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EFFECTS OF GASTRIC PLICATION SURGERY ON HEPATIC ENZYME ACTIVITY IN FATTY LIVER DISEASE

ALIREZA SHARIFI[1], SHAHAB DOLATSHAHI[1], MOHAMMAD TALEBPOUR[2], NEDA GORJIZADEH[3*]

1- Department of Internal Medicine, Gastroenterolgy Ward, Sina Hospital, Tehran University of Medical Sciences

2- Department of surgery, Laparoscopic Ward, Sina Hospital, Tehran University of Medical Sciences

3- Department of Internal Medicine,Tehran University of Medical Sciences

***Corresponding author: Neda Gorjizadeh**

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ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) is a severe liver disease that is increasing in prevalence with the worldwide epidemic of obesity. Bariatric surgery is the most reliable method for achieving substantial, sustained weight loss. **Aim:** so the aim of the current study was to determine effects of gastric plication surgery on hepatic enzyme activity in fatty liver disease. **Methods**: The case-series study was performed on32 patients with liver diseases underwent gastricplication surgery. Patients underwent liver biopsy during the surgery. The demographic characteristics of the patients were recorded. The patient's liver biopsy and alkaline phosphatase (ALP), alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) levels were determined prior and 2, 4 and 6 months after surgery. **Results**: the mean age of the patients were 33.92 ± 9.76 years (16-56 years). Average weight and bodymass index of patients were 126.61kg and 45.58 kg/m^2, respectively. Steatosis (37.5%), mild (21.9%), moderate (18.8%) and severe nonalcoholic steatohepatitis (21.9%) were reported in histopathology of liver biopsy. Fifteen patients had fatty liver grade II, before surgery. According to the results, after gastric plication surgery the rate of the normal patients increased after 4 months while the rate of the fatty liver grade I, II and III significantly decreased after 6 months ($P<0.05$).Liver AST and ALT levels significantly

decreased after 2, 4 and 6 months gastric plication surgery (P<0.05).After gastric plication surgery significantly increased hepatic ALP at 2 and 4 months after gastric plication surgery (P<0.05). Gastric plication surgery significantly decreased liver TG and LDL levels after 6 month compared to pre-operation (P<0.05).**Conclusions**: these results suggested the gastric plication surgery is an appropriate surgical procedure in extreme weight loss and effective in normalize liver enzymes.

Keywords: Gastric plication, Liver enzymes,Fatty liver disease

INTRODUCTION

In recent years, the obese population has been rapidly increasing because of increases in diets rich in saturated fat and processed carbohydrates and sedentary lifestyles. The metabolic syndromes that are considered risk factors of arteriosclerotic diseases, such as abnormal glucose tolerance, hyperlipemia, and hypertension, have increased alongside obesity in the developed world (Sasaki et al. 2014). Non-alcoholic fatty liver disease (NAFLD) is a liver phenotype of metabolic syndrome. Factors that affect the morbidity of this disease include genetic background, an epigenetic control mechanism, the fat toxicity of free fatty acid, and a natural immunity system of intestinal bacteria. Also, Non-alcoholic fatty liver disease is the most common cause of liver dysfunction worldwide, and obesity is a well-documented risk factor for the disease. It is highest in populations with preexisting metabolic conditions (Younossi et al. 2014). The incidence of nonalcoholic steatohepatitis in morbidly obese patient's approaches 70%, and 4% of them may have cirrhosis. Mild steatosis, in the majority of cases, remains stable without any further complication. However, patients with fibrosis have a higher risk for cirrhosis, portal hypertension, hepatocarcinoma and death (Cotrim et al. 2009). Therefore, identifying the presence and severity of liver fibrosis in patients with NAFLD is crucial in the guidance of subsequent management.

Alkaline Phosphatases are a group of enzymes found primarily the liver (isoenzyme ALP-$_1$) and bone (isoenzyme ALP-$_2$). There are also small amounts produced by cells lining the intestines (isoenzyme ALP-$_3$), the placenta, and the kidney (in the proximal convoluted tubules). What is measured in the blood is the total amount of alkaline phosphatases released from these tissues into the blood. As the name implies, this enzyme works best at an alkaline pH (a pH of 10), and thus the enzyme itself is inactive in the blood. Alkaline phosphatases act by

splitting off phosphorus (an acidicmineral) creating an alkaline pH (Garen and Levinthal, 1960).The primary importance of measuring alkaline phosphatase is to check the possibility of bone disease or liver disease. Since the mucosal cells that line the bile system of the liver are the source of alkaline phosphatase, the free flow of bile through the liver and down into the biliary tract and gallbladder are responsible for maintaining the proper level of this enzyme in the blood. When the liver, bile ducts or gallbladder system are not functioning properly or are blocked, this enzyme is not excreted through the bile and alkaline phosphatase is released into the blood stream. Thus the serum alkaline phosphatase is a measure of the integrity of the hepatobiliary system and the flow of bile into the small intestine (Kim and Wyckoff, 1991).

Aspartate aminotransferase (AST) is a widely distributed enzyme, which is found in many tissues and organs, with high activity in the liver (Zimmerman et al., 1968). Increased AST activity in the serum is a sensitive marker of liver damage (Meyer and Harvey, 1998). There are two main isoenzymes, mitochondrial and cytosolic, which prevails in the total concentration in the blood plasma because it has a longer half-life (Kramer and Hoffman, 1997). Activity of AST in horses is much higher than in other animals (Cornelius et al., 1958). Alanine aminotransferase (ALT) is a specific cytosol liver enzyme, and its increase in the blood plasma is specific for changes in the liver (Kramer and Hoffman, 1997). ALT activity in the blood plasma is influenced by age and muscle activity (Weigert et al., 1980).

The insulin stimulates specifically lipid from the liver to adipose tissue and it increases the uptake of glucose and changes into fatty acids and TG, VLDL and releases VLDL to circulation. Insulin increases lipoprotein lipase (LPL) which hydrolysis TG to FFA. It also increases FFA adipocyte resorption and TG changing and inhibits lipolysis (Diehl, 2004).Steatosis can cause to steatohepatitis possibly due to FFA oxidation by hepatocellular mitochondria. There are certain benefits of weight loss in NAFLD resolve (Mun et al. 2001). Weight loss improves insulin sensitivity and reduces the incidence and severity of NAFLD. (Dixon et al. 2004). The risk of liver damage is strongly related to patient weight and the FFA release is been increased by adipose tissue lipolysis (Lee et al, 1995). The preferred method for weight loss is important. Biochemical and histological abnormalities of liver disease may be better after weight loss due to gastric restrictive surgery (Dixon et al.

2004). However, such findings are often associated with weight loss due to using of a low calorie diet and gastric surgery (Andersen et al. 1991).

Based on the literature, scarce information exists on effect of the gastric plication surgery on hepatic enzyme activity in fatty liver disease. So, the hypothesis of the current study was to determine effect of the gastric plication surgery on hepatic AST, ALT and ALP as well as body weight and body mass index (BMI) in fatty liver disease patients.

MATERIAL AND METHODS

This prospective cross-sectional study was conducted between patients admitted to Sina hospital, Tehran at 2013-14. Inclusion criteria include plication stomach surgery, absence of liver diseases such as viral hepatitis, autoimmune hepatitis, cirrhosis, hemochromatosis, Wilson's disease, alpha-one antitrypsin deficiency, no renal disease. Sampling was done in a convenient and accessible. Required lab tests and liver sonography were obtained before surgery. Liver biopsy was done concurrently during surgery. The patients were followed by lab test and liver ultrasonography at 2, 4 and 6 months after surgery and were compared with before surgery.

Biomarkers for Liver Functions Tests

The liver samples obtained and the tissue alkaline phosphatase (ALP), alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) were determined using commercial detecting kits (Reitman and Frankel, 1957; Belfield and Goldberg, 1971). Also, serumhigh-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglycerides (TG) levels were determined using commercial detecting kits.

Statistical analyses

Data for age, sex, height, weight, BMI, laboratory and ultrasound and pathology were analyzed by repeated measure two-way analysis of variance(ANOVA) using SPSS 16.0 for Windows (SPSS, Inc., Chicago, IL, USA). For treatment showing a main effect by ANOVA, means compared by Tukey–Kramer test. $P<0.05$ was considered as significant differences between treatments.

RESULTS

Anthropometric data in patients is presented in table 1. According to the results, the mean age of the patients was 33.92 ± 9.76 years (16-56 years). Also, 28 (87.5%) of the patients was female while only 4 (12.5%) of them was male. Average weight and body mass index of patients were 126.61kg and 45.58 kg/m^2, respectively.

The body weight of the patients suffering fatty liver grading after gastric plication

surgery is presented in figure 1. As seen, gastric plication surgery significantly decreased body weight after 6 months compared to the initial time (before the surgery) (P<0.05).

The BMI of the patients suffering fatty liver grading after gastric plication surgery is shown in figure 2. According to the results, no significant difference detected on BMI of the patients after gastric plication surgery (P>0.05).

Frequency of fatty liver grading in liver sonography is presented in figure 3. As seen, after gastric plication surgerythe rate of the normal patients increased after 4 months while the rate of the fatty liver grade I, II and III significantly decreased after 6 months (P<0.05).

As seen in figure 4, liver AST and ALT levels significantly decreased after 2, 4 and 6 months gastric plication surgery (P<0.05).

As seen, after gastric plication surgery significantly increased hepatic ALP at 2 and 4 months after gastric plication surgery while had no effect on hepatic ALP levels after 6 months (P>0.05).

Effects of the gastric plication surgery on liver biomarkers in fatty liver patients are shown in table 2. According to the data, hepatic AST, ALT levels significantly decreased (P<0.05) while ALP levels remained unchanged after gastric plication surgery (P>0.05). Furthermore,gastric plication surgery significantly decreased liver TG and LDL levels after 6 month compared to pre-operation (P<0.05).

Table 1: Anthropometric data in patientsgastric plication surgery

Variables	Mean ± SD (%)
Age (year)	33.92 ± 9.76 (11.20 %)
Sex(male)	4 (12.5%)
(female)	28 (87.5%)
Weight (kg)	126.61 (45.58%)
BMI (Kg/m^2)	45.58
Diabetes Mellitus	2 (6.3%)
Hypertension	8 (25%)
Hyperlipidemia	6 (18.8%)
Hypothyroidism	6 (18.8%)
Steatosis	12 (37.5)
Mild NASH	7 (21.9)
Moderate NASH	6 (18.8
Severe NASH	7 (21.9%)
Normal liver	0 (0.0%)
fatty liver grade I	8 (25.0%)
fatty liver grade II	15 (46.9%)
fatty liver grade II	9 (28.1%)
AST (U/L)	31.66
ALT (U/L)	42.00
ALP (U/L)	181.88
HDL (mg/dL)	46.06
LDL (mg/dL)	122.06
TG (mg/dL)	208.53
Fasting glucose (mg/dl)	95.69

BMI: body mass index; NASH: nonalcoholicsteatohepatitis;AST: aspartate transaminase; ALT: alanine transaminase; ALP: alkaline

phosphatase; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: Triglycerides.

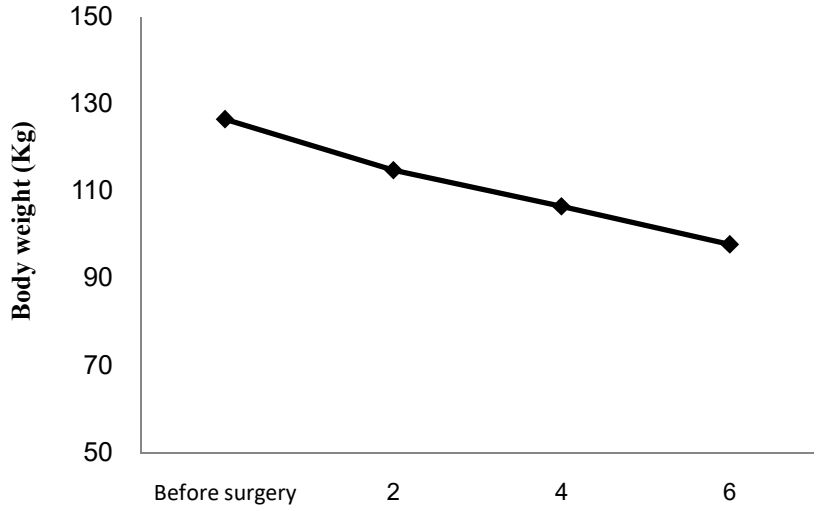

Figure 1: The body weight of the patients sufferingfatty liver grading after gastric plication surgery

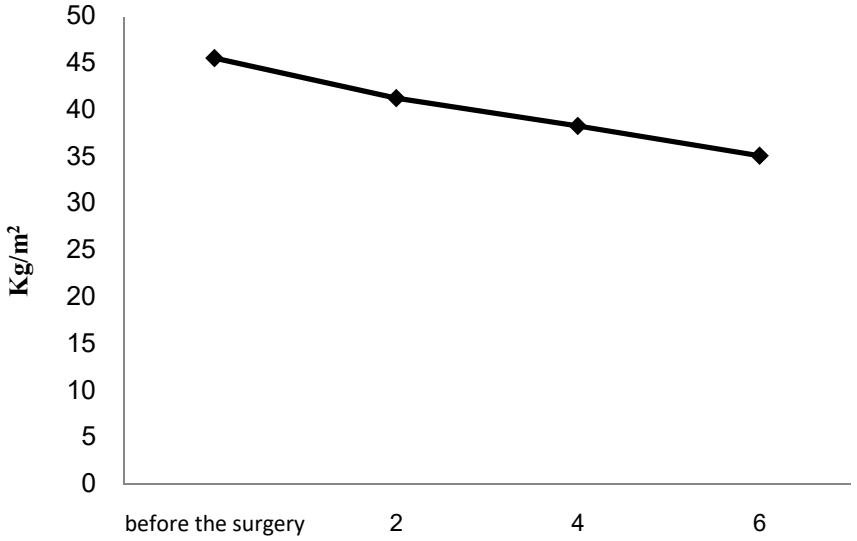

Figure 2: The BMI of the patients sufferingfatty liver grading after gastric plication surgery. BMI: body mass index

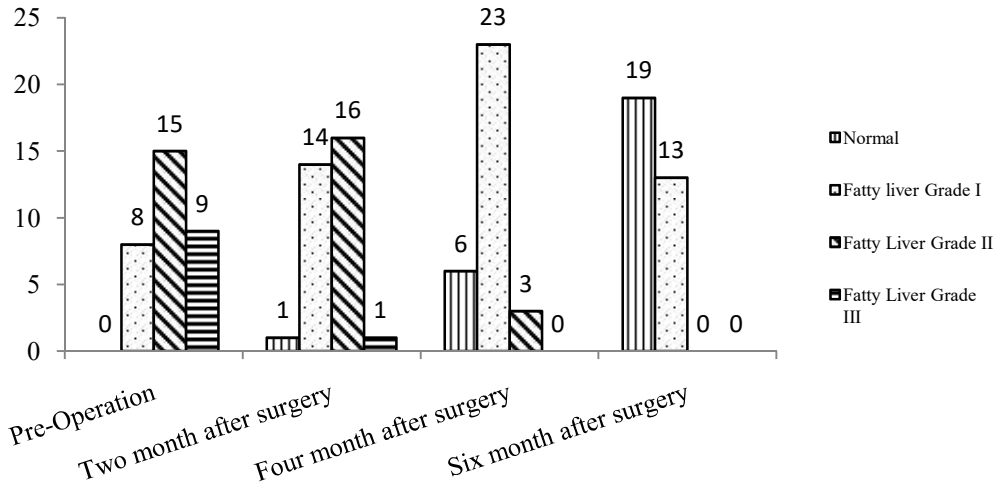

Figure 3: Frequency of fatty liver grading in liver sonography after gastric plication surgery in fatty liver patients

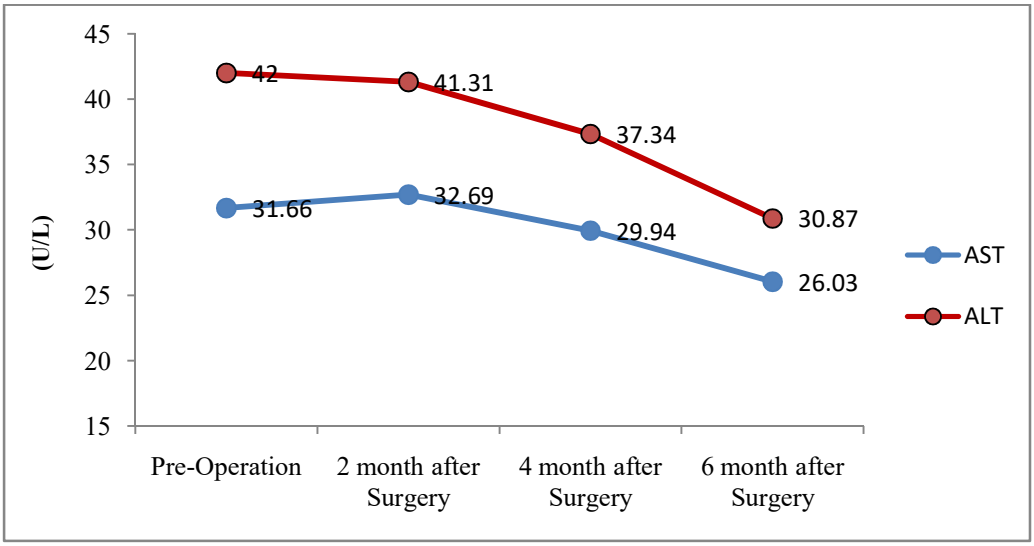

Figure 4. Liver test at pre-operation andafter gastric plication surgery in fatty liver patients. ALT: alanine aminotransferase; AST: aspartate aminotransferase

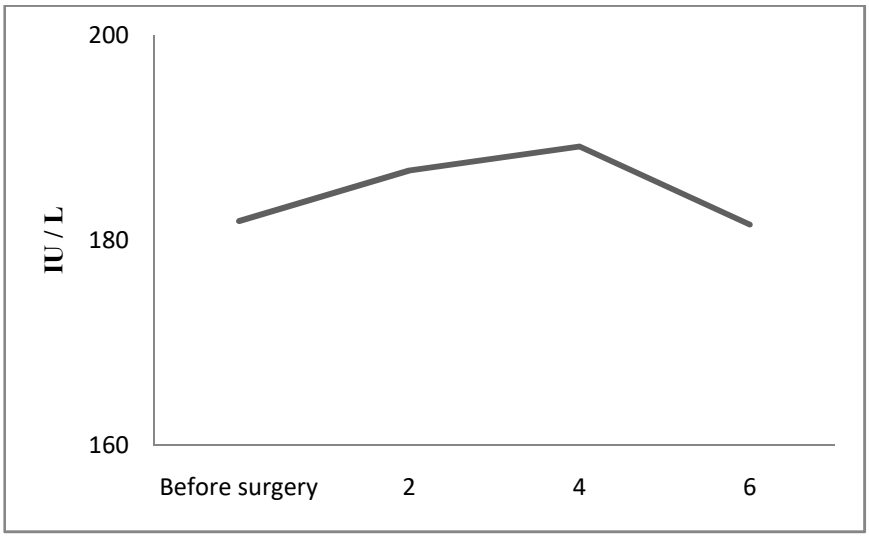

Figure 5. Liver ALP levels at pre-operationand after gastric plication surgery in fatty liver patients. ALP: alkaline phosphatase

Table 2: Effects of the gastric plication surgery on liver biomarkers in fatty liver patients

Variables	Post-operation (Mean ± SD)				
	Pre-operation	2 month	4 month	6 month	Pvalue
AST (U/L)	31.66 (15.87)	32.69 (16.66)	29.94 (10.90)	26.03 (7.86)	0.04
ALT (U/L)	42.00 (21.40)	41.31 (20.51)	37.34 (16.18)	30.87 (10.62)	0.04
ALP (U/L)	181.88 (64.50)	186.78 (54.33)	189.12 (55.88)	181.53 (47.07)	0.61
HDL (mg/dL)	46.06 (9.09)	46.75 (8.07)	46.75 (8.08)	47.81 (8.38)	0.70
LDL (mg/dL)	122.06 (23.64)	116.22 (18.90)	112.59 (17.32)	105.44 (15.35)	0.04
TG (mg/dL)	208.53 (128.44)	199.56 (104.74)	194.09 (95.43)	171.94 (83.71)	0.03

AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; HDL; high-density lipoprotein; LDL, low-density lipoprotein; TG, Triglycerides.

DISCUSSION

To our knowledge this is the first report on effect of the gastric plication surgery on hepatic AST, ALT and ALP in fatty liver disease patients. As observed in this study, liver AST and ALT levels significantly

decreased after 2, 4 and 6 months gastric plication surgery.After gastric plication surgery significantly increased hepatic ALP at 2 and 4 months after gastric plication surgery while had no effect on hepatic ALP levels after 6 months.

With the increasing prevalence of obesity worldwide, NAFLD has become the most common cause of liver disease in developed countries (Haynes et al. 2004). In this regard, Luyckx, et al (1998) studied 528 cases that 74% of them were diagnosed with fatty liver. In 69 patients who underwent liver biopsy after weight loss, 45% of the biopsies were normal (compared with 13% before surgery, $p< 0.0001$). They concluded that weight loss after gastric plication surgery reduced liver steatosis but it seemed that can lead to increased hepatic lobular inflammation.Jaskiewicz's (2006), in 59 obese cases were obtained liver biopsy sample during gastric plication surgery. The data were shown steatosis in 96% of them. Weight loss was high in 1th year after surgery but slowed after that. Future biopsy showed significant improvement in degenerative and inflammatory disorder of liver until 8 month after surgery.

Cholestasis is characterized by an accumulation of compounds that cannot be excreted because of occlusion or obstruction of the biliary tree. Hence, the serum concentration of substances (bile pigments, enzymes, bile salts) that normally are present within or eliminated via bile will increase in cholestatic conditions. The ALP, gamma glutamyltranspeptidase (GGT), and conjugated bilirubin, all of which require a clear biliary tree for elimination, will be elevated (Yamada et al. 2010).

Conversely, necrosis of hepatocytes following a viral or toxic insult to the liver (eg, acetaminophen overdose or viral hepatitis) will cause primarily an elevation of enzymes found within the hepatocyte, such as the aminotransferases (ALT and AST). In hepatocellular disease, the serum levels of GGT and ALP do not rise to the same degree as the aminotransferases (Popov and Lim, 2015). In hepatocellular disease, the reduced bile flow that ensues from necrosis of the hepatocytes also causes a mild rise in serum markers of obstruction (ALP, GGT). The two basic types of liver disease can be distinguished early in the course of the disease process, but more often, the underlying type of liver disease is diagnosed by interpretation of a constellation of clinical and laboratory criteria, including liver biopsy (Popov and Lim, 2015). These enzymes catabolize the reversible transfer of the alpha-amino group of the amino acids alanine and aspartic acid to the alpha-keto group of

alphaketoglutaric acid, leading to the formation of pyruvic acid (ALT) and oxaloacetic acid (AST). ALT is more specific for the presence of liver disease because it is found only in low concentrations in other tissues eg, muscle. Conversely, AST is present in high concentrations in many tissues, including cardiac and skeletal muscle, kidney, pancreas, and erythrocytes (Popov and Lim, 2015).

In NASH patients, researchers observed the effects on serum ALT and AST of continuous treatment with a combination of Bifidobacterium (Bifidobacteriumlongum) and fructo-oligosaccharide for six months (He et al. 2016). In this study, the patients were divided in two groups according normal or abnormal liver ultrasonography 6 month after surgery. ALT and AST serum level were increased in normal group then decreased gradually but in abnormal group, AST and ALT level were not increased. Alk-P serum level was increased to 2th month after surgery in both groups and was decreased gradually in abnormal group. It can be concluded ALK-P may elevate after surgery until 4th month, although liver ultrasonography may normal. In 4th month, It can be expected significant decreasing in liver enzyme after surgery due to liver histological improvement. 4th month after gastric plication surgery can be proposed as cut-off-point to improvement of liver enzyme.In conclusion according to the findings the gastric plication surgery is an appropriate surgical procedure in extreme weight loss and can be effective in reducing liver enzymes. Of course, liver enzymes reduction was observed in all patients four month after surgery. This note is more researches required in this field.

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