# Association of Hepatitis B Virus Serological Markers with Glycemic Control and Diabetes Duration in Type 1 and Type 2 Diabetes Patients in the Najaf Government

**Baneen Abdul Hadi Jalaout[1] and Saif Jabbar Yasir[2]**

[1] MSc in Medical Microbiology, Faculty of Medicine, University of Kufa, Najaf, Iraq. Email: baneena.alhamdani@student.uokufa.edu.iq.

[2] Ph. D. in Medical Microbiology, Faculty of Medicine, University of Kufa, Najaf, Iraq. Email: saif.alshehmani@uokufa.edu.iq.

**Corresponding Author Email: baneena.alhamdani@student.uokufa.edu.iq**

***Abstract :***

**Background**: Diabetes mellitus (DM) and hepatitis B virus (HBV) infection are two major global health concerns. Growing evidence suggests a possible association between chronic viral infections and glucose metabolism disorders. **Objective:** To investigate the association between HBV serological markers and glycemic control, as measured by fasting blood glucose levels and the duration of diabetes, among patients with type 1 and type 2 diabetes mellitus. **Subjects and methods**: A cross-sectional study was performed from July to October 2024. The serum was taken from 200 individuals. All of the patients were tested using an ELISA technique for HBc IgG and by an immunochromatographic assay for HBsAb, HBsAg, HBcAb, HBeAg, and HBeAb. The statistical analysis approach was conducted using SPSS version 26. **Results**: HBcAb-positive diabetic patients showed significantly higher fasting blood glucose levels (P=0.044). HBcIgG was detected in 83 out of 200 patients, mainly in those with 5–15 years of diabetes duration (P = 0.049). No significant association was found between HBV markers and diabetes type.**Conclusions**: a potential link between HBV exposure and impaired glycemic control , suggesting a possible role of chronic HBVexposure in the progression of metabolic dysfunction over time This suggests that the activation of a previous HBV infection may be an underlying factor in the progression of diabetes mellitus or the development of pre-existing conditions and the relationship between HBV and glycemic markers may be independent of diabetes type.

**Keywords:** Hepatitis B virus, Diabetes mellitus, Anti-HBc IgG, Anti-HBs, ELISA

## Introduction

Hepatitis B virus has the capacity of generating various types of antigens, like core, surface, and envelope antigens, the key features of which are their immunogenicity, which can mediate an immune response **[1]**. Despite the success of immunization strategies and the reduction in HBsAg seroprevalence since 2000, the hepatitis B virus continues to be a widespread worldwide health concern due to the ongoing complications associated with chronic infection, which continue to contribute significantly to morbidity and mortality. Annually mortality rate due to cancer and liver cirrhosis is 820,000 people, demonstrating the seriousness of being infected with this hepatitis virus **[2]**. The simultaneous presence of HBV infection and diabetes mellitus represents a life-threatening situation that demands urgent attention **[3]**. Diabetes mellitus is a chronic disease characterized by an imbalance in glucose homeostasis.

The link between hepatitis B and diabetes mellitus is still a topic of contention. Studies have been conducted on the rising occurrence of HBV, but there is less evidence on its connection with diabetes patients. Diabetic patients are susceptible to viral infections because of their impaired T lymphocyte numbers, which weaken their immune system. Individuals with diabetes mellitus are at a considerably greater risk of acquiring infectious diseases, including bacterial, fungal, parasitic, and viral infections. This susceptibility is due to impaired cellular immunity and dysfunction of phagocytes caused by high blood sugar levels and reduced blood flow. Among the viruses, hepatitis B and C are the most widespread **[4]**.

There is limited information on the correlation between HBV indicators, infection conditions, and subtypes of DM. The recent study investigation of Iraqi individuals aged 18–80 years yielded several interesting findings. This study aims to investigate the relationship between hepatitis B virus (HBV) serological markers and

fasting blood glucose (FBG) levels in adult patients, aiming to explore whether HBV infection may influence glucose homeostasis and the duration of diabetes, among patients with type 1 and type 2 diabetes mellitus.

## Methods

### Methodology and data collection process

The current study is a cross-sectional research project included only Iraqi participants who were medical patients in the specialized endocrinology and diabetes center at the Al-Sader Teaching Hospital in Najaf city from July to October 2024. The study comprised 200 patients (either type 1 or type 2 only DM based on a clinical diagnosis by an endocrinologist and serological tests). The patients' data were obtained through the implementation of a questionnaire and the collection of a blood sample. The specimens were obtained by extracting approximately 10 mL of venous blood from every participant.

Blood samples were placed into a gel tube and allowed to coagulate at room temperature for thirty minutes. The serum was extracted using centrifugation and thereafter divided into 1.5-ml Eppendorf tubes. A part of the serum was immediately utilized for a fasting blood glucose test. The other part was then preserved in a refrigerator at a temperature of -80°C for immunological investigation until further examination. Enzyme-linked immunosorbent assays (ELISA) and rapid diagnostic tests are the main methods used in clinical laboratories to find HBV serological markers. A fraction of the serum was used for a human hepatitis B virus panel test (five panel kit): HBc Ab, HBs Ag, HBs Ab, HBe Ag, HBe Ab (Eugene Biotech/China), After that, an ELISA method (Sun Long Biotech, China) was used to find a qualitative HBc IgG.

The measurement of fasting plasma glucose (FPG) was conducted using an enzymatic colorimetric method and a kit available commercially from Spinreact, a company in Spain. The procedures for all tests were conducted according to the instructions outlined in the kit's manual. Before enrolling in the research study, all patients received a comprehensive briefing on the study's aims and objectives and were then given their informed consent to participate.

**Statistical analysis**

The statistical analysis in this study was conducted with Version 26 of the Statistical Package for the Social Sciences (SPSS). The relationship between categorical data was illustrated using chi square. The findings are displayed in tables and figures, accompanied by a descriptive narrative, utilizing MS Word and Excel 2016.

**Ethics Committee approval**

The ethics council of the University of Kufa's Faculty of Medicine gave its approval before starting this research project. All participants gave their consent, and the Al-Sader Teaching Hospital in the province of Najaf gave its approval.

**Limitations of this research**

Firstly, obtaining the individual's HBV vaccination history through self-reporting poses a potential risk of bias recall. Secondly, the limitation of the study is its restriction to a single center with a small sample size.

**Results**

The present study included a sample of 200 patients, who had undergone testing for HBV infection between July and October 2023, was screened to detect the

presence of HBc Ab, HBsAg, HBsAb, HBeAg, HBeAb, Hbc IgG, . Fig 1 presents an overview of the general scheme followed in this investigation. Patients who tested positive for HBsAg, and patients with inadequate clinical data were excluded. This study found that 10.5% of patients who tested negative for HBsAg, but positive for HBc IgG were also positive for HBs Ab. The study also revealed that 75.5% of patients had HBc IgG, 77% had HBc Ab, 10.5% had HBs Ab, and 16.5% had Hbe Ab.

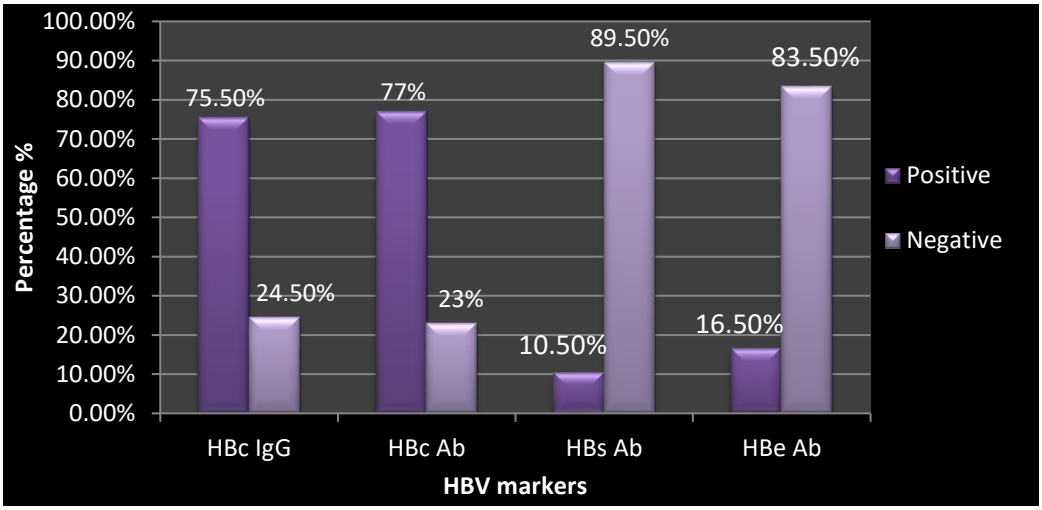


**Figure (1):** Distribution of HBV biomarkers in diabetes mellitus patients

Individuals who tested positive for HBc IgG had a substantially higher mean rank level of FBG [104.31 (mg/dl)] compared to individuals who tested negative for HBc IgG [88.77 (mg/dl)]. Additionally, the disparity was statistically nonsignificant (P = 0.102). The patients who tested positive for HBc Ab had a considerably higher average rank level of FBG [105.00 (mg/dl)] compared to the patients who tested negative for HBc Ab [85.43 mg/dl]. Simultaneously, the disparity was assessed statistically significant as demonstrated by a p-value of 0.044. As seen in table (1).

**Table (1):** Association between HBV markers and level of blood sugar

| | | positive | | Negative | | Test statistics |
|---|---|---|---|---|---|---|
| | | N | Mean Rank | N | Mean Rank | |
| **FBG (mg/dl)** | HBc IgG | 151 | 104.31 | 49 | 88.77 | P= 0.102<br>Z=-1.634- |
| | HBc Ab | 154 | 105.00 | 46 | 85.43 | P=**0.044***<br>Z=-2.012- |
| | HBs AB | 21 | 95.50 | 179 | 101.09 | P=0.676<br>Z=-0.419- |
| | HBe Ab | 33 | 86.05 | 167 | 103.36 | P=0.116<br>Z=-1.570- |
| *Probability value (level of significance <0.05) , P values were computed via the Mann-Whitney test, FBG:Fasting blood glucose | | | | | | |

**Table (2):** Association between HBV markers and diabetic duration.

| | | | HBc IgG | | HBc Ab | |
|---|---|---|---|---|---|---|
| | | | **Positive N=151** | **Negative N=49** | **Positive N=154** | **Negative N=46** |
| **Duration of diabetes / years** | Less than 5 years | Count | 45 | 6 | 45 | 6 |
| | | % | 88.2% | 11.8% | 88.2% | 11.8% |
| | From 5 to 15 years | Count | 83 | 33 | 86 | 30 |
| | | % | 71.6% | 28.4% | 74.1% | 25.9% |
| | More than 15 years | Count | 23 | 10 | 23 | 10 |
| | | % | 69.7% | 30.3% | 69.7% | 30.3% |
| P value | | | P= 0.049*<br>df= 2<br>$X^2$= 6.050 | | P= 0.076<br>df= 2<br>$X^2$= 5.165 | |
| $X^2$=chi square, p value=probability value (* level of significance at <0.05), df = degree of freedom | | | | | | |

Additionally, there was no significant link found between HBc Ab, HbsAb, Hbe Ab and diabetes duration (P > 0.05).

**Table (3):** Association between HBV markers and duration of diabetic

| | | | HBs Ab | | HBe Ab | |
|---|---|---|---|---|---|---|
| | | | Positive N=21 | Negative N=179 | Positive N=33 | Negative N=167 |
| Duration of diabetes / years | Less than 5 years | Count | 4 | 47 | 9 | 42 |
| | | % | 7.8% | 92.2% | 17.6% | 82.4% |
| | From 5 to 15 years | count | 13 | 103 | 21 | 95 |
| | | % | 11.2% | 88.8% | 18.1% | 81.9% |
| | More than 15 years | Count | 4 | 29 | 3 | 30 |
| | | % | 12.1% | 87.9% | 9.1% | 90.9% |
| P value | | | P=0.765 | | P=0.454 | |
| $X^2$=chi square, p value=probability value (level of significance at <0.05) | | | | | | |

In the present study, it was observed based on the results obtained, as well as the study of the relationship between the diagnosis of anti-HBc IgG and the investigation of HBs antibodies. The table also demonstrates that there were highly significant findings for anti-HBs antibody values among patients who tested positive for anti-HBc IgG, with a p-value of < 0.05.

**Table (4):** Comparison between anti-HBs antibody seropositivity and anti-HBc-IgG results

| | | | HBs Ab | | Total | P value |
|---|---|---|---|---|---|---|
| | | | positive | negative | | |
| HBc IgG | positive | Count | 21 | 130 | 151 | **P=0.006*** df=1 $X^2$=7.614 |
| | | % | 13.9% | 86.1% | 75.5% | |
| | Negative | Count | 0 | 49 | 49 | |
| | | % | 0.00% | 100.0% | 24.5% | |
| | Total | Count | 21 | 179 | 200 | |
| | | % | 100.0% | 100.0% | 100.0% | |

There was no significant association between type of diabetes and HBc IgG, HBc Ab, HBs Ab, or HBe AB positivity, as seen in Tab. 5.

**Table (5):** Association between HBV markers and types of diabetes

| Parameter | | Types of DM | | Total | P value |
|---|---|---|---|---|---|
| | | Type 1 DM | Type 2 DM | | |
| HBc IgG | Positive Count, % | 44(78.6%) | 107(74.3%) | 151(75.5%) | P= 0.529 df= 1 $X^2$= 0.397 |
| | Negative Count, % | 12(21.4%) | 37(25.7%) | 49(24.5%) | |
| HBc Ab | Positive Count, % | 44(78.6%) | 110(71.4%) | 154(77.0%) | P= 0.742 df= 1 $X^2$= 0.108 |
| | Negative Count, % | 12(21.4%) | 34(23.6%) | 46(23.0%) | |
| HBs Ab | Positive Count, % | 4(7.1%) | 17(11.8%) | 21(10.5%) | P= 0.334 df= 1 $X^2$= 0.933 |
| | Negative Count, % | 52(92.9%) | 127(88.2%) | 179(89.5%) | |
| HBe AB | Positive Count, % | 9(13.1%) | 24(16.7%) | 33(16.5%) | P= 0.919 df= 1 $X^2$= 0.010 |
| | Negative Count, % | 47(28.1%) | 120(83.3%) | 167(83.5%) | |
| $X^2$=chi square, p value=probability value (level of significance at <0.05) , df= degree of freedom | | | | | |

## Discussion

Serological markers of HBV infection revealed the highest rate of HBcAb (77%) among diabetes patients screened in the current study. Different with other studies were done in China **[5]** and the US **[15]**, which related the prevalence of HBcAb in diabetic patients of 62.3% and 6.35%, respectively. It is also higher, than

the percentage observed in individuals with diabetes (8.2%), as reported by **[6]**. Significantly surpasses the prevalence among patients in Brazil, which stands at just 16.8%, according to **[1]**. **[7]** found that 54.2% of individuals tested for HbcAb positivity received results, while **[8]** discovered that 15.5% of those tested showed positive results when using anti-HBc as an alternative indicator. The research was conducted in various geographical regions with various sample sizes and did not come to a compromise. Variations in HBV exposure risk, diagnostic method accuracy, study period, sociodemographic characteristics. The variations in antibody frequencies can originate from variations in the assay, sensitivity levels of the technique, sample size, or study methodology.

The present study found that the HBs Ab 21 (10.5%) result was lower than a study conducted in the US population of 19.66% **[15]** of individuals tested positive for HBsAb. In a study conducted in China, the average percentage of HBsAb positivity among diabetic patients was found to be 37% **[5]**, which is higher than the frequency in the current study. A study by **[7]** found an 8.3% positive rate among individuals with HBsAb, which is lower compared to the current study. There are variations in vaccination status, danger indicators, and the rate of HBV infection in the whole population. Due to the serologic window during the incubation period after infection, other studies have not been able to identify infected patients, and this HBs Ab positive result is from an infection that was not vaccinated.

On the other hand, a study by **[9,10]** found that in HBeAg patients greater anti-HBc levels were correlated with recurrence and hindered the attainment of HBsAg seroclearance. For individuals without HBe Ag they enter a period of dormancy marked by a robust immune reaction, where the anti HBc level mirrors the presence of HBc Ag in the liver. **[11]** revealed that this level is also correlated with the transcriptional activities of cccDNA in hepatocytes. HBeAg has been observed in serum as a sign of active viral replication in previous study **[12]**. The current investigation reveals no cases of HBeAg positivity.

Nevertheless, **[13]** indicated that the negativity of HBsAg in the blood does not certify the eradication of the virus. Likewise, **[14]** clearly demonstrated that the HBV genome has a high mutation rate because it doesn't have the proofreading function during the replication period. The inability of HBsAg to be detected in cases of occult hepatitis B, involving as well the presence of covalently closed circular

DNA (cccDNA), is commonly explained by cccDNA being hindered by epigenetic regulation pathways and/or the immune system of the host, which is believed to be its main cause. The data coming from these studies are showing that patients harboring OBI seem to have a higher chance of mutation in pre-S/S region comparing to patient with HBV chronic infection. It is likely that it will lead to a fall in the antigenicity of HBsAg detection or the production/release of HBsAg is going to be altered **[16]**.

The detection of anti-HBc antibodies has been the main diagnostic marker of occult HBV infection in most research studies on HBV reactivation **[17]**. Occult hepatitis B infection (OBI) constitutes both seropositive and seronegative categories according to the presence of serum markers that point at exposure to HBV. People who are seropositive for occult hepatitis B infection (OBI) have anti-HBC and anti-HBs antibodies in their serum specific to the core antigen or/and the surface antigen of hepatitis B, respectively. Such a form of OBI makes up around 80% of all OBI observed **[18]**. The diagnostic method that is the gold standard for identifying occult hepatitis B infection is when HBV genomes are found inside DNA extracted from hepatocytes. Instead, the HBc Ab tests may be applied as an alternative biomarker for OBI screening **[18,19]**.

The study by **[21]** categorized the HBsAg-negative/antibody HBc-positive condition as a phase in the "occult" stage of the disease progression. If HBsAg becomes undetectable, HBc antibodies are identified as the only clinical evidence of past HBV infection. Consider the HBsAg-negative/HBc-Ab-positive status like an OBI stage in the course of the natural HBV infection. Over 90% of people who are anti-HBc positive could have OBI. The "alternative" antiHBc test is considered the most acceptable and practicable marker for occult hepatitis B infection diagnosis **[23]**.

Diabetes patients who are exposed to HBV and have positive HBc Ab show higher levels of FBG, with a significant correlation ($P < 0.05$) in the present study. Furthermore, HBV infection can exacerbate diabetic patients' glucose control and raise their risk of hyperglycemia **[23,24,25]**. Hyperglycemia in diabetes mellitus is believed to induce impairment of the immunological reaction, resulting in inadequate control of the increase of invading microorganisms in individuals with diabetes. Consequently, individuals with diabetes are recognized to be more predisposed to

infections. The rising prevalence of Type 2 Diabetes (T2D) would lead to an increase in the occurrence of infectious illnesses as well as comorbidities **[26]**. The fasting plasma glucose levels of individuals with diabetes type 2 and adult-onset autoimmune diabetes were greater than those of the controls ($P < 0.05$) compared to patients with adult-onset autoimmune diabetes, but with a shorter duration of diabetes ($P < 0.01$) in those with the chin (Lu et al., 2017), which agrees with current study results.

As the virus does not show symptoms, the complications could happen when the patient has been sick for a long period **[27]**. As **[28]** found out, DM, along with HBV infection, generates liver complications including cirrhosis, hepatocellular carcinoma, and even death. From the 200 patients with a duration of diabetes ranging from 5 to 15 years, the HBc IgG was detected as positive in as many as 83 patients. The statistical evaluation resulted in a considerable result ($P = 0.049$) in the present study. In 2021, **[29]** made a study of the relationship between the duration of diabetes and the higher risk of HBV infections, and it was found out that patients who have been diabetic longer than six years had a greater risk of getting the infection compared to the ones who have normal blood glucose levels. This is consistent with the current study results. Individuals who have CHB infection or test positive for HBc Ab may be at a higher risk of developing diabetes. This association may have been influenced by many metabolic factors as well as age, according to **[30]**.

The relationship between HBV exposure and a prolonged duration of DM might be considered a cumulative danger of being exposed to the virus, likely due to the management of the condition, as DM itself does not lead to hepatitis B. The co-related existence of HBV infection and longer DM duration has been documented in the Polish study of 2002 **[31]**, the Turkish one in 2008 **[32]**, and the Nigerian one of 2016 **[33]**. In contract, the investigation done in Italy showed the absence of a correlation between the infection and the DM duration **[21]**. The results of the **[34]** study showed that there was no significant $P = 0{,}892$ relationship between the length of DM and HBV infection. That most individuals with diabetes were exposed to HBV infection within ten years of DM.

In present study show that in people with diabetes type 2, the incidence of HBV markers was not significantly greater compared to individuals with type 1 diabetes. Though DM has long been known to increase the risk of many co-

morbidities, such as chronic liver disease, a connection between HBV-related liver dysfunction and Type 2 DM development has just recently been identified. According to theories, viral hepatitis may affect important liver-regulated metabolic processes that are linked to the onset of diabetes mellitus (DM) through the interaction of inflammatory mechanisms brought on by liver infection, which in turn causes insulin resistance and glycometabolic dysfunction. According to a **[6]** meta-analysis, those who have HBV infection have a higher chance of developing diabetes than those who do not. **[35]** research revealed that among 733 diabetic patients in an Iranian population, 12.82% tested positive for HBcAb and 3.82% tested positive for HBsAg. The difference in HBcAb seroprevalence between diabetic patients and non-diabetic controls was not statistically significant (P = 0.23).

This study aligns with the findings of **[34]**, which indicated a prevalence of HBV in Type 1 (n = 1, 3.3%) and Type 2 (n = 4, 3.4%) with a non-significant p-value of 0.994. The occurrence of hepatitis B in this study may be attributed to variations in geographical location or the challenge of detecting infected individuals during the serologic window in the incubation period post-infection. This could be due to the activation of insulin resistance linked to persistent inflammatory reactions triggered by HBV infection, as well as the excess production of nitric oxide and tumor necrosis factor-α in the liver. These factors are implicated in impairing insulin metabolic action, damaging β-cells in the pancreas through HBV replication, and causing glycometabolism disorders because of hepatic damage from HBV infection **[36,30]**. **[27]** revealed that vaccination is a crucial and successful strategy for controlling and preventing it. The national immunization program has significantly reduced the disease's occurrence.

## Conclusion

The study revealed a statistically significant association between HBcAb positivity and elevated fasting blood glucose levels, indicating a potential link between HBV exposure and impaired glycemic control. Additionally, HBcIgG was significantly associated with a diabetes duration of 5 to 10 years, suggesting a possible role of chronic HBV exposure in the progression of metabolic dysfunction over time.

This suggests that the activation of a previous HBV infection may be an underlying factor in the progression of diabetes mellitus or the development of pre-existing conditions. No significant differences were observed in the distribution of HBV markers between type 1 and type 2 diabetes, indicating that the relationship between HBV and glycemic markers may be independent of diabetes type. These findings underscore the importance of considering viral comorbidities in diabetic care and metabolic monitoring.

**References**


1. Arrelias CCA, Rodrigues FB, Torquato MTDCG, Teixeira CRS, Rodrigues FFL, Zanetti ML. 2018. Prevalence of serological markers for hepatitis and potential associated factors in patients with diabetes mellitus. Rev Lat Am Enfermagem. Nov 29;26: e3085.
2. Lazarevic, I., Banko, A., Miljanovic, D., & Cupic, M. (2023). Clinical Utility of Quantitative HBV Core Antibodies for Solving Diagnostic Dilemmas. Viruses. 15(2), 373.
3. Mirzaei M, Rahmaninan M, Mirzaei M, Nadjarzadeh A, Dehghani Tafti AA. (2020) Epidemiology of diabetes mellitus, pre-diabetes, undiagnosed and uncontrolled diabetes in Central Iran: results from Yazd health study. BMC Public Health. 20(1):166.
4. Gutiérrez-Grobe Y, Ponciano-Rodríguez G, MéndezSánchez N. 2017.Viral hepatitis infection and insulin resistance: a review of the pathophysiological mechanisms. Salud Publica Mex. [Internet]. 2011 [cited Jul 10, 2017]; 53Suppl1:S46-51.
5. Lu J, Hou X, Tu H, Tang Z, Xiang Y, Bao Y, et al. (2017). Chronic hepatitis B virus infection status is more prevalent in patients with type 2 diabetes. J Diabetes Investig. 8(4):619–625.
6. Schillie SF, Xing J, Murphy TV, Hu DJ. 2012. Prevalence of hepatitis B virus infection among persons with diagnosed diabetes mellitus in the United States, 1999-2010. J Viral Hepat 19(9):674-6.
7. Ndako JA, Nwankiti OO, Olorundare JO, Ojo SKS, Okolie CE, Olatinsu O, Dojumo VT. 2021.Studies on the serological markers for hepatitis B virus infection among type 2 diabetic patients. J Clin Lab Anal. Jan;35(1): e23464.
8. Saitta, C.; Pollicino, T.; Raimondo, G. (2022). Occult Hepatitis B Virus Infection: An Update, Viruses. 14(7), 1504.

9. Chi H, Li Z, Hansen BE, Yu T, Zhang X, Sun J, et al. (2019). Serum level of antibodies against Hepatitis B core protein is Associated with Clinical Relapse after discontinuation of Nucleos(t)ide Analogue Therapy. Clinical Gastroenterology and Hepatology, 17(1):182–191.
10. Tseng, C.H.; Hsu, Y.C.; Chang, C.Y.; Tseng, T.C.; Wu, M.S.; Lin, J.T.; et al. (2018). Quantification of serum hepatitis B core antibody topredict off-entecavir relapse in patients with chronic hepatitis B. J. Formos. Med. Assoc. 117(10), 915–921.
11. Guner R, Karahocagil M, Buyukberber M, Kandemir O, Ural O, Usluer G et al. 2011.Correlation between intrahepatic hepatitis B virus cccDNA levels and other activity markers in patients with HBeAg-negative chronic hepatitis B infection. Eur J Gastroenterol Hepatol. 23(12):1185-91.
12. Zhang H, Li Q, Sun J, et al. (2011). Seroprevalence and risk factors for hepatitis b infection in an adult population in Northeast China. Int J Med Sci,8(4):321-331.
13. Caviglia, G. P., Olivero, A., Ciancio, A., Tandoi, F., Troshina, G., Rosso, C et al., (2020). Analytical and clinical evaluation of a novel assay for anti-HBc IgG measurement in serum of subjects with overt and occult HBV infection. Diagnostic Microbiology and Infectious Disease. 96(4), 114985.
14. Yan L, Zhang H, Ma H, Liu D, Li W, Kang Y, et al. (2015). Deep sequencing of hepatitis B virus basal core promoter and precore mutants in HBeAg-positive chronic hepatitis B patients. Sci Rep.5:17950. doi: 10.1038/srep17950.
15. Huang, J., Ou, Y., Lin, J., Karnchanasorn, R., Feng, W., Samoa, R., Chuang, M., & Chiu, K. C. (2015). The Impact of Hepatitis B Vaccination Status on the Risk of Diabetes, Implicating Diabetes Risk Reduction by Successful Vaccination. PLoS ONE, 10(10).
16. Zhang, H., Yang, Z., Zhang, W., Niu, Y., Li, X., Qin, L., & Su, Q. (2017). White blood cell subtypes and risk of type 2 diabetes. Journal of Diabetes and its Complications, 31(1), 31-37.
17. Cholongitas E, Haidich AB, Apostolidou-Kiouti, F, Chalevas P, Papatheodoridis GV. 2018. Hepatitis B virus reactivation in HBsAg-negative, anti-HBc-positive patients receiving immunosuppressive therapy: a systematic review. Ann Gastroenterol. Jul-Aug;31(4):480-490.

18. Raimondo G, Allain JP, Brunetto MR, Buendia MA, Chen DS, Colombo M, Craxi A, Donato F, Ferrari C, Gaeta GB, Gerlich WH, Levrero M, Locarnini S, Michalak T, Mondelli MU, Pawlotsky JM, Pollicino T, Prati D, Puoti M, Samuel D, Shouval D, Smedile A, Squadrito G, Trepo C, Villa E, Will H, Zanetti AR, Zoulim F (2008) Statements from the Taormina expert meeting on occult hepatitis B virüs infection. J Hepatol. 49:652–657
19. Raimondo, G.; Locarnini, S.; Pollicino, T.; Levrero, M.; Zoulim, F.; Lok, A.S.; et al. (2019). Update of the statements on biology and clinical impact of occult hepatitis B virus infection. J. Hepatol. 71(2), 397–408.
20. Pollicino, T., and Caminiti, G. (2021). HBV-integration studies in the clinic: role in the natural history of infection. Viruses 13 (3), 368.
21. Sangiorgio L, Attardo T, Gangemi R, Rubino C, Barone M, Lunetta M.2000. Increased frequency of HCV and HBV infection in type 2 diabetic patients. Diabetes Res Clin Pract. [Internet]. 2000 [cited Feb 11, 2017]; 48(2):147-51.
22. Wang C, Xue R, Wang X, Xiao L and Xian J (2023) High-sensitivity HBV DNA test for the diagnosis of occult HBV infection: commonly used but not reliable. Front. Cell. Infect. Microbiol. 13:1186877.
23. Gundling F, Seid H, Strassen I, Haller B, Siegmund T, Umgelter A, et al. (2013). Clinical manifestations and treatment options in patients with cirrhosis and diabetes mellitus. Digestion. 87(2):75-84.
24. Gutiérrez-Grobe Y, Ponciano-Rodríguez G, MéndezSánchez N. 2017.Viral hepatitis infection and insulin resistance: a review of the pathophysiological mechanisms. Salud Publica Mex. [Internet]. 2011 [cited Jul 10, 2017]; 53Suppl1:S46-51.
25. Lecube A, Hernández C, Genescà J, Simó R. 2006.Glucose abnormalities in patients with hepatitis C virus infection: epidemiology and pathogenesis. Diabetes Care.; 29(5):1140-9.
26. Berbudi, A., Rahmadika, N., Tjahjadi, A. I., & Ruslami, R. 2020. Type 2 Diabetes and its Impact on the Immune System. Current Diabetes Reviews, 16(5), 442-449.
27. Komatsu H. (2014). Hepatitis B virus: where do we stand and what is the next step for eradication? World J Gastroenterol. 20(27):8998.
28. Younossi, Z., Kochems, K., Curran, D., & Bunge, E. M. (2017). Should adults with diabetes mellitus be vaccinated against hepatitis B virus? A systematic

review of diabetes mellitus and the progression of hepatitis B disease. Human Vaccines & Immunotherapeutics, 13(11), 2695-2706.

29. Han B, Liu W, Yang S, Wang S, Du J, Liu Y, Cui F. 2021.Association between self-monitoring of blood glucose and hepatitis B virus infection among people with diabetes mellitus: a cross-sectional study in Gansu Province, China. BMJ Open. Oct 7;11(10): e048463.
30. Lei S, Chen S, Zhao X, Zhang Y, Cheng K, Zhang X, et al. (2020). Hepatitis B virus infection and diabetes mellitus: the Kailuan prospective cohort study in China. Hepatol Int,14 (5):743–753.
31. Halota W, Muszyńska M, Pawłowska M. 2017. Hepatitis B virus serologic markers and anti-hepatitis B vaccination in patients with diabetes. Med Sci Monit. [Internet]. 2002 [cited Nov 26, 2017]; 8(7):516-9.
32. Gulcan A, Gulcan E, Toker A, Bulut I, Akcan Y.2008. Evaluation of risk factors and seroprevalence of hepatitis B and C in diabetic patients in Kutahya, Turkey. J Investig Med; 56(6):858-63.
33. Onyekwere CA, Ogbera AO, Dada AO, Adeleye OO, Dosunmu AO, Akinbami AA, et al. 2016.Hepatitis C Virus (HCV) Prevalence in Special Populations and Associated Risk Factors: A Report from a Tertiary Hospital. Hepat Mon.16(5): e35532.
34. Kombi PK, Agasa SB, Mukonkole JPM, Bome LB, Bokele CA, Tshilumba CK. (2018) Seroprevalence of hepatitis B and C virus infections among diabetic patients in Kisangani (North-eastern Democratic Republic of Congo). Pan Afr Med J. Nov 2; 31:160.
35. Farshadpour, F., Taherkhani, R., & Saberi, F. (2022). Molecular evaluation of hepatitis B virus infection and predominant mutations of pre-core, basal core promoter and S regions in an Iranian population with type 2 diabetes mellitus: A case–control study. BMC Infectious Diseases, 22.
36. Cai C, Zeng J, Wu H, Shi R, Wei M, Gao Y, et al. (2015). Association between hepatitis B virus infection and diabetes mellitus: a meta-analysis. Exp Ther Med. 10(2):693–698.
37. Kaya, S. Y., & Kaya, A. (2020). Age Specific Hepatitis B Surface Antigen (HBsAg) and AntiHBs Seroprevalence among Patients Admitted to a State Hospital, Viral Hepatitis Journal ,26(2):85-87.