*Research Article / Araştırma Makalesi*

# Analysis of Hepatitis B and C Seroprevalence and Anti-Hbs Antibody Titers in Type 2 Diabetic Patients with and without Diabetic Foot Ulcers

## Diyabetik Ayak Ülseri Olan ve Olmayan Tip 2 Diyabetli Hastalarda Hepatit B ve C'nin Seroprevalansı ile Anti-Hbs Antikor Titrelerinin Analizi

Huseyin KARAASLAN [1], Ceylan KESKIN [2]

[1]Harran University, School of Medicine, Department of Endocrinology, Sanliurfa, TÜRKİYE
[2]Harran University, School of Medicine, Department of Internal Medicine, Sanliurfa,TÜRKİYE

**Abstract**

**Background:** Infection with parenterally transmitted viruses, such as hepatitis B and C viruses, is thought to be more common in patients with type 2 diabetes for several reasons. Diabetic foot ulcers are a serious complication of diabetes that can lead to more frequent hospital admissions, longer hospital stays and the need for more invasive procedures. Given their complicated conditions, we hypothesized that the prevalence of hepatitis B and C infections might be higher in patients with diabetic foot ulcers.
**Materials and Methods:** A total of 440 patients with type 2 diabetes, 220 with diabetic foot ulcers (group 1) and 220 without (group 2), who were tested for hepatitis B surface antigen (HBsAg), anti-HBs and anti-hepatitis C antibodies (anti-HCV), were retrospectively included in the study. Anti-HBs titers <10 IU/mL were defined as lack of protective immunity, titers of 10-99 IU/mL were considered protective, and titers of ≥100 IU/mL were considered high immunity.
**Results:** HBsAg seropositivity was detected in 7 patients (3.2%), both in group 1 and group 2 (p=1.0). The presence of anti-HCV seropositivity was detected in 5 patients (2.3%) in group 1 and in 3 patients (1.4%) in group 2 (p=0.724). A titer of less than 10 mIU/mL of anti-HBs antibody was found in 118 (55.4%) patients in group 1 and in 112 (52.6%) patients in group 2 (p=0.609).
**Conclusions:** No significant differences were observed in HBsAg, anti-HCV, or relative anti-HBs seropositivity between type 2 diabetic patients with and without diabetic foot ulcer. It was found that 54.0% of patients with type 2 diabetes had anti-HBs antibody titers below 10 mIU/mL.

**Key Words:** Type 2 diabetes mellitus, Hepatitis B, Hepatitis C, Anti-HBs

**Öz**

**Amaç**: Tip 2 diyabetli bireylerde, hepatit B ve C virüsleri gibi parenteral yolla bulaşan virüslerin neden olduğu enfeksiyonlar daha yaygın görülebilmektedir. Diyabetik ayak ülserleri, artan sayıda hastaneye yatış ihtiyacı, invaziv prosedür gereksinimi ve uzayan yatış süreleri ile ilişkili olan diyabetin kronik ve ciddi bir komplikasyonudur. Komplike durumları göz önüne alındığında, diyabetik ayak ülserli bireylerde hepatit B ve C enfeksiyonlarının prevalansının daha yüksek olabileceğini varsayarak bu çalışmaya planladık.
**Materyal ve Metod:** HBV yüzey antijeni (HBsAg), anti-HBs ve anti-hepatit C antikor (anti-HCV) düzeyleri bakılmış olan 220'si diyabetik ayak ülseri olan (grup 1) ve olmayan 220 kişi (grup 2) olmak üzere toplam 440 tip 2 diyabet hastası, retrospektif olarak çalışmaya dahil edildi. Anti-HBs titrelerinin <10 IU/mL olması bağışıklığın yokluğu, 10-99 IU/mL olması koruyucu bağışıklık ve ≥100 IU/mL titreler ise yüksek bağışıklığın varlığı olarak kabul edildi.
**Bulgular:** HBsAg seropozitifliği her iki grupta benzer bir şekilde 7'şer hastada (%3.2) tespit edildi (p=1.0). Grup 1'de 5 hastada (%2.3), grup 2'de ise 3 hastada (%1.4) anti-HCV seropozitifliği saptandı (p=0.724). Grup 1'de 118 (%55.4) hastada, grup 2'de ise 112 (%52.6) hastada anti-HBs antikor titrelerinin 10 mIU/mL'nin altında seyrettiği tespit edildi (p=0.609).
**Sonuç:** Diyabetik ayak ülseri olan ve olmayan tip 2 diyabet hastaları arasında HBsAg, anti-HCV veya göreceli anti-HBs antikor seropozitifliği açısından anlamlı bir fark saptanmadı. Hastaların önemli bir kısmında (%54.0) anti-HBs antikor titrelerinin düşük (10 mIU/mL'nin altında) olduğu tespit edildi.

**Anahtar Kelimeler:** Tip 2 diyabetes mellitus, Hepatit B, Hepatit C, Anti-HBs

**Corresponding Author / Sorumlu Yazar**

**Dr. Huseyin KARAASLAN**
Harran University School of Medicine,
Department of Endocrinology
Osmanbey Campus, 63290,
Haliliye/Sanliurfa/TÜRKİYE

**E-mail:** huseyinkaraaslan@hotmail.com

**Received / Geliş tarihi:** 04.04.2024

**Accepted / Kabul tarihi:** 11.07.2024

**DOI:** 10.35440/hutfd.1464459

## Introduction

Hepatitis B virus (HBV) infection is one of the leading causes of chronic liver disease (CLD) and remains endemic in many countries despite widespread vaccination efforts. As with HBV, the hepatitis C virus (HCV) can also cause liver fibrosis, hepatocellular carcinoma (HCC), and liver-related deaths (1). In 2019, it is estimated that the global prevalence of chronic HBV infection was 4.1% and chronic HCV infection was 0.8% for all ages (2, 3). In a study conducted in Turkey in 2015, the incidence of HBV and HCV infections was reported as 4.0% and 1.0%, respectively (4). In more recent studies, the prevalence of HBV infection has been reported to be declining, with a detection rate of 2.5% in 2018 and 1.9% in 2020 (5,6) Infection with parenterally transmitted viruses, such as HBV and HCV, is believed to be more common in patients with type 2 diabetes (T2DM) for several reasons. These reasons include frequent hospitalizations and invasive procedures, regular blood tests, and the potential misuse of fingertip devices (7-14). Further, T2DM has adverse effects on HBV and HCV-related liver infections and is associated with an increased risk of hepatic fibrosis, cirrhosis, and HCC (15, 16).

Diabetic foot ulcers (DFUs) usually occur as a serious complication of uncontrolled and prolonged diabetes. Patients with DFU have a higher mortality rate and require an increasing number of hospital visits, hospitalizations and invasive procedures (17). The increased prevalence of HBV and HCV infections and associated risk factors in DM patients has been well documented in many studies. Despite this, there are no data regarding the prevalence of HBV and HCV infections in patients with DFU. Given their complicated conditions, we hypothesized that the prevalence of HBV and HCV infection may be higher and anti-HBs antibody titres may be lower in patients with DFU. In addition, as there are very few studies on the seroprevalence of HBV and HCV as well as anti-HBs seropositivity in patients with DM worldwide, particularly in Turkey, we believe that our study will make a valuable contribution to the existing literature in this area.

## Materials and Methods

This study was conducted in accordance with the Declaration of Helsinki and approved by the clinical research ethics committee (date: 07.08.2023, number: HRÜ/23.14.22). Medical records of T2DM patients hospitalized in our endocrinology clinic from 2020 to 2022 were retrospectively reviewed. Since there were a limited number of patients with type 1 diabetes, they were excluded from the study. In addition, individuals with acute viral hepatitis, decompensated liver disease, malignancy, and those receiving immunosuppressive treatment were excluded from the study due to their potential impact on antibody responses.

Consequently, 440 patients (220 with DFU and 220 without DFU) whose HBV surface antigen (HBsAg), anti-HBs and hepatitis C antibody (anti-HCV) levels were tested as part of the viral serological examination were included in the study. Those with DFU were categorized as group 1, while those without DFU were categorized as group 2. Anti-HBs titers <10 IU/mL were defined as lack of protective immunity, titers of 10-99 IU/mL were considered protective, and titers of ≥100 IU/mL were considered high immunity (18). In our laboratory, the upper limit of anti-HBs titers was 1,000 IU/ml and patients with an anti-HBs titer >1,000 IU/ml were considered above the upper limit. Besides age and gender, glycated hemoglobin A1c (HbA1c), serum creatinine (sCr), estimated glomerular filtration rate (eGFR), sedimentation and C-reactive protein (CRP) levels were also recorded.

### *Statistical Analysis*

The statistical analyses were conducted using SPSS (version 20.0, SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to check the normality of continuous variables. According to the distribution of the data, the mean±standard deviation or median and interquartile range were calculated. Categorical data were represented by numbers and percentages. The continuous variables were analyzed using independent samples t-tests or Mann-Whitney U tests, based on their distribution. We compared categorical variables with the Chi-square test.

## Results

The study analysed data from 440 patients with T2DM, of whom 233 (53%) were females and 207 (47%) were males. The percentage of male patients in group 1 (53.6%) was significantly higher than in group 2 (40.5%) (p=0.006). The mean age was 60.8±9.2 years in group 1 and 59.1±9.7 years in group 2 (p=0.057) (Table 1).

In the viral serological examination, HBsAg seropositivity was detected in seven patients (3.2%), both in group 1 and group 2. Despite anti-HCV seropositivity being detected in 5 patients (2.3%) in group 1 and in 3 patients (1.4%) in group 2, this difference was not statistically significant (p=0.724). Additionally, there was no significant difference in anti-HBs antibody titers between the two groups (p=0.964). A comparison of hepatitis B and C seroprevalence between groups is illustrated in Table 2.

A titer of less than 10 mIU/mL of anti-HBs antibody was found in 118 (55.4%) patients in group 1 and in 112 (52.6%) patients in group 2. There were no significant differences between the two groups in terms of relative anti-HBs seropositivity (p=0.609) (Table 3).

**Table 1.** Clinical characteristics of the study groups

| Variables | Total (n=440) | Group 1 (n=220) | Group 2 (n=220) | p |
|---|---|---|---|---|
| Age (years) | 59.9±9.5 | 60.8±9.2 | 59.1±9.7 | .057 [a] |
| Gender (male), n(%) | 207 (47.0) | 118 (53.6) | 89 (40.5) | .006 [b] |

*Data are expressed as the mean and standard deviation or the number (%) of patients.*
*A p<0.05 was considered significant. Significant p values between group 1 and 2 are highlighted in bold. a Independent samples t-test. b Chi-square test.*

**Table 2.** Comparison of hepatitis B and C seroprevalence between groups

| Variables | Total | Group1 | Group 2 | p-value |
|---|---|---|---|---|
| HBsAg (+), n (%) | 14 (3.2) | 7 (3.2) | 7 (3.2) | 1.0 [a] |
| Anti-HBs (IU/mL) | 7.2 (0.6-114) | 7.7 (0.8-78) | 6.2 (0.5-134) | 0.964 [b] |
| Anti-HCV (+), n (%) | 8 (1.8) | 5 (2.3) | 3 (1.4) | .724 [a] |

*Abbreviations: HBsAg, hepatitis B surface antigen; anti-HBs, antibodies against HBsAg, anti-HCV, hepatitis C antibody*
*Data are expressed as the number (%) of patients or median (first and third quartile) values.*
*a: Chi-square test, b: Mann-Whitney U test*

**Table 3.** Comparison of the relative levels of anti-HBs seropositivity between groups (for HBsAg-negative individuals)

| Variables | Total (n=426) | Group1 (n=213) | Group 2 (n=213) | p |
|---|---|---|---|---|
| Anti-HBs (<10 IU/mL), n (%) | 230 (54.0) | 118 (55.4) | 112 (52.6) | 0.609 [a] |
| Anti-HBs (10-100 IU/mL), n (%) | 85 (20.0) | 44 (20.7) | 41 (19.2) | |
| Anti-HBs (>100 IU/mL), n (%) | 111 (26.0) | 51 (23.9) | 60 (28.2) | |

*Data are expressed as the number (%) of patients. A p<0.05 was considered significant.*
*a: Chi-square test*

## Discussion

This study revealed that the prevalence of HBsAg and anti-HCV seropositivity was higher in patients with T2DM compared to those in the general population screenings. It was also found that 230 (54.0%) patients with T2DM had anti-HBs antibody titers below 10 mIU/mL. No significant differences were observed in HBsAg, anti-HCV, or relative anti-HBs seropositivity between T2DM patients with and without DFU.

Vaccination is the most effective way to prevent HBV infection and its complications. It is documented that universal vaccination against HBV significantly reduces the prevalence of acute and chronic HBV infection as well as the incidence of HCC and hepatic events (19, 20). WHO recommends hepatitis B vaccination for all newborns, children up to 18 years of age, and adults at high risk of infection (21). In the United States, the Centers for Disease Control and Prevention (CDC) recommends the hepatitis B vaccine for all newborns, children up to age 18, adults 19-59 years of age, and adults 60 and older who are at high-risk for infection (22). Post-vaccination immunity should be assessed using a method that allows the determination of the protective level of anti-HBs (≥10 mIU/mL). People with anti-HBs levels below 10 mIU/mL after receiving a full dose of HBV vaccine are recommended to re-vaccinate according to their risk status (23).

We found an overall HBsAg seropositivity of 3.2% (14/440) in the present study. A significant decrease in chronic HBV infection, particularly among children, has been observed since the introduction of the hepatitis B vaccine. It is estimated that there was a 31.3% decrease in prevalence across all ages between 1990 and 2019. Along with this significant decline over the years, there are also large regional differences in HBsAg seropositivity. The Western Pacific region had the highest prevalence of 7.1%, followed by the African region with 6.5%. The lowest prevalence of 1.1% was found in the Europe region (2). The prevalence of HBV in Turkey is higher than in European countries and is one of the countries with an intermediate prevalence of HBV (24). Following the introduction of a universal vaccination programme for all children and high-risk groups in Turkey in 1998, a decline in prevalence has been observed (25). According to the TURHEP study conducted in 2015, HBsAg was found in 4% of 5,460 participants from both rural and urban areas, with a higher prevalence in eastern regions. In the Southeastern Anatolia Region, where our study was conducted, the HBsAg positivity rate was found to be 7.3%, notably higher than the results obtained in our study (4). This may be partly due to the general decline in HBsAg positivity rates observed over the years. In 2018, another study found that there was a 2.5% prevalence of HBsAg positivity in Turkey, based on 61,943 volunteers from 73 provinces (5). A further study published in 2020, in which 1,486 patients were screened, showed that the seropositivity rate for HBsAg was 1.9% (6). However, it's important to note that the prevalence studies mentioned above were carried out in the general adult population, not in specific patient groups. The rate of HBsAg seropositivity in our study (3.2%) was higher than that found in general population studies in recent years. It should be noted that there are very few studies evaluating HBsAg seropositivity in patients with DM in our country. A study published in 2008, compared the HBsAg seropositivity rates of 630 diabetics and 314 non-diabetics. The results showed that 5.1% of diabetics were seropositive, while only 3.8% of non-diabetics were seropositive (10). In another study published in 2017, it was found that 3.7% of diabetics and 0.8% of non-diabetics were seropositive for HBsAg (p<0.001) (11). These results are consistent with our findings and reveal a decrease in HBsAg seropositivity over the years in Turkey.

Vaccination against HBV is recommended for all patients with DM who are under the age of 60. For diabetics over 60 years of age with an anti-HBs level below 10 mIU/mL, vaccination may also be recommended, depending on their physician's advice (23). Older adults have impaired vaccine responses, and this impairment is further demonstrated in older adults with DM, particularly those with comorbid kidney disease. Although patients with DM have an adequate humoral immune response to vaccination, an impaired cellular response may account for less robust antibody production

following hepatitis B vaccination (26). In a study comparing adults with and without T2DM, it was found that patients with T2DM had lower antibody response rates compared to healthy controls. Although a lower antibody response was associated with increasing age and BMI, advanced age was reported as the most clinically significant factor. For this reason, it is recommended to receive the hepatitis B vaccine as soon as possible after the diagnosis of DM (27). In our study, we found that 230 patients (54.0%) had anti-HBs antibody titers below 10 mIU/mL. However, we lacked information regarding our patients' vaccination history and did not assess anti-HBc IgG levels. As a result we were unable to determine whether this response in patients with protective anti-HBs levels (>10 mIU/mL) was triggered by the vaccine or a previous HBV infection. In a recent study conducted by Kaya et al., it was found that the rate of anti-HBs seropositivity in the general population was 54.2%. Moreover, the study revealed that this rate was approximately 70% among individuals under 30 years old, while it dropped to below 40% in those over 30 years old. It has also been observed that anti-HBs seropositivity begins to rise again after the age of 70, probably due to increased exposure to HBV (6). Another similar study published in 2016 found that the seropositivity of anti-HBs was 85.5% in the age group of 0-12, 25% in the age group of 20-50, and 41% in individuals over 50 years old. It was believed that the high anti-HBs seropositivity in the younger age group was a result of the national vaccination program initiated in Turkey in 1998. It was also thought that the higher seropositivity observed in the older age group was associated with increased exposure to HBV (28).

According to data from the WHO in 2019, the estimated global prevalence of HCV infection in the general population is 0.8%. The mortality rate from hepatitis C has decreased since 2019 due to the availability of more effective antiviral treatment options. However, it is estimated that 78% of HCV infections remain undiagnosed. In this regard, screening programs have been recommended to eliminate the disease, particularly in high-risk individuals (3). In Turkey, the prevalence of HCV infection is generally estimated to be low, at about 1% (4). Evidence suggests that patients with DM are at a higher risk of HCV infection, which may be related to either the disease itself or frequent parenteral exposure (10-14). Despite this, only a limited number of studies have been conducted on the prevalence of HCV infection among DM patients in Turkey. In our study, we found that the prevalence of HCV infection in patients with DM was 1.8%. Although we observed a higher prevalence of HCV infection in patients with DFU compared to those without (2.3% versus 1.4%), this difference was not statistically significant. Our result is higher than the reported prevalence of HCV infection in the general Turkish population, which is 1% (4). According to three separate studies conducted in the Turkish population in 2008, 2015 and 2017, the prevalence of HCV infection in patients with DM was found to be 3.2%, 3.3% and 2.2%, respectively (10-12). The prevalence of HCV infection in our study (1.8%) was found to be lower than in previous studies. The decline over the years can be explained by improved screening strategies, increased awareness of effective prevention methods, and the availability of more effective treatment options against HCV infection. However, this decrease may vary depending on the patient profiles included in the studies and regional differences.

***Strengths and Limitations of the Study***

Our study had some limitations. Firstly, the study is retrospective, conducted in a single center, and the number of patients included is relatively small. Secondly, since we were unable to examine the levels of anti-HBc antibodies, we could not determine whether the positivity in patients who tested positive for anti-HBs was a result of the vaccine or a previous infection. Our study stands out as one of the few studies conducted in Turkey to investigate the prevalence of HBV and HCV infection and anti-HBs levels in patients with T2DM. This study is also the first to compare viral serology between diabetic patients with and without DFU.

## Conclusion

No significant differences were observed in HBsAg, anti-HCV, or relative anti-HBs seropositivity between T2DM patients with and without DFU. It was found that 54.0% of patients with T2DM had anti-HBs antibody titers below 10 mIU/mL. In addition, the rates of HBsAg and anti-HCV seropositivity in our study were higher than those reported in screenings of the general healthy population in Turkey in recent years.

***Ethical Approval:*** This study was conducted in accordance with the Declaration of Helsinki and approved by the clinical research ethics committee (Date: 07.08.2023, Number: HRÜ/23.14.22).

***Author Contributions:***
*Concept: H.K., C.K.*
*Literature Review: H.K., C.K.*
*Design : H.K., C.K.*
*Data acquisition: C.K.*
*Analysis and interpretation: H.K.*
*Writing manuscript: H.K., C.K.*
*Critical revision of manuscript: H.K., C.K.*

***Conflict of Interest:*** *The authors have no conflicts of interest to declare.*

***Financial Disclosure:*** *Authors declared no financial support.*

## References

1. Kanda T, Goto T, Hirotsu Y, Moriyama M, Omata M. Molecular Mechanisms Driving Progression of Liver Cirrhosis towards Hepatocellular Carcinoma in Chronic Hepatitis B and C Infections: A Review. Int J Mol Sci. 2019;20:1358.
2. GBD 2019 Hepatitis B Collaborators. Global, regional, and national burden of hepatitis B, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Gastroenterol Hepatol. 2022;7(9):796-829.
3. Cui F, Blach S, Manzengo Mingiedi C, Gonzalez MA, Sabry Alaama A, Mozalevskis A, et al. Global reporting of progress towards elimination of hepatitis B and hepatitis C. Lancet Gastroenterol Hepatol. 2023;8(4):332-342.

4. Tozun N, Ozdogan O, Cakaloglu Y, Idilman R, Karasu Z, Akarca U, et al. Seroprevalence of hepatitis B and C virus infections and risk factors in Turkey: a fieldwork TURHEP study. Clin Microbiol Infect. 2015;21:1020–1026.
5. Tosun S, Balık İ, Tabak F, Saltoğlu N, Örmeci N, Şencan İ, et al. Evaluation of risk factors associated with HBsAg and anti-HCV seropositivity: Results of a nationwide population-based epidemiological survey study in Turkey. Mediterr J Infect Microb Antimicrob, 2018; 7: 34.
6. Kaya SY, Kaya A. Age Specific Hepatitis B Surface Antigen (Bag) and Anti-HBs Seroprevalence among Patients Admitted to a State Hospital. Viral Hepat J. 2020;26: 85-87.
7. Ndako JA, Nwankiti OO, Olorundare JO, Ojo SKS, Okolie CE, Olatinsu O, et al. Studies on the serological markers for hepatitis B virus infection among type 2 diabetic patients. J Clin Lab Anal. 2021;35:e23464.
8. Zhang X, Zhu X, Ji Y, Li H, Hou F, Xiao C, et al. Increased risk of hepatitis B virus infection amongst individuals with diabetes mellitus. Biosci Rep. 2019;39:BSR20181715.
9. Reilly ML, Schillie SF, Smith E, Poissant T, Vonderwahl CW, Gerard K, et al. Increased risk of acute hepatitis B among adults with diagnosed diabetes mellitus. J Diabetes Sci Technol. 2012;6:858-866.
10. Gulcan A, Gulcan E, Toker A, Bulut I, Akcan Y. Evaluation of risk factors and seroprevalence of hepatitis B and C in diabetic patients in Kutahya, Turkey. J Investig Med. 2008;56:858-863.
11. Gisi K, Cetinkaya A, Ozkaya M, Kantarceken B, Gisi G, Koroglu S. Hepatitis B and C seroprevalence in patients with diabetes mellitus and its relationship with microvascular complications. Prz Gastroenterol. 2017;12(2):105-110.
12. Korkmaz H, Kesli R, Onder Pamuk B, Ipekci SH, Terzi Y, Kebapcilar L. Assessment of evidence for positive association and seroprevalence of hepatitis B and C in diabetic patients in a developing country. J Investig Med. 2015;63(2):251-257.
13. Jadoon NA, Shahzad MA, Yaqoob R, Hussain M, Ali N. Seroprevalence of hepatitis C in type 2 diabetes: evidence for a positive association. Virol J. 2010;7:304.
14. Ba-Essa EM, Mobarak EI, Al-Daghri NM. Hepatitis C virus infection among patients with diabetes mellitus in Dammam, Saudi Arabia. BMC Health Serv Res. 2016;16:313.
15. Saeed MJ, Olsen MA, Powderly WG, Presti RM. Diabetes Mellitus is Associated With Higher Risk of Developing Decompensated Cirrhosis in Chronic Hepatitis C Patients. J Clin Gastroenterol. 2017;51:70–76.
16. Huang YW, Wang TC, Lin SC, Chang HY, Chen DS, Hu JT, et al. Increased risk of cirrhosis and its decompensation in chronic hepatitis B patients with newly diagnosed diabetes: a nationwide cohort study. Clin Infect Dis. 2013;57:1695-1702.
17. Chen L, Sun S, Gao Y, Ran X. Global mortality of diabetic foot ulcer: A systematic review and meta-analysis of observational studies. Diabetes Obes Metab. 2023;25:36-45.
18. Pondé RAA. Expression and detection of anti-HBs antibodies after hepatitis B virus infection or vaccination in the context of protective immunity. Arch Virol. 2019;164:2645-2658.
19. Wong GL, Hui VW, Yip TC, Liang LY, Zhang X, Tse YK, et al. Universal HBV vaccination dramatically reduces the prevalence of HBV infection and incidence of hepatocellular carcinoma. Aliment Pharmacol Ther. 2022;56:869-877.
20. Miglietta A, Quinten C, Lopalco PL, Duffell E. Impact of hepatitis B vaccination on acute hepatitis B epidemiology in European Union/European Economic Area countries, 2006 to 2014. Euro Surveill. 2018;23:17-00278.
21. Hepatitis B vaccines: WHO position paper – July 2017. Wkly Epidemiol Rec. 2017;92:369-392.
22. Conners EE, Panagiotakopoulos L, Hofmeister MG, Spradling PR, Hagan LM, Harris AM, et al. Screening and Testing for Hepatitis B Virus Infection: CDC Recommendations - United States, 2023. MMWR Recomm Rep. 2023;72:1-25.
23. Schillie S, Harris A, Link-Gelles R, Romero J, Ward J, Nelson N. Recommendations of the Advisory Committee on Immunization Practices for Use of a Hepatitis B Vaccine with a Novel Adjuvant. MMWR Morb Mortal Wkly Rep. 2018;67:455-458.
24. Madihi S, Syed H, Lazar F, Zyad A, Benani A. A systematic review of the current hepatitis B viral infection and hepatocellular carcinoma situation in Mediterranean Countries. BioMed Res Int. 2020;2020:7027169.
25. Akarca US, Baykam N, Güner R, Günşar F, İdilman R, Kaymakoğlu S, et al. Eliminating Viral Hepatitis in Turkey: Achievements and Challenges. Viral Hepat J. 2022;28:47-54.
26. Schillie SF, Spradling PR, Murphy TV. Immune response of hepatitis B vaccine among persons with diabetes: a systematic review of the literature. Diabetes Care. 2012;35:2690-2697.
27. Van Der Meeren O, Peterson JT, Dionne M, Beasley R, Ebeling PR, Ferguson M, et al. Prospective clinical trial of hepatitis B vaccination in adults with and without type-2 diabetes mellitus. Hum Vaccin Immunother. 2016;12:2197-2203.
28. Guclu E, Ogutlu A, Karabay O. A Study on the Age-Related Changes in Hepatitis B and C Virus Serology. Eurasian J Med. 2016;48:37-41.