | 105.77 | 62.85 | 30.13 | 95.57 | 63.74 | -6.50 | 133.98 | 0.826 |
| Cholesterol | 3.11 | 2.24 | 3.99 | 3.18 | 2.12 | 4.25 | 2.99 | 1.28 | 4.70 | 0.934 |
| Triglycerides | 3.13 | -1.00 | 7.26 | 4.25 | -2.58 | 11.07 | 1.15 | 0.29 | 2.02 | 0.503 |
| Creatinine | 93.24 | 45.98 | 140.51 | 111.62 | 40.94 | 182.29 | 61.40 | 28.94 | 93.86 | 0.512 |
| Hb | 10.48 | 7.99 | 12.97 | 10.48 | 7.73 | 13.23 | 10.47 | 5.08 | 15.85 | 806 |
| Platelet | 130.60 | 99.55 | 161.64 | 139.44 | 107.66 | 171.2 | 114.7 | 49.75 | 179.59 | 0.681 |
| Tacrolimus | 3.55 | 2.04 | 5.064 | 3.53 | 1.51 | 5.54 | 3.59 | 0.82 | 6.36 | 0.965 |

Table 1: Drug, blood indices and biochemical characteristics by fasting status during Ramadan

Fasting status and the biochemical and hematological indices associations during Ramadan: We ran a bivariate analysis using simple linear mixed regression models to examine whether fasting predicted the absolute values of several biochemical, and hematological values. We detected no significant difference fast in any of the biochemical, and hematological indices between

patients who fasted and patients who did not (Table 1). Furthermore, we compared those who observed fasting and those who did not, using the clinical relevant cutoff values to classify patients accordingly to those with normal and abnormal values. We did not detect a significant excess of abnormal values in any of measured biochemical, and hematological indices. There is no significant change in The Model for End-Stage Liver Disease (MELD) score, which is a reliable measure of mortality risk in patients with end-stage liver disease, in both groups or intragroupal in transplant recipient before and after Ramadan (Data not in table).

Ramadan and the biochemical changes, associations: In order to examine whether altered eating habits during Ramadan would affect the biochemical, and hematological profiles of the patients regardless of whether the patients observed fasting or not, we examined the bivariate association between the biochemical functions and the time of the blood sample acquisition, comparing (before Ramadan, and after Ramadan) to during Ramadan. We detected significantly higher albumin ($P<0.0001$), total proteins ($P<0.0001$), cholesterol ($P<0.0001$), creatinine ($P=0.04$), hemoglobin ($P<0.0001$), and platelet count ($P<0.0001$), before Ramadan, and after Ramadan compared to during Ramadan (Table 2). However, when patients were classified according to whether the biochemical, and hematological indices were considered as clinically abnormal or not, none of the indices were significantly different by Ramadan status (Data not in tables).

| | All | | Before Ramadan | | During Ramadan | | After Ramadan | | P value |
|-----------------|--------|-------|----------------|-------|----------------|-------|---------------|-------|---------|
| | Mean | SE | Mean | SE | Mean | SE | Mean | SE | |
| Albumin | 39.25 | 0.82 | 40.61 | 0.69 | 34.21 | 3.71 | 39.46 | 0.69 | <0.0001 |
| Total bilirubin | 19.59 | 3.29 | 19.62 | 3.23 | 17.81 | 6.14 | 20.12 | 3.62 | 0.105 |
| Total protein | 70.26 | 1.21 | 71.69 | 0.75 | 58.43 | 7.11 | 72.09 | 0.94 | <0.0001 |
| ALP | 136.75 | 13.23 | 124.73 | 12.39 | 145.34 | 28.44 | 145.64 | 15.33 | 0.343 |
| AST | 48.22 | 5.46 | 47.06 | 4.78 | 44.95 | 9.60 | 50.36 | 6.87 | 0.724 |
| ALT | 50.75 | 11.24 | 46.60 | 8.16 | 63.21 | 20.46 | 49.57 | 10.79 | 0.238 |
| Cholesterol | 4.11 | 0.16 | 4.23 | 0.15 | 3.11 | 0.42 | 4.27 | 0.14 | <0.0001 |
| Triglycerides | 2.75 | 0.78 | 1.34 | 0.10 | 3.13 | 1.98 | 3.95 | 1.45 | 0.207 |
| Creatinine | 98.54 | 10.25 | 98.33 | 7.34 | 93.24 | 22.79 | 100.30 | 10.65 | 0.036 |
| Hb | 12.65 | 0.27 | 12.97 | 0.21 | 10.48 | 1.20 | 13.02 | 0.25 | <0.0001 |
| Platelet | 155.16 | 7.70 | 157.46 | 7.97 | 130.60 | 14.97 | 160.34 | 7.63 | <0.0001 |
| Tacrolimus | 4.70 | 0.24 | 4.83 | 0.22 | 3.55 | 0.72 | 4.92 | 0.24 | 0.017 |

Table 2: Drug, blood indices and biochemical characteristics by time of the sample

Tacrolimus level changes by observing fasting and by Ramadan: There was no significant difference in tacrolimus levels ($P=0.96$) between those who observed fasting and the control group, during Ramadan (Table 1).

We further examined whether fasting affected the clinically relevant preferred normal values. Interestingly, those who observed fasting, were less likely to have abnormal Tacrolimus levels (OR (95% CI), 0.2(.05,.85), $P=0.028$). The odds of high (abnormal), or low (abnormal) Tacrolimus levels were higher among those who did not observe fasting compared to those who did not observe fasting (OR 6.42, $P=0.083$ and OR 9.33, $P=0.093$ respectively).

We detected significantly higher tacrolimus levels ($P=0.02$), before Ramadan (mean (SE) 4.83 (0.22)), and after Ramadan (mean SE) 4.92 (0.24)), compared to during Ramadan (mean (SE) 3.55 (0.72)) (Table 2).

The abnormal tacrolimus levels were less likely to be encountered before and after Ramadan compared to during Ramadan (OR 0.38, $P=0.003$ and OR 0.40, $P=0.008$ respectively).

The likelihood of low (abnormal) Tacrolimus levels, but not of high (abnormal) Tacrolimus levels, were statistically borderline higher during Ramadan compared to before Ramadan (OR 2.45, $P=0.063$ and OR 1.07, $P=0.909$ respectively) and marginally higher during Ramadan compared to after Ramadan (OR 2.38, $P=0.099$ and OR 1.05, $P=0.939$ respectively).

Liver transplant

We examined whether there is a difference between transplant patients and stable chronic liver disease patients biochemical and hematological indices during Ramadan. In the unadjusted analysis, there was no significant difference between the two groups in any of the biochemical or hematological values. (Data not in tables)

Predictors of abnormal biochemical and hematological indices among patients with a liver transplant: We ran models adjusted for fasting age, gender, nationality, fasting status, time of the sample acquisition, duration since the transplant and transplant type to determine predictors of abnormal biochemical and hematological indices.

Only fasting status and nationality predicted abnormal total bilirubin, such that those who observed fasting and non-Qatari nationals had a higher likelihood of abnormal total bilirubin (OR 12.82, $P=0.005$ and OR 4.65, $P=0.018$ respectively).

Of note, those who observed fasting were less likely to have abnormal ALT levels compared to those who did not fast (OR 0.14, $P=0.003$ respectively).

Fasting age was the only predictor of cholesterol and triglycerides abnormal levels, such that older patients were more likely to develop abnormal cholesterol and triglycerides levels.

No other characteristic predicted any other abnormal biochemical and hematological indices. (Data not in tables)

Discussion

Ramadan fasting is a unique model of prolonged intermittent fasting without any calorie restriction, in which Muslims all over the world abstain from food and water from dawn to sunset for 29 or 30 days each year. Based on Islamic principles, patients are exempted from fasting during Ramadan, however, many liver transplant recipient ask about the safety of fasting during Ramadan. Transplant patients are at increased risk of adverse effects related to fasting due to their underlying illness and immunosuppressive medication.

While, no deleterious effect was reported in liver function in healthy fasting subjects, mild changes in liver function and significant short term changes in the portal blood flow were reported in cirrhotic patients [8]. These changes were attributed to changes in cytokines and alteration in circadian rhythms of hormones.

All the existing literature was on kidney transplant recipients and we did not find any study regarding deleterious Effect of prolonged intermittent fasting in other transplant patients, and until recently little was known of medication compliance and adverse effect during Ramadan.

Our study revealed that most of the laboratory parameters in liver transplant recipients with normal functioning graft showed no statistically significant difference compared to non-fasting transplant recipient or even their own pre- fasting parameters apart from a rise in the serum bilirubin.

Similar to previous reports in healthy subjects, the liver recipient in our study showed decreased BMI. Many studies have shown that significant weight loss occurs during dawn-to sunset Ramadan fasting, but the cause is unclear because total daily caloric intake during Ramadan fasting appears to be the same compared to non-fasting status [9]. Increased phosphatidylcholine levels observed at the 4th week of dawn-to-sunset fasting, may play a critical role in reduction of BMI and in turn the prevention of fatty liver [10].

In our study and In accordance with previous reports in healthy subjects, a physiological decrease was noticed in albumin, total proteins, cholesterol, and creatinine, with fasting, but still within normal range and similar in both groups.

Up to date, the safety, immunosuppressive changes and outcome of Ramadan fasting, not studied in liver transplant recipient, yet. In kidney transplant recipient, it is reported that The concentration of immunosuppressive drugs tends to remain stable, and biochemical parameters do not change significantly [11]. Only one author reported of adverse effects due to 176 cyclosporine toxicity, but no kidney loss has been documented [12]. In our study, the patients reported excellent Compliance with immunosuppressive medications, and we did not find a significant change in immunosuppressive levels among both groups. Interestingly, the fasting group, was less likely to have abnormal Tacrolimus levels during Ramadan, which reflects patients' compliance. None of our patient reported immunosuppressive toxicity or other adverse effects.

Fasting status was a predictor of abnormal bilirubin level in our modeling. In experimental fasting, an increase in indirect bilirubin occurs 15 h after fasting, which return to normal after a regular or carbohydrate meal only, but not protein or fat diets [13,14]. Significant rise in the serum bilirubin after Ramadan, was reported by different studies which focused on liver function in cirrhotic patients [15]. Also, Nasiri, *et al.* 2010, reported a statistically significant increase in bilirubin level in normal and healthy Iranian student compared to pre-Ramadan level these changes were within the normal range and clinically insignificant and he explain these changes by cytokines and alteration in circadian rhythms of hormones during fasting [16].

Similar to previous reports in healthy subjects, No significant changes in hematological profile, were seen in our liver transplant recipient and stable serum ferritin indicating that iron stores are not significantly disturbed [17]. The seasonal and geographic variations, in temperature and fasting hours, are the main limitations of the results of the current study.

In conclusion, no adverse effects observed on liver function. In the current study, we did not find a significant baseline characteristics that can suggest liver recipient, who are predisposed to any deterioration in liver function. The patients with stable graft function, in the absence of cirrhosis, can fast safely. We suggest to increase Dietary intake of protein, which may overcome the decrease in total protein during fasting.

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