Analysis of hepatitis B and C virus infections amongst members of the Dental National Health Insurance Society in the Oita Prefecture

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Abstract. In Japan, ~3 million individuals are estimated to be infected with hepatitis B virus (HBV) or hepatitis C virus (HCV). The rates of hepatitis virus infection amongst dentists is higher than that amongst other healthcare workers due to increased exposure to both saliva and blood. However, an efficient method for the testing of hepatitis virus infections amongst dentists remains to be established. The aim of the present study was to examine the rate of hepatitis virus infection amongst dental healthcare workers (DHWs) by introducing a health checkup that included screening for HBV and HCV infections. A total of 1,834 members of the Dental National Health Insurance Society in the Oita Prefecture, consisting of dentists and other employees, were tested for hepatitis B surface antigen (HBsAg), antibodies to HBsAg (anti‑HBs) and antibodies to HCV (anti‑HCV) during routine medical checkups. Anonymized data, including the age, sex, occupation (dentist or employee), and presence of a hepatitis virus marker, was collected and analyzed. The positive rates of HBsAg, anti‑HBs and anti‑HCV in the study sample were 0.6, 44.1 and 0.5%, respectively; the positive rates were higher amongst dentists than the employees. Furthermore, the positive rates of HBsAg and anti‑HCV increased with age and were higher in subjects aged 50-79 (1.7-2.2%). The positive rate of presence of anti‑HBs was significantly higher in the dentists compared with employees (56.4 vs. 39.6%; respectively; P<0.0001). The three factors associated with anti‑HB positivity were HBsAg negativity, occupation (dentist) and age (20-29 years) with adjusted odds ratios of 8.29, 2.27 and 1.59, respectively (P<0.05). These results suggest that introducing a hepatitis virus examination during routine health checkups of DHWs may prove useful in identifying infected individuals.

Introduction

According to the World Health Organization (WHO), worldwide, ~2 billion individuals have been infected with hepatitis B virus (HBV) and ~257 million individuals remain chronically infected [defined as hepatitis B surface antigen (HBsAg)-positive] (1). An estimated 887,000 individuals die due to complications associated with hepatitis B, such as cirrhosis and hepatocellular carcinoma (HCC) each year. In addition, ~71 million individuals have been infected with hepatitis C virus (HCV) worldwide, and ~399,000 of these die annually (2).

In Japan, the estimated number of individuals infected with HBV and HCV is ~3 million. Despite a gradual decrease in the mortality rates due to HCC, ~30,000 individuals die of HCC annually, and 80% of these cases are caused by HBV and HCV (3-6). The Oita Prefecture, located in Kyushu in western Japan, has a high death rate due to HCC, based on the statistics obtained from the Ministry of Health, Labor and Welfare (Fig. 1).

The advent of direct antiviral agents has significantly improved the treatment outcomes of HCV infection (7-10). Nucleoside analogs can also significantly suppress HBV replication, leading to a reduction in cirrhosis decompensation and HCC (11-13). At present, the largest challenge faced in Japan regarding hepatitis infection is the identification of individuals with undiagnosed HCV and HBV infections.

In Japan, the Industrial Safety and Health Act was enacted in 1972 to ensure the safety and health of workers in the workplace. Article 66 of this law stipulates that ‘The employer shall, as provided for by the Ordinance of the Ministry of Health, Labour and Welfare, have medical examinations of workers conducted by a physician’ (14). This general medical checkup must be performed annually during a period of
employment. By law, all workers must undergo a periodical medical examination with the same included checks; however, serological testing for HCV and HBV are non-statutory medical examination checks and are not required by law.

Infection control in dental medical institutions is an important issue as dental healthcare workers (DHWs) often come in contact with the blood and saliva of patients. DHWs are at high risk due to occupational exposure to blood-borne pathogens, such as HBV, HCV and human immunodeficiency virus (HIV). The risk of transmission from HBV-, HCV- and HIV-positive patients is 3-30, 3 and 0.3%, respectively (15).

In our previous study, it was reported that DHWs do not always have sufficient knowledge regarding hepatitis viruses, and Japanese dentists present with a high rate of HBV infection and low HB vaccine coverage (16-18). In the United States, HB vaccination has been recommended for all healthcare workers since 1982, but in Japan, mandatory HB vaccination for healthcare workers has not yet been formalized. In Japan, HB vaccination was started in certain medical institutions in 1986 (19), but there was a large difference between facilities and there were no specific guidelines. In 2009, the Japanese Society for Infection Prevention and Control clarified vaccine guidelines for medical personnel (20), and the standardization of HB vaccination is progressing nationwide.

To the best of our knowledge, there are no recent large-scale surveys in Japan since our previous study on hepatitis virus infections in DHWs in the Fukuoka Prefecture in 2008 (17). In the present study, the rates of hepatitis virus infections amongst DHWs in the Oita Prefecture in Kyushu were investigated, where the mortality rate as a result of HCC is high. The results of the present study may prove useful in developing strategies for promoting and maintaining the health of DHWs.

Materials and methods

Subjects. A total of 1,834 members of the Dental National Health Insurance Society in the Oita Prefecture, consisting of dentists and other employees (dental hygienists, dental assistants, dental technicians and clerks), were tested for hepatitis virus during periodic medical examinations at medical institutions contracted by the Dental National Health Insurance Society between April 2018 and March 2019. Written informed consent regarding the submission of the results of the medical examination to a third party for health management and effective use was obtained from each subject. The 1,834 subjects (530 males and 1,304 females) were aged 18-91 years, with a mean age and standard deviation of 44.5±14.6 years (median age, 44.0 years) (Table I). There were 493 dentists and 1,341 employees.

Study design. The results of the medical examination were provided to each individual in a sealed letter from the medical institution. Anonymized data, including the age, sex, occupation (dentist or other employee) and presence/proportion of hepatitis virus markers, were collected and analyzed. The data collected for this study was anonymized by the Dental National Health Insurance Society in the Oita Prefecture.

Screening for viral hepatitis (anti-HCV, HBsAg and anti-HBs). The serum antibody to HCV (anti-HCV) levels were measured using a fully automated chemiluminescent enzyme immunoassay (CLEIA) kit (Lumipulse II HCV; Fujirebio, Inc.; cat. no. 295977); samples with a cut-off index (C.O.I.) of >1.0 were considered positive for the anti-HCV antibody.

HBsAg was detected using a Lumipulse HBsAg-HQ assay (Fujirebio Inc.; cat. no. 291153; C.O.I., 0.005 IU/ml) and HBsAg antibody (anti-HBs) levels were determined using a Lumipulse HBsAb-N (Fujirebio Inc.; cat. no. 296493; C.O.I. 10 mIU/ml). Measurements were performed using a fully automated CLEIA system (Lumipulse G1200; Fujirebio Inc.), according to the manufacturer's protocols (21,22).

Comparison of the results of the present study with previously published data (5). Regarding the HCV and HBV infection rates, 1,753 (18-69 years) out of 1,834 subjects were compared with the results of 2,727,727 Japanese blood donors (16-69 years) in the study by Tanaka et al (5).

Statistical analysis. All data are expressed as the mean ± standard deviation. Differences between the two groups were analyzed using a Mann-Whitney U test, Wilcoxon signed-rank test and a Fisher's exact test. The adjusted odds ratios were calculated using univariate and multivariate logistical regression analysis. All statistical analyses were performed using JMP version 13 (SAS Institute, Inc.). P<0.05 was considered to indicate a statistically significant difference.

Results

Univariate analysis of hepatitis virus infection. The number of subjects who were positive for HBsAg, anti-HBs and anti-HCV were 11 (0.6%), 809 (44.1%) and 9 (0.5%), respectively (Table I). The positive rate for anti-HBs was significantly higher in dentists than in the employees (56.4 vs. 39.6%, respectively; P<0.0001).
Univariate analysis demonstrated significant associations between the positive and negative markers of viral hepatitis amongst the subjects (Table II). A significant difference in mean age was observed between the HBsAg-positive and negative subjects (P=0.0135). Furthermore, a significantly higher number of HBsAg-negative subjects were positive for anti-HBs (P=0.0283; Table II). Significant differences in sex (P=0.0207) and mean age (P=0.0034) were observed between the anti-HCV-positive and -negative subjects. Similarly, significant differences in sex (P=0.0001) and occupation (P<0.0001) were observed between the anti-HBs-positive and negative subjects, and there was a significantly higher number of anti-HBs-negative subjects who were positive for HBsAg (P=0.0283).

Age-specific prevalence of HBsAg and anti-HCV. The age-specific prevalence of the markers of HBV and HCV infection are shown in Table III. The positive rates of HBsAg and anti-HCV increased with age. The positive rates of HBsAg and anti-HCV were compared between 1,753 out of 1,834 subjects (18-69 years of age) in the present study and 2,727,727 blood donors (<70 years of age) in a study by Tanaka et al (5); the positive rate of HBsAg was significantly higher amongst subjects aged 50-59 years old than amongst the age-matched blood donors (P=0.0177). The positive rate was highest among dentists aged 50-59 (1.7%) and 70-79 (1.7%), and other dental employees aged 60-69 (2.2%).

Similarly, the positive rate of anti-HCV was significantly higher among subjects who were in their 60s in the present study when compared with the blood donors (P=0.0019). The highest rates were observed in dentists and employees who were in their 60-69 (2.2%).

Age-specific prevalence of anti-HBs. The age-specific prevalence of the anti-HBs marker is shown in Fig. 2. The presence or absence of vaccination amongst the subjects in the present study could not be investigated. The rate of anti-HBs positivity amongst dentists decreased with age from 75.0% in subjects aged 20-29 years old to 30% in those aged 80 years old and over (Fig. 2). Alternatively, the rate of anti-HBs positivity amongst the employees was low at all ages, particularly in those who were <20 years of age (Fig. 2).

Multivariate analysis of anti-HBs positivity. All variables in the univariate analysis were included in the multivariate analysis (Table IV). Based on the multivariate analysis, three factors [HBsAg negativity, occupation (dentist) and age (20-29 years old)] were found to be associated with anti-HBs positivity with adjusted odds ratios of 8.29, 2.27 and 1.59, respectively (P<0.05).

Discussion

HBV, HCV and HIV are some of the most common and dangerous pathogens that spread through blood in medical
HBV is the most infectious type of virus that causes blood-borne infections, and it can survive on dry environmental surfaces for >7 days (23). Dental workers are at increased risk of needle-stick injuries resulting in exposure to the blood and body fluids of potentially infected patients. In a previous study, exposure to needle-stick injuries was reported in 70.3% of dentists and 77.2% of dental hygienists and assistants in Japan (24). In Canada, an average of 1.5 mucous membrane exposures and 3 percutaneous injuries per a dentist were reported per year (25). The rate of acquiring an HBV infection through HBV-contaminated needles is high, 12% (26) to 60% (27), in unvaccinated individuals. Dentists have been reported to present with the highest rates of HBV infection amongst healthcare workers (28). The prevalence of HBsAg amongst dentists was reported to be significantly higher (45%) than amongst doctors (35.8%) and blood donors (20%) (28). Furthermore, the seroprevalence of HBV infections amongst dentists was 12.1% in Japan (17), 2.4% in Malaysia (29), 13% in Korea (29), 10.8% in Brazil (30), 9-14% in the USA (31) and 7% in Germany (32). In a previous study consisting of 1,628 Iranian DHWs, the positive rates of HBsAg, anti-hepatitis B virus core antigen (anti-HBc), anti-HBs, anti-HCV and anti-HIV were found to be 0.42, 4.97, 88.53, 0.06 and 0%, respectively; 94.28% of the subjects were reported to be vaccinated against HBV (33). The authors emphasized that prevalence of HBV infection among DHWs was lower than that in the general population, but permanent vigilance and educational programs addressing blood-borne viruses infection among dentists are necessary (33).

In our 2017 study, an anonymous online survey and interview with members of the Japanese Society of Dental Practice Administration was performed in order to evaluate the recognition of the problems associated with hepatitis amongst dental healthcare workers (17). The positive rate of anti-HBc increased with age from 2.9% for individuals aged 30-39 to 100% in individuals aged 70-79 (5.6% in individuals aged 40-49, 29.4% in individuals aged 50-59 and 85.7% in individuals aged 60-69) in the previous study (17). Furthermore, less than half (48.2%) of the participants had been vaccinated against hepatitis B; 16 (25.4%) out of the 63 unvaccinated DHWs were found to be anti-HBc positive (17).

In one of our previous studies conducted in 2007, 141 DHWs in the Fukuoka Prefecture (northern Kyushu in Japan) were screened for the presence of HBV and HCV infections; amongst them, 17 subjects (12.1%) were anti-HBc positive (17). The positive rate of anti-HBc increased with age from 2.9% for individuals aged 30-39 to 100% in individuals aged 70-79 (5.6% in individuals aged 40-49, 29.4% in individuals aged 50-59 and 85.7% in individuals aged 60-69) in the previous study (17). Furthermore, less than half (48.2%) of the participants had been vaccinated against hepatitis B; 16 (25.4%) out of the 63 unvaccinated DHWs were found to be anti-HBc positive (17).

**Table II. Distribution of HBsAg, anti-HCV and anti-HBs in positive and negative subjects.**

|          |          | Positive, n=11 | Negative, n=1,823 | P-value |
|----------|----------|----------------|-------------------|---------|
| A, HBsAg | Sex, male/female, n (%) | 4/7 (36.4/63.6) | 526/1,297 (28.9/71.1) | NS |
|          | Age, mean ± SD, years | 54.3±11.4 | 43.6±14.8 | 0.0135* |
|          | Occupation, dentist/employee, n (%) | 4/7 (36.4/63.6) | 489/1,334 (26.8/73.2) | NS |
|          | Anti-HBs, positive/negative, n (%) | 1/10 (9.1/90.9) | 808/1,015 (44.3/55.7) | 0.0283* |
|          | Anti-HCV, positive/negative, n (%) | 0/11 (0/100) | 9/1,814 (0.5/99.5%) | NS |

| B, Anti-HCV |          | Positive, n=9 | Negative, n=1,825 | P-value |
|-------------|----------|----------------|-------------------|---------|
|            | Sex, male/female, n (%) | 6/3 (66.7/33.3) | 524/1,301 (28.7/71.3) | 0.0207 |
|            | Age, mean ± SD, years | 58.4±13.2 | 43.6±14.7 | 0.0034b |
|            | Occupation, dentist/employee, n (%) | 4/5 (44.4/55.6) | 489/1,336 (26.8/73.2) | NS |
|            | HBsAg, positive/negative, n (%) | 0/9 (0/100) | 11/1,814 (0.6/99.4) | NS |
|            | Anti-HBs, positive/negative, n (%) | 3/6 (33.3/66.7) | 806/1,019 (44.2/55.8) | NS |

| C, Anti-HBs |          | Positive, n=809 | Negative, n=1,025 | P-value |
|-------------|----------|----------------|-------------------|---------|
|            | Sex, male/female, n (%) | 271/538 (33.5/66.5) | 259/766 (25.3/74.7) | 0.0001c |
|            | Age, mean ± SD, years | 43.6±14.9 | 43.8±14.7 | NS |
|            | Occupation, dentist/employee, n (%) | 278/531 (56.4/39.6) | 215/1,336 (43.6/60.4) | <0.0001c |
|            | HBsAg, positive/negative, n (%) | 1/808 (0.1/99.9) | 10/1,015 (1.0/99.0) | 0.0283a |
|            | Anti-HCV, positive/negative, n (%) | 3/806 (0.4/99.6) | 6/1,019 (0.6/99.4) | NS |

*P<0.05, **P<0.01, ***P<0.001. HBsAg, hepatitis B surface antigen; anti-HB, antibody to HBsAg; HCV, hepatitis C virus; NS, not significant; SD, standard deviation. Differences between the two groups were analyzed using a Mann-Whitney U test, Wilcoxon signed-rank test and a Fisher's exact test.
dentists, and found that 26.8% of the subjects had not been immunized against hepatitis B. Additionally, male dentists had a significantly higher risk and knowledge deficits scores than female dentists, and the directors of the dental clinics presented with significantly higher risk and knowledge deficits scores than dentists working at university hospitals (18).

In the United States, a case of HBV transmission from one patient to another during tooth extraction was reported in 2007 (34). It was identified as a nosocomial infection due to the matching of the HBV nucleotide sequence between the two patients. Similarly, a case of acute hepatitis C following dental

| Table III. Age-specific prevalence of HBsAg and anti-HCV. |   |   |
|----------------------------------------------------------|---|---|
| **A, HBsAg**                                             |   |   |
| Subjects in the present study                            |   |   |
| Age, years                                              | n | HBsAg-positive, n (%) | n | HBsAg-positive, n (%) | n | HBsAg-positive, n (%) |
| 18-19                                                    | 7 | 0 (0)                   | 0 | -                     |
| 20-29                                                    | 388 | 0 (0)                   | 4 | 0 (0)                 |
| 30-39                                                    | 384 | 1 (0.3)                 | 74 | 0 (0)                 |
| 40-49                                                    | 391 | 2 (0.5)                 | 97 | 1 (1.0)               |
| 50-59                                                    | 359 | 5 (1.4)                 | 115 | 2 (1.7)              |
| 60-69                                                    | 224 | 2 (0.9)                 | 135 | 0 (0)                |
| 70-79                                                    | 71 | 1 (1.4)                 | 58 | 1 (1.7)              |
| ≥80                                                      | 10 | 0 (0)                   | 10 | 0 (0)                |
| Total                                                    | 1,834 | 11 (0.6)               | 493 | 4 (0.8)               |
| First-time blood donors between 2007 and 2011            | n | HBsAg-positive, n (%) |
| Total                                                    | 2,720,727 | 5,469 (0.2) |

| **B, Anti-HCV**                                          |   |   |
|----------------------------------------------------------|---|---|
| Subjects in the present study                            |   |   |
| Age, years                                              | n | Anti-HCV positive, n (%) | n | Anti-HCV positive, n (%) | n | Anti-HCV positive, n (%) |
| 18-19                                                    | 7 | 0 (0)                   | 0 | -                     |
| 20-29                                                    | 388 | 1 (0.3)                 | 4 | 0 (0)                 |
| 30-39                                                    | 384 | 0 (0)                   | 74 | 0 (0)                 |
| 40-49                                                    | 391 | 1 (0.3)                 | 97 | 0 (0)                 |
| 50-59                                                    | 359 | 1 (0.3)                 | 115 | 0 (0)                |
| 60-69                                                    | 224 | 5 (2.2)                 | 135 | 3 (2.2)              |
| 70-79                                                    | 71 | 1 (1.4)                 | 58 | 1 (1.7)              |
| ≥80                                                      | 10 | 0 (0)                   | 10 | 0 (0)                |
| Total                                                    | 1,834 | 9 (0.5)                | 493 | 4 (0.8)               |
| First-time blood donors between 2007 and 2011            | n | Anti-HCV positive, n (%) |
| Total                                                    | 2,720,727 | 4,440 (0.2) |

| **Note:** Anti-HCV: Antibodies to hepatitis C virus; anti-HBs, antibody to hepatitis B surface antigen. Differences between the subjects in the present study and the first-time blood donors were compare using a Fisher’s exact test. |

Table IV. Multivariate analysis of factors associated with anti-HBs-positivity.

| Factor                        | Odds ratio | 95% Confidence interval | P-value |
|-------------------------------|------------|-------------------------|---------|
| HBsAg negative                | 8.29       | 1.55-153.38             | <0.0001 |
| Occupation, dentist           | 2.27       | 1.82-2.83               | <0.0001 |
| Age group, 20-29              | 1.59       | 1.25-2.01               | 0.0002  |

*P<0.01, *P<0.001. HBsAg, hepatitis B surface antigen.
treatment was suspected in Japan in 2017 (35). Only 59.8% of patients with HBV- and HCV-infected liver disease declared the presence of a hepatitis virus infection whilst undergoing dental treatment (36). The most common reason for not declaring the presence of a hepatitis viral infection at a dental clinic was because the dentist had not enquired regarding the possibility of an underlying disease (71.2%).

The Japanese Society for Infection Prevention and Control recommends that hepatitis B vaccination must be given to all medical personnel who are sensitive to hepatitis B in a medical institution, if there is a possibility of their coming in contact with a patient (or the blood or body fluids of a potentially infected patient) (37,38). Unfortunately, it is not legally required for DHWs to be tested for the hepatitis virus or be vaccinated against hepatitis B in Japan. Furthermore, there is a dearth of recent epidemiological data on hepatitis virus infections amongst Japanese DHWs.

In the present study, the examination of hepatitis virus markers as health check items was first introduced by the Dental National Health Insurance Society in the Oita Prefecture, which includes dentists and employees. A total of 20 (11 HBsAg-positive and 9 anti-HCV-positive subjects) were found to be HBV and HCV-infected. In addition, the infection rate was particularly high amongst those aged 50-79. The positive rate of anti-HBs was 44.1% (dentists vs. employees, 56.4 vs. 39.6%). This ratio was lower than that observed in our survey conducted in the Fukuoka Prefecture in 2007 (51.8%) (17). It was estimated that the vaccination rate was lower amongst dental employees than dentists, although the presence or absence of HB vaccination in the current study could not be confirmed.

HCV RNA has been detected in 6.1% (39) to 18% (40) of the dental instruments and in the saliva of patients with hepatitis C (41,42). HCV transmission in dental healthcare settings is preventable using standard precautions, including injection safety, although no vaccine for the prevention of HCV infection is available thus far. Dentists should receive vaccinations against hepatitis B to avoid the risk of HBV infection. Unvaccinated dentists have been reported to be 5x more likely to be infected with HBV than vaccinated dentists (31). In the present study, the anti-HBs-positive DHWs were nearly 8.3 times more likely to be HBsAg negative than the anti-HBs-negative DHWs. According to Banatvala and Van Damme (43), the primary objective of vaccination against hepatitis B is to prevent infection and thereby reduce the incidence of persistent HBV infections and chronic liver diseases; in addition, the elimination of the pool of chronic carriers limits the transmission of the infection to susceptible contacts. A previous survey reported that 8.8% of a total of 283 dentists were not vaccinated, primarily due to a lack of information, thus indicating that educational campaigns are required to assist in reducing the transmission of HBV (44).

As of December 31, 2018, there were 104,908 dentists in Japan, and the majority of these (90,105 dentists) worked as dentists in clinics (45). However, information disclosure and education about hepatitis is not sufficient, as it is estimated that several Japanese dentists have not yet been tested for hepatitis virus (17,18). Therefore, it is important to increase HCV and HBV testing rates and HBV vaccination rates for dentists (46). This can be achieved by educating dental workers about hepatitis. The method used to test for assessing hepatitis infection in the present study may prove useful in the future. In
addition, the Dental National Health Insurance Society has a ‘Hepatitis B vaccination subsidy system’, which subsidizes the cost of the HBV vaccinations, and it is recommended that awareness of this system amongst DHWs should be increased.

The present study has several limitations. First, it was not possible to determine if a Dhw had been vaccinated against hepatitis B, and data on the antibody titers were not available. Second, the outcomes of 11 HBsAg-positive and 9 anti-HCV-positive subjects were not evaluated.

In conclusion, the rate of hepatitis virus infection amongst the 1.834 DHWs in the Oita Prefecture of Japan was determined in the present study. The positive rates of HBsAg, anti-HBs and anti-HCV were 0.6%, 44.1% and 0.5%, respectively; furthermore, the rates were higher amongst dentists than among the other associated employees. These findings highlight the importance of identifying untreated hepatitis individuals amongst DHWs who have not yet been tested for HBV or HCV in order to prevent and provide early treatment for the disease.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

YN interpreted data, performed the statistical analysis and wrote the manuscript. TK collected data from participants. HN made a substantial contribution to the conception and design of the study, and made critical revisions to the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Oita Dental Association (approval no. 2020-1) and was performed in accordance with the Declaration of Helsinki. Written informed consent regarding the submission of the results of the medical examination to a third party for health management and effective use was obtained from each subject.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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BIOMEDICAL REPORTS 14: 23, 2021
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