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# The Effects of Proton Pump Inhibitors For Dispeptic Complaints In Patients With Nonalcoholic Steatohepatitis

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**ABSTRACT**

As the most common liver disease in recent years, nonalcoholic fatty liver disease (NAFLD) has gained great importance. In recent years, a close relationship with insulin resistance has been shown in the pathogenesis of NAFLD and its severe form, NASH. This study aimed to observe the effects of proton pump inhibitors (PPIs) on insulin resistance and hepatosteatosis by causing hypergastrinemia.

Forty-two patients diagnosed with steatohepatitis were included in the study. Seventeen of the 42 patients were followed up with dietary therapy alone, and 25 were followed up with diet+PPI for 2 months due to accompanying dyspeptic complaints. Biochemical and anthropometric measurements of the patients were made before and after the treatment.

Levels of the following parameters decreased significantly after treatment in cases followed only with diet: total cholesterol (p=0.009), low-density lipoprotein (LDL) (p=0.007), weight (p=0.004), waist circumference (p=0.006), and body mass index (BMI) (p=0.026). Whereas, there was a significant decrease in the levels of alanine transaminase (ALT) (p=0.005), aspartate transaminase (AST) (p=0.009), total cholesterol (p=0.020), low-density lipoprotein (LDL) (p=0.031), and waist circumference (p=0.008) after treatment with diet+PPI. After two months, the increase in the mean insulin resistance levels (HOMA-IR) in the diet group was significantly higher than the increase of mean HOMA-IR levels in the diet+PPI group (p=0.02). In conclusion, a significant improvement in liver enzymes was observed in patients with Nonalcoholic steatohepatitis with 2 months of pantoprazole treatment added to dietary management.

**Keywords:** Nonalcoholic steatohepatitis, Proton pump inhibitors, Insulin resistance

## Introduction

Nonalcoholic steatohepatitis (NASH) was first described in 1980 by Ludwing et al. by observing liver biopsy findings of nonalcoholic patients being the same as those in alcoholic hepatitis (1). NASH is currently seen as the most common cause of asymptomatic liver enzyme elevation. NASH is a metabolic syndrome characterized by chronic liver disease with mostly obesity and insulin resistance and macrovesicular fat accumulation in the liver without alcohol intake (2). The histological spectrum of liver disease can range from fatty changes alone to steatohepatitis, cirrhosis, and liver failure. The most common illnesses associated with NASH are obesity, impaired glucose tolerance, type 2 diabetes, and hyperlipidemia (3). Although the pathogenesis of NASH is not known precisely, it has been observed that these individuals have both an increase in insulin levels and insulin resistance (2). The presence of insulin resistance also causes hepatotoxicity with the rise of serum fatty acids and free oxygen radicals (4). It is thought that drugs that increase insulin sensitivity may be effective in treating NASH (5). In recent studies, PPIs, which are frequently preferred in treating patients with dyspeptic complaints, reduce gastric acid on the one hand and increase gastrin secretion, which has an incretin effect on pancreatic beta-cells (6). Gastrin promotes beta-cell differentiation in the pancreas, potentially increasing beta cell regeneration while reducing apoptosis (7). Our study aimed to observe the changes in steatohepatitis in patients with NASH who were given PPI due to dyspeptic complaints.

## Materials and Methods

Adult women and men over 18 years old who

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applied to Van YYU Medical Faculty Internal Medicine and subspecialty outpatient clinics for steatohepatitis were included in the study. For the diagnosis of steatohepatitis, the presence of an increase in liver function tests (AST, ALT) together with an increased fatty liver based on ultrasonographic examination was observed in patients who did not drink alcohol. Among the patients, those who have acute or chronic viral hepatitis, autoimmune hepatitis, congenital hepatitis, osteoporosis, kidney disease, malignancy, and those who have used statins, glucocorticoids, alcohol, vitamin supplements, $H_2$ receptor blockers, bismuth salts, proton pump inhibitors, and antibiotics in the last 3 months were excluded. Patients who did not have accompanying dyspeptic complaints deemed suitable for diet therapy and those given PPI and diet therapy for dyspeptic complaints were re-evaluated after 2 months of treatment. Among PPIs, pantoprazole, which is fully metabolized in the liver and has minimal potential for drug interactions, was preferred. Without interfering with the treatment protocol and indication of the patients, laboratory values, such as fasting blood glucose, C-peptide, insulin, AST, ALT, ALP, GGT, total cholesterol, LDL, HDL, Triglyceride, HOMA-IR, weight, and waist circumference were measured, and BMI was calculated before and 2 months after the treatment. The Abbott Architect i4000 hormone device (Abbott Laboratories, IL, ISA) was used in the study for biochemical analyses.

**Statistical Analysis:** Normal distribution of the continuous study variables was checked with the Shapiro-Wilk's test ($n<50$) and Skewness-Kurtosis values; parametric tests were used because the assumptions were met. Descriptive statistics for continuous variables were expressed as mean and standard deviation. The Independent Samples T-test was used to compare measurements between groups. In the calculations, the statistical significance level was taken as 5%, and the SPSS (IBM SPSS for Windows, Ver.24) software was used for statistical analysis.

## Results

Laboratory values such as fasting blood glucose, C-peptide, insulin, AST, ALT, ALP, GGT, total cholesterol, LDL, HDL, triglyceride, HOMA-IR and weight, waist circumference, and BMIs were measured in 42 patients before and after treatment, who were admitted to the Internal Medicine and subspecialty outpatient clinics of our hospital with steatohepatitis and had an indication for diet or diet+PPI for 2 months. While 15 of the patients were receiving only diet therapy, 27 received diet+PPI treatment. The GGT levels could be measured in 42 patients before treatment and 41 patients after treatment. The fasting insulin before treatment and the percentage after treatment could be measured in 41 participants. There was no significant difference between all baseline treatment parameters in both the diet and diet+PPI groups, indicating that the groups were formed homogeneously (Table 1).

**Pre and Post Treatment Values of Patients on Diet:** Of the 17 patients in the diet group, 8 were male, and 9 were female. Their mean age was 38.29 (17-52). The decreases in weight, waist circumference, total cholesterol, and BMI after treatment were significant (p-values 0.004, 0.006, 0.09, and 0.026, respectively). Biochemical parameters of the 17 diet patients included in our study before and after treatment and averages of weight measurements and p values are given in Table 2.

**Pre and Post Treatment Values in Patients Using Diet and Proton Pump Inhibitors:** Of the 25 diet and proton pump patients, there were 11 males and 14 females. Their mean age was 41.76 (25-58) years. After the treatment, the decrease in waist circumference, ALT, AST, total cholesterol, and LDL values were significant (p-values 0.008, 0.005, 0.009, 0.020, and 0.031, respectively). Pre-treatment and post-treatment biochemical parameters, averages of weight measurements, and p-values of the 25 patients who received diet+PPI are given in Table 3.

**Comparison of The Differences Between The Pre-Treatment and Post-Treatment Laboratory Values of Patients Under Diet and Diet + PPI Treatment:** The difference in insulin changes between the diet group and the diet+PPI group was significant, and the increase in insulin in the diet group was higher than the increase in insulin in the diet+PPI group ($p=0.041$). The difference in C- peptide change between the diet group and the diet+PPI group was significant. C-peptide increased in the diet

group, while C- peptide decreased in the diet+PPI group ($p=0.024$). The HOMA-IR change between the diet group and the diet+PPI group was significant. The increase in HOMA-IR in the diet group was greater than the increase in the diet+PPI group ($p=0.002$). Although it was notable that the patients in the diet group lost weight, HOMA IR levels were increased.

**Tablo 1.** Descriptive Statistics and Comparisons of The Differences of Patients Under Diet Group and Diet+PPI Group

| Parameters | Diet<br>Mean (Min-Max) | Diet+PPI<br>Mean (Min-Max) | p |
|---|---|---|---|
| Weight (kg) | 84.81 (56.1-114) | 81.42 (49.4-113) | 0.484 |
| Waist Circumference(cm) | 107.59 (80-127) | 108.16 (90-144) | 0.889 |
| Fasting Blood Glucose (mg/dL) | 118.41 (67-457) | 94.28 (72-135) | 0.201 |
| Fasting Insulin (μU/mL) | 9.69 (0.8-19.3) | 12.78 (5.1-58) | 0.266 |
| C-Peptide(ng/mL) | 2.23 (0.05-3.5) | 3.42 (1.4-15) | 0.116 |
| ALT(IU/L) | 70.41 (33-106) | 73.2 (34-162) | 0.773 |
| AST(IU/L) | 44.41 (25-87) | 46.32 (22-108) | 0.762 |
| GGT(IU/L) | 89.84 (35.4-381) | 79.01 (3.8-275) | 0.664 |
| ALP (IU/L) | 232.53 (126-604) | 246.32 (35-1101) | 0.795 |
| Total Cholesterol(mg/dL) | 224.88 (160-316) | 205.24 (33-310) | 0.266 |
| LDL(mg/dL) | 135.24 (77-220) | 133 (40-218) | 0.37 |
| HDL(mg/dL) | 43.88 (29-65) | 41.72 (22-95) | 0.637 |
| Triglyceride(mg/dL) | 230.82 (72-562) | 183.44 (81-362) | 0.154 |
| BMI(kg/m$^2$) | 29.58 (19.3-33.6) | 28.9 (19.6-43.3) | 0.683 |
| HOMA-IR | 2.41 (0.78-5.38) | 3.00 (0.92-12.73) | 0.5 |

AST: Aspartate transaminase, ALT: Alanine transaminase, GGT: γ-Glutamyltransferase, ALP: Alkaline phosphatase, HDL: High -Density Lipoprotein BMI: Body Mass Index, HOMA-IR: HOMA for insulin resistance, LDL: Low-Density Lipoprotein

**Table 2.** Descriptive Statistics and Comparisons of The Differences Before and After Treatment In The Diet Group

| Parameters | Before treatment<br>(Mean±SD) | After treatment<br>(Mean±SD) | p |
|---|---|---|---|
| Weight(kg) | 84.81±13.78 | 83.05±13.33 | 0.004 |
| Waist Circumference(cm) | 107.59±10.58 | 102.88±10.48 | 0.006 |
| Fasting Blood Glucose(mg/dL) | 118.41±91.29 | 119.53±87.09 | .839 |
| Fasting Insulin(μU/mL) | 9.69±4.06 | 18.75±24.20 | .148 |
| C-Peptide(ng/mL) | 2.23±0.79 | 2.38±0.80 | .166 |
| ALT(IU/L) | 70.41±21.69 | 59.82±30.43 | .173 |
| AST(IU/L) | 44.41±15.19 | 35.82±12.28 | .070 |
| GGT(IU/L) | 89.84±83.87 | 55.81±37.46 | .108 |
| ALP(lU/L) | 232.53±117.11 | 223.59±111.49 | .102 |
| Total Cholesterol(mg/dL) | 224.88±41.53 | 206.88±41.44 | .009 |
| LDL(mg/dL) | 135.24±36.95 | 124.41±36.95 | .107 |
| HDL(mg/dL) | 43.88±12.12 | 42.00±10.49 | .311 |
| Triglyceride(mg/dL) | 230.82±130.68 | 200.76±94.63 | .291 |
| BMI(kg/m$^2$) | 29.58±4.68 | 28.96±4.23 | .026 |
| HOMA_IR | 2.4106±1.11569 | 6.2704±9.86026 | 0.137 |

AST: Aspartate transaminase, ALT: Alanine transaminase, GGT: γ-Glutamyltransferase, ALP: Alkaline phosphatase, HDL: High -Density Lipoprotein BMI: Body Mass İndex, HOMA-IR: HOMA for insulin resistance, LDL: Low-Density Lipoprotein

**Table 3.** Descriptive Statistics and Comparisons of The Differences Before and After Treatment In The Patient Group Using Diet+PPI

| Parameters | Before treatment (Mean±SD) | After treatment (Mean±SD) | p |
|---|---|---|---|
| Weight (kg) | 81.424±16.1150 | 80.804±16.8932 | 0.315 |
| Waist Circumference(cm) | 108.16±14.320 | 105.84±14.159 | 0.008 |
| Fasting Blood Glucose(mg/dL) | 94.28±16.074 | 97.24±18.277 | 0.324 |
| Fasting Insulin (µU/mL) | 12.776±10.7250 | 12.949±7.6133 | 0.906 |
| C-Peptide (ng/mL) | 3.4200±2.98454 | 2.8400±1.50776 | 0.191 |
| ALT(IU/L) | 73.20±35.294 | 51.68±27.735 | 0.005 |
| AST(IU/L) | 46.32±22.505 | 35.88±17.910 | 0.009 |
| GGT(IU/L) | 79.01±72.798 | 62.68±64.852 | 0.100 |
| ALP(lU/L) | 246.32±194.511 | 211.44±81.481 | 0.420 |
| Total Cholesterol(mg/dL) | 205.24±62.952 | 186.32±53.494 | 0.020 |
| LDL(mg/dL) | 133.00±47.089 | 112.52±40.952 | 0.031 |
| HDL(mg/dL) | 41.72±15.865 | 39.92±12.186 | 0.414 |
| Triglyceride(mg/dL) | 183.44±80.752 | 178.60±87.258 | 0.784 |
| BMI( $kg/m^2$) | 28.900±5.6258 | 27.668±7.8174 | 0.258 |
| HOMA_IR | 3.0025±2.45664 | 3.2062±2.22706 | 0.516 |

FBG: Fasting Blood Glucose, AST: Aspartate transaminase, ALT: Alanine transaminase, GGT: γ-Glutamyltransferase, ALP: Alkaline phosphatase, HDL: High -Density Lipoprotein BMI: Body Mass Index, HOMA-IR: HOMA for insulin resistance, LDL: Low-Density Lipoprotein

Tis show that insulin resistance increases in the diet group despite weight loss. Besides, although the patients lost weight, AST and ALT levels did not change. Comparison of the differences between the Pre-Treatment and Post-Treatment laboratory values of patients under diet and diet PPI treatment p values are given in Table 4.

## Discussion

The increase in NASH prevalence parallels obesity and diabetes in all age groups (8). The common problem blamed in these diseases is shown as increasing insulin resistance. Insulin has direct and indirect damage to the liver. The indirect effect is increased liver fat accumulation associated with an early-onset hyperinsulinemic state. Its immediate effect is oxidative stress caused by insulin (9,10). The HOMA-IR in our study was 2.7, and the mean value of fasting insulin was 11.7, which was higher than normal. In the survey conducted by Marchesini et al. on 92 patients with NASH, 43% of the patients were obese, and 55% had diabetes. In this study, insulin resistance was significantly associated with central obesity, not with increased BMI (11). In our study, 42% of the patients had obesity, and 33% had diabetes. There was no correlation between BMI and insulin resistance. While a statistically significant weight loss occurred in patients in the diet group (p=0.04), weight loss was not substantial in the diet+PPI group. Despite the greater weight loss in patients who received diet therapy, their fasting insulin levels were elevated. This increase in fasting insulin was more significant than the increase in insulin in the diet+PPI group (p=0.04). In parallel with the increase in fasting insulin, HOMA-IR values indicating insulin resistance of the patients in the diet group were high. Insulin resistance is one of the commonly used factors in explaining the pathogenesis of NASH. The development of insulin resistance causes an increase in free fatty acid (FFA) production in the liver and an increase in fat entry to hepatocytes from glucose that cannot be taken up by peripheral adipocytes and monocytes. In addition, insulin has a direct oxidative stress effect on the liver, and insulin achieves these effects regardless of weight (9,10). Although there was weight loss in the diet group, the possible reason for not having a significant decrease in liver enzymes was the increased insulin and insulin resistance in this group. Although there was not enough weight loss in the diet+PPI group, insulin resistance and insulin sensitivity did not change, but a statistically significant decrease was found in liver enzymes (AST and ALT) (p=0.09, p=0.05). Hypergastrinemia ocurs as a result of the decline in the gastric acid secretion of proton pump inhibitors. The study by

**Table 4.** Comparison of The Differences Between The Pre-Treatment And Post-Treatment Laboratory Values of Patients Under Diet and Diet + PPI Treatment

| Parameters | Treatment | n | Mean | Std. Deviation | p |
|---|---|---|---|---|---|
| Δ _weight(kg) | Diet | 17 | 1.7588 | 2.15582 | 0.854 |
| | Diet+PPI | 25 | 0.62 | 3.02021 | |
| Δ _ waistcircumference(cm) | Diet | 17 | 4.7059 | 6.13152 | 0.078 |
| | Diet+PPI | 25 | 2.32 | 3.99708 | |
| Δ _FBG(mg/dL) | Diet | 17 | -1.1176 | 22.31838 | 0.404 |
| | Diet+PPI | 25 | -2.96 | 14.70397 | |
| Δ _Insulin(μU/mL) | Diet | 17 | -9.0529 | 24.54448 | 0.041 |
| | Diet+PPI | 25 | -0.1728 | 7.25238 | |
| Δ _c-peptide(ng/mL) | Diet | 17 | -0.1512 | 0.42956 | 0.024 |
| | Diet+PPI | 25 | 0.58 | 2.15735 | |
| Δ_ALT(IU/L) | Diet | 17 | 10.5882 | 30.57176 | 0.936 |
| | Diet+PPI | 25 | 21.52 | 35.04773 | |
| Δ_AST(IU/L) | Diet | 17 | 8.5882 | 18.27245 | 0.469 |
| | Diet+PPI | 25 | 10.44 | 18.40534 | |
| Δ _GGT( IU/L) | Diet | 16 | 31.975 | 74.92841 | 0.357 |
| | Diet+PPI | 25 | 16.328 | 47.77278 | |
| Δ _ALP (IU/L) | Diet | 17 | 8.9412 | 21.26755 | 0.215 |
| | Diet+PPI | 25 | 24.88 | 151.47478 | |
| Δ _Total_Cholesterol | Diet | 17 | 18 | 25.16198 | 0.177 |
| | Diet+PPI | 25 | 18.92 | 38.02951 | |
| Δ _LDL(mg/dL) | Diet | 17 | 10.8235 | 26.16351 | 0.084 |
| | Diet+PPI | 25 | 20.48 | 44.58897 | |
| Δ _HDL(mg/dL) | Diet | 17 | 1.8824 | 7.41521 | 0.713 |
| | Diet+PPI | 25 | 1.8 | 10.83205 | |
| Δ _TG(mg/dL) | Diet | 17 | 30.0588 | 113.59273 | 0.681 |
| | Diet+PPI | 25 | 4.84 | 87.42982 | |
| Δ _BMI( kg/m$^2$) | Diet | 17 | 0.6235 | 1.05032 | 0.247 |
| | Diet+PPI | 25 | 1.232 | 5.26361 | |
| Δ _HOMA_IR | Diet | 17 | -3.8598 | 10.17009 | 0.002 |
| | Diet+PPI | 25 | -0.2036 | 1.54515 | |

FBG: Fasting Blood Glucose, AST: Aspartate transaminase, ALT: Alanine transaminase, GGT: γ-Glutamyltransferase, ALP: Alkaline phosphatase, HDL: High -Density Lipoprotein, BMI: Body Mass Index, HOMA-IR: HOMA for insulin resistance, LDL: Low-Density Lipoprotein, TG: Triglyceride

Ahmet Gürbüz and his friends found a 51% increase in the amount of gastrin, using lansoprazole for 1 month (12). The incretin-mimetic effect of gastrin has been shown in previous studies. It has been demonstrated that increased gastrin in PPI use can delay pancreatic beta-cell destruction with its insulin-releasing and trophic effect on the pancreas and can cause beta-cell neogenesis by trans-differentiation from pancreatic ductus cells (13,14). In our study, we could not show an increase in insulin secretion in patients using PPIs. However, although there was an increase in insulin resistance in the patient group we followed up with diet only, there was no increase in insulin resistance in our patients who used diet+PPI. We think that the decrease we found in liver enzymes is related to the increase in insulin sensitivity. We conclude that this effect is likely to be achieved by gastrin via stimulating functional improvement and neogenesis in the beta cells of the pancreas. More controlled studies are needed to better understand these responses.

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