Relationship between non-alcoholic fatty liver disease and periodontal disease: a review and study protocol on the effect of periodontal treatment on non-alcoholic fatty liver disease

Chieko Kudo 1 *, Takaomi Kessoku 1, Yohei Kamata 1, Koichi Hidaka 1, Takeo Kurishashi 1, Tomoyuki Iwasaki 1, Shogo Takashiba 1, Toshiro Kodama 1, Toshiyuki Tamura 3, Atsushi Nakajima 2 and Masato Minabe 1

1 Division of Periodontology, Department of Oral Function & Restoration, Graduate School of Dentistry, Kanagawa Dental University, 82 Inaoka-cho, Yokosuka, Kanagawa 238-8580, Japan
2 Department of Gastroenterology and Hepatology, Yokohama City University Graduate School of Medicine, 3-9 Fukaura, Kanazawa-ku, Yokohama 236-0004, Japan
3 Department of Comprehensive Dentistry, Kanagawa Dental University, 3-31-6 Tsunurya-cho, Kanagawa, Yokohama, Kanagawa 221-0835, Japan
4 Department of Internal medicine, Yokohama Clinic, Kanagawa Dental University, 3-31-6 Tsunurya-cho, Kanagawa, Yokohama, Kanagawa 221-0835, Japan
5 Iwasaki Internal Medicine Clinic, 1-1-5 Furuyokohama1F, Kamishikawa, Hodogaya-ku Yokohama, Kanagawa 240-0042, Japan
6 Department of Pathophysiology - Periodontal Science, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8525, Japan
7 Department of Implantology and Periodontology, Graduate School of Dentistry, Kanagawa Dental University, 3-31-6 Tsunurya-cho, Kanagawa, Yokohama, Kanagawa 221-0835, Japan

Abstract

Non-alcoholic fatty liver disease (NAFLD) is a chronic liver disease that is prevalent worldwide. Non-alcoholic steatohepatitis (NASH) is an advanced form of NAFLD and carries the risk of progression from hepatic inflammation and fibrosis to cirrhosis and hepatocellular carcinoma. Pathological mechanisms of NAFLD have been proposed, such as the two-hit hypothesis and the multiple parallel hit hypothesis. Periodontal disease is a chronic infectious disease of the tissues surrounding the teeth that result in tooth loss. Several reports have indicated that periodontal infection is related to NAFLD. NAFLD and periodontal disease are chronic inflammatory conditions that are known as ‘silent diseases’. Therefore, both conditions need to be detected early and treated under collaborative medical and dental care in order to prevent progression to NASH. For this purpose, further investigations in humans on the relationship between NAFLD and periodontal disease and on the effect of periodontal treatment on NAFLD are necessary. In this paper, studies on the relationship between NAFLD and periodontal disease are reviewed and a clinical study investigating the effect of periodontal treatment on NAFLD is introduced.

Introduction

Several studies in recent years have reported on the relationship between systemic disease and periodontal disease [1,2]. It has been reported that chronic periodontal disease is related to conditions, such as diabetes mellitus (DM), atherosclerosis and heart disease [3-6]. We have previously reported that infection with periodontal pathogens is associated with the progression of atherosclerosis [7].

Fatty liver disease, which is one of the causes of atherosclerosis [8,9], includes non-alcoholic fatty liver disease (NAFLD) and alcoholic fatty liver disease (AFLD) [10]. NAFLD (in which fat accumulates in the liver without a history of drinking or immune system disease) has gained attention worldwide. NAFLD includes simple steatosis and non-alcoholic steatohepatitis (NASH), which is characterized by a chronic and progressive liver pathology [11]. The prevalence of NAFLD in the American general adult population is 10%-40% and that of NASH is approximately 2%-5% [12].

Recent animal and human investigations have indicated that NAFLD/NASH is related to periodontal disease [13,14]. As patients with liver or periodontal disease have few subjective and early symptoms, the diseases are often severe when they are discovered at medical institutions. [15,16]. Therefore, early detection and treatment under collaborative medical and dental care is important to prevent progression to NASH, which may then develop into cirrhosis or liver cancer. Further investigations in humans on the relationship between NAFLD and periodontal disease and on the effect of periodontal treatment on NAFLD are desired.

This paper reviews studies on NAFLD and periodontal disease.
disease and briefly introduces our clinical study design: ‘A study on the relationship between NAFLD and periodontal disease and on the effect of periodontal disease on NAFLD’. The University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) identifier is UMIN000022079.

NAFLD/NASH and its treatment

NAFLD is a chronic liver disease that occurs in people who drink little or no alcohol and is prevalent worldwide. It is a spectrum of conditions that includes simple steatosis (which has a good prognosis) and NASH. NASH may progress from hepatic inflammation and fibrosis to cirrhosis and hepatocellular carcinoma [17,18]. It has been reported that the main factors for the histological progression of NASH are fibronectin immunohistochemistry, hypertensin, diabetes, low-density lipoprotein (LDL) cholesterol and body-mass index (BMI) [19-24]. It is also reported that 67-78% of individuals with a BMI of 30 or greater have NAFLD [25,26]. NAFLD is closely related to DM and metabolic syndrome [27,28]. In addition, it has been demonstrated that patients with NAFLD and DM are prone to hepatic inflammation, and the consequent hyperglycaemia, hyperinsulinaemia and hyperlipidaemia promote the progression of atherosclerosis [29].

As a pathological mechanism of NAFLD, the ‘two-hit’ hypothesis has long been proposed [30]. The ‘first hit’ is represented by the action of hyperinsulinaemia and insulin resistance, accompanying obesity, which leads to liver steatosis and increases the absolute non-esterified fatty acid uptake in the liver and esterification to form triglycerol. At the ‘second hit’, hepato-cytotoxic factors and genetic predisposition lead to progression to NASH [31]. In recent years, a ‘multiple parallel hits’ hypothesis has been proposed, in which a variety of factors, such as cytokines derived from adipose tissue and the intestinal tract, and dietary factors may play a central role [32]. Multiple hits induce adipokine secretion, endoplasmic reticulum and oxidative stress at the cellular level that subsequently induce hepatic steatosis, inflammation and fibrosis, among which oxidative stress is considered as the major promoter of necroinflammation in NASH through lipid peroxidation [33,34].

General treatment for NASH includes lifestyle modifications such as weight loss through diet and exercise [35]. Pharmacological therapies using agents such as insulin sensitizers, vitamin E and obestetholic acid are also administered. However, there is still no approved drug for the treatment of NAFLD [35,36].

Periodontal disease and its treatment

Periodontal disease is an infectious disease of the gums and tissues surrounding the teeth and causes tooth loss due to destruction of tooth-supporting tissues. It has been reported that the incidence rate of periodontitis is over 47% in adults in the United States of America [37]. More than 700 bacterial species or phyotypes have been detected in the oral cavity [38]. Some species/complexes are closely associated with advanced periodontal lesions, such as Porphyromonas gingivalis (P. gingivalis), Treponema denticola, Tannerella forsythia, Prevotella intermedia, Parvimonas micra, Fusobacterium nucleatum, Eubacterium nodatum and Aggregatibacter actinomycetemcomitans [39,40]. Among them, P. gingivalis, a Gram-negative anaerobic bacterium, is the major aetiological agent that contributes to periodontal disease progression and bone and tissue destruction [41,42]. The lipopolysaccharide (LPS) cell-wall component of P. gingivalis is one of the virulence factors that trigger a wide range of host responses, including the production of pro-inflammatory cytokines, anti-inflammatory cytokines and chemokines [43]. These cytokines and inflammatory mediators have important roles in the progression of periodontitis during a stage in which host immune and inflammatory responses lead to the destruction of periodontal tissue under the influence of multiple behavioural, environmental and genetic factors [44].

Recently, the number of studies which demonstrate that chronic periodontal disease (persistent low-grade infection of periodontal pockets by Gram-negative bacteria) is associated with increased DM, atherosclerosis, heart disease, liver cirrhosis and other systemic diseases via the bloodstream has been increasing [3-6]. It has also been suggested that DM and atherosclerosis improve through periodontal treatment [45-55]. Clozza E et al. [56] reported the case of the periodontal management in end-stage liver disease undergoing liver transplantation. At the same time, it has been mentioned that periodontal therapy delivered in close interaction with the referring physicians is important. Hence, it has been proposed that the prevention and management of periodontal disease under collaborative medical and dental care for patients with conditions such as atherosclerosis, DM and liver disease are important [57-63].

The main purpose of periodontal treatment is to control periodontal infection [64]. At first, instruction on the correct way to brush teeth is given to the patient with periodontal disease. Supra- and sub-gingival bacterial plaque/biofilm and calculus are then removed with periodontal scaling and root planning is performed [65].

The relationship between NAFLD and periodontal disease

Recently, studies on the relationship between NAFLD and periodontal disease have been published.

Research on Japanese university students has suggested that young males with periodontal disease had significantly increased levels of alanine aminotransferase (ALT) [66]. Also, clinical research in healthy Japanese women has demonstrated that the incidence of periodontal disease in females was significantly increased in individuals with elevated serum levels of aspartate aminotransferase (AST), ALT and cholesterol [67]. Furthermore, it has been reported from an observational study of annual workplace health check-ups at a company in Japan that an association between periodontal disease and the combination of elevated ALT and metabolic syndrome was confirmed in males [68]. It has also been suggested that in Japanese adults with severe periodontal disease and no drinking habit, serum levels of γ-glutamyl transferase (GGT), a liver biochemical parameter, are high [69].

In vivo study, it was demonstrated that areas of fibrosis with proliferation of hepatic stellate cells and collagen formation were observed in mice with P. gingivalis infection that were fed a high fat diet. In addition, it has been reported that in steatotic hepatocytes, expression of toll-like receptor 2 (TLR2), one of the P. gingivalis-LPS receptors, was upregulated. P. gingivalis-LPS further increased mRNA levels of the palmitate-induced inflammasome and proinflammatory cytokines in steatotic hepatocytes [13]. That is to say, dental infection with P. gingivalis exacerbated the pathological progression of NASH from simple steatohepatitis to steatohepatitis with fibrosis through upregulation of the P. gingivalis-LPS-TRLR pathway and activation of inflammasomes. Iliivski V et al. [70] suggested that biomarkers of oxidative stress in the liver were elevated in mice with periodontitis induced by P. gingivalis. Interestingly, Huang Y et al. reported that periodontitis contributes to adipose tissue inflammation through the nuclear factor-κB, B, c-Jun amino-terminal kinase and...
extracellular-signal regulated kinase pathways to promote insulin resistance in a rat model [71]. This mechanism by which periodontitis affects the inflammatory response and systemic insulin resistance in the white adipose and liver tissues may be related to the ‘first hit’ of the two-hit hypothesis which is considered as pathological mechanism of NAFLD. Recently, evidence in mice has shown that disturbance of the composition of gut microbiota by orally derived periodontopathic bacteria such as P. gingivalis may be a causal mechanism linking periodontitis and systemic disease including NAFLD [72-74].

Yoneda et al. [14] reported that the detection frequency of P. gingivalis in the saliva of patients with NAFLD and NASH was significantly higher than that of non-NAFLD control subjects. In addition, they presented preliminary findings showing that non-surgical periodontal treatments in 10 patients with NAFLD for 3 months improved liver function parameters such as serum levels of AST and ALT. Taking all of this into account, it is thought that infection with periodontal pathogens mainly composed of P. gingivalis is associated with fibrosis severity in patients with NAFLD and that the prevention and eradication of P. gingivalis infection through periodontal treatment may have a beneficial effect upon NASH.

We therefore hypothesized that treatment of oral infection, including P. gingivalis infection, by periodontal treatment in patients with NAFLD would ameliorate NAFLD-related clinical markers, and we started a clinical study to confirm this under collaborative medical and dental care.

The clinical study design

Objectives

The objectives are to investigate periodontal disease morbidity in patients with NAFLD and to assess the effect of periodontal treatment on NAFLD, under medical and dental collaborative care in Kanagawa Prefecture in Japan.

Study design and outcome measures

This is a prospective, multicentre, observational, cohort study. Enrolment of participants occurs at four institutes: Yokohama City University Hospital, Kanagawa Dental University Hospital Yokohama Clinic, Kanagawa Dental University Hospital and Iwasaki Internal Medicine Clinic. The study population is ambulatory medical patients and periodontal patients. The former are patients with NAFLD under consultation in the internal medicine or gastroenterology departments who are registered at collaborative investigation facilities, and the latter are patients who have not had treatment at a medical clinic but have been diagnosed as having periodontal disease by the department of periodontics and who are registered at collaborative investigation facilities (Figure 1).

Systemic examinations of fatty liver-related diseases and periodontal examinations will be performed at baseline by the individual physicians and dentists. Relationships between fatty liver-related clinical markers and periodontal clinical markers will be analysed statistically using the examination data. Periodontal treatment including scaling, root planning and instruction in proper home care techniques will be administered to the patients who consent to treatment. During periodontal treatment at the dental institutions, systematic observation will be continued with all patients given nutrition and exercise education at the medical institutions. Individual systemic examination results of fatty liver-related diseases and periodontal examination results will be compared before and after periodontal treatment.

The primary endpoint is ALT level. Secondary outcomes are levels of AST, gamma-glutamyl transpeptidase (γGTP) and albumin.

Inclusion criteria

Participant eligibility includes those aged at least 20 years old who have been diagnosed with NAFLD by routine ultrasound in the internal medicine or gastroenterology departments and who have also had a diagnosis of periodontal disease from specialists in periodontal diseases (a periodontal probing depth of 4 mm or more at any probing site in a periodontal examination).

Exclusion criteria

Participants will be excluded if they have:

- An alcohol intake of more than 20 g/day;
- Unstable NAFLD;
- An unstable medication situation;
- Hepatitis C;
- Hepatitis B;
- Autoimmune hepatitis;
- Primary biliary cirrhosis;
- Sclerosis cholangitis;
- Hemochromatosis;
- Alpha-antitrypsin deficiency;
- Wilson disease;
- A history of dental visits within the past 6 months;
- A history of antibiotic use within the past 6 months;
- A history of poor compliance with treatment.

Information collection including lifestyle of participants

Participants will answer a questionnaire about items such as the following: age, sex, height, weight, systemic history, information about medicines, smoking history, tooth brushing habits and the presence or absence of bruxism.

Systemic examination for fatty liver-related diseases

Participants will have blood tests and imaging examinations at the medical institutions. The blood test will include white blood count, red blood count, platelet count and levels of triglyceride, high-density lipoprotein cholesterol (HDL-C), LDL-C, AST, ALT, γGTP, albumin, fasting blood glucose, glycosylated haemoglobin (HbA1c) according to the National Glycohemoglobin Standardization Program (NGSP), C-reactive protein (CRP) and high-sensitivity CRP (hs-CRP). The imaging examination will be performed to confirm the presence or absence of fatty liver disease by ultrasonography or FibroScan®.

Clinical examination for periodontal disease

Participants will have the following periodontal examinations at the dental institutions: the amount of P. gingivalis in saliva by quantitative polymerase chain reaction (qPCR) and the periodontal disease infection level and severity. The periodontal disease infection level will be determined using a serum immunoglobulin G (IgG) antibody titre test for P. gingivalis FDC381 using an enzyme-linked immunosorbent
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assay (ELISA) [75]. Periodontal disease severity will be examined by probing pocket depths, clinical attachment levels, gingival bleedings on probing at six sites per tooth using a calibrated periodontal probe and the stability of the teeth.

Statistical analysis

The relationship between NAFLD severity (fatty liver-related clinical markers in systemic examinations) and periodontal disease severity (periodontal clinical markers in periodontal examinations) at baseline will be analysed by univariate analysis. In addition, risk factors for NAFLD will be analysed by multivariate analysis using lifestyle factors and fatty liver-related and periodontal clinical markers. Next, the comparison of systemic and periodontal examination results before and after periodontal treatment will be analysed by paired t-test for parametric data and Wilcoxon’s signed-rank test for non-parametric data.

Future perspective

If the study hypothesis is confirmed, periodontal treatment
may contribute to preventing the progression of fibrosis in patients with early NASH and mild fibrosis and to reducing the dose of drug therapy in patients with severe NASH. In future, we will establish an oral infection management system under collaborative medical and dental care to inhibit progression from NAFLD to NASH and aim to contribute to the promotion of good health from the dental side.

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