Evaluation of the Relationship between Insulin Resistance and HBV DNA Level in Patients with HBeAg-negative Chronic HBV Infection (Natural Course Phase 3)

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ABSTRACT

Background and aims: Chronic hepatitis B (CHB) infection is an important cause of morbidity and mortality worldwide with an increased risk of liver failure, cirrhosis, and hepatocellular carcinoma. Hepatitis B virus (HBV) DNA level, the marker of viral load in the host, is a parameter affected by host factors. In this study, we investigated the relationship between HBV DNA level and insulin resistance as a host factor.

Methods: In this study, 146 patients diagnosed with “HBeAg-negative chronic HBV infection” (natural course phase 3, inactive carrier) according to the European Association for the Study of the Liver (EASL) 2017 guidelines were retrospectively analyzed and demographic, anthropometric, histopathological, radiological and laboratory data of the patients were recorded. Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) levels of the patients were calculated, and according to the value, the patients were divided into two groups as insulin resistant and non-insulin resistant. All parameters, including HBV DNA, were evaluated and compared between the two groups.

Results: 77 patients (52.7%) were insulin resistant with a HOMA-IR value of 2.5 or more. The remaining 69 patients (47.3%) whose HOMA-IR value less than 2.5 were non-insulin resistant. The median HBV DNA was 410 IU in the insulin-resistant group and 350 IU in the other group, and there was no statistical significance between the two groups (p = 0.537). HBV DNA level was only positive correlated with HBsAg level and negatively correlated with anti-HBs level and age (p < 0.005). Compared to the non-insulin resistant group, body mass index (BMI), presence of hepatosteatosis on ultrasonography (USG), fasting blood sugar, fasting insulin, total protein, gamma glutamyl transferase (GGT), triglyceride (TG), very-low-density lipoprotein (VLDL), uric acid level, triglyceride/high-density lipoprotein (HDL) ratio were significantly higher and HDL levels were significantly lower in the insulin-resistant group (p < 0.005). GGT levels and TG/HDL ratio were found to be higher in patients with hepatosteatosis on ultrasonography than in patients without hepatosteatosis (p < 0.005). TG/HDL ratio was found to be an independent factor in predicting insulin resistance and every 1 unit increase of this ratio increases the risk of developing insulin resistance 2.1 times.

Conclusion: In this study, no significant relationship was found between insulin resistance and HBV DNA levels in chronic inactive HBV carriers. In addition, insulin resistance was observed more frequently in these patients compared to the general population, and insulin resistance was found to be associated with high BMI, hepatosteatosis rate, VLDL, TG, GGT, total protein, uric acid, TG/HDL ratio, and low HDL. TG/HDL ratio was found to be successful in predicting insulin resistance.

Keywords: HBV DNA, Hepatitis B, Homeostasis model assessment, Insulin resistance, Triglyceride/HDL ratio, Viral load.

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INTRODUCTION

HBV Infection is an important cause of morbidity and mortality, affecting 240 million people worldwide, causing liver failure, cirrhosis, and hepatocellular carcinoma (HCC).¹,² CHB infection is a dynamic process, and consists of 5 different phases, according to Hepatitis B e antigen (HbeAg). HBV DNA, alanine aminotransferase (ALT) levels and the degree of inflammation in the liver. “HBeAg Negative Chronic HBV Infection” (phase 3, inactive carrier phase) is one of the five phases characterized by the presence of antibodies to HBeAg, HBV DNA level less than 2000 IU/ml, and normal ALT values. In the current phase, patients rarely have HBV levels of more than 2000 IU/ml but less than 20,000 IU/ml. When liver biopsy is obtained, necroinflammatory activity and fibrosis are absent or minimally detected.

In addition to being an important indicator of separating CHB phases, HBV DNA level, the marker of the viral load in the host, is also important by creating an indication of antiviral therapy above a certain level, by participating in cirrhosis pathogenesis and HCC carcinogenesis. HBV DNA-level measurement is recommended for routine monitoring during the follow-up of CHB patients and the level is affected by many host factors.³,⁴

Insulin resistance can be defined as a subnormal biological response to normal insulin concentrations. The underlying causes

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are generally obesity, stress-related contraregulatory hormone imbalance, lipodystrophy, and various drugs. It is frequently accompanied by diabetes, metabolic syndrome, and nonalcoholic fatty liver disease (NAFLD) in which insulin resistance is the key mechanism and found to be positive above 75%. Insulin resistance can be practically measured with the HOMA-IR score.

The relationship between chronic hepatitis C infection and insulin resistance has been clearly demonstrated and insulin resistance has been identified as a risk factor in liver fibrosis, reduction of the permanent response in interferon alpha-based treatment, and HCC development. Unfortunately, the relationship between CHB and insulin resistance has not been revealed so clearly. The aim of this study was to investigate the relationship between insulin resistance as a host factor and the HBV DNA level in phase 3 CHB patients. In addition to HBV DNA levels, anthropometric and demographic values, liver function tests, cholestasis and coagulation parameters, lipid panel, AFP levels, other viral markers, and radiological and histopathological findings were also evaluated.

**METHODS**

**Patients and Study Design**

Our research was a single-center retrospective cross-sectional study. The study was conducted at Ankara University School of Medicine, Gastroenterology Outpatient Clinic. We retrospectively reviewed all the natural course phase 3 patients between June 1, 2017, and October 01, 2019. Only patients over 18 years old and meet “HBeAg Negative Chronic HBV Infection” criteria according to EASL 2017 guidelines (patients with antibodies to HBeAg, HBV DNA level less than 2000 IU/ml and normal ALT value, or normal ALT value, HBV DNA level 2000 to 20,000 IU/ml, no or minimal necroinflammatory activity and fibrosis in the liver), with regular control and with laboratory data, especially HBV DNA, fasting glucose and insulin on admission were included. Patients under the age of 18, whose laboratory data were not available; who used antiviral therapy or drugs that will affect insulin resistance (oral antidiabetic, insulin, steroids, etc.) or more than 20 grams of alcohol daily; with cirrhosis (histological diagnosis or patients with characteristic cirrhosis findings in physical examination, laboratory, or ultrasonography), active malignancy, simultaneous antibody to hepatitis C virus and/or antibody to human immunodeficiency virus positivity, stage 3 and above chronic kidney disease (glomerular filtration rate <60), Wilson, hereditary hemochromatosis, biopsy-proven autoimmune hepatitis, and pregnant women were excluded. Following these criteria, 146 participants were enrolled. For each patient, retrospectively collected data, including patient demographics and clinical and laboratory variables, were abstracted from the medical records at baseline.

Parameters evaluated within the scope of these examinations in patients are age, gender, height, body weight, liver biopsy (if performed), hepatobiliary ultrasonography, fasting blood glucose, fasting insulin, uric acid, total protein, albumin, total and direct bilirubin, aspartate aminotransferase (AST), ALT, GGT, alkaline phosphatase (ALP), lactate dehydrogenase LDH, lipid profile (total cholesterol, LDL, HDL, VLDL, TG, and TG/HDL ratio), HBV DNA level, hepatitis B surface antigen (HBsAg), antibody to HBsAg (Anti-HBs), HBeAg, antibody to HBeAg (Anti-HBe), antibody to hepatitis D virus (Anti-HDV), alfa-feto protein (AFP), and international normalized ratio (INR). BMI of patients was calculated by dividing body weight in kilograms by the square of height in meters. Insulin resistance was calculated with the HOMA-IR score, fasting blood glucose value in mg/dl was multiplied by the fasting insulin value in uIU/ml, and the resulting value was divided by the constant 405. HOMA-IR scores of 2.5 and above were evaluated as positive for insulin resistance, values below 2.5 were evaluated as negative for insulin resistance.

The patients were divided into two groups as those with and without insulin resistance and these groups were evaluated as study groups. It was investigated whether there was a significant difference between the two groups in terms of the HBV DNA level and the other parameters mentioned above and also whether there was a correlation between HBV DNA level and insulin resistance or not.

**Statistical Analyses**

The research data were uploaded to the computer and evaluated via SPSS (Statistical Package for Social Sciences) for Windows 22.0 (SPSS Inc, Chicago, IL). Descriptive statistics are presented as median (IQR), frequency distribution, and percentage. In the evaluation of categorical variables, Pearson chi-squared test and Fisher’s final test were used. The suitability of variables to normal distribution was examined using visual (histogram and probability graphs) and analytical (Kolmogorov-Smirnov test) methods. Mann-Whitney U test was used as a statistical method to find the statistical significance between the two independent groups for the variables that were found not to conform to the normal distribution. The relationship between the variables was evaluated with the Spearman correlation test. Correlation coefficient was evaluated as a weak relationship between 0 and 0.25, moderate relationship between 0.26 and 0.50, strong relationship between 0.51 and 0.75, and very strong relationship between 0.76 and 1.00.

In the multivariate analysis, independent predictors for predicting insulin resistance were analyzed with logistic regression analysis using the possible factors identified in previous analyses. Hosmer-Lemeshow test was used for model fitting. Statistical significance level was accepted as $p < 0.05$.

**Results**

A total of 146 patients were included in the study. The median age of the patients was 52 (41.8–57.0) and 63% were female and 37% were male. The median BMI of the patients was 27.6 (24.1–30.1) kg/m². In ultrasonographic examination, 57.2% of 138 patients had hepatosteatosis. The results of ultrasonography were 42.8% normal, 32.6% grade 1 hepatosteatosis, 22.5% grade 2 hepatosteatosis, and 2.2% grade 3 hepatosteatosis (Table 1). Insulin resistance was present in 77 (52.7%) of the patients, but not in the remaining 69 (47.3%) and these were accepted as study groups. The distribution of some descriptive and clinical features among the study groups is presented in Table 1. The BMI value of the patients with insulin resistance (median 28.2) was significantly higher than those without insulin resistance (median 26.3) ($p = 0.027$). Similarly, the percentage of hepatosteatosis in USG in insulin resistant group (66.7%) was significantly higher than those without insulin resistance (47%) ($p = 0.019$). On the other hand, there was no statistically significant difference between the study groups in terms of age, gender, and biopsy results ($p > 0.05$) (Table 1).

Fasting blood sugar, uric acid, total protein, GGT, fasting insulin, VLDL, TG, and TG/HDL ratio values of patients with insulin resistance were significantly higher and HDL value was significantly lower than in patients without insulin resistance (Table 2). There was no statistically significant difference between the study groups in terms of albumin, total bilirubin, direct bilirubin, ALT, AST, LDH, ALP, INR, AFP, total cholesterol, and LDL values ($p > 0.05$) (Table 2).
### Table 1: Distribution of some descriptive characteristics among patients with and without insulin resistance

| Characteristic                  | Total | Insulin resistance | p     |
|---------------------------------|-------|--------------------|-------|
| **Age (years), median (IQR)**   | 146   | 52 (41.8–57.0)     | 0.275 |
| **Gender, n (%)**               | 146   | 77                 | 69    |
| Male                            | 54 (37.0) | 29 (37.7)      | 25 (36.2) | 0.858 |
| Female                          | 92 (63.0) | 48 (62.3)       | 44 (63.8) |
| **BMI (kg/m²), median (IQR)**   | 134   | 27.6 (24.1–30.1)   | 0.027*|
| **Biopsy, n (%)**               | 34    | 17                 | 17    |
| Grade I, Stage 0                | 3 (8.9) | 0                 | 3 (17.6) |
| Grade II, Stage 0               | 11 (35.4) | 4 (35.2)      | 5 (29.4) |
| Grade II, Stage I               | 2 (5.9) | 2 (11.8)         | 0     |
| Grade III, Stage 0              | 7 (20.6) | 4 (23.5)     | 3 (17.6) |
| Grade III, Stage I              | 2 (5.9) | 1 (5.9)          | 1 (5.9) |
| Grade IV, Stage 0               | 6 (17.6) | 3 (17.6)      | 3 (17.6) |
| Normal                          | 1 (2.9) | 0                 | 1 (5.9) |
| Steatohepatitis                 | 2 (5.9) | 1 (5.9)          | 1 (5.9) |
| **USG, n (%)**                  | 138   | 72                 | 66    |
| Grade I HS                      | 45 (32.6) | 27 (37.5)     | 18 (27.3) | 0.101 |
| Grade II HS                     | 31 (22.5) | 18 (25.0)     | 13 (19.7) |
| Grade III HS                    | 3 (2.2) | 3 (4.2)          | 0     |
| Normal                          | 59 (42.8) | 24 (33.3)      | 35 (53.0) |
| **Hepatosteatosis on USG, n (%)** | 138 | 72               | 66  |
| Positive                        | 79 (57.2) | 48 (66.7)  | 31 (47.0) | 0.019*|
| Negative                        | 59 (42.8) | 24 (33.3)  | 35 (53.0) |

*p < 0.05; n, number of patients; %, percent of column; IQR, interquartile range (25–75%); BMI, body-mass index; USG, ultrasonography; HS, hepatosteatosis.

### Table 2: Distribution of some laboratory values among patients with and without insulin resistance

| Laboratory Value          | Total | Insulin resistance | p     |
|---------------------------|-------|--------------------|-------|
| **FBS**                   | 146   | 89 (83.8–95.0)     | <0.001**|
| **Uric acid**             | 143   | 4.9 (4.2–5.6)      | 0.006**|
| **Total protein**         | 145   | 73.3 (70.2–75.6)   | <0.001**|
| **Albumin**               | 145   | 43.7 (42.1–45.2)   | 0.088  |
| **Total bilirubin**       | 146   | 0.60 (0.48–0.78)   | 0.383  |
| **Direct bilirubin**      | 146   | 0.11 (0.09–0.15)   | 0.415  |
| **ALT**                   | 146   | 19 (15–25)         | 0.347  |
| **AST**                   | 146   | 20 (18–23)         | 0.302  |
| **GGT**                   | 146   | 18 (14–25)         | 0.002**|
| **LDH**                   | 146   | 183 (160–209)      | 0.248  |
| **ALP**                   | 146   | 73 (62–86)         | 0.163  |
| **Fasting insulin**       | 146   | 11.6 (8.6–15.7)    | <0.001**|
| **INR**                   | 143   | 1.01 (0.97–1.05)   | 0.529  |
| **AFP**                   | 146   | 2.75 (1.72–4.77)   | 0.122  |
| **Total cholesterol**     | 131   | 206 (174–237)      | 0.155  |
| **HDL**                   | 131   | 50 (43–58)         | 0.004**|
| **LDL**                   | 131   | 130 (106–153)      | 0.117  |
| **VLDL**                  | 131   | 24 (15–33)         | 0.002**|
| **TG**                    | 131   | 118 (77–160)       | 0.001**|
| **TG/HDL**                | 131   | 2.32 (1.45–3.59)   | <0.001**|

*p < 0.05; **p < 0.01; n, number of patients; IQR, interquartile range (25–75%); FBS, fasting blood sugar; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; INR, international normalized ratio; AFP, alfa fetoprotein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein; TG, triglycerides.
The median of TG/HDL of the patients with insulin resistance was 2.74 (1.65–4.25), the median of TG/HDL ratio of the patients without insulin resistance was 1.80 (1.05–3.07), and the difference was statistically significant ($p < 0.001$). The median of TG/HDL ratio and GGT of patients with hepatosteatosis in USG is 2.88 (IQR: 1.70–3.80) and 20 (15–29), respectively. The median of TG/HDL ratio and GGT of patients without hepatosteatosis in USG is 1.69 (IQR: 1.05–3.07) and 17 (13–21), respectively. Patients with hepatosteatosis in USG had a significantly higher TG/HDL ratio and GGT ($p = 0.001$, $p = 0.009$, respectively) (Fig. 1).

The median value of HBsAg was 4044 (1094–4794), anti-HBs was 1.22 (0.28–3.49) and HBV-DNA 366 (43–1400) in the study. Anti-HDV positivity was detected in 2.1% of the patients (3 patients). HBsAg, Anti-HBs, HBeAg, Anti-HBe values, anti-HDV and HBV-DNA positivity, and HBV-DNA values were not significant different between the study groups ($p > 0.05$) (Table 3).

The independent effect of some possible predictors on predicting insulin resistance was evaluated by multivariate logistic regression analysis. The presence of insulin resistance was included as a dependent variable; hepatosteatosis in USG, BMI, uric acid, total protein, GGT, VLDL, and TG/HDL ratio were included as independent variables. It was determined that TG/HDL ratio had an independent effect on predicting insulin resistance ($p = 0.043$) and not all other variables ($p > 0.05$). A unit increase in TG/HDL ratio increased the risk of developing insulin resistance 2.1 times.

![GGT value according to hepatosteatosis status in USG](image)

**Fig. 1:** GGT value according to hepatosteatosis status in USG

A positive correlation was found between HOMA-IR score and BMI ($r = 0.32$), uric acid ($r = 0.26$), GGT ($r = 0.32$), VLDL ($r = 0.33$), TG ($r = 0.35$), TG/HDL ($r = 0.36$), ALT ($r = 0.21$), ALP ($r = 0.20$), total cholesterol ($r = 0.20$), and LDL ($r = 0.21$). A negative correlation was found between the HOMA-IR score and HDL ($r = −0.20$), AFP ($r = −0.20$) ($p < 0.05$). No statistically significant relationship was found between the HOMA-IR value and age and all other laboratory parameters ($p > 0.05$).

A statistically significant positive correlation between the HBV-DNA value and HBsAg ($r = 0.45$) and a negative correlation between age ($r = −0.25$) and Anti-HBs ($r = −0.17$) were found in the study ($p < 0.05$). There was no statistically significant relationship between the HBV-DNA value and BMI value and all other laboratory parameters ($p > 0.05$) (Fig. 2).

**Discussion**

This retrospective study revealed that there is no significant relationship between HBV DNA value and insulin resistance status in patients with HBeAg negative Chronic HBV Infection. Our study is important because it examines the relationship of insulin resistance with various parameters in a specific patient group, inactive carriers.

There are different values in studies for the prevalence of insulin resistance. In a study from Thai, it was found to be 25.1% in men and 21.5% in women. Although there are no data currently for Turkey, in our study, the frequency of insulin resistance in inactive HBV carriers was found to be 52.7% and this was higher than in the general population.

In their study with 7880 nondiabetic patients, Lee et al. determined that CHB patients have higher HOMA-IR values and CHB is associated with insulin resistance. The result, which is similar to our study, is based on the theory that HBX protein may play a prominent role in hepatic steatosis and inflammation by disrupting the insulin signal pathway. On the other hand, in their meta-analysis, Wang et al. reported that metabolic syndrome was observed less frequently in HBV patients. Therefore, in contrast to chronic HCV infection, the relationship between HBV and insulin resistance is still unclear and appears to be elucidated by studies involving pathogenesis. It is known that coexistence of CHB and metabolic syndrome increases the development of HCC and cirrhosis. For this reason and according to our study, it seems appropriate to evaluate patients with CHB in terms of insulin resistance or metabolic syndrome components.

In our study, hepatosteatosis was detected by ultrasound in 57.2% of the patients. Among patients with insulin resistance,
hepatosteatosis rate was higher than those without insulin resistance. Similarly, in the study consisting of CHB patients performed by Yun et al., it was reported that steatosis was detected in 51.2% of the patients and HOMA-IR, TG, and insulin levels were high in the group with steatosis, and it was emphasized that HOMA-IR and TG levels were independent risk factors for steatosis. With all these results, caution should be exercised for NAFLD in inactive CHB carriers with high HOMA-IR values or clinically considered insulin resistance.

Insulin resistance was calculated with the HOMA-IR score, which is widely used in clinical practice and studies. HOMA-IR score is known to be correlated with the gold standard method hyperinsulinemic euglycemic clamp test. In our study, we found that some laboratory findings and BMI are associated with insulin resistance. The differences in GGT, uric acid, and lipid profile were found to be compatible with the literature. In the study of Nejatinamini et al., it was found that those with metabolic syndrome had high uric acid levels and a 1 mg/dl increase caused a 2-fold increase in the risk of metabolic syndrome. The underlying mechanisms may be that uric acid decreases the endothelial nitric oxide level and disrupts perfusion or the hyperinsulinemic condition disrupts uric acid excretion with tubulopathy. In a study with CHB patients, it was stated that AST, ALP, and GGT increased in correlation with the HOMA-IR score and that ALP and GGT were found higher in patients with NAFLD. Also, in this study, similar to our findings, AST, ALT, GGT, and HOMA-IR correlated with the degree of hepatosteatosis. The reason for this is that GGT is an indicator of excess fat storage in the liver and excess fat tissue in the liver leads to hepatic insulin resistance and then systemic insulin resistance. Another mechanism is that GGT plays an important role in oxidation due to its participation in glutathione metabolism. High GGT level is an indirect indicator of the cell’s need for antioxidation. Therefore, the high BMI index in the group with insulin resistance is also compatible with the current literature.

High TG and low HDL are among the diagnostic criteria of insulin resistance syndrome. In our study, TG/HDL ratio is higher both in the group with insulin resistance and in the patients with hepatosteatosis. We proved that 1 unit increase in TG/HDL ratio increased the insulin resistance risk 2.1 times. In many studies, including the NHANES 2019, it was observed that the TG/HDL ratio is a reproducible, strong and inexpensive method which correlates with the HOMA-IR score in demonstrating insulin resistance; however, it seems reasonable to determine the cutoff value according to ethnicity. TG/HDL ratio is associated with

![Fig. 2: Relationship between HBV-DNA and age, HBsAg, anti-HBs](image_url)
increased cardiovascular risk because it reveals the atherogenic and protective lipid ratio and is parallel to the small dense LDL level known as atherogenic lipoprotein. To our knowledge, we are the first study in the literature to examine TG/HDL in inactive CHB patients. In our study, the median of HBV DNA was 366 IU and there was no significant difference between the groups. Although there are contradictory results in the literature, there is no relationship between insulin resistance, metabolic syndrome or hepatosteatosis, and HBV DNA level, as presented in our study. In the study of Pais et al., steatosis was reported to be unrelated to HBV DNA level. In a study conducted by Dai et al., it was found that 44.2% of CHB patients had insulin resistance and CHB patients with insulin resistance had higher BMI and ALT values but there is no difference in HBV DNA levels. In the study of Wong et al., in accordance with our study, it was proved that HBV DNA level did not have a significant relationship with NAFLD in 91 CHB patients. However, in a study by Janicko et al., a significantly high HBV DNA level was found in individuals with metabolic syndrome, but the number of patients was limited to 55. In the study conducted by Jarcuska et al., HBV DNA was found to be higher in HBV patients with metabolic syndrome compared to the group without the metabolic syndrome. In pathophysiology, it has been shown that factors that activate the gene phosphoenoxypruvate carboxykinase and HBV promoter complex are similar. At the same time, hepatic glucose production is increased and HBV gene replication increases due to high resistin and low adiponectin levels in insulin resistance. In contrast, in a Chinese study with HBsAg negative CHB patients, it was found that patients with histology-proven steatosis had lower HBV DNA values. They cited the study published in 1997 showing that insulin suppresses HBV gene expression in cell cultures as evidence of this situation. In summary, the relationship between HBV DNA and insulin resistance appears to be contradictory. This may be due to the fact that viremia appears in waves in HBsAg negative patients and the measurements made during this time are misleading to see the whole picture.

When the relationship of parameters with HBV DNA was examined, a positive correlation with HBsAg and negative correlation with anti-HBs and age was found. The relationship between HBV DNA and HBsAg is compatible with the literature. In addition, it is stated that the loss of HBsAg is also a treatment target, such as the suppression of HBV DNA to undetectable levels. Although the HBsAg measurement we used in the study is not quantitative, currently studies on quantitative measurements are also being conducted. The decrease in HBV DNA level with age may be related to 1 to 3% spontaneous HBsAg loss or seroconversion annually seen in phase 3 patients, and additional studies are needed for this interpretation.

Our study has some limitations. The most important one is measuring the insulin resistance with the one-time HOMA-IR method which can be affected by short-term exercise and nutrition status. Instead of diagnosing hepatosteatosis by ultrasonography, which is a subjective method, histological evaluation could be more scientifically reliable. The study was planned retrospectively cross-sectional and if it was prospective, the cause–effect relationship could be examined more clearly.

The study has several strengths. It is remarkable to study insulin resistance with a group that has not undergone antiviral treatment that will primarily affect the HBV DNA level, thereby enabling a more reliable examination of the relationship. It is also important to examine the TG/HDL ratio in patients with CHB. To the best of our knowledge, it is also the only study in the literature that examines only inactive HBV carrier patients by grouping them according to their insulin resistance status and comparing their various parameters including anthropometric, radiologic, laboratory, and viral measurements.

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