

The role of dentists in controlling hepatocellular carcinoma in Japan (Review)

YUMIKO NAGAO^{1,2}

¹Department of Public Health, Graduate School of Medicine, Juntendo University, Bunkyo-ku, Tokyo 113-8421;

²Department of Pathology & Microbiology, Faculty of Medicine, Saga University, Saga 849-8501, Japan

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Abstract. In Japan, the method of treatment for hepatitis is well established due to the high rates of hepatitis C. However, the identification of patients with hepatitis who do not receive appropriate treatment poses a major problem. Some patients with this disease may need to consult with a dentist due to the development of extrahepatic manifestations, such as lichen planus, in the oral cavity. Alternatively, the dentist might discover patients with untreated hepatitis C and hepatitis B during routine dental examination. In such cases, the patient should be referred to a hepatologist for further examinations and treatment. Thus, dentists are required to act as ‘gatekeepers of hepatitis’. Furthermore, Japanese dentists need to increase hepatitis B vaccine coverage for infection control. By acting as a ‘care coordinator of hepatitis’, the dentist will be able to contribute to the eradication of liver cancer in Japan, thereby eliminating the discrimination and prejudice against patients with hepatitis. Dentists need to have a deep understanding of liver disease from the viewpoints of both nosocomial infection control and treatment of oral diseases.

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Correspondence to: Professor Yumiko Nagao, Department of Public Health, Graduate School of Medicine, Juntendo University, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan
E-mail: y.nagao.qd@juntendo.ac.jp

Abbreviations: OLP, Oral lichen planus; HCV, hepatitis C virus; HBV, hepatitis B virus; Anti-HBc, hepatitis B core antibody; HCC, hepatocellular carcinoma; IFN, interferon; DAA, direct-acting antivirals; SVR, sustained virologic response

Key words: dentist, lichen planus, hepatitis B virus, hepatitis C virus, hepatocellular carcinoma

1. Introduction

According to the World Health Organization (WHO), the number of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections worldwide in 2015 was 257 million and 71 million, respectively (1,2). It is predicted that the number of patients who develop complications such as liver cirrhosis and hepatocellular carcinoma (HCC), due to persistent infections with HBV and HCV, will peak in 2030-2035. Thus, the goal is to diagnose 90% and treat 80% of the HBV and HCV patients by 2030 in order to eliminate this disease (3). HCC, which accounts for the majority of primary liver cancers, is one of the most common cancers worldwide and a leading cause of cancer-related death (4). HCC rates are the highest in East and South-East Asia and Northern and Western Africa and lowest in South-Central Asia and Northern, Central, and Eastern Europe (4). Furthermore, HCC is the leading cause of death in patients with HCV infection (5,6). Approximately 80% of HCCs result from infections with HBV and HCV in Japan (7-10). Hepatitis C and its complications are the leading causes of HCC.

An interferon (IFN)-free oral agent called direct antiviral agent (DAA) is the first choice of treatment for effectively eliminating HCV (11). DAA treatment has enabled many patients to achieve sustained virologic response (SVR) with few side effects (12-15). In addition, it reduces the incidence of chronic hepatitis C (16) and HCC (17), and mortality (18). Only nine countries (Australia, France, Iceland, Italy, Japan, South Korea, Spain, Switzerland, and the United Kingdom) are on track toward eliminating HCV by 2030, based on their current rates of diagnosis and treatment (19). Nucleotide analog therapy suppresses HBV replication (20), and leads to a reduction in both cirrhosis decompensation and HCC (21-23).

However, it is estimated that approximately 3 million people are infected with HBV and HCV in Japan; moreover, approximately 780,000 people have latent infections without their knowledge. Among the HCV-infected people, an estimated 470,000 people visit medical institutions, 300,000 people are unaware of the fact that they are infected, and 250,000 to 750,000 people are aware of the infection but not receiving treatment in the country (24). In order to eradicate HCC, it is necessary to improve the examination rate of the hepatitis virus and encourage infected patients to receive treatment.

However, discrimination and prejudice against people infected with hepatitis virus exist. A national survey involving

1,705 people with viral hepatitis revealed that dental clinics were the most common places for discrimination against infected patients (25). In a previous study, we reported the prevalence of prejudice and discrimination among HBV/HCV-infected individuals; of the 69 patients with viral liver disease, 76.8% revealed a psychological burden and 20.3% experienced prejudice and discrimination by healthcare workers (26). Prejudice was most prevalent within the dental clinic setting (50%). The presence or absence of prejudice experienced by the patient from a healthcare worker was found to be significantly associated with the psychological burden ($P=0.0255$).

2. Dental care and viral hepatitis

The dental clinic is often visited by patients with underlying diseases. In Japan, the number of elderly patients who undergo dental examination is increasing with the increase in age, and at least one in three patients who undergo dental examinations is over 65 years old (27). Furthermore, a significant number of patients with HCV infection in Japan are over the age of 65 (28), and a large proportion of them present with complications such as cirrhosis or HCC (29).

Dentists need to have in-depth knowledge about liver disease from the viewpoints of both nosocomial infection control and treatment of oral diseases. Dentists often come in contact with the patient's saliva and blood. Unlike a general medical office, a dental office is often polluted by suspended matter from teeth and prostheses. In addition, dentists frequently have accidents due to punctures from sharp dental instruments and injection needles; 70.3% of dentists and 77.2% of dental hygienists and assistants are reported to have been exposed to needle stick injuries in Japan (30). Dentists are known to have significantly higher HBV infection rates than other healthcare workers (31). According to the results of our survey in 2007, the positive rates of hepatitis B core antibody (anti-HBc) among Japanese dentists increased with age (85.7% in their 60s and 100% in their 70s; average rate, 12.1%) (32). The coverage of the hepatitis B vaccine was only 48.2%, and 25.4% of those who did not receive the vaccine were positive for anti-HBc (32). These findings indicate that dentists may be routinely exposed to HBV.

In 2017, an online survey involving members of the Japanese Society of Dental Practice Administration found that 26.8% of dentists were not vaccinated against hepatitis B (33). Statistical analyses showed that male dentists had significantly higher scores for risk behavior of infection control ($P=0.002$) and knowledge deficit scores of hepatitis ($P=0.031$) than female dentists. Furthermore, general dentists had significantly higher risk scores for infection control ($P<0.001$) and knowledge deficit scores ($P=0.014$) than those working in university hospitals.

Pakistan (34), Poland (35), India (36), and Iran (37) have reported the knowledge and attitudes about hepatitis virus among dentists. In Poland, a survey of 192 dentists revealed that a relatively high percentage (25%) refused to provide services to infected patients with HBV, HCV and HIV due to concerns about their health (35). A cross-sectional study conducted in India to assess the knowledge and awareness about HCV among dental health-care professionals found a statistically significant association between mean knowledge scores and gender, education level, and experience (36). A

cross-sectional study from Iran showed that the knowledge, attitudes, and practices (KAP) of dentists with regard to HBV, HCV, and HIV were influenced by their age, work experience, and year of graduation (37). Dentists less than 30 years of age, longer work experience, and those who graduated after 2006 displayed superior knowledge and attitude.

It is impossible to detect the presence or absence of infectious diseases in all patients in a general dental practice. Therefore, it is important for the dentist to obtain detailed and accurate medical histories from patients and take appropriate precautions. We have previously reported that only 59.8% of patients with viral liver disease self-disclose their infection at the dental clinic (38). The most common reason for not disclosing was because the dentist did not enquire about the condition of the liver. It is vital to pay attention to bleeding tendencies associated with liver cirrhosis (39), drug administration, and hypoalbuminemia (40,41) while providing dental treatment to patients with liver disease.

3. Oral lichen planus and hepatitis C virus

Oral lichen planus (OLP) is a T-cell mediated chronic inflammatory mucosal disorder with different clinical characteristics, and can be classified into six types as follows: Reticular, plaque, atrophic, erosive, and bullous (42). It occurs predominantly in adults over 40 years of age, and is characterized by the presence of long-term, painful areas on the oral mucous membrane (Fig. 1).

HCV has been shown to affect many tissues other than the liver (43-46). The HCV-related extrahepatic manifestations include renal disease (such as mixed cryoglobulinemia and membrane proliferative glomerulonephritis), metabolic dysfunction (such as cardiovascular disease and type 2 diabetes), lymphoma (non-Hodgkin's lymphoma), skin and membrane disease (such as porphyria cutanea tarda and lichen planus), thyroid disease (such as Hashimoto's thyroiditis and Grave's disease), and autoimmune diseases (Sjögren's syndrome). Studies have revealed that 38-76% of patients with chronic HCV infection develop at least one extrahepatic manifestation during the course of the disease (47-49).

Of the many extrahepatic manifestations, OLP (50,51), Sjögren's syndrome (52-54), and oral cancer (55,56) have been associated with HCV (57,58). The results of four meta-analysis showed that patients with HCV infection were 2.8-6.1 times more likely to develop OLP compared to controls (59-62). Furthermore, HCV-positive OLP patients might be at a higher risk of presenting with malignant transformation (63). The prevalence of HCV infection in patients with OLP varies considerably (range, 4-62%) based on the region; however, it is particularly high (62%) in Japan (50).

In a previous study, we showed the histopathological disappearance of OLP when HCV was eliminated by IFN therapy (64). On the other hand, IFN therapy may trigger the onset of OLP (65-67) or sometimes act as an aggravating factor (66,68,69). Recent studies have demonstrated improvements in OLP after the elimination of HCV via DAA treatment (70-75). Su *et al* (76) reported that patients with chronic HCV infection had a significantly higher risk of oral cancer than patients without HCV infection, and that antiviral therapy with pegylated IFN (PegIFN)/ribavirin (RBV) significantly reduced the risk of oral cancer. In addition to OLP and

Table I. Characteristics of the studies where the examination and treatment of liver disease were recommended by a dentist.

Report	Area (prefecture)	Method	Subjects	Investigation period	(Refs.)
One	Fukuoka	Retrospective study	Patients visiting T Dental Clinic in Fukuoka prefecture	1 year and 9 months	74
Two	Yamaguchi and Shimane	Prospective study	Patients visiting 12 medical institutions consisting of 11 dental clinics in the Yamaguchi prefecture and one oral and maxillofacial surgery center in the Shimane prefecture	3 months	88
Three	Ehime	Prospective study	Patients visiting 35 dental clinics in Ehime prefecture	3 months	89



Figure 1. Clinical appearance of oral lichen planus (A, right buccal mucosa; B, left buccal mucosa; C, tongue; and D, lower lip) in patients at Saga University Hospital, Japan. White lace-like (reticular) lesions and erosions were observed on the buccal mucosae (A and B) of a patient with fatty liver and diabetes mellitus. Severe erosions with symptoms of contact pain on the tongue (C) of a patient with HCV-related liver cirrhosis and HCC, and erosion on lower lip (D) of a patient with chronic hepatitis C. HCV, hepatitis C virus; HCC, hepatocellular carcinoma.

oral cancer, SVR leads to substantial reductions in extrahepatic manifestations such as cryoglobulinemia vasculitis, malignant B-cell lymphoproliferative diseases, insulin resistance, diabetes, mixed cryoglobulinemia, and glomerulonephritis (77,78).

The detection and proliferation of HCV in oral tissues, including the normal oral mucosa and those affected by OLP and oral cancer, have been reported previously (79-81). However, virus detection is not a direct factor in the development of OLP. The onset of OLP due to HCV depends on three factors: Viral (82-85), host (86), and drugs (69,70).

4. Efforts to identify untreated hepatitis patients through dentistry

In Japan, various measures have been taken to improve the coverage rate of the hepatitis virus test. According to the

Basic Guidelines on Hepatitis Measures, all citizens are required to undergo hepatitis virus testing once in a lifetime. However, the national testing rate for these viruses is only ~60% (87). Despite the increase in the eradication rate of HCV following the introduction of DAAs, issues concerning the establishment of an efficient pick-up and follow-up system for people infected with hepatitis virus remain unsolved. It is challenging to improve the screening rate of the hepatitis virus and build a follow-up system for hepatitis virus-positive persons.

Several untreated hepatitis patients have been identified during routine dental treatment in several parts of Japan in retrospective and prospective studies (Fig. 2 and Table I) (74,88,89).

The identification of untreated hepatitis through dentistry.

Ninety new patients who visited the T Dental Clinic in Fukuoka prefecture from May 2015 to February 2017 for the treatment of oral mucosal diseases (average age, 68.9 years \pm 13.1 years) were included in a retrospective study (74). The main oral diseases were OLP (39 cases), leukoplakia (7 cases), head and neck cancer (4 cases), oral candidiasis (8 cases) Sjögren's syndrome (4 cases), and taste disorders (3 cases). Fifty-one (56.7%) of the 90 subjects were referred to a hepatologist or a family doctor, by an oral surgeon, to evaluate the liver disease for the presence or absence of HCV or HBV infection. The prevalence of anti-HCV was 29.4% (15/51). The oral surgeon was able to encourage 12 (80%) out of 15 anti-HCV-positive patients to undergo treatment for hepatitis. All patients with HCV infection (and OLP-complications) who received DAA treatment following referral from a dental clinic achieved SVR. In Japan, general dentists do not perform blood tests due to issues with medical insurance. Nonetheless, dentists can detect untreated viral hepatitis patients among those with oral mucosal diseases or a history of hepatitis in cooperation with the medical doctors.

A prospective study that encourages the identification of patients with untreated hepatitis through dentistry.

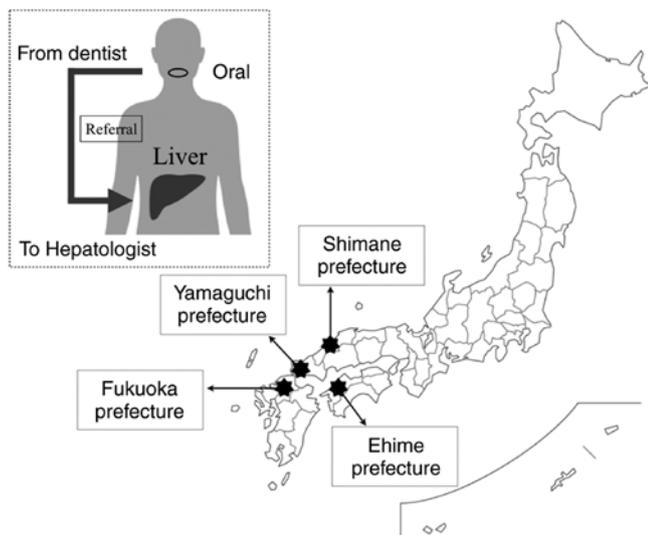


Figure 2. The research areas where the examination and treatment of liver disease were recommended by a dentist. Dentists promoted the examination and treatment of hepatitis virus infection among patients who visited the dental clinics in the prefectures (black stars on the map). Each of the three studies was conducted after approval by the Ethics Committee (74,88,89). A study conducted in four prefectures in Japan (Fukuoka prefecture, Yamaguchi prefecture, Shimane prefecture, and Ehime prefecture) and comprising 48 medical institutions reported that the dentist serves the role of a gatekeeper for the treatment of a number of liver diseases.

We conducted prospective studies to determine whether a general dentist could recommend hepatitis testing to patients who visited a dental clinic (88,89). Twelve clinics ($n=5,091$ patients), including 11 dental clinics in Yamaguchi prefecture and one institution for oral surgery in a hospital in Shimane prefecture, were included in the study by the end of October 2017 (88). The number of patients who visited a dentist, the number of HCV- and HBV-infected patients, the number of OLP patients, the rate of HCV infection in OLP patients, and the number of patients referred to a family doctor for consultation regarding liver diseases over a period of 3 months were recorded. Consequently, 73% of OLP patients were encouraged to undergo examinations for liver disease and hepatitis virus infection. One patient was referred to the medical department for untreated liver disease and achieved SVR with DAA treatment.

In the same clinical study conducted at 35 dental clinics in the Ehime prefecture ($n=19,077$ patients), 42 OLP, 69 HCV-infected, and 76-HBV-infected patients were identified over the 3-month period (89); 66.7% of the OLP patients were recommended to undergo tests for liver disease and 47.6% of the OLP patients were identified with the disease. HCV-related liver disease was the most common finding (70%), and 78.6% of the patients had persistent HCV infection ($P=0.0287$). Currently, general dentists are educating their patients about hepatitis, and are promoting the referral of untreated hepatitis patients to hepatologists in the Ehime prefecture.

5. Conclusions

Oral lesions are known to be associated with liver disease. Thus, the dentist is expected to play a role as a 'gatekeeper of hepatitis'. The promotion of the examination and treatment

of HBV and HCV infections by dentists aids in providing appropriate treatment for the oral condition and in the reduction of the incidence of liver cancer. If the number of people infected with hepatitis virus decreases, the problems of discrimination and prejudice will be resolved. Thus, in-depth knowledge about hepatitis by the dentist and strong cooperation with the medical department are required to promote these activities. In order to increase the knowledge about hepatitis and the number of HB vaccinations among dentists, it is necessary to conduct workshops on the prevention of nosocomial infections, which should be attended by dentists. Since April 2018, only those medical institutions that meet the standards that stipulate nosocomial infection control are permitted to calculate a new basic medical examination fee in Japan. If the criteria are not met, the method of subtraction is adopted. The standard requirements are as follows: i) the establishment of an adequate system for the replacement of each patient and the cleaning and sterilization of the dental equipment using dedicated tools; ii) the establishment of a system to support the dental treatment for patients with infectious diseases; iii) the presence of at least one full-time dentist who can regularly attend the outpatient training for infection prevention measures every four years; iv) the provision of in-hospital training, such as standard preventive measures for the prevention of nosocomial infections, for employees; v) the provision of information about the measures that need to be taken to prevent nosocomial infection in the hospital; and vi) The submission of a report about the implementation status of nosocomial infection control to the directors of the Regional Bureau Health and Welfare, once a year.

In Japan, the Dental National Health Association to which dentists and their employees participate has a 'Hepatitis B Vaccination Subsidy Program' that subsidizes the cost of HB vaccination. In order to increase the number of HB vaccinations for dentists, this grant system should be widely announced.

The structure of dental illness in Japan has changed drastically due to improvements in oral hygiene and the aging population; hence, there is an increasing need for dental care depending on the patient's condition. Dentists must disseminate interventions by acting as coordinators for HCV infection.

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Authors' contributions

YN conceived and designed the review, analyzed the relevant literature and wrote the manuscript. YN critically revised the

manuscript and produced the figures. The author read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Informed consent for publication of the images was obtained from the patient.

Competing interests

The author declares that they have no competing interests.

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