Cystic Fibrosis-Related Diabetes, Periodontitis, and Quality of Life in Adults with Cystic Fibrosis

Alaa Abdulrahman Alkhateeb

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Reading Committee:

Donald L. Chi, Chair

Lloyd A. Mancl

Kathleen J. Ramos

Dace L. Trence

Program Authorized to Offer Degree:

Oral Health Sciences

University of Washington

Abstract

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Alaa Abdulrahman Alkhateeb

Chair of the Supervisory Committee:

Donald L. Chi

Department of Oral Health Sciences

There are few studies on the oral health of individuals with cystic fibrosis (CF), even though poor oral health is a potential contributor to worsening chronic health conditions. Periodontitis, the inflammation of hard tissues that support and anchor the teeth, is a source of infection that could compromise the respiratory health of individuals with CF. Periodontitis is independently associated with increased systemic inflammation and is a complication of diabetes. CF-related diabetes (CFRD) is a common comorbidity of CF impacting up to 50% of adults with CF. Other CF-related comorbidities like asthma and bone diseases as well as CF-related treatments like continued use of inhaled medications can also increase one's risk for periodontitis. To date, there is no study that evaluated whether CFRD and other CF-related medical factors are associated with

increased risk of periodontitis, nor whether the presence of periodontitis impact the quality of life of adults with CF.

The main objectives of this dissertation were to: 1) identify CF-related correlates of periodontitis in adults with CF; 2) evaluate the association between CFRD and periodontitis; 3) compare the periodontal health of adults with CF to matched non-CF controls, accounting for diabetes status; and 4) evaluate the impact of periodontitis on the quality of life of adults with CF. We designed a cross-sectional study of adults with CF (age ≥ 18 years) who were recruited from the Adult CF Center at the University of Washington, Seattle, WA, U.S.A. A single study visit was scheduled for study participants at the Regional Clinical Dental Research Center at the University of Washington School of Dentistry. Study visit included a full periodontal examination and self-administered oral health and diet surveys. Periodontitis was defined using the U.S. Centers for Disease Control and Prevention and the American Academy of Periodontology case definition. We assessed the oral health-related quality of life (OHRQoL) for adults with CF using the Oral Health Impact Profile 14 and the cystic fibrosis-related quality of life (CFRQoL) using the Cystic Fibrosis Questionnaire Revised. We utilized the 2013-2014 National Health and Nutrition Examination Survey to form non-CF control groups. Non-CF controls were frequency matched to adults with CF on age, sex, diabetes status, and insulin status. We used the Fisher's exact test, the Mann-Whitney test, the Kruskal-Wallis test, and the Spearman rank correlation for hypotheses testing.

Our analyses did not identify CF-related correlates of periodontitis for adults with CF. Rather, correlates of periodontitis identified in our study are similar to previously reported correlates in the general population. Within the study population with CF, CFRD was not significantly associated with periodontitis. However, compared to healthy non-CF controls, adults with CF with and without CFRD had significantly higher prevalence of periodontitis despite having higher markers of socioeconomic status than healthy non-CF controls. In addition, both CF groups with and without CFRD had similar periodontitis prevalence to non-CF controls with diabetes, even though the non-CF controls with diabetes had significantly higher glucose levels than the two CF groups. Periodontitis was not associated with OHRQoL or CFRQoL for adults with CF. However, our analyses showed disparities in OHRQoL and in CFRQoL for adults with CF by socioeconomic status.

Evaluating the impact of CF-related comorbidities and treatments on the periodontal health of adults with CF is the next step to understanding the oral health needs of this medically vulnerable population. Future studies should evaluate if an interaction between different CF-related medical factors explains the difference in periodontitis by CF status found in our study. Furthermore, it is critical to ensure adequate diversity of future study populations with CF–particularly in terms of race, socioeconomic status, dental care access, and CF phenotypes–to identify barriers to optimal periodontal health that is general for all adults with CF.

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LIST OF ABBREVIATIONS

ASA-24	Automated self-administered 24-hour dietary assessment tool
BMI	Body mass index
CAL	Clinical attachment loss
CDC/AAP	Centers for Disease Control and Prevention and the American Academy of Periodontology
CF	Cystic fibrosis
CFQ-R	Cystic fibrosis questionnaire revised
CFRD	Cystic fibrosis-related diabetes
CFRQoL	Cystic fibrosis-related quality of life
CFTR	Cystic fibrosis transmembrane regulator
COVID-19	Coronavirus disease of 2019
DII	Dietary inflammatory index
DM	Diabetes mellitus
FEV_1% predicted	Forced expiratory volume in one second percent predicted
HbA1c	Glycated hemoglobin
HIPAA	Health insurance portability and accountability Act
HRQoL	Health-related quality of life
IQR	Interquartile ranges
kg/m^2	Kilogram per square meter
mg/L	Milligram per liter
NHANES	National Health and Nutrition Examination Survey

OGTT	Oral glucose tolerance test
OHIP-14	Oral health impact profile 14
OHRQoL	Oral health-related quality of life
PD	Periodontal pocket depth
SD	Standard deviation

Acknowledgements

The submission of this dissertation marks an exciting final milestone in my graduate school training at the University of Washington (UW). In addition to learning about cystic fibrosis (CF), diabetes, periodontitis, statistics, and how to lead a clinical study, I have gained important knowledge on how to participate in interdisciplinary research work and how to engage with the scientific community.

I acknowledge with gratitude the participants of this study, who without whom this dissertation would not be possible. Meeting study participants and learning from their experience with CF was a highlight of completing this dissertation. I have been inspired by the commitment of study participants to advancing CF research by continuing to participate in CF research. I also acknowledge the staff at the Regional Clinical Dental Research Center at the UW School of Dentistry, especially the center director Marilynn Rothen, RDH, MS. In addition to her role as the clinical examiner in this study, Ms. Rothen has provided expertise in developing study protocols and attaining the human subject research approval from the UW Institutional Review Board. I would also thank Ms. Rothen for her exceptional support throughout my time at UW and for being a role model for all dental hygiene educators. I also thank the staff at the UW CF Foundation Research Development Program and the UW Adult CF Center for being a great source of support in the completion of this project. The data presented in this dissertation were collected with the support from the National Center For Advancing Translational Sciences of the National Institutes of Health (Grant Number: UL1 TR002319), by the

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science to help elevate the life of those who are disproportionally impacted by health disparities. I'm also very grateful to Dr. Chi for creating an inclusive and motivating lab environment. Being in a such positive environment has motivated me to excel in my roles as a researcher. Dr. Chi was also a great support to me during the challenging time of completing my dissertation during a global pandemic in addition to being away from my family. While I have been lucky to have made many mentors and role models throughout my training at UW, I attribute my success in graduate school and the exceptional time I had at UW, in a large part, to Dr. Chi.

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Dedication

For my favorite people, Abdulrhaman Alkhateeb and Noral Alarifi

Chapter 1. Introduction

1.1. Cystic fibrosis

Cystic fibrosis (CF) is a life-limiting autosomal recessive disease caused by defects in the cystic fibrosis transmembrane regulator (CFTR) gene (1). Defects in the CFTR result in abnormal transport of chloride and bicarbonate across the cell membrane, affecting several organ systems including respiratory, digestive, endocrine, and reproductive systems (2). The main cause of morbidity and mortality for individuals with CF is respiratory diseases resulting from overproduction and accumulation of mucus in the lungs. In the U.S., there are more than 35,000 individuals with CF and about 1,000 new cases diagnosed every year (3).

Since the 1930's, CF clinical management was focused on multifaceted symptomatic treatments and extensive prophylactic daily treatments (4). Significant advancements in CF therapies were achieved with the introduction of CFTR modulating therapy designed to correct the basic defect caused by CFTR mutations. In 2019, there was a breakthrough in CF therapy when the U.S. Food and Drug Administration approved a triple combination therapy (elexacaftor/tezacaftor & ivacaftor) that is mostly recognized for restoring the protein function defected by mutation on the Fdel508 gene (the most prevalent CFTR mutation), making the therapy suitable for use by around 90% of individuals with CF (5). The significant advancements in CF diagnosis and treatments over the years have steadily extended the median predicted survival for individuals with CF from a few months following diagnosis to 50 years, as observed for individuals with

CF registered in the U.S. CF Foundation patient registry in the years 2016 to 2020 (1). Despite advancements in CF diagnosis and treatments, individuals with CF are at high risk of respiratory infections, and many are involved with daily complex and time-consuming medical treatments that can impact quality of life (6).

1.2. Periodontitis

Periodontitis is a bacterial-induced inflammation characterized by destruction of the tooth–supporting tissues that leads to the development of periodontal pockets, alveolar bone loss, tooth mobility and eventually tooth loss (7). Periodontitis is the leading cause of tooth loss in the U.S. for adults ages 30 years or older (8). The host response to periodontal bacteria can be modified by behavioral factors, systemic diseases, and medications (7). Epidemiological data from the National Health and Nutrition Examination Survey (NHANES) 2009 to 2012 estimated that 46% of the U.S. adult population ages 30 years and older had periodontitis and around 9% had severe periodontitis (8). The prevalence of periodontitis increases with age and is higher in males, Hispanics and non-Hispanic Black adults, smokers, adults with diabetes, adults with low socioeconomic status, and adults with low educational attainment (8).

Periodontitis is independently associated with increased systemic inflammation and is identified as a comorbidity to several chronic diseases such as diabetes mellitus, cardiovascular disease, and chronic obstructive pulmonary diseases (9–11). The correlations between these chronic conditions and periodontitis can be explained by shared risk factors like increased systemic inflammation and impaired innate and

acquired immunity as a result of chronic conditions leading to exaggerated host response to periodontal pathogens. Periodontitis can be a source of infection that could compromise the respiratory health of individuals with CF, as studies showed an increased risk of micro-aspiration of oral bacteria and links between oral infections and decreased lung function in individuals with lung diseases (12–14). The potential links between oral health and respiratory health have not been formally studied in adults with CF.

1.3. CF-related diabetes and other CF-medical factors as potential risk factors for periodontitis

CF-related medical factors like CF-related diabetes (CFRD), systemic inflammation associated with frequent lung infections, asthma, anxiety, depression, bone disease, and chronic use of inhaled medications present a high-risk profile for periodontitis (7,10,14–16). CFRD is a common comorbidity in individuals with CF (17,18). By adulthood, 40% to 50% of individuals with CF are diagnosed with CFRD and another 30% have glucose impairment (prediabetes). Potential biological mechanisms linking diabetes and periodontitis include periodontal bacteria triggering a host defense response, which increases diabetes-induced systemic inflammation and leads to periodontal tissue destruction (9,19–21). The association between diabetes and periodontitis may also be bidirectional. Longitudinal studies showed treatment of periodontitis was associated with improved glycemic control (22,23). Despite the strong links between diabetes mellitus and periodontitis, it is unknown if CFRD impacts the periodontal health of adults with CF.

Other CF-related medical factors described above may also increase an individual's risk of periodontitis through different systemic, local, and behavioral mechanisms. First, systemic mechanisms like increased immunological response associated with asthma and decreased bone density in the case of bone diseases create a favorable environment for exaggerated host immune response and increased severity of periodontal tissue destruction (11,16). Second, CF-related medical factors may increase the risk of periodontitis through local mechanisms such as continued use of dry-mouth inducing treatments like inhaled medications and anti-depressants. This leads to decreased mechanical cleansing of saliva and increased accumulation of dental plaque, increasing the risk of periodontitis (16,24). Third, potential behavioral mechanisms include reduced oral hygiene practices and reduced utilization of dental care, both of which have been associated with chronic medical conditions (25,26). For instance, studies showed increased prevalence of dental-related anxiety for individuals with generalized anxiety disorder and an association between anxiety, avoiding dental visits, and irregular oral hygiene practices (15,27). Moreover, a retrospective study of Medicaid-enrolled children with CF showed that children with CF were significantly less likely to utilize dental care than their counterparts without CF (26). This difference in dental care utilization might be attributed to a diversion of resources whereby the expensive and time-consuming CF-related health care prevents directing resources to dental care for individuals with CF. Another potential explanation is that individuals with CF consider CF clinics as their medical home, at which they may not be receiving recommendations for establishing dental homes, recommendations they might

otherwise receive during primary care visits (28). To date, there are no published studies on the access to dental care and determinants of dental care utilization for adults with CF.

Despite the potential CF-related risk profile described above, the majority of studies of the periodontal health of individuals with CF reported lower periodontal disease rates compared to controls and attributed this finding to the chronic use of antibiotics to treat lung infections (29–31). However, these studies are old, did not include full-mouth comprehensive periodontal examinations, and were mainly focused on children and adolescents, an age group with low risk of periodontal disease. Only one study exclusively focused on adults with CF and showed more than half of the study population had periodontal disease (32). To date, no study has evaluated whether the above-mentioned CF-related risk profile is associated with periodontitis in adults with CF.

1.4. Periodontitis and health-related quality of life

Health-related quality of life (HRQoL) describes the broader impact of a medical condition on patients' physical, social, and emotional functioning (33,34). Studies showed periodontitis is associated with low HRQoL independent of other oral conditions (7). While tooth mobility and tooth loss–signs of severe periodontitis–are the major symptoms associated with lower quality of life, studies have also showed clinical measures of periodontitis (e.g., deep periodontal pockets and increased clinical attachment loss) to be associated with lower HRQoL (35,36). Generally, the impact of

periodontitis on the HRQoL of adults with chronic medical conditions is not well studied, and no known studies have assessed the impact of periodontitis on the quality of life of adults with CF.

1.5. Study goal

The primary goal of this study is to evaluate how CFRD and other CF-related medical factors are associated with the periodontal health of adults with CF and whether periodontitis is associated with low health related quality of life in this medically vulnerable population.

1.6. Study objectives and hypotheses

There are currently no published studies that evaluated the determinants of periodontal health for adults with CF. The objectives of this dissertation were to: 1) identify CF-related correlates of periodontitis in adults with CF; 2) evaluate the association between CFRD and periodontitis; 3) compare the periodontal health of adults with CF to matched non-CF controls, accounting for diabetes status; and 4) evaluate the impact of periodontitis on the quality of life of adults with CF.

Through primary cross-sectional clinical and survey data collection from adults with CF (age ≥18 years) and secondary data analysis of NHANES data we tested the following hypotheses:

1) CF-related medical factors are associated with increased periodontitis in adults with CF.

2) Adults with CFRD have a higher prevalence of periodontitis than adults with CF with no CFRD.
3) Periodontal health differs by CF and diabetes status.
4) Periodontitis is associated with low oral health-related quality of life.
5) Periodontitis is associated with low CF-related quality of life.

1.7. Clinical and research significance

This pilot study provides work to date in studying the periodontal health of adults with CF and advances our understanding of the determinants of oral health and health related quality of life for adults with CF that could help inform new standards of dental clinical care for this medically vulnerable population. Our analyses also provide a new perspective of the association between diabetes and periodontitis by studying it in a new population, which helps define future research priorities for studying this association, particularly in the context of complex health conditions like CF.

Chapter 2. Description of The Periodontal Health of Adults with Cystic Fibrosis Clinical Study.

2.1. Study design overview

This was a cross-sectional study. We recruited adults with CF (age ≥ 18 years) from the Adult CF Center at the University of Washington, Seattle, WA, U.S.A., from November 2019 to June 2021. A HIPAA waiver of consent was approved by the Institutional Review Board at the University of Washington to allow for a medical record screening to identify eligible study participants. We obtained informed consent and HIPAA authorization from participating adults with CF at the study visit to allow for subsequent abstraction of medical record data for study variables. The study was approved by the Institutional Review Board at the University of Washington (protocol no: 00007976).

2.2. Study population

Inclusion criteria included: a confirmed diagnosis of CF; 18 years and older; able to provide written informed consent; and able to complete surveys in English (**Figure 2.1**). There were four exclusion criteria. First, because of the high contagion risk for adults with CF, we excluded adults with active infection with *Burkholderia cenocepacia* or *Mycobacterium abscessus* in the prior two years. Second, to reduce potential bias of adverse impact of steroids on blood glucose level and the impact of pulmonary exacerbations on quality of life, we excluded adults with pulmonary exacerbation requiring intravenous antibiotics or systemic steroids in the prior 4 weeks. Third, because smoking is a strong risk factor for periodontitis, and smoking is rare among adults with CF, we excluded adults with a history of smoking to avoid potential effect

modification of the association between CFRD and periodontitis that we could not adjust for. Fourth, for adults who need prophylactic antibiotics for dental exams, the benefit of being in an observational dental study did not outweigh the risk of taking prophylactic antibiotics. Thus, we excluded adults who needed prophylactic antibiotics for dental visits.

2.3. Study procedures

There were six study procedures in the single study visit: 1) recruitment and consent, 2) oral health survey, 3) diet assessment, 4) oral hygiene assessment, 5) periodontal screening, and 6) medical record abstraction (**Figure 2.2**).

2.3.1. Recruitment and consent

Based on the inclusion and exclusion criteria described above, we identified 140 eligible adults with CF who were invited to participate in the study by the study principal investigator or a research coordinator by phone, email, or in-person during a CF clinical visit. A single two-hour study visit was then scheduled at the Regional Clinical Dental Research Center at the University of Washington School of Dentistry. The study visit included a self-administered oral health and diet surveys and periodontal screening performed by a registered dental hygienist. We followed the Cystic Fibrosis Foundation and the American Dental Association guidelines for infection control. If an adult with CF had unmet dental treatment needs, we gave them a referral to the University of Washington School of Dentistry. We provided oral hygiene instruction at the end of the

study visit. Enrolled adults with CF were given a $95 incentive as a reimbursement for their time and parking costs and an oral hygiene kit.

2.3.2. Oral health survey

We administered a 22-item survey instrument in English. The survey included questions on sociodemographic factors (race, ethnicity, household income, education level, food insecurity, dental insurance), history of dental care utilization, and personal oral hygiene habits. We designed the survey using REDCap™, and adults with CF used an iPad to complete the survey. Oral health survey is included in **Supplementary Table 2.1**.

2.3.3. Diet assessment

We collected 24-hour dietary recalls using the Automated Self-Administered 24-Hour (ASA-24) dietary assessment tool. ASA-24 is a web-based tool developed by the National Cancer Institute and is a practical and cost-effective alternative to the standard interviewer-administered 24-hour dietary recall (37). Adults with CF completed the ASA-24 based on their dietary intake on the previous day of the study visit. The diet assessment in this study specifically focused on the inflammatory potential using the Dietary Inflammatory Index (DII). A description of the design and development of the original DII was previously reported (38). The current study incorporated the latest version of DII, which represents an improved scoring algorithm based on an extensive review of the literature and of world food consumption data from several countries (39). Briefly, a total of 45 food parameters (types of food and nutrients) derived from dietary data were assigned inflammatory effect scores based on the research findings from

1,943 selected articles, published from 1950 to 2010, examining the role of the food parameters on six established inflammatory biomarkers (IL-1ß, IL-4, IL-6, IL-10, TNF-a, and C-reactive protein). World food consumption data, based on 11 diverse populations around the world, were used to generate a mean and a standard deviation for each food parameter. An individual's diet was then linked to the world food database as a z-score, calculated by subtracting the standard global mean and dividing by its standard deviation. This z-score was then converted to a centered percentile score to minimize the risk of right skewing. The centered percentile score for each food parameter was multiplied by its respective inflammatory effect score generating a specific food parameter DII. The DII scores for each food parameter was then summed to create an overall DII score for an individual. An overall DII score could be positive or negative. Higher positive DII scores indicate a more pro-inflammatory diet, and negative scores imply a more anti-inflammatory diet.

To calculate DII for adults with CF, we utilized 28 out of the 45 food parameters used in the original study (38), for which we had dietary intake data collected. These parameters included total calories, total fat, saturated fat, monounsaturated fat, polyunsaturated fat, omega-3 fatty acids, omega-6 fatty acids, protein, carbohydrate, fiber, alcohol, cholesterol, niacin, thiamin, vitamin A, vitamin B2, vitamin B6, vitamin B12, vitamin C, vitamin D, vitamin E, iron, magnesium, selenium, zinc, folic acid, ß carotene, and caffeine. We calculated the total DII scores per 1000 calories of food consumed to control for the effect of variations in total energy intake across participants.

2.3.4. Oral hygiene assessment

We assessed oral hygiene using the Silness-Löe plaque index (40). We assessed the presence of dental plaque on four surfaces (mesial, distal, buccal, and lingual) of six teeth (maxillary right first molar, maxillary right lateral incisor, maxillary left first premolar, mandibular left first molar, mandibular left lateral incisor, and mandibular right first premolar). A tooth surface was scored in the following manner: 0= no plaque;1= plaque may only be recognized by running a probe across the tooth surface above the gingival margin; 2= moderate accumulation of soft deposits visible with the naked eye; 3= an abundance of soft matter within the gingival pocket, on the tooth, or gingival margin. Consistent with previous studies, the mean plaque score was computed across examined surfaces and used to determine the oral hygiene category as in the following: 0.00-0.09= excellent oral hygiene; 0.10-0.99= good oral hygiene; 1.00-1.99= fair oral hygiene; 2.00-3.00= poor oral hygiene (40).

2.3.5. Periodontal screening

At the beginning of the study visit, we reviewed health history data obtained from the medical record to confirm there were no contradictions to conducting a dental examination.

Each adult with CF received a full-mouth periodontal examination using a manual UNC-15 periodontal probe. Two periodontal measures were assessed at six sites per tooth (disto-buccal, mid-buccal, mesio-buccal, disto-lingual, mid-lingual, and mesio-lingual) for all teeth present, excluding third molars (41). The first measure was periodontal pocket

depth (PD), defined as the distance in millimeters (mm) from the free gingival margin to the bottom of periodontal sulcus. Second, gingival margin level is the distance in mm from the free gingival margin to the cementoenamel junction. Gingival margin level takes a negative value if the free gingival margin is apical (i.e., toward the tooth root) to the cementoenamel junction; zero value if the free gingival margin is at the level of cementoenamel junction; and a positive value if the free gingival margin is coronal (i.e., toward the tooth crown) to the cementoenamel junction. All measurements of PD and gingival margin level were rounded to the lowest whole mm. Then clinical attachment loss (CAL) was calculated by subtracting gingival margin level from PD using the following equation: CAL = PD – (+/–) gingival margin level.

2.3.6. Medical record abstraction

We abstracted sociodemographic data including age, sex, and health insurance type. We abstracted medical data including CF-transmembrane conductance regulator (CFTR) genotype, most recent forced expiratory volume in one second percent predicted (FEV_1% predicted), referral and evaluation for lung transplant, comorbidities (CFRD, bone disease (osteoporosis and/or osteopenia), pancreatic insufficiency, anxiety, depression), glycated hemoglobin (HbA1c), body mass index (BMI), C-reactive protein, and current medication use (CFTR modulator, antibiotic, non-antibiotic inhaled medications). CFTR modulator therapy was defined as (triple CFTR modulator therapy (elexacaftor/tezacaftor/ivacaftor), other CFTR modulator therapy (ivacaftor, lumacaftor/ivacaftor, or tezacaftor/ ivacaftor), or none. We defined antibiotic use as current use of oral or inhaled antibiotic (yes/no).

2.3.7. Sample size calculation

The sample size calculation was determined based on the differences in clinical measures of periodontitis (PD, CAL) between adults with CFRD and adults with CF without CFRD. In the diabetes literature, differences range from two to three standard deviations (SD) in PD and CAL (8). According to studies of the periodontal health of adults with diabetes, 1 SD corresponds to 0.6 mm in PD, and 1 mm in CAL (42). The difference of 1 SD in the periodontal measures between adults with CFRD and adults with CF without CFRD was the basis of our sample size calculation. To be able to detect a 1 SD difference with a power of 0.8 using significance level of 0.05, a minimum sample size of 17 individuals per group is needed (CFRD and CF without diabetes).

Figure 2.1. Identification and enrollment of adults with CF.

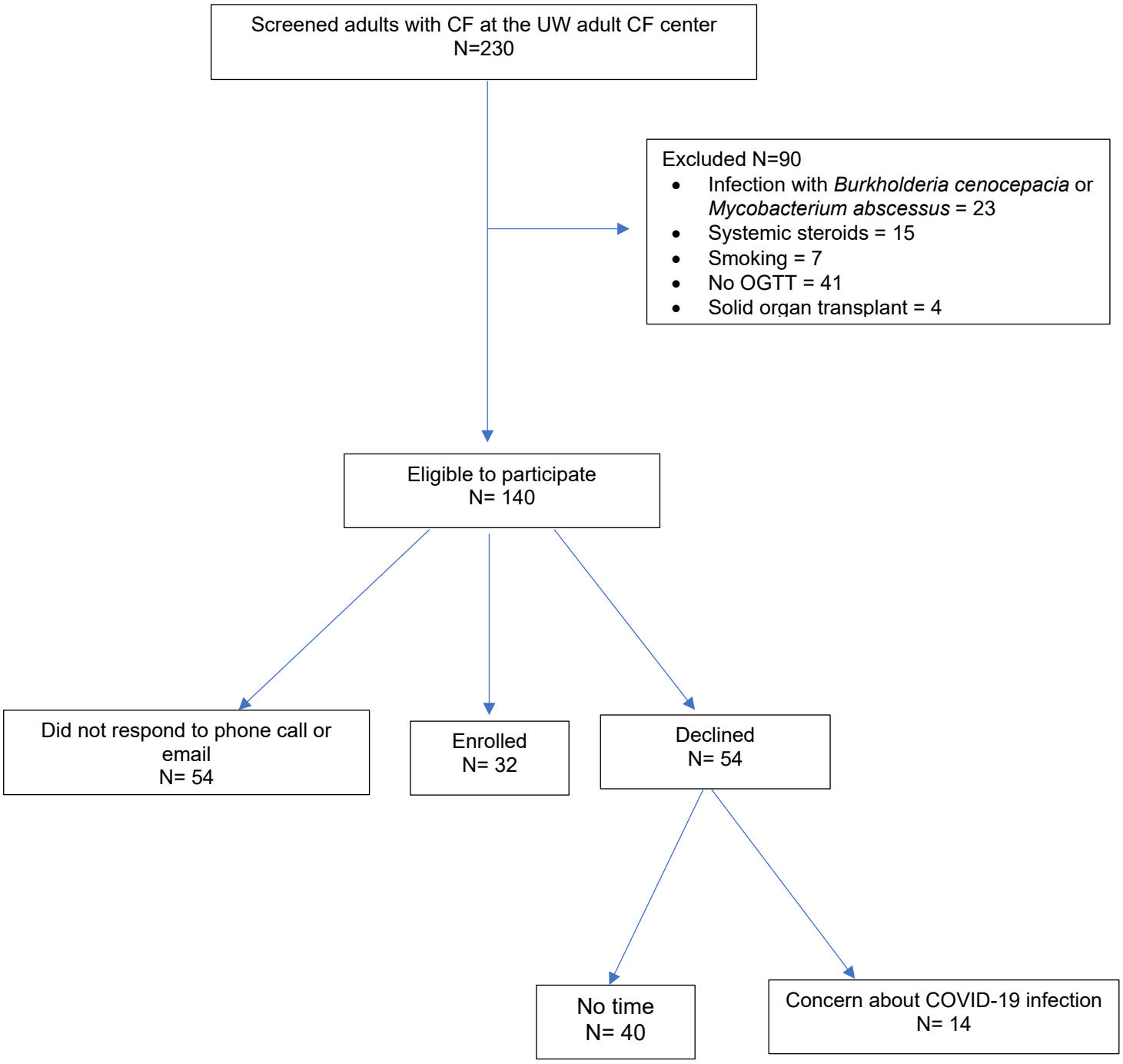
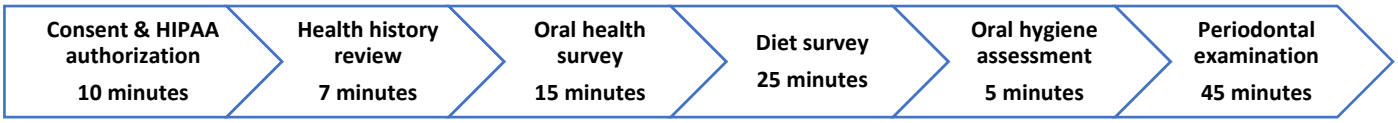


Figure 2.2. Sequence and duration of study procedures for adults with CF during a single study visit.



Supplementary Table 2.1. Oral health survey for adults with CF.

Survey question	Answer choices
Part 1: Oral Health	
1. Overall, how would you rate the health of your teeth and gums?	- Excellent - Very good - Good - Fair - Poor - I don't know
2. Do you think you might have gum disease?	- Yes - No - I don't know
3. Have you ever had treatment for gum disease such as scaling and root planing, sometimes called "deep cleaning"?	- Yes - No - I don't know
4. Have you ever had any teeth become loose on their own, without an injury?	- Yes - No - I don't know
5. Have you ever been told by a dental professional that you lost bone around your teeth?	- Yes - No - I don't know
6. During the past three months, have you noticed a tooth that doesn't look right?	- Yes - No - I don't know
7. Which of the following types of home care products do you use? (Check all that apply)	- Regular toothbrush - Electric toothbrush - Floss - Interdental brush - Waterpik - Other
8. How often do you brush your teeth?	- More than once a day - Once a day - A few times a week - Once a week - Never - I don't know
9. How often do your teeth or gums bleed when they are brushed?	- Always - Sometimes - Never - I don't know
10. Do you floss your teeth?	- Yes - No
11. How often do you floss your teeth?	- More than once a day - Once a day - A few times a week - Once a week - I don't know
12. How often do your teeth or gums bleed when you use dental floss?	- Never - Sometimes - Always
13. Have you ever used tobacco?	- Yes - No
14. Do you have dental insurance?	- Yes - No

15. When was the last time you visited a dentist?	- 6 months ago or less - More than 6 months, but not more than 1 year ago - More than 1 year ago - More than 3 years ago - I have never been to the dentist
16. During the past 12 months, was there a time when you needed dental care but could not get it at that time?	- Yes - No
Part 2: Miscellaneous Questions	
17. What is your date of birth	- mm/dd/yyyy
18. What is your race/ethnicity? (Check all that apply)	- American Indian or Alaska Native Asian - Black or African American - Native Hawaiian or Pacific Islander - White or Caucasian - Other
19. Are you Hispanic or Latino(a)?	- Yes - No
20. What is the highest level of schooling you completed?	- Less than high school - High school, GED, or equivalent - Some college - 4-year college degree - More than 4-year college degree
21. Do you receive assistance to pay for food (like SNAP or food stamps)?	- Yes - No
22. What is the estimated total annual income of all people in your household?	- Less than $20,000 - $20,000 to $29,999 - $30,000 to $49,999 - $50,000 to $69,999 - $70,000 to $89,999 - More than $90,000 - I don't know - I prefer not to answer

Chapter 3. Correlates of Periodontitis in Adults with Cystic Fibrosis

Authors

Alaa A. Alkhateeb [a]

Lloyd A. Mancl [a]

Kathleen J. Ramos [b]

Georgios A. Kotsakis [c,d]

Dace L. Trence [e]

Marilynn L. Rothen [a]

Donald L. Chi [a,f] (Chair)

[a] Department of Oral Health Sciences, School of Dentistry, University of Washington, Seattle, WA, USA.

[b] Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, University of Washington, Seattle, WA, USA.

[c] Department of Periodontics, Dental School, University of Texas Health at San Antonio, San Antonio, TX, USA.

[d] Department of Global Health, University of Washington, Seattle, WA, USA.

[e] Division of Metabolism, Endocrinology, and Nutrition, Department of Medicine, University of Washington, Seattle, WA, USA.

[f] Department of Health Systems and Population Health, School of Public Health, University of Washington, Seattle, WA, USA.

Abstract

Background and objective: Individuals with cystic fibrosis (CF) present with several periodontitis risk factors like CF-related diabetes, asthma, bone disease, anxiety, depression, increased systemic inflammation associated with frequent lung infections, and chronic use of inhaled medications. Despite this risk profile, most studies of CF and periodontal health report lower periodontal disease rates in individuals with CF compared to non-CF controls and attribute this difference to the frequent use of antibiotics to treat lung infections. However, these studies are old, do not include a full-mouth periodontal exam, and focus on children and adolescents with CF, an age group for which the prevalence of periodontal disease is low. To date, no study has evaluated whether the high-risk profile described above is associated with increased periodontitis in adults with CF. Thus, we hypothesized that the above CF-related risk profile is associated with increased periodontitis in adults with CF.

Methods: We conducted a pilot cross-sectional study of adults with CF (age ≥18 years) at a single CF center in Seattle, Washington, USA (N=32). We assessed two periodontal measures (periodontal pocket depth (PD) and clinical attachment loss (CAL)). Our outcome was periodontitis defined following the U.S. Centers for Disease Control and Prevention and the American Academy of Periodontology as the presence of at least two interproximal sites with CAL ≥3 mm, and two or more interproximal sites with PD ≥4 mm (not on the same tooth) or one site with PD ≥5 mm. CF-related medical factors and other sociodemographic factors and oral health behaviors were assessed as potential correlates of periodontitis. We also assessed the associations between the abovementioned correlates and clinical periodontal measures (PD, CAL). We used the

independent samples t-test, the Fisher exact test, and the exact chi square test for hypothesis testing.

Results: Sixty percent of adults with CF had periodontitis. There were no significant associations between CF-related medical factors and periodontitis: CF-related diabetes (P=0.49), asthma (P=0.68), bone disease (P=0.99), anxiety (P=0.70), depression (P=0.99), C-reactive protein (P=0.10), inhaled medication use (P=0.99), and antibiotic use (P=0.99). Of the non-CF related correlates, age and daily flossing were significantly associated with increased CAL (age *r*= 0.39, 95% CI=0.034,0.67; P=0.028), (daily flossing, median CAL: daily flossing 2.0mm vs. no daily flossing 1.5mm; P= 0.004).

Conclusions: Contrary to our hypothesis, CF-related medical factors were not associated with periodontitis in adults with CF. Rather, the correlates of periodontitis identified in our study are similar to previously reported correlates in the general population. This suggests adults with CF are not at higher risk of periodontitis than the general population. Future studies should consider a multicenter approach to increase the diversity of study population with CF to verify the generalizability of our study findings.

3.1. Introduction

Cystic Fibrosis (CF) is a life-limiting autosomal recessive disease that affects multiple organ systems (1). The main cause of morbidity and mortality in individuals with CF is respiratory disease resulting from accumulation of thick mucus in the lungs (2). In the U.S., there are more than 35,000 individuals with CF and about 1,000 new cases diagnosed every year (3). Historically, individuals with CF died during childhood. Now, as a result of the advancement in diagnosis and treatment, more than half of the CF population is 18 years and older, and the median survival age of individuals with CF is 44.4 years (1).

Periodontitis is a result of host immune response to dysbiosis of the commensal oral microbiota leading to inflammation and disease of hard tissues that support and anchor the teeth creating deep periodontal pockets (7). Over time in patients with periodontitis, the bone around the teeth is lost, leading to tooth loss. Periodontitis is the leading cause of tooth loss in US adults ages 30 years or older (8). Periodontitis has a negative impact on quality of life and overall well-being (35,43) and is independently associated with increased systemic inflammation compromising general health (44). Periodontitis is a source of infection that could compromise the respiratory health of individuals with CF. Studies have demonstrated an increased risk of micro-aspiration of oral bacteria and links between oral infections and decreased lung function in individuals with lung diseases (12,13,45–47). Potential links between oral health and respiratory health have not yet been studied in adults with CF.

CF-related comorbidities and treatments like CF-related diabetes (CFRD), increased systemic inflammation associated with frequent lung infections, asthma, bone disease, anxiety, depression, and chronic use of inhaled medications potentially increase one's risk of developing periodontal disease (7,10,14,15). Despite this risk profile, most studies of CF and periodontal health reported lower periodontal disease rates in individuals with CF compared to non-CF controls and attributed this difference to the frequent use of antibiotics to treat lung infections (29,31,48). Collectively, these studies form the current knowledge base of CF and periodontal health. However, these studies are outdated (1977-2009), did not include a comprehensive periodontal examination, and were mainly focused on children and adolescents, an age group for which the prevalence of periodontal disease is low. Only one study had exclusively focused on adults with CF and showed more than half of the study population had periodontal disease (32). To date, no study has evaluated whether the CF-related risk profile described above is associated with increased periodontitis in adults with CF. Thus, in this study we hypothesized that the above CF-related risk profile is associated with increased periodontitis in adults with CF. This study is a continuation of efforts to better understand the oral health needs of individuals with CF that would help inform new standards of dental clinical care for this medically vulnerable population.

3.2. Methods

3.2.1. Study design and participants

This was a cross-sectional study of adults with CF ages ≥18 years recruited from a single adult CF center in Seattle, WA. The single study visit included a full mouth

periodontal exam and diet and oral health surveys. A complete description of the cross-sectional study design, procedures, and inclusion and exclusion criteria of adults with CF were previously described in **Chapter 2.**

3.2.2. Outcome measure

Based on the periodontal exam findings, we created a binary variable to indicate whether an adult with CF had periodontitis (yes/no), a complete description of the periodontal exam was previously described in **Chapter 2**. Periodontitis was defined using the U.S. Centers for Disease Control and Prevention and the American Academy of Periodontology (CDC/AAP) case definition, which is based on periodontal pocket depth (PD) and clinical attachment loss (CAL) (49). The (CDC/AAP) case definition indicates that mild periodontitis is defined by the presence of two or more interproximal sites with CAL ≥3 mm and two or more interproximal sites with PD ≥4 mm (not on the same tooth), or one site with PD ≥5 mm. Moderate periodontitis is defined as the presence of two or more interproximal sites with CAL ≥4 mm (not on the same tooth), or two or more interproximal sites with PD ≥5 mm (not on the same tooth). Severe periodontitis is defined as the presence of two or more interproximal sites with CAL ≥6 mm (not on the same tooth) and ≥1 interproximal site with PD ≥5 mm. Our outcome was any periodontitis (yes/no) despite severity of the disease.

3.2.3. Predictor variables

We adapted the multifactorial oral health risk factor model for individuals with CF by *Chi, et al.* (13) to identify correlates of periodontitis in adults with CF (**Figure 3.1**). We focused

on CF-related medical correlates including CF-transmembrane conductance regulator (CFTR) genotype, CFRD, bone disease, anxiety, depression, CFTR modulator use, antibiotic use, inhaled medication use, most recent forced expiratory volume in one second percent predicted (FEV_1% predicted), body mass index (BMI), and C-reactive protein. We also evaluated other non-CF correlates of periodontitis that were grouped in two major domains: sociodemographic (age, sex, household income, health insurance, and dental insurance), and oral health behaviors (oral hygiene status, brushing, flossing, dental care utilization, unmet dental treatment needs, and dietary inflammatory index (DII)). Description of correlates are presented in the (**Supplementary Table 3.1.**). Supplementary Table 3.1 also summarizes whether correlates were formally tested in previous studies or were tested as new hypotheses in this study.

3.2.4. Data analysis

We used descriptive statistics to report on study variables using means and standard deviations (SD) for normally distributed quantitative variables, medians and interquartile ranges (IQR) for non-normally distributed quantitative variables, and frequencies and percentages for categorical variables.

For hypothesis testing, first, we assessed the associations between potential correlates and periodontitis status. We used independent samples t-test for normally distributed quantitative variables, the Mann-Whitney test for non-normally distributed quantitative variables, the Fisher exact test for binary variables, and exact chi-square test for categorical variables. Second, we assessed the associations between potential

correlates and clinical measures of periodontitis (PD, CAL). We used Spearman rank correlation for continuous variables, the Mann-Whitney test for binary variables, and the Kruskal-Wallis test for categorical variables.

Because this was a pilot study and hypothesis generating, no adjustment was made for multiple statistical tests. Statistical significance was set at 0.05 for all statistical analysis and all tests were two-sided.

3.3. Results

3.3.1. Study population

Of the 140 eligible individuals, we enrolled 32 adults with CF; 54 individuals did not respond to phone and email invitations; and 54 individuals declined. The main reasons for not participating were lack of time (N=40) and concerns related to the risk of COVID-19 infection (N=14).

The median (IQR) age at the time of the study visit was 30 (28 – 38) years (range: 22 to 63 years), 63% were female, 97% were white, and 6% were Hispanic or Latino (**Table 3.1**). In terms of health insurance, 25% were publicly insured (Medicaid or Medicare) and 75% had private or dual health insurance (both public and private). Ninety-one percent of study population had dental insurance. Nine percent reported food insecurity, 28% had an annual household income less than $70,000, and 66% had completed at least a 4-year college degree.

Forty-one percent of the study population were homozygous for the F508del CFTR mutation, 47% were F508del heterozygous, and 13% had other mutations. The mean±SD FEV_1% predicted for the study population was 74.1±21.9%. Only one adult with CF had been referred and evaluated for lung transplantation. Forty-seven percent of the study population had CFRD, 84% had pancreatic insufficiency, 31% had bone disease, 28% had anxiety, and 31% had depression. The median (IQR) of BMI for the study population was 23.1 (21.1 – 27.4) kg/m^2; the median (IQR) of HbA1c was 5.6 (5.4 – 6.2) %, and the median (IQR) of C-reactive protein was 2.1 (0.7 – 5.7) mg/L.

In terms of oral hygiene status, 22% had excellent oral hygiene, 72% had good oral hygiene, and 6% had fair oral hygiene. Twenty-five percent of the study population had not been to a dentist in over a year, and another 25% could not get needed dental treatment because of lack of insurance or inability to pay for dental care. Eighty-eight percent reported tooth brushing at least once per day, and 25% reported daily flossing.

3.3.2. Correlates of periodontitis

Sixty percent of study population had periodontitis. Twenty-eight percent had mild periodontitis and 31% had moderate periodontitis (**Table 3.2**). There was no association between CF-related medical factors and periodontitis (**Table 3.3**). Age and daily flossing were positively associated with CAL (age, r= 0.39, 95% CI=0.034,0.67; P=0.028), (daily flossing, median CAL: daily flossing 2.0mm vs. no daily flossing 1.5mm; P= 0.004) (**Table 3.5**).

3.4. Discussion

This is the first study to evaluate correlates of periodontitis in adults with CF. Our findings showed CF-related comorbidities and treatments were not associated with periodontitis. Rather, the identified correlates of periodontitis in this study are similar to previously reported correlates in the general population.

Medical factors like CFRD, asthma, bone disease, anxiety, depression, increased systemic inflammation, and frequent inhaled medication use present a high-risk profile for periodontitis (7,10,14,15), but these factors were not associated with periodontitis for adults with CF in our study. This is inconsistent with studies that showed the above risk profile to be associated with increased risk of periodontal disease through several mechanisms (**Figure 3.1**). These include systemic mechanisms like hyperglycemia-induced systemic inflammation in the case of diabetes, local mechanisms like reduced saliva and increased dental plaque accumulation associated with dry mouth-inducing medications, and behavioral mechanisms like reduced oral hygiene practices and dental care utilization associated with dental fear in the case of anxiety (10,14,15,24). The lack of associations between the above risk profile and periodontitis in our study can be explained by the fact that we evaluated these associations in a CF-population with low risk of periodontitis. The majority of adults with CF in our study were non-Hispanic whites, with relatively high socioeconomic status, had dental insurance, had mild CF lung disease, reported frequent utilization of preventive dentistry, maintained optimal oral hygiene, and those with diabetes had good diabetes control. All of these factors are associated with low risk of periodontitis (8,21,50,51) which likely had mitigated the

potential risk proposed by the CF-related comorbidities and treatments discussed above. In addition, our analysis showed no association between antibiotic use and periodontitis. Thus, the lack of association between the CF-related risk profile and periodontitis in our study cannot be explained by the frequent use of antibiotics to treat lung infections as proposed by previous studies (29,31,48). Lastly, the small sample size in our study prevented the detection of moderate association between the CF-related risk profile and periodontitis. Thus, future studies should consider a multicenter approach to increase the size and diversity of study population to allow for powered analyses of correlates of periodontitis for adults with CF.

Our study identified two correlates of periodontitis in adults with CF which are similar to findings in the general population. Age was positively associated with CAL (i.e., more attachment loss with older age). This is consistent with findings in the general population (8). Age is not a causative factor of CAL (i.e., CAL is not a natural outcome of aging), rather age represents the cumulative effect of untreated inflammation overtime and continued exposure to risk factors like bone disease, abnormal glucose level, and systemic inflammation associated with chronic comorbidities that are more prevalent in older age (52). Older adults with CF might be disproportionally disadvantaged in this context given the above-mentioned CAL risk factors present at a young age in individuals with CF (3). While our current analysis did not show an association between the above-mentioned risk factors and CAL, the small sample size of the current study prevented ruling out an interaction between these factors on periodontal health. The increased CAL with age observed in our study underscores the

importance of oral health promotion to maintain life-long optimal oral health for adults with CF especially with the increased survival associated with highly effective CF therapeutics (3).

Daily flossing was associated with greater CAL. This indicates that flossing might be less efficient in removing subgingival plaque from deep pockets and the prevention of hard tissues inflammation and bone loss. This finding is in support of the latest *European Federation of Periodontology* conclusion that stated flossing is only efficient in areas with no CAL, and that flossing should only be recommended for areas where an interdental brush will not pass through the interproximal area without trauma (44,53). Another potential explanation of increased CAL in adults with CF who reported daily flossing, is that those with increased CAL might be aware of the presence of periodontal disease and as a result are more committed to interdental cleaning to prevent further disease.

The lack of association between CF-related medical factors and periodontitis in our study suggests that adults with CF are at the same risk of periodontitis as the general population. However, given that more than half of the study population had mild to moderate periodontitis and the fact that even the mild form of periodontitis acts as a systemic inflammatory stressor compromising the general health (54), it is important to ensure optimal oral health for adults with CF. This can be enhanced by incorporating oral health assessment and education with regular CF care. In terms of future research priorities, larger studies with a more diverse study population especially non-white

adults with CF, adults with severe CF phenotype, and adults with low-income status are needed to verify whether our finding of prevalent, but not severe, periodontitis is typical for adults with CF.

There were four main limitations to our study. First, the study had limited power because of small sample size and lack of a control group. The sample size was determined based on the study primary goal of assessing the association between CFRD and periodontitis, thus the assessment of correlates of periodontitis might be underpowered. Enrollment of adults with CF and clinical data collection were adversely impacted by the COVID-19 pandemic and related public health guidelines. Second, to avoid confounding in the association between diabetes and periodontitis, we excluded adults with CF who were treated with steroids in the last 4 weeks. Thus, our study did not include individuals with advanced CF disease who experience frequent pulmonary exacerbations which bias our study population toward individuals with milder phenotype of CF. Third, we conducted our study at a single site. Most of our study population was white, had relatively high socioeconomic status, and had dental insurance. Thus, our findings were potentially biased toward adults with CF with low risk for periodontitis. Multicenter studies are needed to increase sample size and participant diversity, especially race, ethnicity, and household income (15). Fourth, our data were cross-sectional. Thus, our study did not capture variations in correlates over time (e.g., antibiotic use, diet). Longitudinal studies could help to definitively identify correlates of periodontitis in adults with CF.

In conclusion, most of adults with CF had mild to moderate periodontitis. Our study did not show CF-related correlates of periodontitis, which implies that adults with CF have the same risk of periodontitis as the general population. Longitudinal studies with larger sample size and control groups are needed to confirm our study findings.

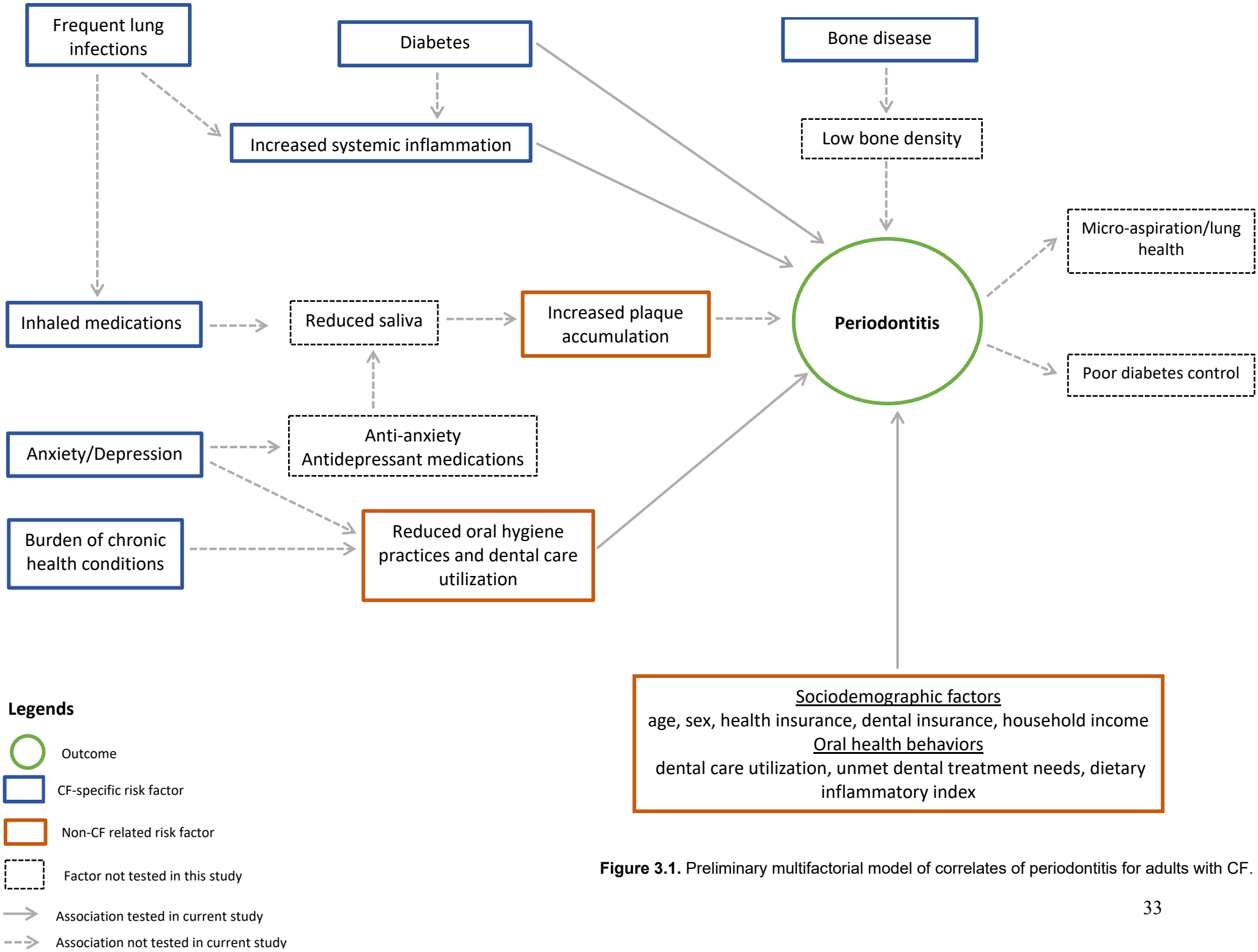


Figure 3.1. Preliminary multifactorial model of correlates of periodontitis for adults with CF.

Tables

Table 3.1. Sociodemographic, medical, and dental characteristics of adults with CF (N=32).

Characteristics	N= 32
Sociodemographic	
Age (years) (Median (IQR))	30.0 (28.0-38.0)
Sex (N (%))	
Female	20 (62.5)
Male	12 (37.5)
Race (N (%))	
White	31 (96.9)
Black or African American	1 (3.1)
Ethnicity (N (%))	
Hispanic/Latino	2 (6.3)
Health Insurance (N (%))	
Public	8 (25.0)
Private or dual	24 (75.0)
Dental insurance (N (%))	29 (90.6)
Food insecurity (N (%))	3 (9.4)
Annual household income (US$) (N (%))	
<$70,000	8 (27.6)
≥$70,000	21 (72.4)
Declined to answer	3
Education level (N (%))	
High school, GED, or equivalent	4 (12.5)
Some college	7 (21.9)
4-year college degree	11 (34.4)
More than 4-year college degree	10 (31.3)
Medical	
CF genotypes (N (%))	
F508del homozygous	13 (40.6)
F508del heterozygous	15 (46.9)
Other mutations	4 (12.5)
FEV1% predicted (mean ± SD)	74.1±21.9
Referred for lung transplant (N (%))	1 (3.1)

Comorbidities (N (%))	
CF-related diabetes	15 (46.9)
Pancreatic insufficiency	27 (84.4)
Asthma	8 (25.0)
Bone disease	10 (31.3)
Anxiety	9 (28.1)
Depression	10 (31.3)
Body Mass Index (kg/m^2) (median (IQR))	23.1 (21.1-27.4)
Hemoglobin A1c (median (IQR))	5.6 (5.4-6.2)
C-reactive protein (median (IQR))	2.1 (0.7-5.7)
Medications (N (%))	
CFTR modulator therapy	
Elexacaftor/tezacaftor/ivacaftor	18 (56.3)
Other modulator therapies [a]	10 (31.3)
None	4 (12.5)
Antibiotic	23 (71.9)
Inhaled medications	27 (84.4)
Dental (N (%))	
Oral hygiene status [b]	
Excellent	7 (22.0)
Good	23 (72.0)
Fair	2 (6.3)
Last dental visit [c]	
Less than one year	24 (75.0)
One year or more	5 (15.6)
Three years or more	3 (9.4)
Unable to get needed dental treatment [c]	8 (25.0)
Tooth brushing frequency [c]	
Less than once a day	4 (12.5)
Once a day	13 (40.6)
Two or more times a day	15 (46.9)
Daily flossing [c]	8 (25.0)
Dietary Inflammatory Index (median (IQR))	0.54 (–0.34-1.3)

[a] Other CFTR modulator therapy= ivacaftor, lumacaftor/ivacaftor, or tezacaftor/ ivacaftor.

[b] Oral hygiene status was defined based on Silness-Löe index plaque index.

[c] Self-reported.

Table 3.2. Description of periodontal health of adults with CF (N=32).

Periodontitis severity [a]	**N (%)**
No periodontitis	13 (40.6)
Mild periodontitis	10 (31.3)
Moderate periodontitis	9 (28.1)
Clinical Periodontal measures	**Mean±SD**
Periodontal pocket depth (mm)	2.4±0.14
Clinical attachment loss (mm)	1.7±0.29

[a] **Mild periodontitis:** ≥2 interproximal sites with attachment loss ≥3 mm, and ≥2 interproximal sites with pocket depth ≥4 mm (not on same tooth) or one site with pocket depth ≥5 mm. **Moderate periodontitis:** ≥2 interproximal sites with attachment loss ≥4 mm (not on same tooth), or ≥2 interproximal sites with pocket depth ≥5 mm (not on same tooth).

Table 3.3. CF-related medical correlates of periodontitis in adults with CF (N=32).

	Periodontitis		P-value [a]
correlates	**Yes**	**No**	
CF-related medical factors			
CF genotypes (N (%))			0.92
F508del homozygous	8 (61.5)	5 (38.5)	
F508del heterozygous	9 (60.0)	6 (40.0)	
Other mutations	2 (50.0)	2 (50.0)	
FEV1% predicted (mean ± SD)	72.7±20.0	76.1±25.2	0.69
Referred for lung transplant (N (%))			0.99
Yes	1 (100.0)	0 (0.00)	
No	18 (58.1)	13 (41.9)	
Comorbidities (N (%))			
CF-related diabetes			0.49
Yes	10 (66.7)	5 (33.3)	
No	9 (52.9)	8 (47.1)	
Asthma			0.68
Yes	4 (50.0)	4 (50.0)	
No	15 (62.5)	9 (37.5)	
Bone disease			0.99
Yes	6 (60.0)	4 (40.0)	
No	13 (59.1)	9 (40.9)	
Anxiety			0.70
Yes	6 (66.7)	3 (33.3)	
No	13 (56.5)	10 (43.5)	
Depression			0.99
Yes	6 (60.0)	4 (40.0)	
No	13 (59.1)	7 (40.9)	
Body Mass Index (kg/m^2) (median (IQR))	22.7 (21.3-26.9)	23.3 (20.6-29.1)	0.97
Hemoglobin A1c (median (IQR))	5.6 (5.4-6.2)	5.9 (5.3-6.3)	0.83

C-reactive protein (median (IQR))	2.7 (1.1-6.0)	0.8 (0.5-2.9)	0.10
Medications			
CFTR modulator therapy			0.93
Elexacaftor/tezacaftor/ivacaftor	11 (61.1)	7 (38.9)	
Other modulators therapies [b]	6 (60.0)	4 (40.0)	
None	2 (50.0)	2 (50.0)	
Antibiotic			0.99
Yes	14 (60.9)	9 (39.1)	
No	5 (55.6)	4 (44.4)	
Inhaled medications			0.99
Yes	16 (59.3)	11 (40.7)	
No	3 (60.0)	2 (40.0)	

[a] Independent samples t-test was used for normally distributed continuous variables, Mann-Whitney test for skewed continuous variables, Fisher exact test for binary variables, and exact chi square test for other categorical variables.

[b] Other CFTR modulator therapy= ivacaftor, lumacaftor/ivacaftor, or tezacaftor/ ivacaftor.

Table 3.4. Sociodemographic and oral health behavior correlates of periodontitis in adults with CF (N=32).

	Periodontitis		P-value [a]
correlates	**Yes**	**No**	
Sociodemographic			
Age (years) (Median (IQR))	30.0 (29.0-39.0)	29.0 (26.5-31.5)	0.14
Sex (N (%))			0.71
Female	11 (55.0)	9 (45.0)	
Male	8 (66.7)	4 (33.3)	
Race (N (%))			0.41
White	19 (63.1)	12 (38.7)	
Black or African American	0 (0.0)	1 (100.0)	
Ethnicity (N (%))			0.99
Hispanic/Latino	1 (50.0)	1 (50.0)	
Not Hispanic/Latino	18 (60.0)	12 (40.0)	
Health Insurance (N (%))			0.99
Public	5 (62.5)	3 (37.5)	
Private or dual	14 (58.3)	10 (41.7)	
Dental insurance (N (%))			0.99
Yes	17 (58.6)	12 (41.4)	
No	2 (66.7)	1 (33.3)	
Food insecurity (N (%))			0.99
Yes	2 (66.7)	1 (33.3)	
No	20 (69.0)	9 (31.0)	
Annual household income (US$) (N (%))			0.22
<$70,000	3 (37.5)	5 (62.5)	
≥$70,000	14 (66.7)	7 (33.3)	
Declined to answer	2	1	
Education level (N (%))			0.63
High school, GED, or equivalent	2 (50.0)	2 (50.0)	
Some college	3 (42.9)	4 (57.1)	

4-year college degree	8 (72.7)	3 (27.3)	
More than 4-year college degree	6 (60.0)	4 (40.0)	
Oral health behaviors (N (%))			
Oral hygiene status [b]			0.75
Excellent	5 (71.4)	2 (28.6)	
Good	13 (56.5)	10 (43.5)	
Fair	1 (50.0)	1 (50.0)	
Last dental visit [c]			0.96
Less than one year	10 (41.7)	14 (58.3)	
One year or more	3 (60.0)	2 (40.0)	
Three years or more	2 (66.7)	1 (33.3)	
Unable to get needed dental treatment [c]			0.99
Yes	5 (62.5)	3 (37.5)	
No	16 (66.7)	8 (33.3)	
Tooth brushing frequency [c]			0.32
Less than once a day	2 (50.0)	2 (50.0)	
Once a day	6 (46.2)	7 (53.8)	
Two or more times a day	11 (73.3)	4 (26.7)	
Daily flossing [c]			0.42
Yes	6 (75.0)	2 (25.0)	
No	13 (54.2)	11 (45.8)	
Dietary Inflammatory Index (median (IQR))	0.32 (–0.58 - 1.2)	0.76 (0.12-2.0)	0.31

[a] Independent samples t-test was used for normally distributed continuous variables, Mann-Whitney test for skewed continuous variables, Fisher exact test for binary variables, and exact chi square test for other categorical variables.

[b] Oral hygiene status was defined based on Silness-Löe index plaque index

[c] Self-reported

P-Value < 0.05 is **bolded**

Table 3.5. Correlates of clinical measures of periodontitis in adults with CF (N=32).

Correlates	Clinical Measures of Periodontitis [a]			
	Periodontal pocket depth		Clinical attachment loss	
	Correlation coefficient (95%CI) or median (IQR)	P-value	Correlation coefficient (95%CI) or median (IQR)	P-value
Sociodemographic				
Age	0.078 (–0.29,0.43)	0.67	0.39 (0.034,0.67)	**0.028**
Sex		0.88		0.21
Female	2.4 (2.3-2.4)		1.5 (1.5-1.7)	
Male	2.4 (2.3-2.5)		1.7 (1.5-2.0)	
Health insurance		0.56		0.85
Public	2.4 (2.3-2.6)		1.6 (1.5-1.9)	
Private or dual	2.4 (2.3-2.4)		1.6 (1.5-1.9)	
Dental insurance		0.35		0.20
Yes	2.4 (2.3-2.4)		1.6 (1.5-1.9)	
No	2.6 (2.4-2.6)		1.5 (1.3-1.6)	
Household income		0.12		0.097
<$70,000	2.3 (2.3-2.4)		1.5 (1.3-1.7)	
≥$70,000	2.4 (2.3-2.5)		1.7 (1.5-2.0)	
Medical characteristics				
CFTR genotype		0.16		0.78
F508del homozygous	2.4 (2.4-2.4)		1.6 (1.5-1.7)	
F508del heterozygous	2.3 (2.3-2.4)		1.6 (1.5-2.1)	
Other mutations	2.3 (2.3-2.6)		1.6 (1.2-2.0)	
FEV1% predicted	–0.24(–0.55,0.13)	0.19	0.004 (–0.36,0.36)	0.98
Comorbidities				
CF-related diabetes		0.65		0.14
Yes	2.4 (2.3-2.5)		1.7 (1.5-2.1)	
No	2.4 (2.3-2.4)		1.5 (1.5-1.8)	
Asthma		0.49		0.51
Yes	2.4 (2.3-2.5)		1.7 (1.5-1.9)	
No	2.4 (2.3-2.4)		1.6 (1.5-1.9)	
Bone disease		0.81		0.50
Yes	2.4 (2.2-2.6)		1.7 (1.5-2.1)	
No	2.4 (2.3-2.4)		1.6 (1.5-1.8)	
Anxiety		0.31		0.71
Yes	2.4 (2.2-2.6)		1.7 (1.5-1.8)	

No	2.4 (2.3-2.4)		1.6 (1.5-2.1)	
Depression		0.28		0.66
Yes	2.4 (2.3-2.7)		1.7 (1.5-1.8)	
No	2.4 (2.3-2.4)		1.6 (1.5-2.0)	
CFTR modulator therapy		0.81		0.99
Elexacaftor/tezacaftor/ivacaftor	2.4 (2.3-2.5)		1.6 (1.5-1.9)	
Other modulators therapies [b]	2.3 (2.2-2.5)		1.8 (1.4-2.2)	
None	2.3 (2.2-2.5)		1.6 (1.2-2.0)	
Antibiotic use		0.22		0.40
Yes	2.4 (2.3-2.5)		1.7 (1.5-2.0)	
No	2.3 (2.3-2.4)		1.6 (1.4-1.8)	
Body mass index (kg/m²)	0.082 (–0.28,0.43)	0.65	–0.13 (–0.47,0.24)	0.47
C-reactive protein (mg/L)	0.13 (–0.27,0.50)	0.51	–0.053 (–0.43,0.34)	0.79
Oral health behaviors				
Oral hygiene status [c]		0.11		0.44
Excellent	2.3 (2.3-2.4)		1.7(1.5-1.8)	
Good	2.4(2.3-2.4)		1.6(1.5-2.0)	
Fair	2.6(2.5-2.7)		1.7(1.7-1.7)	
Tooth brushing [d]		0.27		0.51
Less than once a day	2.4 (2.3-2.5)		1.6 (1.2-1.9)	
Once a day	2.4 (2.3-2.5)		1.7 (1.5-2.0)	
Two or more times a day	2.3 (2.3-2.4)		1.5 (1.5-1.8)	
Daily flossing [d]		0.57		**0.004**
Yes	2.3 (2.3-2.5)		2.0 (1.7-2.2)	
No	2.4 (2.3-2.4)		1.5 (1.5-1.7)	
Time of last dental visit [d]		0.13		0.84
Less than one year	2.4 (2.3-2.4)		1.7 (1.5-1.9)	
One year or more	2.5 (2.2-2.6)		1.6 (1.5-2.0)	
Three years or more	2.3 (2.3-2.3)		1.5 (1.3-1.5)	
Frequency of preventive dental care [d]		0.92		0.60
Less than once per year	2.4 (2.2-2.5)		1.5 (1.5-1.8)	
Once per year	2.4 (2.3-2.6)		1.6 (1.5-2.1)	
Twice per year or more	2.4 (2.3-2.4)		1.7 (1.5-1.8)	
Unable to get needed dental treatment [d]		0.98		0.12
Yes	2.3 (2.3-2.5)		1.5 (1.5-1.6)	
No	2.4 (2.3-2.4)		1.7 (1.5-2.0)	
Dietary inflammatory index	0.047 (–0.34,0.42)	0.81	–0.10 (–0.47,0.29)	0.61

[a] Correlation coefficient (95% CI) for continuous variables and median (IQR) for binary and categorical variables. Spearman rank correlation for quantitative variables, the Man-Whitney test for binary variables, and Kruskal-Wallis for categorical variables.

[b] Other CFTR modulator therapy= ivacaftor or tezacaftor/ ivacaftor& ivacaftor.

[c] Oral hygiene status was defined based on Silness-Löe index plaque index.

[d] Self-reported.

P-Value < 0.05 is **bolded**.

Supplementary Table 3.1. Description of correlates of periodontitis.

Correlate	Variable	Type	Unite/Value	Instrument	Reference
CF-related medical	CFTR genotype	Categorical	- F508del homozygous - F508del heterozygous - Other mutations	Medical records	New hypothesis
	CF severity (FEV 1-predicted)	Continuous	- Percent (%)	Medical records	(Takeuchi K et al., 2018)
	CF-related diabetes	Binary	- Yes/ No	Medical records	(Liu Y et al.,2018)
	Pancreatic insufficiency	Binary	- Yes/ No	Medical records	New hypothesis
	Bone disease	Binary	- Yes/ No	Medical records	(Guiglia R et al., 2013)
	Anxiety	Binary	- Yes/ No	Medical records	(Kisely S et al., 2016)
	Depression	Binary	- Yes/ No	Medical records	(Kisely S et al., 2016)
	CF modulators use	Categorical	- Elexacaftor/tezacaftor/ivacaftor - Other modulators - None	Medical records	New hypothesis
	Antibiotic use	Binary	- Yes/ No	Medical records	New hypothesis
	Inhaled medication use	Binary	- Yes/ No	Medical records	(Te-Chun Shen et al., 2017)
	BMI	Continuous	- kg/m^2	Medical records	(Eke PI et al., 2012), (Liu Y et al.,2018)
	C-reactive protein	Continuous	- mg/L	Medical records	(Demmer RT et al., 2012)
Sociodemographic	Age	Continuous	- Years	Medical record	(Eke PI et al., 2015), (Lee JH et al., 2016)
	Sex	Binary	- Male - Female	Medical record	(Eke PI et al., 2015), (Lee JH et al., 2016)
	Health insurance	Categorical	- Public - Private - Dual (public, private)	Medical records	(Kinane DF et al., 2006)
	Dental insurance	Binary	- Yes/ No	Questionnaire	(Kinane DF et al., 2006)
	Income	Categorical	- Less than $20,000 - $20,000 to $29,999 - $30,000 to $49,999 - $50,000 to $69,999 - $70,000 to $89,999 - More than $90,000 - I don't know - I prefer not to answer	Questionnaire	(Kinane DF, et al., 2006)
Oral health behaviors	Brushing frequency	Categorical	- More than once a day - Once a day - A few times a week - Once a week - Never - I don't know	Questionnaire	(Chapple ILC et al., 2015)
	Flossing	Binary	- Yes/ No	Questionnaire	(Chapple ILC et al., 2015)
	Unmet dental treatment need	Binary	- Yes/ No	Questionnaire	New hypothesis
	Time of last dental check-up	Categorical	- 6 months ago or less - More than 6 months, but not more than 1 year ago - More than 1 year ago - More than 3 years ago - I have never been to the dentist	Questionnaire	(Lee JH et al., 2016)
	Frequency of preventive dental care	Categorical	- Less than once per year - Once per year - Twice per year or more	Questionnaire	(Lee JH et al., 2016)
	Dietary inflammatory index	Continuous	- ASA24	Questionnaire	New hypothesis

Supplementary Table 1.2. Lower respiratory microbiology for adults with CF (N=32).

Microbiology [a]	**N (%)**
Pseudomonas aeruginosa	20 (62.5)
Staphylococcus aureus - methicillin sensitive (MSSA)	11 (34.4)
Staphylococcus aureus - methicillin resistant (MRSA)	10 (31.3)
Stenotrophomonas maltophilia	6 (18.8)

[a] Any positive sputum culture in the prior 12 months.

Supplementary Table 3.3. List of antibiotic and inhaled medication used by adults with CF (N=32).

Medication category	Medication name	Route
Antibiotic	Amoxicillin	Oral
	Azithromycin	Oral
	Aztreonam Lysine	Inhaled
	Colistimethate Sodium	Inhaled
	Levofloxacin	Oral
	Minocycline	Oral
	Tobramycin	Inhaled
Non-antibiotic inhaled medications	Albuterol Sulfate	Inhaled
	Beclomethasone	
	Budesonide	
	Budesonide / Formoterol	
	Ciclesonide	
	Dornase Alfa	
	Fluticasone propionate	
	Fluticasone-Salmeterol	
	Ipratropium-Albuterol	
	Levalbuterol	
	Levalbuterol Tartrate	

Chapter 4. Cystic Fibrosis-Related Diabetes and Periodontitis in Adults with Cystic Fibrosis

Authors

Alaa A. Alkhateeb [a]

Lloyd A. Mancl [a]

Kathleen J. Ramos [b]

Georgios A. Kotsakis [c,d]

Dace L. Trence [e]

Marilynn L. Rothen [a]

Donald L. Chi [a,f] (Chair)

[a] Department of Oral Health Sciences, School of Dentistry, University of Washington, Seattle, WA, USA.

[b] Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, University of Washington, Seattle, WA, USA.

[c] Department of Periodontics, Dental School, University of Texas Health at San Antonio, San Antonio, TX, USA.

[d] Department of Global Health, University of Washington, Seattle, WA, USA.

[e] Division of Metabolism, Endocrinology, and Nutrition, Department of Medicine, University of Washington, Seattle, WA, USA.

[f] Department of Health Systems and Population Health, School of Public Health, University of Washington, Seattle, WA, USA.

Abstract

Background and objective: Cystic fibrosis-related diabetes (CFRD) is a unique type of diabetes that affects up to 50% of adults with cystic fibrosis (CF). The prevalence and severity of periodontitis are both significantly higher in adults with diabetes than adults without diabetes. Our previous work indicates that adults with CF are not at greater risk for periodontitis, but it is unknown if CFRD impacts the periodontal health of adults with CF. The goals of this pilot study were to assess the association between CFRD and periodontitis and to compare the prevalence of periodontitis in adults with CF to non-CF controls, accounting for diabetes status.

Methods: We conducted a cross-sectional study of the association between CFRD and periodontitis in adults with CF (age ≥ 18 years) at a single CF center in Seattle, Washington, USA (N=32). CFRD was defined based on an established diagnosis by a physician following the American Diabetes Association diagnostic criteria. Our outcome was periodontitis defined following the U.S. Centers for Disease Control and Prevention and the American Academy of Periodontology case definition as the presence of at least two interproximal sites with clinical attachment loss ≥3 mm, and two or more interproximal sites with periodontal pocket depth ≥4 mm (not on the same tooth) or one site with periodontal pocket depth ≥5 mm. We compared periodontitis prevalence between adults with CF grouped by CFRD status (N=32). We used the 2013-2014 National Health and Nutrition Examination Survey to form two non-CF control groups (with and without diabetes). Non-CF controls were frequency matched to adults with CF on age, sex, diabetes status, and insulin use. Because NHANES periodontal data were only available for adults ages 30 years and older, we focused our analysis that included

non-CF controls on this age group (CF N=19, non-CF N=54). Based on CF and diabetes status, we compared periodontitis prevalence across four groups: CFRD, CF and no diabetes, non-CF with diabetes, and non-CF and no diabetes (healthy). We used the Fisher's exact test for hypotheses testing.

Results: There was no association between CFRD and periodontitis for adults with CF ages 22-63 years (CFRD 67% vs. CF no diabetes 53%; P=0.49), this was also true for those ages 30 years and older (CFRD 78% vs. CF no diabetes 60%; P=0.63). The prevalence of periodontitis for the two CF groups, with and without CFRD, were higher than the prevalence of periodontitis for healthy controls (CFRD 78% vs. healthy 7%; P<0.001), (CF no diabetes 60% vs. healthy 7%; P=0.001) and not significantly different than periodontitis prevalence for non-CF controls with diabetes (CFRD 78% vs. non-CF with diabetes 56%; P=0.43), (CF no diabetes 60% vs. non-CF with diabetes 56%; P=0.99).

Conclusion: Our study did not show a statistically significant association between CFRD and periodontitis. Regardless of their diabetes status, adults with CF had significantly higher prevalence of periodontitis than healthy controls and similar prevalence to non-CF controls with diabetes. Additional studies with larger sample size and concurrent non-CF controls are needed to confirm our study findings.

4.1. Introduction

Cystic fibrosis-related diabetes (CFRD) affects up to 50% of adults with cystic fibrosis (CF) (17,55). CFRD adversely impacts the lung health, nutritional status, quality of life, and survival of individuals with CF (18,55). CFRD is a unique type of diabetes mellitus (DM) that shares similarities with major DM types (55,56). DM complications like retinopathy and nephropathy occurs in CFRD but with less frequency and severity than other DM types (56).

Periodontitis, defined as the inflammation of hard tissues supporting the teeth, is commonly associated with DM (21). Potential biological mechanisms linking DM and periodontitis include periodontal bacteria triggering a host defense response, which increases diabetes-induced systemic inflammation and leads to periodontal tissue destruction (19). The prevalence and severity of periodontitis are both significantly higher in U.S. adults with DM than those without DM (21). In addition, studies showed that hyperglycemia (poorly controlled DM) is associated with increased colonization of periodontal bacteria and poorer periodontal treatment outcomes (57,58). Despite the strong links between DM and periodontitis (9), it is unknown if CFRD impacts the periodontal health of adults with CF, and as a result, if adults with CFRD are in need of interventions aimed at promoting oral health.

In theory, adults with CF are at high risk for periodontitis because of increased systemic inflammation associated with frequent lung infections, asthma, anxiety, depression, bone disease, and chronic use of inhaled medications, all of which are risk factors of

periodontitis (7,14,15). However, our pilot analysis of periodontitis risk factors for adults with CF showed that the abovementioned factors were not associated with periodontitis (unpublished) (59). This indicates that adults with CF would have similar periodontal health as adults without CF. However, this hypothesis has not yet been tested. In this study we hypothesized the following: 1) CFRD is associated with periodontitis, 2) periodontitis rates differ by CF and diabetes status.

4.2. Methods

4.2.1. Study design and study population.

This was a cross-sectional study with a historical control group. We included all enrolled adults with CF (age ≥ 18 years) in our analysis of the association between CFRD and periodontitis. A complete description of the cross-sectional study design, procedures, and inclusion and exclusion criteria of adults with CF are detailed previously in **Chapter 2**.

A historical control group without CF was identified from the 2013-2014 National Health and Nutrition Examination Survey (NHANES). 2013-2014 NHANES periodontal examination data was only available for participants ages ≥30 years, thus our control group was focused on this age group. NHANES participants were included in the study if they had complete documentation of periodontal examinations, laboratory tests for diabetes, medical history questions for diabetes, and interviews assessing demographics. We excluded NHANES participants with impaired glucose tolerance, smokers, and pregnant women. NHANES does not include a variable for CF. Thus, to

avoid including adults with CF from NHANES in our control groups, we excluded NHANES participants who reported chronic obstructive respiratory diseases and chronic bronchitis. Non-CF controls were frequency matched to adults with CF on age, sex, diabetes status, and insulin use (**Figure 4.1**).

4.2.2. Control data procurement

For non-CF controls in the 2013-2014 NHANES, we obtained sociodemographic data (age, sex, race, ethnicity, income level, education level), medical data (diabetes status, glycated hemoglobin (HbA1c), body mass index (BMI)), and periodontal measures (periodontal pocket depth (PD) and clinical attachment loss (CAL)). Periodontal measures were collected using the same protocol used for adults with CF described in **Chapter 2** (60).

4.2.3. Comparison groups

Based on CFRD status, adults with CF were grouped into two groups (CFRD, no CFRD). CFRD was defined based on an established diagnosis by a physician following the American Diabetes Association diagnostic criteria using an Oral Glucose Tolerance Test (OGTT) of 200 mg/dL or greater or glycated hemoglobin (HbA1c) greater than 6.5%. We recruited adults with CFRD with insulin use. Adults without CFRD were defined based on normal OGTT within the last two years. For non-CF controls, diabetes status was defined based on self-reported diabetes and HbA1c.

Based on CF status and diabetes status (CF-diabetes status) we grouped study participants into four groups: CFRD, CF and no diabetes, non-CF with diabetes, and no CF and no diabetes (healthy).

4.2.4. Outcome measure

Based on the periodontal exam findings (**Chapter 2**), we defined periodontitis following the U.S. Centers for Disease Control and Prevention and the American Academy of Periodontology (CDC/AAP) case definition (49). Mild periodontitis is defined by the presence of two or more interproximal sites with CAL ≥3 mm and two or more interproximal sites with PD ≥4 mm (not on the same tooth), or one site with PD ≥5 mm. Moderate periodontitis is defined as the presence of two or more interproximal sites with CAL ≥4 mm (not on the same tooth), or two or more interproximal sites with PD ≥5 mm (not on the same tooth). Severe periodontitis is defined as the presence of two or more interproximal sites with CAL ≥6 mm (not on the same tooth) and ≥1 interproximal site with PD ≥5 mm. Our outcome was any periodontitis (yes/no).

4.2.5. Data analysis

We used descriptive statistics to report on study variables using means and standard deviations (SD) for normally distributed quantitative variables, medians and interquartile ranges (IQR) for non-normally distributed quantitative variables, and frequencies and percentages for categorical variables. We presented descriptive data for all study population with CF and for adults with CF grouped by CFRD status (yes/no). We also presented descriptive data for study population with and without CF grouped by

diabetes status. To test for differences in the study variables, we used the independent samples t-test for normally distributed quantitative variables, the Mann-Whitney test for non-normally distributed quantitative variables, the Fisher's exact test for binary variables, and the exact chi-square test for categorical variables.

For hypothesis testing, first, we used the Fisher's exact test to assess the association between CFRD and periodontitis for all enrolled adults with CF ages 22-63 years. Second, we used the exact chi-square test to assess the association between CFRD and periodontitis severity for adults with CF. Third, we used the independent samples t-test to assess differences in means of clinical periodontal measures (PD, CAL) between adults with CF grouped by CFRD status. Fourth, we used the Fisher's exact test to compare the prevalence of periodontitis between adults with CF ages 30 years and older grouped by CFRD status and non-CF controls with and without diabetes. Fifth, we used the Welch's analysis of variance with the Games-Howell post hoc test to assess for between groups differences in PD and CAL for the four CF-diabetes groups and adjust for multiple testing. We reported the difference in means and 95% CI. Because NHANES periodontal data was only available for adults ages 30 years and older, we focused our analysis that included non-CF controls on this age group (CF N=19, non-CF N=57).

Statistical significance was set at 0.05 for all statistical analysis and all tests were two-sided. Data were analyzed using Statistical Package for the Social Sciences (SPSS) 19.0 for Mac.

4.3. Results

4.3.1. Study population

4.3.1.1. Adults with CF

Of the 140 eligible individuals, we enrolled 32 adults with CF; 54 individuals did not respond to phone and email invitations; and 54 individuals declined. The main reasons for not participating were lack of time (N=40) and concerns related to the risk of COVID-19 infection (N=14).

The median (IQR) age at the time of the study visit was 30 (28 – 38) years (range: 22 to 63 years), 63% were female, 97% were white, and 6% were Hispanic or Latino (**Table 4.1**). In terms of health insurance, 25% were publicly insured (Medicaid or Medicare) and 75% had private or dual health insurance (both public and private). Ninety-one percent of study population had dental insurance. Nine percent reported food insecurity, 66% had completed at least a 4-year college degree, and 28% had an annual household income less than $70,000.

Forty-one percent of adults with CF were homozygous for the F508del CF mutation, 47% were F508del heterozygous, and 13% had other mutations. The mean±SD forced expiratory volume in one second percent predicted (FEV_1% predicted) for the study population was 74.1±21.9%. Only one adult with CF had been referred and evaluated for lung transplantation. Forty-seven percent of the study population had CFRD, 84% had pancreatic insufficiency, 31% had bone disease, 28% had anxiety, and 31% had

depression. The median (IQR) HbA1c for the study population with CF was 5.6 (5.4 – 6.2) %, and the median (IQR) body mass index (BMI) was 23.1 (21.1 – 27.4) kg/m^2.

Twenty-five percent of the study population had not been to a dentist in over a year, and 25% could not get needed dental treatment because of lack of insurance or inability to pay for dental care. Eighty-seven percent reported tooth brushing at least once per day, and 25% reported daily flossing.

Compared to the CF group without diabetes, the CFRD group had a higher proportion of adults with pancreatic insufficiency (CFRD 100% vs. CF no diabetes 71%; P=0.046), a higher proportion of adults with antibiotic use (CFRD 93% vs. CF no diabetes 53%; P=0.018), and a higher median HbA1c (median: CFRD 6.2% vs. CF no diabetes 5.4%; P<0.001). There were no differences in other sociodemographic and behavioral characteristics between the two CF groups.

4.3.1.2. Non-CF controls

Compared to the non-CF group, the CF group ages 30 years and older had a higher proportion of white adults (CF 100% vs. non-CF 67%; P=0.038) (**Table 4.2**); a lower proportion of adults with annual income of lower than $70,000 (CF 17% vs. non-CF 52%; P=0.013); and a lower median BMI (CF 23.4 kg/m^2 vs. non-CF 28.4 kg/m^2 ; P=0.002).

4.3.2. Outcome measure

4.3.2.1. Periodontitis and CFRD in adults with CF

CFRD was not associated with periodontitis (CFRD 67% vs. no CFRD 53%; P=0.49). CFRD was also not associated with periodontitis severity (P=0.57) (**Table 4.3**). Adults with CF with and without CFRD had similar means of clinical periodontal measures (PD: CFRD 2.4±0.11 mm vs. no CFRD 2.4±0.13 mm; P=0.58), (CAL: CFRD 1.8±0.33mm vs. no CFRD 1.7±0.28 mm; P=0.18)

4.3.2.2. Periodontitis and CF-Diabetes status

The prevalence of periodontitis for the two CF groups, with and without CFRD, ages 30 years and older were significantly higher than the prevalence of periodontitis for the healthy control group (CFRD 78% vs. healthy 7%; P<0.001), (CF no diabetes 60% vs. healthy 7%; P=0.001) (**Table 4.4**) and not significantly different than the prevalence of periodontitis for the non-CF control group with diabetes (CFRD 78% vs. non-CF with diabetes 56%; P=0.43) (CF no diabetes 60% vs. non-CF with diabetes 56%; P=0.99).

Our analysis of variance showed significant differences in PD and CAL between the four CF-diabetes groups (PD F=161.9; P<0.001), (CAL F=15.5; P<0.001). Compared to healthy controls, both CF groups had significantly deeper PD (CFRD vs. healthy: mean difference=1.3, 95CI%=1.1,1.5; P<0.001), (CF no diabetes vs. healthy: mean difference=1.3, 95CI%=1.1,1.5; P<0.001), and significantly greater CAL (CFRD vs. healthy: mean difference=0.66, 95CI%=0.30,1.0; P<0.001), (CF no diabetes vs. healthy: mean difference=0.51, 95CI%=0.23,0.80; P<0.001) (**Table 4.5**). The two CF groups had

significantly deeper PD than non-CF controls with diabetes (CFRD vs. non-CF with diabetes: mean difference=0.91, 95CI%=0.60,1.2; P<0.001), (CF no diabetes vs. non-CF with diabetes: mean difference=0.90, 95CI%=0.58,1.2; P<0.001), but similar CAL (CFRD vs. non-CF with diabetes: mean difference=0.09, 95CI%= – 0.66,0.52; P=0.97), (CF no diabetes vs. non-CF with diabetes: mean difference= – 0.06, 95CI%= – 0.62,0.50; P=0.99).

4.4. Discussion

To our knowledge this is the first study to assess the association between CFRD and periodontitis and to include non-CF controls in the assessment of the periodontal health of adults with CF. There were two main findings. First, among adults with CF, CFRD was not significantly associated with periodontitis. Second, both CF groups (with and without CFRD) ages 30 years and older had higher prevalence of periodontitis than healthy controls and similar prevalence of periodontitis to non-CF controls with diabetes, despite adults with CF having higher markers of socioeconomic status than non-CF controls.

First, CFRD was not significantly associated with periodontitis. This finding is inconsistent with studies of non-CF adults with DM that showed increased prevalence and severity of periodontitis with DM (8,21). There are four potential interconnected explanations of the lack of association between CFRD and periodontitis in our study. First, periodontitis is associated with poorly controlled diabetes. Studies showed that the prevalence and severity of periodontitis were increased with HbA1c of 8.0% and higher

(61). Our CFRD group had an overall well-controlled diabetes, only two adults with CFRD had HbA1c higher than 8.0% and two-thirds of adults with CFRD had HbA1c of less than 6.5%. Second, temporary hyperglycemia occurs in the absence of CFRD for adults with CF, which is mainly related to steroid treatment of pulmonary exacerbations (18,55,62). Studies of non-CF adults showed that prediabetes, indicated by glucose level that is higher than normal but lower than diabetes level, was associated with increased periodontitis (58). The fluctuation in glucose levels in adults with CF without CFRD might have mitigated the difference in periodontitis by CFRD status in our study. Third, the majority of our study population were white, had relatively high socioeconomic status, had dental insurance, maintained optimal oral hygiene and reported frequent utilization of preventive dentistry, all of which are factors associated with low risk of periodontitis (8,51). Thus, these factors might have served as preventive measures and lessened the impact of CFRD on periodontal health for our study population. Finally, the lack of a significant association between CFRD and periodontitis in our study is likely because of the small sample size and limited power. Among adults with CF, CFRD was associated with 14% increase in periodontitis, but the difference was not statistically significant. Future studies of CFRD and periodontal health should include a larger and more diverse population with CF including non-whites, adults with low socioeconomic status, adults with limited dental care access, adults with severe CFRD, and collect longitudinal data to account for the impact of steroid use and episodes of hyperglycemia on the periodontal health of adults without CFRD.

Second, regardless of their CFRD status adults with CF had higher prevalence of periodontitis than healthy controls and similar prevalence of periodontitis as non-CF controls with diabetes, despite having higher socioeconomic markers than non-CF controls. There are two potential explanations of this finding. First, adults with CF without CFRD are at higher risk of prediabetes than non-CF adults without diabetes (62), which potentially increased their risk of periodontitis. Adults with CF without CFRD in our study had significantly higher median HbA1c than healthy controls. Because we defined the CF group without CFRD based on normal OGTT in the last two years, there was a potential risk of misclassification as some of adults with CF without CFRD might had developed undiagnosed prediabetes that was not captured in our study. Increased HbA1c is independently associated with increased periodontitis in the general population (21). However, increased HbA1c by itself does not fully explain the difference in the prevalence of periodontitis in our study, as adults with CF without CFRD had a significantly lower HbA1c than adults with CFRD who had a significantly lower HbA1c than non-CF controls with diabetes, yet the three groups had similar prevalence of periodontitis. The second potential explanation is that the impact of increased HbA1c for adults with CF might had been amplified by other risk factors for periodontitis like increased systemic inflammation associated with frequent lung infections, frequent use of inhaled medications and antibiotics, and the presence of other comorbidities like asthma, bone disease, anxiety, and depression (7,14–16). While our previous analysis of CF-related risk factors for periodontitis showed that these factors were not associated with periodontitis (59), our analysis did not include a non-CF control group and was not powered to test for interaction between these risk factors. Longitudinal studies with

concurrent non-CF controls are needed to measure the impact of glucose fluctuation and test for interaction between the above-mentioned periodontitis risk factors on the periodontal health of adults with CF.

Our study showed that despite their CFRD status adults with CF are at similar risk of periodontitis as non-CF adults with diabetes, a well-defined high-risk group for periodontitis. This indicates that having either CF or diabetes is a potential risk factor for periodontitis. In addition, while not statistically significant, our findings suggest a potential interaction between CF and diabetes as our study group with CFRD had the highest prevalence of periodontitis compared to the other study groups (adults with CF without diabetes and non-CF controls with and without diabetes). Collectively, these observations are particularly concerning for adults with CF given that periodontitis is linked to poor diabetes control and increased systemic inflammation, both of which are risk factors for poor CF outcomes (10,63,64). In addition, studies have demonstrated an increased risk of micro-aspiration of oral bacteria and links between oral infections and decreased lung function in individuals with lung diseases (12,45–47). Collectively, these data call for strategies to ensure optimal oral health for adults with CF. Strategies should focus on increase oral health awareness, facilitation of dental care access, and further clinical research. First, oral health awareness for adults with CF can be improved by integrating oral health promotion as part of the CF care at clinical and community level. Routine CF care can include promotion of oral health by conducting regular dental screenings and discussions of the importance of optimal oral health to the maintenance of general health and quality of life. CF advocacy organizations proved to be successful

in promoting health related practices for individuals with CF (65). These organizations can partner with dentists and dental hygienists to promote efforts to build resources and provide education to meet the oral health needs of adults with CF. In hospital settings with dental clinics, pairing dental visits with the routine CF care visits might be an efficient way to increase dental care utilization for adults with CF. As part of dental care, behavioral interventions like motivational interviewing should be utilized with the goal of defining barriers to optimal oral health and ways to mitigate the potential impact of CF disease and related treatments on oral health. Finally, the current literature is inadequate to form an evidence-based dental care recommendations specific for adults with CF. There is a need for longitudinal multicenter studies with a representative sample of all adults with CF to build a framework of CF-related risk factors for dental diseases that would guide clinical care recommendations.

There are three important considerations in the interpretation of our comparison of periodontal health by CF status. First, while the CF groups had a higher prevalence of periodontitis than healthy controls, clinically, all groups had mild to moderate periodontitis (**Supplementary Table 4.1**). Second, while adults with CF with and without CFRD had significantly deeper PD than non-CF controls with diabetes, CAL level was the same for all three groups (CFRD, CF no diabetes, non-CF with diabetes), thus the three groups had similar periodontitis prevalence. The deeper PD with similar CAL levels clinically suggests increased gingival overgrowth for adults with CF. We did not formally assess gingival overgrowth in our current analysis. However, this warrant future investigations of the prevalence and causes of gingival overgrowth in adults with CF as

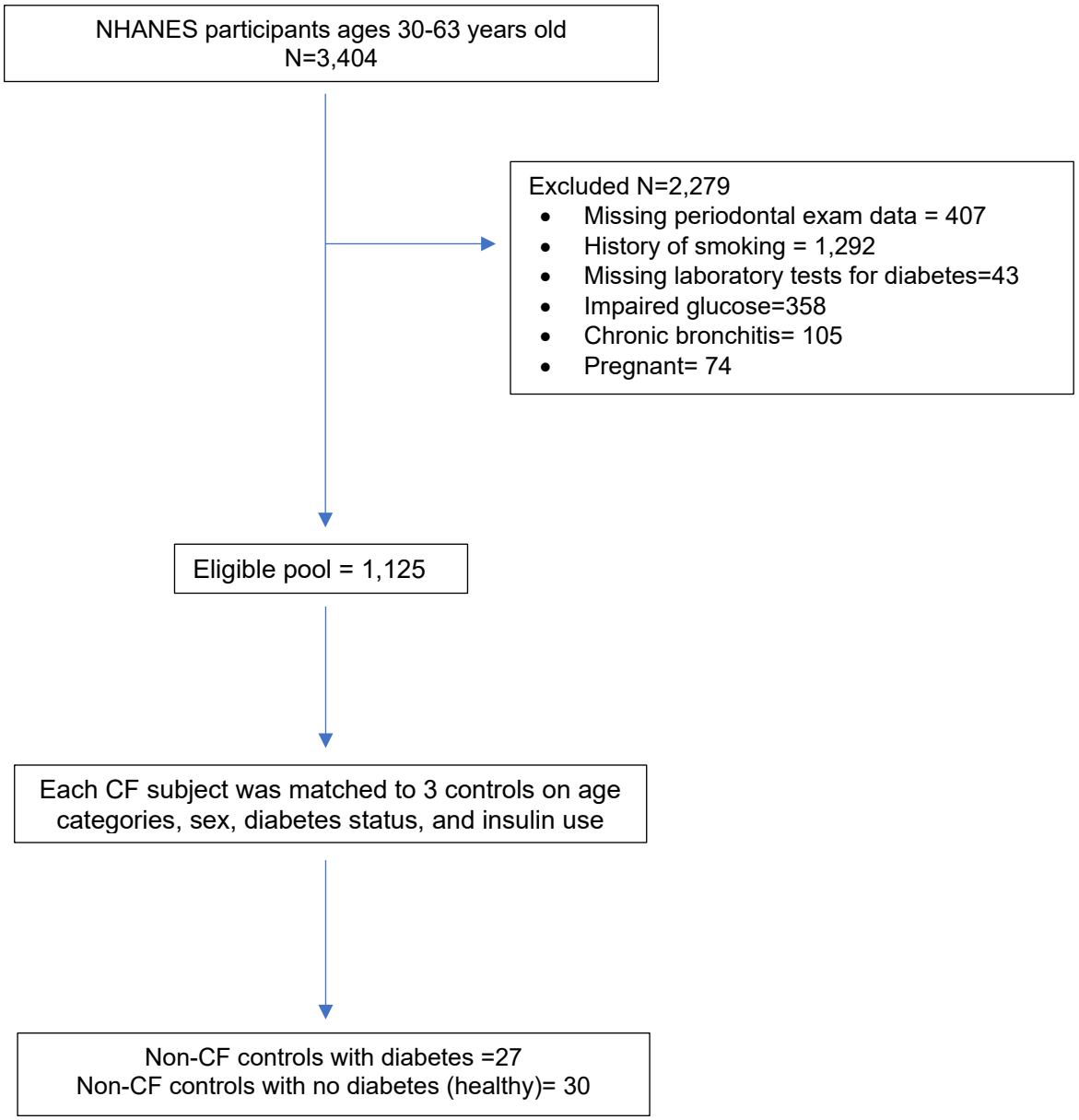
gingival overgrowth is a risk factor for poor oral hygiene increasing the risk of periodontal disease (66). Third, while the non-CF control groups formed using a nationally representative data source, the non-CF groups do not represent all adults enrolled in NHANES. For example, the non-CF groups did not include older adults (≥65 years) and adults with history of smoking (two groups with high risk for periodontitis). Thus, our analyses did not reflect the risk of periodontitis in the US adults. According to the latest NHANES analysis, around half of the US population had periodontitis with increased risk in men, smokers, Hispanics, non-Hispanic Black people, obese, and adults with severe diabetes, majority are not represented in our non-CF control groups (21,67,68).

There were five main limitations to our study. First, the study had limited power because of small sample size. Enrollment of adults with CF and clinical data collection were adversely impacted by the COVID-19 pandemic and related public health guidelines. Second, the time of diabetes screening for adults without CFRD was not uniformed in our study. We identified adults with CF without CFRD based on a normal OGTT result within the last two years. Episodes of glucose abnormality are common in adults with CF without CFRD, proposing a potential confounding factor of the association between diabetes and periodontitis that we did not account for in this study (62). We opted for the two-year time for an OGTT due to the low adherence to annual OGTT in CF clinic populations (69). Out of the 90 individuals excluded from our study, 41 individuals were excluded because they did not have an OGTT in the last two years. Future studies should use a standardized approach to define adults without CFRD. Third, to avoid

confounding in the association between diabetes and periodontitis, we excluded individuals with CF who were treated with steroids for pulmonary exacerbations in the last 4 weeks. Thus, our study did not include individuals with advanced CF disease who experience frequent pulmonary exacerbations which bias our study population toward a healthier population with CF. Fourth, we conducted our study at a single site. Most of our study population was white, with a relatively high socioeconomic status, and had dental insurance, all of which are factors associated with low risk of periodontitis (8). Multicenter studies are needed to increase sample size and population diversity, especially race, ethnicity, and income. Finally, the study included a historical control group which hinder the ability to include all variables in our models. Examples include socioeconomic factors like dental insurance and comorbidities associated with periodontitis like cardiovascular diseases, anxiety, and depression.

In conclusion, CFRD was not associated with periodontitis. However, adults with CF with and without CFRD had higher prevalence of periodontitis than healthy controls and similar prevalence of periodontitis as non-CF controls with diabetes, despite having higher markers of socioeconomic status than non-CF controls. There is a need for larger, multicenter, longitudinal studies to understand how CF-related comorbidities and treatments impact the oral health of adults with CF. These data are needed to update dental care recommendations for adults with CF and to develop interventions aimed at improving the oral and systemic health and the quality of life of this vulnerable population.

Figure 4.1. Identification of non-CF controls from NHANES 2013-2014.



Tables

Table 4.1. Sociodemographic, medical, and dental characteristics of adults with CF grouped by CFRD status (N=32).

	Overall N= 32	Cystic Fibrosis-Related Diabetes		
		Yes N= 15	No N= 17	P-value [a]
Sociodemographic characteristics				
Age (years) (Median (IQR))	30.0 (28.0-38.0)	30.0 (28.0-39.0)	30.0 (28.5-32.5)	0.86
Sex (N (%))				0.29
Female	20 (62.5)	11 (73.3)	8 (47.1)	
Male	12 (37.5)	4 (26.7)	9 (52.9)	
Race (N (%))				0.47
White	31 (96.9)	14 (93.3)	15 (100.0)	
Black or African American	1 (3.1)	1 (6.7)	0 (0.0)	
Ethnicity (N (%))				
Hispanic/Latino	2 (6.3)	1 (6.7)	1 (5.9)	
Health Insurance (N (%))				0.42
Public	8 (25.0)	5 (33.3)	3 (17.6)	
Private or dual	24 (75.0)	10 (66.7)	14 (82.4)	
Annual household income (US$) (N (%))				0.99
<$70,000	8 (27.6)	4 (30.8)	4 (25.0)	
≥$70,000	21 (72.4)	9 (69.2)	12 (75.0)	
Declined to answer	3	2	1	
Education level (N (%))				0.30
High school, GED, or equivalent	4 (12.5)	3 (20.0)	1 (5.9)	
Some college	7 (21.9)	3 (20.0)	4 (23.5)	
4-year college degree	11 (34.4)	3 (20.0)	8 (47.1)	
More than 4-year college degree	10 (31.3)	6 (40.0)	4 (23.5)	
Food insecurity (N (%))	3 (9.4)	2 (13.3)	1 (5.9)	0.59
Dental insurance (N (%))	29 (90.6)	12 (80.0)	17 (100.0)	0.09
Medical characteristics				
CF genotypes (N (%))				0.76
F508del homozygous	13 (40.6)	7 (46.7)	6 (35.3)	
F508del heterozygous	15 (46.9)	6 (40.0)	9 (52.9)	
Other mutations	4 (12.5)	2 (13.3)	2 (11.8)	
FEV1% predicted (mean ± SD)	74.1±21.9	71.2±20.8	76.7±23.2	0.25
Referred for lung transplant (N (%))	1 (3.1)	1 (7.1)	0 (0.0)	0.33
Comorbidities (N (%))				

Pancreatic insufficiency	27 (84.4)	15 (100.0)	12 (70.6)	**0.046**
Bone disease	10 (31.3)	7 (46.7)	3 (17.6)	0.13
Anxiety	9 (28.1)	5 (33.3)	4 (23.5)	0.70
Depression	10 (31.3)	6 (40.0)	4 (23.5)	0.45
Hemoglobin A1c (median (IQR))	5.6 (5.4-6.2)	6.2 (5.9-7.3)	5.4 (5.3-5.6)	**<0.001**
Body Mass Index (kg/m^2) (median (IQR))	23.1 (21.1-27.4)	22.9 (20.5-26.9)	23.3 (21.4-28.1)	0.62
C-reactive protein (mg/L) (median (IQR))	2.1 (0.70-5.7)	3.0 (0.85-7.6)	1.6 (0.58-3.0)	0.13
Medications (N (%))				
CFTR modulator therapy				0.31
Elexacaftor/tezacaftor/ivacaftor	18 (56.3)	9 (60.0)	9 (52.9)	
Other modulators therapies [b]	10 (31.3)	3 (20.0)	7 (41.2)	
None	4 (12.5)	3 (20.0)	1 (5.9)	
Antibiotic	23 (71.9)	14 (93.3)	9 (52.9)	**0.018**
Dental characteristics (N (%))				
Last dental visit [c]				0.15
Less than one year	24 (75.0)	10 (66.7)	14 (82.4)	
One year or more	5 (15.6)	2 (13.3)	3 (17.6)	
Three years or more	3 (9.4)	3 (20.0)	0 (0.0)	
Unable to get needed dental treatment [c]	8 (25.0)	5 (33.3)	3 (17.6)	0.42
Tooth brushing frequency [c]				0.76
Less than once a day	4 (12.5)	2 (13.3)	2 (11.8)	
Once a day	13 (40.6)	7 (46.7)	6 (35.3)	
Two or more times a day	15 (46.9)	6 (40.0)	9 (52.9)	
Daily flossing [c]	8 (25.0)	5 (33.3)	3 (17.6)	0.42

[a] Independent samples t-test was used for normally distributed continuous variables, Mann-Whitney test for skewed continuous variables, Fisher exact test for binary variables, and exact chi square test for categorical variables.

[b] Other CFTR modulator therapy= ivacaftor, lumacaftor/ivacaftor, or tezacaftor/ ivacaftor.

[b] Self-reported

P-Value < 0.05 is **bolded**

Table 4.2. Sociodemographic and medical characteristics of adults with CF and 2013-2014 NHANES non-CF controls ages 30 years and older grouped by CF status and diabetes status (N=76).

	Overall			Diabetes					
	CF (N= 19)	Non-CF (N=57)	P-value [a]	Yes			No		
				CF (N=9)	Non-CF (N=27)	P-value [a]	CF (N=10)	No-CF (N=30)	P-value [a]
Age (years) (Median (IQR))	33.0 (30.0-52.0)	38 (31.0-47.0)	0.51	39.0 (30.5- 53.0)	42.0 (38.0-50.0)	0.28	31.5 (30.0-45.5)	31.0 (30.0-35.0)	0.89
Sex (N (%))			0.99			0.99			0.99
Female	11 (57.9)	33 (57.9)		7 (77.8)	21 (77.8)		4 (40.0)	12 (40.0)	
Male	8 (42.1)	24 (42.1)		2 (22.2)	6 (22.2)		6 (60.0)	18 (60.0)	
Race (N (%))			**0.038**			0.08			0.38
Mexican American	0 (0.0)	10 (17.5)		0 (0.0)	7 (25.9)		0 (0.0)	3 (10.0)	
White	19 (100)	38 (66.7)		9 (100.0)	14 (51.9)		10 (100.0)	24 (80.0)	
Other /multiracial	0 (0.0)	9 (15.8)		0 (0.0)	6 (22.2)		0 (0.0)	3 (10.0)	
Ethnicity (N (%))			0.27			0.40			0.56
Hispanic/Latino	1 (5.3)	11 (19.3)		1 (11.1)	8 (29.6)		0 (0.0)	3 (10.0)	
Annual household income (US$) (N (%))			**0.013**			0.053			0.14
<$70,000	3 (16.7)	28 (51.9)		1 (12.5)	14 (53.8)		2 (20.0)	14 (50.0)	
≥$70,000	13 (83.3)	26 (48.1)		7 (87.5)	12 (46.2)		8 (80.0)	14 (50.0)	
Declined to answer or missing	1	3		1	1		0	2	
Education level (N (%))			0.15			**0.006**			0.85
Less than high school	0 (0.0)	9 (15.8)		0 (0.0)	7 (25.9)		0 (0.0)	2 (6.7)	
High school, GED, or equivalent	1 (5.3)	6 (10.5)		0 (0.0)	4 (14.8)		1 (10.0)	2 (6.7)	
Some college	6 (31.6)	20 (35.1)		3 (33.3)	11 (40.7)		3 (30.0)	9 (30.0)	
4-year college degree or more	12 (63.1)	22 (38.6)		6 (66.7)	5 (18.5)		6 (60.0)	17 (56.7)	
Body Mass Index (kg/m^2) (Median (IQR))	23.4 (21.5-26.9)	28.4 (25.7-35.2)	**0.002**	24.3 (21.8-27.3)	32.9 (27.7-38.4)	**0.003**	22.8 (21.4-27.7)	26.2 (22.5-32.0)	0.15
Hemoglobin A1c (Median (IQR))	5.7 (5.4-6.2)	5.5 (5.1- 7.5)	0.78	6.1 (5.8-6.6)	7.5 (6.4-8.8)	**0.008**	5.5 (5.3-5.7)	5.1 (5.0-5.3)	**0.007**

[a] The Mann-Whitney test for skewed continuous variables, Fisher exact test for binary variables, and exact chi square test for other categorical variables.

P-Value < 0.05 is **bolded**

Table 4.3. Description of periodontitis severity and clinical periodontal measures of adults with CF grouped by CFRD status (N=32).

	Overall	**CFRD**		
	N=32	**Yes**	**No**	
		N=15	**N=17**	
	N (%)	**N (%)**	**N (%)**	**P-value** [a]
Periodontitis severity				0.57
No periodontitis	13 (40.6)	5 (33.3)	8 (47.1)	
Mild periodontitis	10 (31.3)	4 (26.7)	6 (35.3)	
Moderate periodontitis	9 (28.1)	6 (40.0)	3 (17.6)	
Severe periodontitis	0 (0.0)	0 (0.0)	0 (0.0)	
Periodontal measure	**Mean ±SD**	**Mean ±SD**	**Mean ±SD**	**P-value** [b]
Periodontal pocket depth (mm)	2.4±0.14	2.4±0.11	2.4±0.13	0.58
Clinical attachment loss (mm)	1.7±0.30	1.8±0.33	1.7±0.28	0.18

[a] Exact chi square test

[b] Independent samples t-test

Table 4.4. Prevalence of periodontitis for adults with CF ages 30 years and older grouped by CFRD status compared to non-CF controls with and without diabetes (N=76).

CF-Diabetes group	Periodontitis	
	%	P-value [a]
CFRD vs. healthy	77.8% vs. 6.7%	**<0.001**
CF no diabetes vs. healthy	60.0% vs. 6.7%	**0.001**
Non-CF with diabetes vs. healthy	55.6% vs. 6.7%	**<0.001**
CFRD vs. non-CF with diabetes	77.8% vs. 55.6%	0.43
CF no diabetes vs. non-CF with diabetes	60.0% vs. 55.6%	0.99

[a] Fisher's exact test.

Healthy= no CF and no diabetes

Table 4.5. Difference in means of clinical periodontal measures for adults with CF ages 30 years and older grouped by CFRD status compared to non-CF controls with and without diabetes (N=76).

CF-Diabetes group	Periodontal pocket depth		Clinical attachment loss	
	Difference (95% CI)	P-value [a]	Difference (95% CI)	P-value [a]
CFRD vs. healthy	1.3 (1.1,1.5)	**<0.001**	0.66 (0.30,1.0)	**<0.001**
CF no diabetes vs. healthy	1.3 (1.1,1.5)	**<0.001**	0.51 (0.23,0.80)	**<0.001**
Non-CF with diabetes vs. healthy	0.39 (0.06,0.71)	**0.014**	0.57 (0.04,1.1)	**0.029**
CFRD vs. non-CF with diabetes	0.91 (0.60,1.2)	**<0.001**	0.09 (–0.50,0.67)	0.97
CF no diabetes vs. non-CF with diabetes	0.90 (0.58,1.2)	**<0.001**	– 0.06(–0.62,0.50)	0.99

[a] Games-Howell post hoc test

Healthy= no CF and no diabetes

P-Value < 0.05 is **bolded**

Supplementary Table 4.1. Periodontitis severity and clinical periodontal measures for adults with CF and non-CF controls ages 30 years and older grouped by CF-diabetes status (N=76).

Periodontitis severity [a]	**CFRD** **N=9** **N (%)**	**CF- no diabetes** **N=10** **N (%)**	**Non-CF with diabetes** **N=27** **N (%)**	**Healthy** **N=30** **N (%)**
No periodontitis	2 (22.2)	4 (40.0)	12 (44.4)	28 (93.3)
Mild periodontitis	2 (22.2)	4 (40.0)	1 (3.7)	2 (6.7)
Moderate periodontitis	5 (55.6)	2 (20.0)	10 (37.0)	0 (0.0)
Severe periodontitis	0 (0.0)	0 (0.0)	4 (14.8)	0 (0.0)
Periodontal measure	**Mean ±SD**	**Mean ±SD**	**Mean ±SD**	**Mean ±SD**
Periodontal pocket depth (mm)	2.4±0.11	2.4±0.13	1.5±0.56	1.1±0.28
Clinical attachment loss (mm)	1.8±0.32	1.7±0.28	1.7±0.97	1.2±0.28

[a] Defined following the U.S. Centers for Disease Control and Prevention and the American Academy of Periodontology case definition.

Chapter 5. Periodontitis and Quality of Life in Adults with CF

Authors

Alaa A. Alkhateeb [a]

Lloyd A. Mancl [a]

Kathleen J. Ramos [b]

Georgios A. Kotsakis [c,d]

Dace L. Trence [e]

Marilynn L. Rothen [a]

Donald L. Chi [a,f] (Chair)

[a] Department of Oral Health Sciences, School of Dentistry, University of Washington, Seattle, WA, USA.

[b] Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, University of Washington, Seattle, WA, USA.

[c] Department of Periodontics, Dental School, University of Texas Health at San Antonio, San Antonio, TX, USA.

[d] Department of Global Health, University of Washington, Seattle, WA, USA.

[e] Division of Metabolism, Endocrinology, and Nutrition, Department of Medicine, University of Washington, Seattle, WA, USA.

[f] Department of Health Systems and Population Health, School of Public Health, University of Washington, Seattle, WA, USA.

Abstract

Background and objective: Health-related quality of life (HRQoL) is an important clinical and research outcome that describes the impact of a health condition on an individual's overall well-being as well as on physical, social, and psychological functioning. Adults with cystic fibrosis (CF) present with several periodontitis risk factors like CF-related diabetes, asthma, bone disease, and chronic use of inhaled medications. Both CF and periodontitis impact HRQoL independently. In this study, we sought to evaluate the interconnection between the impacts of CF and periodontitis on HRQoL by evaluating the oral health related quality of life (OHRQoL) of adults with CF and the impact of periodontitis and other dental-behavioral factors on CF related quality of life (CFRQoL). We also evaluated other sociodemographic and medical correlates of OHRQoL and CFRQoL.

Methods: We conducted a pilot cross-sectional study of adults with CF (age ≥ 18 years) at a single CF center in Seattle, Washington, USA (N=32). Periodontitis was defined using the U.S. Centers for Disease Control and Prevention and the American Academy of Periodontology case definition. HRQoL was measured using two measures: 1) OHRQoL using the Oral Health Impact Profile 14 (OHIP-14), 2) CFRQoL using the Cystic Fibrosis Questionnaire Revised (CFQ-R). We used the Mann-Whitney test to assess differences in median scores of OHIP-14 and CFQ-R domains for adults with CF grouped by periodontitis status. We used the Mann-Whitney test, the Kruskal-Wallis test, and the Spearman rank correlation to assess correlates of OHRQoL and CFRQoL.

Results: Adults with CF reported good OHRQoL. Across the OHIP-14 domains, the median score was 2.0, indicating that occasionally oral health impacted social, physical,

and psychological functioning of adults with CF. Median OHIP-14 and CFQ-R domain scores did not differ by periodontitis status. Markers of low socioeconomic status, anxiety, and depression were significantly associated with worse domain scores of both measures of HRQoL.

Conclusion: Adults with CF reported good OHRQoL. Contrary to our hypothesis, periodontitis was not associated with low HRQoL in adults with CF. There were potential disparities in HRQoL of adults with CF by socioeconomic status. Additional larger studies are needed to confirm these findings.

5.1. Introduction

Quality of life is a self-assessment of well-being in reference to physical health, mental health, social, environmental, and economic factors (33). Health-related quality of life (HRQoL) is an important clinical and research outcome that describes the impact of a specific health condition on an individual's overall well-being as well as on physical, social, and psychological functioning (34). HRQoL measures can be disease-specific, like cystic fibrosis (CF) related quality of life (CFRQoL) (70) or body system-specific like oral health related quality of life (OHRQoL) (71). HRQoL measures have become increasingly important in health care to ensure that programmatic and patient-centered goals, which are used to guide health care planning and allocation of health care resources, are tracked and measured (34).

CF is a life-limiting autosomal recessive disease caused by defects in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, impacting all mucus-producing organs, including the lungs, pancreas, sinuses, and reproductive system (2,3). In the U.S., there are more than 35,000 individuals with CF, and approximately 1,000 new cases are diagnosed every year. Despite the dramatic improvement in prognosis and survival as a result of highly effective CF-therapeutics, individuals with CF are at high risk for respiratory infections. CF care involves complex and time-consuming medical treatments that can impact QoL (3). Older age, decreased lung function, low BMI, CF-related diabetes (CFRD), anxiety, and depression are all factors associated with low CFRQoL for adults with CF (6,72).

Periodontitis, defined as inflammation of tooth supporting structures (alveolar bone, periodontal ligament), can also adversely affect HRQoL (7). Tooth mobility and tooth loss are late signs of severe periodontitis, and both are associated with low OHRQoL by limiting function. Studies have also shown clinical measures of periodontitis (e.g., deep periodontal pockets, increased clinical attachment loss) to be associated with low OHRQoL (36). In the general population, OHRQoL decreases with older age, low socioeconomic status, and with the presence of chronic conditions like diabetes and chronic obstructive pulmonary diseases (23,73).

Recent studies have shown that the oral health of children and adolescents with CF declines with age, as indicated by increased oral disease prevalence and decreased OHRQoL (13,74). This trend is particularly concerning in the context of increased survival of individuals with CF and the fact that with age an individual may accumulate adverse effects of periodontitis risk factors like CFRD, asthma, bone disease, and chronic use of inhaled medications (7,75). To date, it is unknown whether the trend of decreased OHRQoL with age shown in younger individuals with CF continues into adulthood and whether the high-risk profile for periodontitis impacts the HRQoL of adults with CF. Thus, the goals of this pilot study of adults with CF were to: 1) evaluate the OHRQoL, 2) assess the association between periodontitis and HRQoL (OHRQoL and CFRQoL), 3) identify sociodemographic, medical, and behavioral correlates of HRQoL (OHRQoL and CFRQoL).

Understanding the association between oral health and quality of life in adults with CF is a continuation of efforts to better understand the dental care needs of individuals with CF and help guide future research aimed at promoting oral health in this medically vulnerable population.

5.2. Methods

5.2.1. Study design and participants

This was a cross-sectional study of a convenience sample of adults with CF aged (≥18 years). A complete description of the cross-sectional study design, procedures, and inclusion and exclusion criteria of adults with CF are described previously in **Chapter 2.**

5.2.2. Conceptual model

We developed a preliminary conceptual model in which 14 potential correlates of HRQoL were identified and organized into three domains: sociodemographic, medical, and behavioral (**Figure 5.1**). The model also shows the hypothesized association between periodontitis and HRQoL.

5.2.3. Outcome measures

5.2.3.1. OHRQoL

We assessed OHRQoL using the Oral Health Impact Profile 14 (OHIP-14), a 14-item patient-centered and symptom-based survey that measures seven different domains of oral health over the last year (71). OHIP-14 is a valid and reliable instrument of OHRQoL (Cronbach α= 0.30 to 0.75; test-retest stability *r*= 0.72 to 0.78) (76). The

seven domains are: functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability, and handicap. Each domain includes two OHIP-14 items. Each item is graded on a 5-point scale: 0= never, 1= hardly ever, 2= occasionally, 3= fairly often, 4= very often. We reported domain scores which range from 0 to 8 with higher scores indicating worse OHRQoL.

5.2.3.2. CFRQoL

We used the Cystic Fibrosis Questionnaire Revised (CFQ-R) to assess CFRQoL. CFQ-R is a validated disease-specific HRQoL instrument for adolescents and adults with CF. The CFQ-R is a 50-item survey that evaluates functioning across 12 domains over the previous two weeks with good reliability (Cronbach α= 0.67 to 0.94) and acceptable test-retest stability (*r*= 0.45 to 0.90) (34,77). CFQ-R assesses nine HRQoL domains (physical functioning, vitality, emotion, eating, treatment burden, health perceptions, social functioning, body image, role functioning); and 3 symptoms (weight, respiratory symptoms, and digestive symptoms). Response choices include ratings of frequency and difficulty on five different 4-point scale (e.g., 1=always, 2=often, 3=sometimes, 4=never). Each item is summed to generate a domain score then the domain score is standardized. Domain scores range from a minimum of 0 to a maximum of 100, with higher scores representing better CFRQoL (70). The minimal clinically important difference in CFQ-R is four points (78).

5.2.4. Correlates of HRQoL

5.2.4.1. Periodontitis

Based on periodontal exam findings, we created a binary variable to indicate whether an adult with CF had periodontitis (yes/no), a complete description of periodontal exam was previously described in **Chapter 2**. We defined periodontitis following the U.S. Centers for Disease Control and Prevention and the American Academy of Periodontology (CDC/AAP) case definition (49). The CDC/AAP case definition indicates that mild periodontitis is defined by the presence of two or more interproximal sites with clinical attachment loss (CAL) ≥3 mm and two or more interproximal sites with periodontal pocket depth (PD) ≥4 mm (not on the same tooth), or one site with PD ≥5 mm. Moderate periodontitis is defined as the presence of two or more interproximal sites with CAL ≥4 mm (not on the same tooth), or two or more interproximal sites with PD ≥5 mm (not on the same tooth). Severe periodontitis is defined as the presence of two or more interproximal sites with CAL ≥6 mm (not on the same tooth) and ≥1 interproximal site with PD ≥5 mm.

5.2.4.2. Other correlates of HRQoL

We identified potential correlates of HRQoL that were grouped in three major domains (**Figure 5.1**). Sociodemographic domain includes age, sex, household income, and dental insurance (73,79). Medical domain includes CF severity defined using forced expiratory volume in one second percent predicted (FEV_1 % predicted), cystic fibrosis transmembrane regulator (CFTR) modulator use, antibiotic use, CFRD, anxiety, and depression (6,15,72). Dental and behavioral domain includes unmet dental treatment

needs and dietary inflammatory index (DII) (73,80). Description of correlates are presented in (**Supplementary Table 5.1**). Supplementary Table 5.1. also shows whether correlates of HRQoL were formally tested in previous studies or were tested as new hypotheses in this study.

5.2.5 Data analysis

We used descriptive statistics to report on study variables using means and standard deviations (SD) for normally distributed quantitative variables, medians and interquartile ranges (IQR) for non-normally distributed quantitative variables, and frequencies and percentages for categorical variables. We presented descriptive data for the whole study population and for adults with CF grouped by periodontitis status (yes/no).
To test for differences in the study variables between the two study groups, we used independent samples t-test for normally distributed quantitative variables, the Mann-Whitney test for non-normally distributed quantitative variables, the Fisher's exact test for binary variables, and the exact chi-square test for categorical variables.

For hypothesis testing, first, we used the Mann-Whitney test to assess differences in OHIP-14 and CFQ-R domain scores between adults with CF grouped by periodontitis status. Second, we ranked periodontitis severity as (no periodontitis=1, mild periodontitis=2, and moderate periodontitis=3, severe periodontitis=4) and used the Spearman rank correlation to assess the association between periodontitis severity and OHIP-14 and CFQ-R domains. Third, we assessed the association between each of the correlates and each of OHIP-14 and CFQ-R domains. We used the Spearman rank

correlation for continuous variables, the Mann-Whitney test for binary variables, and the Kruskal-Wallis test for categorical variables. Fourth, to account for the significant impact of the triple CFTR modulator therapy on CFRQoL (4,5), we ran additional analyses to assess correlates of CFRQoL for the study population grouped by triple CFTR modulator therapy use. We reported whether significant correlates of CFRQoL found from the above-described analyses were significant for the triple CFTR modulator therapy users.

Because this is a pilot study and hypothesis generating, no adjustment was made for multiple statistical tests. Statistical significance was set at 0.05 for all statistical analysis and all tests were two-sided.

5.3. Results

5.3.1. Study population

Of the 140 eligible individuals, we enrolled 32 adults with CF; 54 individuals did not respond to phone and email invitations; and 54 individuals declined. The main reasons for not participating were lack of time (N=40) and concerns related to the risk of COVID-19 infection (N=14).

The median (IQR) age at the time of the study visit was 30 (28 – 38) years (range: 22 to 63 years), 63% were female, 97% were white, and 6% were Hispanic or Latino (**Table 5.1**). In terms of health insurance, 25% were publicly insured (Medicaid or Medicare) and 75% had private or dual health insurance (both public and private). Ninety-one

percent of study population had dental insurance. Nine percent reported food insecurity, 66% had completed at least a 4-year college degree, and only 28% had an annual household income less than $70,000.

Forty-one percent of the study population were homozygous for the F508del CF mutation, 47% were F508del heterozygous, and 13% had other mutations. The mean±SD FEV_1% predicted for the study population was 74.1±21.9%. Only one adult with CF had been referred and evaluated for lung transplantation. Forty-seven percent of the study population had CFRD, 84% had pancreatic insufficiency, 31% had bone disease, 28% had anxiety, and 31% had depression. The median (IQR) body mass index was 23.1 (21.1 – 27.4) kg/m^2, and the median (IQR) of glycated hemoglobin was 5.6 (5.4 – 6.2) %.

Twenty-five percent of the study population had not been to a dentist in over a year, and 25% could not get needed dental treatment because of lack of insurance or inability to pay for dental care. Eighty-seven percent reported tooth brushing at least once per day, and 25% reported daily flossing.

5.3.2. Periodontitis in adults with CF

Sixty percent of adults with CF had periodontitis, 31% had mild periodontitis, and 28% had moderate periodontitis (**Table 5.2**). The mean±SD of PD was 2.4±0.14mm and of CAL was 1.7±0.30mm. There were no significant differences in sociodemographic,

medical, or dental characteristics between adults with CF grouped by periodontitis status (**Table 5.1**).

5.3.3. HRQoL measures by periodontitis status

Across the seven OHIP-14 domains, the median score was 2.0, indicating that the oral health of adults with CF occasionally impacted their social, physical, and psychological functioning (**Table 5.3**). There were no significant differences in the OHIP-14 or CFQ-R domain scores for adults with CF by periodontitis status. OHIP-14 and CFQ-R domain scores were also not correlated with periodontitis severity.

5.3.4. Correlates of OHRQoL

Public health insurance was the most frequent correlate of OHIP-14. Public health insurance was associated with worse scores in three out of the seven OHIP-14 domains (**Table 5.4**). Compared to adults with CF with private or dual health insurance, adults with CF with public health insurance reported worse median scores in physical pain (public 4.0 vs. private or dual 2.0; P=0.006); psychological discomfort (public 4.0 vs. private or dual 2.0; P=0.016); psychological disability (public 4.0 vs. private or dual 2.0; P=0.005). Adults with CF with annual income less than $70K had worse median score in the physical pain domain (income <$70K 3.0 vs. income ≥$70K 2.0; P=0.008). Adults with CF with no dental insurance reported worse median scores in physical pain (no dental insurance 4.0 vs. dental insurance 2.0; P=0.018) and in psychological disability (no dental insurance 6.0 vs. dental insurance 2.0; P=0.035). Adults with CF who are F508del homozygous reported better median score in social disability than F508del

heterozygous who reported slightly better scores than other mutations (F508del homozygous 1.0, F508del heterozygous 2.0, other genotypes 2.5; P=0.025). Adults with CF with unmet dental treatment needs reported worse median score in physical pain (unmet dental treatment needs 3.5 vs. no unmet dental treatment needs 2.0; P=0.001).

5.3.5. Correlates of CFRQoL

Age was positively associated with the vitality domain of the CFQ-R (vitality *r*=0.52, 95% CI= 0.20,0.74; P=0.002) (**Table 5.5**). Adults with CF with public health insurance had significantly worse scores in the following domains: physical (public 62.5 vs. private or dual 87.5; P=0.014); digestion (public 55.6 vs. private or dual 77.8; P=0.013); health perception (public 66.7 vs. private or dual 88.9; P=0.006); social (public 50.0 vs. private or dual 72.2; P=0.039); and role (public 58.3 vs. private or dual 83.3; P<0.001). Adults with CF with annual household income of less than $70K had significantly worse scores in seven out of the twelve CFQ-R domains; physical (income <$70K 60.4 vs. income ≥$70K 87.5; P=0.004); vitality (income <$70K 45.8 vs. income ≥$70K 66.7; P=0.011); emotion (income <$70K 60.0 vs. income ≥$70K 86.7; P=0.004); treatment burden (income <$70K 44.4 vs. income ≥$70K 66.7; P=0.027); health perception (income <$70K 61.1 vs. income ≥$70K 88.9; P=0.017); body image (income <$70K 50.0 vs. income ≥$70K 77.8; P=0.010); and role (income <$70K 66.7 vs. income ≥$70K 83.3; P=0.003). Adults with CF with no dental insurance reported worse scores in the following domains: physical (no dental insurance 29.2 vs. dental insurance 83.3; P=0.017); health perception (no dental insurance 44.4 vs. dental insurance 77.8; P=0.025); and role (no dental insurance 50.0 vs. dental insurance 75.0; P=0.007).

FEV_1% predicted was positively associated with CFQ-R respiratory domain (*r*=0.39, 95% CI= 0.04,0.66; P=0.027), physical domain (*r*=0.52, 95% CI= 0.20,0.74; P=0.002) and health perception domain (*r*=0.45, 95% CI= 0.11,0.69; P=0.010). Adults with CF with anxiety reported worse median scores in four domains: emotion (anxiety 66.7 vs. no anxiety 86.7; P=0.004); digestion (anxiety 66.7 vs. no anxiety 88.9; P=0.020); social (anxiety 61.1 vs. no anxiety 72.2; P=0.022); and role (anxiety 66.7 vs. no anxiety 83.3; P=0.023). Adults with CF with depression reported worse median scores in the emotion domain (depression 66.7 vs. no depression 86.7; P=0.016), health perception domain (depression 61.1 vs. no depression 88.9; P=0.035), and in the role domain (depression 66.7 vs. no depression 83.3; P=0.025).

Adults with CF with unmet dental treatment needs reported worse scores in eight out of the twelve CFQ-R domains: physical (unmet dental treatment needs 60.4 vs. no unmet dental treatment needs 87.5; P<0.001), vitality (unmet dental treatment needs 45.8 vs. no unmet dental treatment needs 66.7; P=0.040), emotion (unmet dental treatment needs 63.3 vs. no unmet dental treatment needs 83.3; P=0.027), eating (unmet dental treatment needs 72.2 vs. no unmet dental treatment needs 100; P=0.010); digestion (unmet dental treatment needs 61.1 vs. no unmet dental treatment needs 77.8; P=0.039), health perception (unmet dental treatment needs 61.1 vs. no unmet dental treatment needs 88.9; P=0.005); social (unmet dental treatment needs 47.2 vs. no unmet dental treatment needs 72.2; P=0.032); and role (unmet dental treatment needs 62.5 vs. no unmet dental treatment needs 83.3; P=0.001).

5.3.5.1. Correlates of CFRQoL for triple CFTR modulator therapy users

From the above significant correlates, the following correlates were significant for adults with CF with triple CFTR modulator therapy. Public health insurance was significantly associated with worse scores in the following domains: physical (public 45.8 vs. private or dual 89.6; P=0.019); health perception (public 61.1 vs. private or dual 88.9; P=0.015); and role (public 62.5 vs. private or dual 79.2; P=0.002) (**Table 5.7**). Annual household income of less than $70K was significantly associated with worse scores in physical (income <$70K 60.4 vs. income ≥$70K 100; P=0.014); emotion (income <$70K 56.7 vs. income ≥$70K 73.3; P=0.005); and role (income <$70K 66.7 vs. income ≥$70K 75.0; P=0.031). Lack of dental insurance was associated with worse scores in physical (no dental insurance 22.9 vs. dental insurance 87.5; P=0.032); health perception (no dental insurance 33.3 vs. dental insurance 77.8; P=0.022); and role (no dental insurance 54.2 vs. dental insurance 75.0; P=0.038). Anxiety was associated with worse scores in the social (anxiety 61.1 vs. no anxiety 75.0; P=0.049) and role (anxiety 66.7 vs. no anxiety 79.2; P=0.013), and depression was associated with worse scores in the health perception domain (depression 55.6 vs. no depression 88.9; P=0.019) and in the role domain (depression 66.7 vs. no depression 83.3; P=0.017). The presence of unmet dental treatment needs was associated with worse scores in the physical domain (unmet dental treatment needs 58.3 vs. no unmet dental treatment needs 100; P<0.001), emotion domain (unmet dental treatment needs 60.0 vs. no unmet dental treatment needs 73.3; P=0.044), eating domain (unmet dental treatment needs 55.6 vs. no unmet dental treatment needs 100; P=0.011); health perception domain (unmet

dental treatment needs 55.6 vs. no unmet dental treatment needs 88.9; P=0.010); and role domain (unmet dental treatment needs 66.7 vs. no unmet dental treatment needs 83.3; P=0.011).

5.4. Discussion

The aim of this study was to assess the OHRQoL for adults with CF, whether periodontitis is associated with OHRQoL and CFRQoL, and identify sociodemographic, medical, and behavioral correlates of OHRQoL and CFRQoL for adults with CF. There were three main findings. First, adults with CF reported good OHRQoL. Second, periodontitis was not associated with OHRQoL or CFRQoL. Third, markers of low socioeconomic status were significantly associated with low OHRQoL and CFRQoL.

First, adults with CF reported good OHRQoL, indicating that only occasionally oral health status interferes with physical, social, or psychological functioning. While there are no studies to which we can directly compare this finding, it is consistent with a study of the OHRQoL of children and adolescents with CF that showed two-thirds of study population reported good or excellent OHRQoL (74). The good perception of oral health for our study population was consistent with clinical findings of good periodontal health. While more than half of our study population had periodontitis, the majority had mild localized periodontitis, and no participant had severe periodontitis. Another explanation of the good OHRQoL is that our study population had a low risk profile for dental diseases. The majority of adults with CF in our study had a relatively high socioeconomic status, dental insurance, reported frequent utilization of preventive

dentistry, maintained optimal oral hygiene, all of which are factors associated with good oral health and quality of life (51,81). Future studies of OHRQoL should focus on increasing the diversity of study population and make effort to include adults with CF with low socioeconomic status and adults with limited health care access to verify if the good OHRQoL found in our study and in the abovementioned pediatric study (74) is typical for all individuals with CF.

Second, periodontitis was not associated with OHRQoL or CFRQoL of adults with CF in our study. This is inconsistent with studies of the OHRQoL for non-CF adults that showed that periodontitis was associated with lower OHRQoL especially in the pain domains (35,36,80). There are two potential explanations of the lack of association between periodontitis and OHRQoL in our study population. First, an association between periodontitis and low OHRQoL is stronger in the case of severe periodontitis (36). Two-thirds of our study population had no or mild periodontitis. In addition, as mentioned above our study population present with several protective factors for periodontitis (dental insurance, optimal oral hygiene, frequent utilization of dental care). These factors potentially lessened the impact of periodontitis on OHRQoL for our study population. A second explanation is that the impact of CF and related medical regimens on the HRQoL of adults with CF outweigh the impact of periodontitis. Thus, adults with CF might not find the presence of periodontitis to interfere with their HRQoL. However, other oral conditions (e.g., dental caries) might have a stronger impact on the HRQoL of adults with CF than periodontitis. In our study, adults with CF with unmet dental treatment needs had significantly worse scores in eight out of the twelve CFRQoL

domains. All identified unmet dental treatment needs for our study population were related to dental caries. Future studies of oral health and HRQoL should evaluate how other oral diseases, mainly dental caries, impact the HRQoL of adults with CF to further understand links between oral health and systemic health of adults with CF and help define dental care priorities for this medically vulnerable population.

Third, markers of low socioeconomic status (public health insurance, annual income of less than $70K, lack of dental insurance, and inability to receive needed dental treatments due to financial limitations) were significantly associated with low OHRQoL and CFRQoL, especially in the health perception and pain domains. This is consistent with several studies that showed low socioeconomic status to be a barrier in CF clinical and HRQoL outcomes (81) and in oral health outcomes in non-CF adults (8). Disparities in oral health and OHRQoL by socioeconomic status is a long-standing dental public health problem (82). Adults with CF with low socioeconomic status are particularly disadvantaged given the high cost of CF-related health care which may hinder directing resources to dental health care needs (81). For adults with CF with limited dental care access, routine CF clinical visits might be the only available professional health care which makes it a critical opportunity for oral health assessment. Routine oral health assessment is significant for early diagnosis of oral diseases, which are usually asymptomatic and potentially not noticeable by an individual (83). At this stage tooth-saving dental procedures are less extensive and more affordable than at advanced stages of oral diseases. CF care teams can be trained to conduct dental screenings which could be combined with annual health screenings for adults with CF (e.g.,

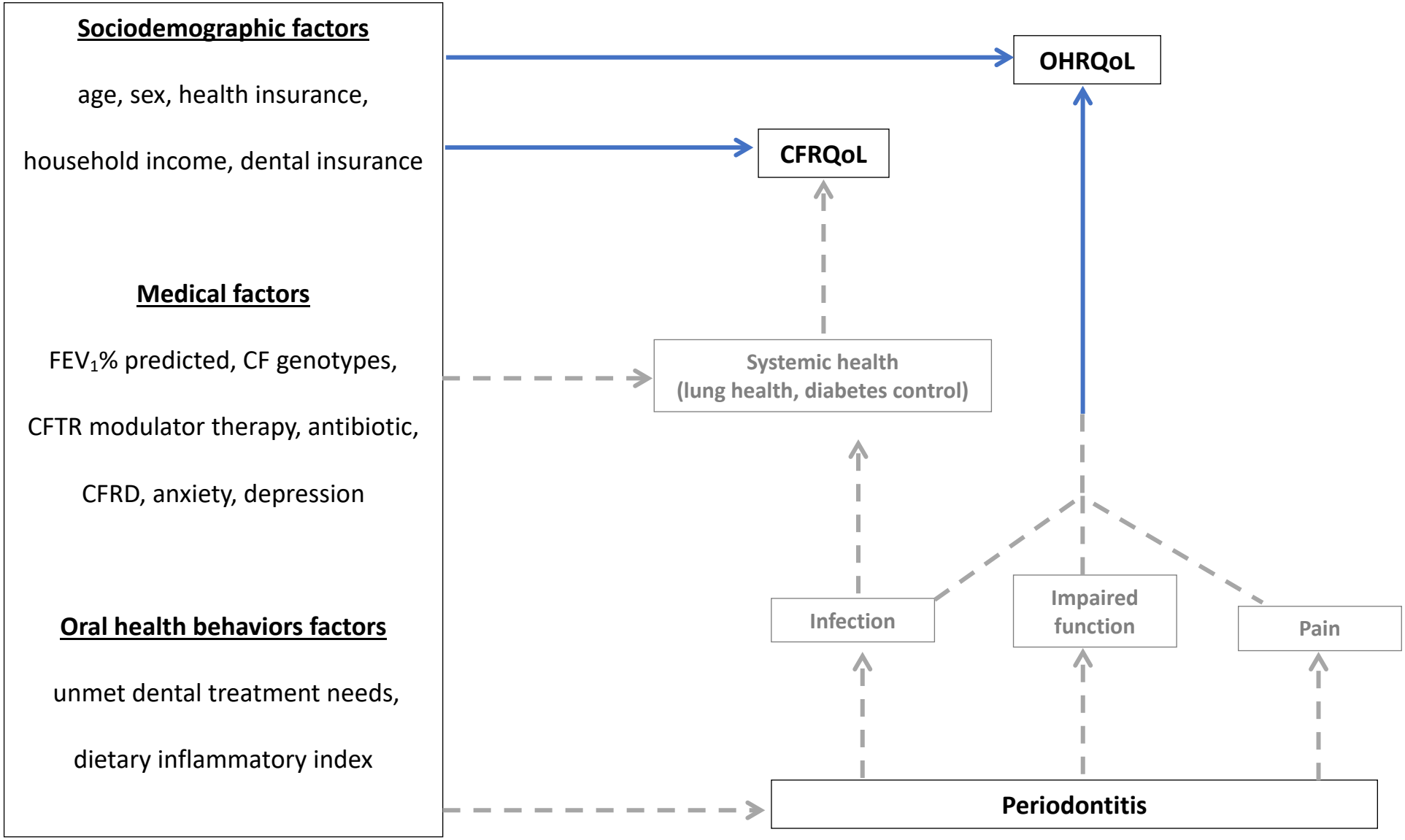
screenings for diabetes and bone disease). Future investigators should identify practical approaches and evaluate the feasibility of implementing oral health assessment as part of the routine CF care with the goal of increasing dental care access especially for adults with CF with low socioeconomic status.

There were limitations to our study. First, the study had limited power because of small sample size and lack of a control group. The sample size was determined based on the study primary goal of evaluating the association between CFRD and periodontitis, thus the assessment of association between periodontitis and HRQoL might be underpowered. The small sample size prevented adjusting for potential confounding variables in the assessment of HRQoL with regression models. Study enrollment and clinical data collection were adversely impacted by the COVID-19 pandemic and related public health guidelines. Second, the clinical significance of using OHIP-14 for the assessment of perceptions of oral health for adults with CF is limited because we only assessed periodontal health. Future studies should take a comprehensive approach and include other oral conditions most importantly dental caries. Third, to avoid confounding in the association between periodontitis and HRQoL, we excluded adults with CF who had a pulmonary exacerbation in the last four weeks. Thus, our study did not include individuals with advanced CF disease who experience frequent pulmonary exacerbations which biased our study population toward healthier individuals with CF. Fourth, we conducted our study at a single site. Most of our study population was white, with relatively high socioeconomic status, and had dental insurance. Thus, our findings were potentially biased toward adults with CF with optimal oral health and quality of life.

Multicenter studies are needed to increase sample size and participant diversity, especially race, ethnicity, and income. Fifth, our data were cross-sectional. Longitudinal studies could help to identify causal factors related to HRQoL in adults with CF.

In conclusion, our study showed adults with CF had good OHRQoL. In addition, periodontitis was not associated with HRQoL. However, there were potential disparities in HRQoL by socioeconomic status for our study population. Multicenter longitudinal studies are needed to confirm our findings and to define strategies to address disparities in oral health and HRQoL for adults with CF.

Figure 5.1. Preliminary multifactorial HRQoL correlates model for adults with CF.



Gray boxes and dashed arrows represent potential mechanisms not evaluated in this study.

Tables

Table 5.1. Sociodemographic, medical, and dental characteristics of adults with CF grouped by periodontitis status (N=32).

	Overall N= 32	Periodontitis [a]		P-value [b]
		Yes N=19	No N= 13	
Sociodemographic characteristics				
Age (years) (Median (IQR))	30.0 (28.0- 38.0)	30.0 (29.0-39.0)	29.0 (26.5-31.5)	0.14
Sex (N (%))				0.71
Female	20 (62.5)	11 (57.9)	9 (69.2)	
Male	12 (37.5)	8 (42.1)	4 (30.8)	
Race (N (%))				0.41
White	31 (96.9)	19 (100.0)	12 (92.3)	
Black or African American	1 (3.1)	0 (0.0)	1 (7.7)	
Ethnicity (N (%))				0.99
Hispanic/Latino	2 (6.3)	1 (5.3)	1 (7.7)	
Health Insurance (N (%))				0.99
Public	8 (25.0)	5 (26.3)	2 (23.1)	
Private or dual	24 (75.0)	14 (73.7)	10 (76.9)	
Dental insurance (N (%))	29 (90.6)	17 (89.5)	12 (92.3)	0.99
Food insecurity (N (%))	3 (9.4)	2 (10.5)	1 (7.7)	0.99
Education level (N (%))				0.63
High school, GED, or equivalent	4 (12.5)	2 (10.5)	2 (15.4)	
Some college	7 (21.9)	3 (15.8)	4 (30.8)	
4-year college degree	11 (34.4)	8 (42.1)	3 (23.1)	
More than 4-year college degree	10 (31.3)	6 (31.6)	4 (30.8)	
Annual household income (US$) (N (%))				0.23
<$70K	8 (27.6)	3 (17.6)	5 (41.7)	
≥$70K	21 (72.4)	14 (82.4)	7 (58.3)	
Declined to answer	3	2	1	
Medical characteristics				
CF genotypes (N (%))				0.92
F508del homozygous	13 (40.6)	8 (42.1)	5 (38.5)	
F508del heterozygous	15 (46.9)	9 (47.4)	6 (46.2)	

Other mutations	4 (12.5)	2 (10.5)	2 (15.4)	
FEV_1% predicted (mean ± SD)	74.1±21.9	72.7±20.0	76.0±25.2	0.69
Referred for lung transplant (N (%))	1 (3.1)	1 (5.3)	0 (0.0)	0.99
Comorbidities (N (%))				
CF-related diabetes	15 (46.9)	10 (52.6)	5 (38.5)	0.49
Pancreatic insufficiency	27 (84.4)	15 (78.9)	12 (92.3)	0.63
Asthma	8 (25.0)	4 (21.1)	4 (30.8)	0.68
Bone disease	10 (31.3)	6 (31.6)	4 (30.8)	0.99
Anxiety	9 (28.1)	6 (31.6)	3 (23.1)	0.70
Depression	10 (31.3)	6 (31.6)	4 (30.8)	0.99
Medications (N (%))				
CFTR modulator therapy:				0.93
Elexacaftor/tezacaftor/ivacaftor	18 (56.3)	11 (57.9)	7 (53.8)	
Other modulators therapies [c]	10 (31.3)	6 (31.6)	4 (30.8)	
None	4 (12.5)	2 (10.5)	2 (15.4)	
Antibiotic	23 (71.9)	14 (73.7)	9 (69.2)	0.99
Body Mass Index (kg/m^2) (Median (IQR))	23.1 (21.1-27.4)	22.6 (21.3-26.9)	23.3 (20.6-29.0)	0.97
Hemoglobin A1c (median (IQR))	5.6 (5.4-6.2)	5.6 (5.4-6.2)	5.9 (5.3-6.3)	0.83
Dental characteristics (N (%))				
Last dental visit [d]				0.96
Less than one year	24 (75.0)	14 (73.7)	10 (76.9)	
One year or more	5 (15.6)	3 (15.8)	2 (15.4)	
Three years or more	3 (9.4)	2 (10.5)	1 (7.7)	
Unable to get needed dental treatment [d]	8 (25.0)	5 (26.3)	3 (23.1)	0.99
Tooth brushing frequency [d]				0.32
Less than once a day	4 (12.5)	2 (10.5)	2 (15.4)	
Once a day	13 (40.6)	6 (31.6)	7 (53.8)	
Two or more times a day	15 (46.9)	11 (57.9)	4 (30.8)	
Daily flossing [d]	8 (25.0)	6 (31.5)	2 (15.4)	0.42
Dietary Inflammatory Index (median (IQR))	0.54 (–0.34-1.3)	0.31 (–0.59-1.2)	0.76 (0.12-2.0)	0.31

[a] Periodontitis defined following the CDC/AAP case definition

[b] Independent samples t-test was used for normally distributed continuous variables, Mann-Whitney test for skewed continuous variables, Fisher exact test for binary variables, and exact chi square test for other categorical variables.

[c] Other CFTR modulator therapy= ivacaftor, lumacaftor/ivacaftor, or tezacaftor/ ivacaftor.

[d] Self-reported

P-Value < 0.05 is **bolded**

Table 5.2. Description of periodontal health of adults with CF (N=32).

Periodontal disease severity [a]	**N (%)**
No periodontitis	13 (40.6)
Mild periodontitis	10 (31.3)
Moderate periodontitis	9 (28.1)
Periodontal health measures	**Mean ±SD**
Periodontal pocket depth (mm)	2.4±0.14
Clinical attachment loss (mm)	1.7±0.30

[a] **Healthy:** No periodontitis, **Mild periodontitis:** ≥2 interproximal sites with attachment loss ≥3 mm, and ≥2 interproximal sites with pocket depth ≥4 mm (not on same tooth) or one site with pocket depth ≥5 mm. **Moderate periodontitis:** ≥2 interproximal sites with attachment loss ≥4 mm (not on same tooth), or ≥2 interproximal sites with pocket depth ≥5 mm (not on same tooth).

Table 5.3. 1) Oral health related quality of life (OHIP-14) and cystic fibrosis related quality of life (CFQ-R) domain scores for adults with CF grouped by periodontitis status (N=32), and 2) correlation between periodontitis severity and OHIP-14 and CFQ-R domain scores.

	Overall	**Periodontitis** [a]			**Periodontal disease severity** [b]	
	N=32	**Yes (N=19)**	**No (N=13)**			
OHIP-14 domains	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	**P-value** [c]	**Correlation coefficient (95% CI)**	**P-value** [d]
Functional limitation	2.0 (0.0-2.0)	2.0 (0.0-2.0)	2.0 (1.0-2.0)	0.73	−0.06 (−0.41,0.30)	0.74
Physical pain	2.0 (2.0-3.0)	2.0 (1.0-3.0)	3.0 (2.0-3.5)	0.32	−0.18 (−0.50,0.19)	0.28
Psychological discomfort	2.0 (2.0-3.8)	2.0 (1.0-4.0)	2.0 (2.0-3.5)	0.72	−0.06 (−0.41,0.30)	0.73
Physical disability	2.0 (0.0-2.0)	2.0 (0.0-2.0)	2.0 (2.0-2.0)	0.064	−0.33 (−0.62,0.03)	0.063
Psychological disability	2.0 (1.3-2.0)	2.0 (1.0-2.0)	2.0 (2.0-3.0)	0.48	−0.13 (−0.46,0.24)	0.49
Social disability	2.0 (0.0-2.0)	2.0 (0.0-2.0)	2.0 (1.5-2.0)	0.13	−0.27 (−0.58,0.10)	0.13
Handicap	2.0 (1.0-2.0)	2.0 (0.0-2.0)	2.0 (2.0-2.0)	0.18	−0.24 (−0.55,0.13)	0.18
CFQ-R domains	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	**P-value** [c]	**Correlation coefficient (95% CI)**	**P-value**[d]
Respiratory	75.0 (52.8-83.3)	77.8 (61.1-83.3)	72.2 (47.2-86.1)	0.67	0.07 (−0.29,0.42)	0.69
Physical	75.0 (62.5-91.7)	83.3 (66.7-91.7)	66.7 (54.2-93.8)	0.44	0.14 (–0.23,0.47)	0.45
Vitality	58.3 (43.8-66.7)	66.7 (50.0-75.0)	50.0 (41.7-66.7)	0.38	0.16 (–0.21,0.48)	0.39
Emotion	73.3 (61.7-91.7)	73.3 (60.0-93.3)	80.0 (63.3-90.0)	0.74	0.06 (−0.41,0.32)	0.75
Eating	100 (88.9-100)	100 (88.9-100)	100 (88.9-100)	0.94	−0.013 (−0.37,0.35)	0.95
Digestion	72.2 (55.6-88.9)	66.7 (55.6-88.9)	77.8 (61.1-100)	0.36	−0.17 (−0.50,0.21)	0.37
Treatment burden	66.7 (44.4-88.8)	66.7 (44.4-88.9)	66.7 (33.3-77.8)	0.51	0.12 (−0.25,0.46)	0.52
Health perception	77.8 (58.3-88.9)	88.9 (66.7-88.9)	66.7 (55.6-88.9)	0.39	0.15 (−0.22,0.49)	0.40
Social	66.7 (61.1-81.9)	66.7 (61.1-83.3)	66.7 (61.1-77.8)	0.94	0.01 (−0.35,0.37)	0.94
Body image	77.8 (55.6-97.2)	77.8 (55.6-100)	55.6 (44.4-88.9)	0.13	0.27 (−0.09,0.57)	0.13
Role	75.0 (66.7-91.7)	83.3 (66.7-91.7)	75.0 (66.7-83.3)	0.38	0.16 (−0.21,0.49)	0.39
Weight	100 (33.3-100)	100 (33.3-100)	66.7 (33.3-100)	0.32	0.18 (−0.19,0.51)	0.32

[a] Periodontal disease refers to both forms of disease (gingivitis and periodontitis)

[b] We ranked periodontal disease as the following (1=healthy, 2=gingivitis, 3=mild periodontitis, 4=moderate periodontitis)

[c] Mann-Whitney test

[d] Spearman rank correlation

P-Value < 0.05 is **bolded**

Table 5.4. Association between sociodemographic, mdeical, oral health behavior correlates and OHIP-14 domains for adults with CF (N=32) [a].

	Functional limitation	Physical pain	Psychological discomfort	Physical disability	Psychological disability	Social disability	Handicap
Age	0.11 (−0.35,0.37)	–0.19 (−0.51,0.18)	–0.04 (−0.40,0.32)	0.04 (−0.33,0.39)	−0.03 (−0.38,0.34)	0.05 (−0.32,0.40)	0.004 (−0.36,0.36)
Sex							
Female	2.0 (0.0-2.0)*	2.0 (0.3-3.0)	2.0 (0.3-3.0)	1.0 (0.0-2.0)*	2.0 (0.0-2.0)*	1.0 (0.0-2.0)	1.5 (0.0-2.0)*
Male	2.0 (2.0-2.8)	2.5 (2.0-4.8)	2.5 (2.0-4.0)	2.0 (2.0-2.0)	2.0 (2.0-4.0)	2.0 (2.0-2.0)	2.0 (2.0-2.0)
Health insurance							
Public	2.0 (2.0-2.0)	4.0 (3.0-6.0)*	4.0 (2.0-6.0)*	2.0 (1.0-6.0)	4.0 (2.0-6.0)*	2.0 (0.0-2.0)	2.0 (2.0-4.0)*
Private or dual	2.0 (0.0-2.0)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	2.0 (0.0-2.0)	2.0 (0.5-2.0)	2.0 (0.0-2.0)	2.0 (0.0-2.0)
Household income							
<$70K	2.0 (2.0-2.0)	3.0 (3.0-4.0)*	2.5 (2.0-4.8)	2.0 (1.3-3.5)	2.0 (2.0-5.5)	2.0 (0.5-2.0)	2.0 (2.0-2.3)
≥$70K	2.0 (0.0-2.0)	2.0 (0.5-2.5)	2.0 (0.5-2.0)	2.0 (0.0-2.0)	2.0 (0.5-2.0)	2.0 (0.0 -2.0)	2.0 (0.0-2.0)
Dental insurance							
Yes	2.0 (0.0-2.0)	2.0 (1.5-3.0)*	2.0 (1.5-3.0)	2.0 (0.0-2.0)	2.0 (1.0-2.0)*	2.0 (0.0-2.0)	2.0 (0.5-2.0)
No	2.0 (1.0-2.0)	4.0 (4.0-5.5)	5.0 (3.5-6.5)	6.0 (3.0-7.0)	6.0 (4.0-7.0)	2.0 (1.0-5.0)	4.0 (2.5-5.5)
FEV_1% predicted	–0.09 (−0.44,0.27)	−0.15 (−0.48,0.22)	0.12 (−0.25,0.46)	0.02 (−0.34,0.38)	−0.10 (−0.37,0.35)	0.008 (−0.35,0.37)	–0.05 (−0.40,0.31)
CF genotypes							
F508del homozygous	2.0 (0.0-2.5)	2.0 (1.5-4.5)	2.0 (1.5-3.5)	2.0 (0.0-2.0)	2.0 (0.5-3.0)	1.0 (0.0-2.0)*	2.0 (0.0-2.0)
F508del heterozygous	2.0 (0.0-2.0)	2.0 (0.0-3.0)	2.0 (0.0-3.0)	2.0 (0.0-2.0)	2.0 (1.0-2.0)	2.0 (0.0-2.0)	2.0 (1.0-2.0)
Other mutations	2.0 (2.0-2.0)	3.0 (2.0-4.0)	3.0 (2.0-4.8)	2.0 (2.0-6.5)	2.5 (2.0-6.8)	2.5 (2.0-6.8)	2.0 (2.0-5.8)
CFTR modulator therapy							
Elexacaftor/tezacaftor/ivacaftor	2.0 (0.0-2.0)	3.0 (1.8-4.3)	2.0 (1.8-4.0)	2.0 (0.0-2.0)	2.0 (0.80-4.0)	2.0 (0.0-2.0)	2.0 (0.0-2.0)

Other modulators [b]	2.0 (1.5-2.0)	2.0 (1.5-2.3)	2.0 (1.5-3.0)	2.0 (0.0-2.0)	2.0 (1.8-2.0)	2.0 (0.0-2.0)	2.0 (1.0-2.0)
None	2.0 (0.5-2.0)	2.0 (0.50-3.5)	3.0 (0.50-4.8)	2.0 (0.5-6.5)	2.5 (0.50-6.8)	2.5 (0.50-6.8)	2.0 (0.50-5.8)
Antibiotic use							
Yes	2.0 (0.0-2.0)	2.0 (2.0-4.0)	2.0 (2.0-3.0)	2.0 (0.0-2.0)	2.0 (2.0-2.0)	2.0 (0.0-2.0)	2.0 (1.0-2.0)
No	2.0 (0.0-2.0)	2.0 (0.0-3.0)	2.0 (0.0-4.0)	2.0 (0.0-2.0)	2.0 (0.5-3.5)	2.0 (0.0-2.0)	2.0 (0.5-2.0)
CF-related diabetes							
Yes	2.0 (0.0-2.0)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	2.0 (0.0-2.0)	2.0 (0.0-2.0)	2.0 (0.0-2.0)	2.0 (0.0-2.0)
No	2.0 (1.0-2.0)	2.0 (2.0-3.5)	2.0 (2.0-4.0)	2.0 (0.5-2.0)	2.0 (2.0-3.0)	2.0 (0.0-2.0)	2.0 (1.5-2.0)
Anxiety							
Yes	2.0 (0.0-2.0)	3.0 (1.8-3.3)	2.0 (1.8-3.3)	2.0 (0.0-2.5)	2.0 (0.8-2.5)	0.0 (0.0-2.0)	2.0 (0.0-2.0)
No	2.0 (0.0-2.0)	2.0 (2.0-3.0)	2.0 (2.0-3.0)	2.0 (1.0-2.0)	2.0 (2.0-2.0)	2.0 (0.0-2.0)	2.0 (2.0-2.0)
Depression							
Yes	2.0 (0.0-2.0)	3.0 (1.8-3.3)	2.0 (1.8-3.3)	2.0 (0.0-2.5)	2.0 (1.8-2.3)	2.0 (0.0-2.0)	2.0 (1.0-2.0)
No	2.0 (0.0-2.0)	3.0 (1.8-3.3)	2.0 (1.8-3.3)	2.0 (0.0-2.5)	2.0 (1.8-2.3)	2.0 (0.0-2.0)	2.0 (1.0-2.0)
Unmet dental treatment needs							
Yes	2.0 (0.50-2.0)	3.5 (3.0-5.5)*	3.5 (2.0-5.8)	2.0 (0.30-5.5)	3.0 (2.0-6.0)*	2.0 (0.0-2.0)	2.0 (1.3-3.8)
No	2.0 (0.0-2.0)	2.0 (1.0-2.0)	2.0 (1.3-3.0)	2.0 (0.0-2.0)	2.0 (1.0-2.0)	2.0 (0.0-2.0)	2.0 (0.30-2.0)
Dietary inflammatory index	–0.08(−0.43,0.29)	–0.11 (−0.47,0.23)	0.04 (−0.33,0.39)	−0.01 (−0.38,0.35)	−0.07 (−0.43,0.30)	−0.01 (−0.37,0.37)	−0.10 (−0.44,0.28)

[a] Correlation coefficient (95% CI) for continuous variables and median (IQR) for binary and categorical variables. Spearman rank correlation was used for quantitative variables, the Man-Whitney test for binary variables, and Kruskal-Wallis for categorical variables.

[b] Other CFTR modulator therapy= ivacaftor, lumacaftor/ivacaftor, or tezacaftor/ ivacaftor.

* P-Value < 0.05

Table 5.5. Association between sociodemographic, mdeical, oral health behavior correlates and CFQ-R domains for adults with CF (N=32) (part 1) [a].

	Respiratory	Physical	Vitality	Emotion	Eating	Digestion
Age	−0.01(−0.37,0.35)	0.09 (−0.28,0.43)	0.52 (0.20,0.74)*	0.32 (−0.04,0.61)	−0.16 (−0.49,0.21)	0.14 (−0.23,0.48)
Sex						
Female	77.8 (62.5-88.9)	75.0 (52.1-90.6)	62.5 (50.0-72.9)	86.7 (66.7-93.3)	100 (72.2-100)	77.8 (55.6-100)
Male	66.7 (44.4-77.8)	83.3 (63.5-100)	54.2 (41.7-66.7)	73.3 (60.0-80.0)	100 (88.9-100)	66.7 (55.6-88.9)
Health insurance						
Public	72.2 (33.3-77.8)	62.5 (25.0-62.5)*	50.0 (41.7 -66.7)	66.7 (53.3-73.3)	100 (44.4-100)	55.6 (55.6-66.7)*
Private or dual	77.8 (61.1-86.1)	87.5 (68.8-95.8)	66.7 (50.0-75.0)	80.0 (66.7-93.3)	100 (88.9-100)	77.8 (61.1-94.4)
Household income						
<$70K	72.2 (36.1-81.9)	60.4 (30.2-62.5)*	45.8 (29.2-56.3)*	60.0 (53.3-71.7)*	100 (55.6-100)	66.7 (55.6-77.8)
≥$70K	77.8 (55.6-80.6)	87.5 (68.8-100)	66.7 (54.2-79.2)	86.7 (73.3-93.3)	100 (88.9-100)	88.9 (61.1-100)
Dental insurance						
Yes	77.8 (61.1-83.3)	83.3 (64.6-95.8)*	66.7 (50.0-70.8)	73.3 (63.3-90.0)	100 (88.9-100)	77.8 (55.6-88.9)
No	50.0 (38.9-72.2)	29.2 (22.9-45.8)	41.7 (33.3-50.0)	73.3 (63.3-83.3)	100 (72.2-100)	55.6 (50.0-61.1)
FEV_1% predicted	0.39 (0.04,0.66)*	0.52 (0.20,0.74)*	−0.06 (−0.41,0.31)	−0.07 (−0.41,0.30)	0.03 (−0.34,0.38)	0.07 (−0.30,0.42)
CF genotypes						
F508del homozygous	77.8 (63.9,91.7)	87.5 (54.2-100)	66.7 (45.8-75.0)	73.3 (63.3-90.0)	100 (100-100)	66.7 (61.1-88.9)
F508del heterozygous	72.2 (50.0-83.3)	70.8 (58.3-91.7)	58.3 (41.73-66.7)	73.3 (60.0-86.7)	88.9 (66.7-100)	77.8 (55.6-100)
Other mutations	66.7 (36.1-76.4)	83.3 (65.6-97.9)	54.2 (43.8-83.3)	86.7 (75.0-98.3)	100 (100-100)	77.8 (58.3-88.9)
CFTR modulator therapy						
Elexacaftor/tezacaftor/ivacaftor	77.8 (66.7-90.3)	81.3 (61.5-100)	54.2 (41.7-66.7)	70.0 (58.3-81.7)	100 (80.6-100)	66.7 (55.6-88.9)

Other modulators [b]	69.4 (58.3-84.7)	75.0 (61.5-88.5)	62.5 (50.0-79.2)	86.7 (70.0-93.3)	100 (97.2-100)	77.8 (55.6-88.9)
None	55.6 (33.3-73.6)	77.1 (53.1-97.9)	62.5 (45.8-72.9)	86.7(81.7-91.7)	100 (66.7-100)	94.4 (63.9-100)
Antibiotic use						
Yes	72.2 (50.0-88.9)	75.0 (50.0-91.7)	66.7 (50.0-75.0)	73.3 (66.7-86.7)	100 (88.9-100)	66.7 (55.6-88.9)
No	77.8 (69.4-83.3)	75.0 (62.5-93.8)	58.3 (33.3-66.7)	80.0 (56.7-93.3)	100 (55.6-100)	77.8 (61.1-94.4)
CF-related diabetes						
Yes	77.8 (50.0-88.9)	70.8 (33.3-91.7)	58.3 (50.0-75.0)	73.3 (66.7-93.3)	100 (88.9-100)	66.7 (55.6-88.9)
No	72.2 (55.6-83.3)	83.3 (62.5-95.8)	58.3 (41.7-66.7)	80.0 (56.7-90.0)	100 (77.8-100)	77.8 (55.6-88.9)
Anxiety						
Yes	77.8 (61.1-91.7)	75.0 (45.8-89.6)	58.3 (37.5-66.7)	66.7 (53.3-73.3)*	100 (72.2-100)	66.7 (55.6-66.7)*
No	72.2 (50.0-83.3)	75.0 (62.5-100)	58.3 (41.7-75.0)	86.7 (73.3-93.3)	100 (88.9-100)	88.9 (55.6-100)
Depression						
Yes	77.8 (66.7-86.1)	72.9 (51.0-87.5)	62.5 (25.0-66.7)	66.7 (53.3-73.3)*	100 (52.8-100)	66.7 (55.6-80.6)
No	72.2 (50.0-83.3)	79.2 (62.5-100)	58.3 (47.9-75.0)	86.7 (71.6-93.3)	100 (88.9-100)	77.8 (55.6-100)
Unmet dental treatment needs						
Yes	75.0 (37.5-81.9)	60.4 (26.0-62.5)**	45.8 (29.2-64.6)*	63.3 (53.3-73.3)*	72.2 (44.4-100)*	61.1 (55.6-66.7)*
No	75.0 (61.1-87.5)	87.5 (70.8-100)	66.7 (50.0-75.0)	83.3 (68.3-93.3)	100 (100-100)	77.8 (58.3-97.2)
Dietary inflammatory index	0.25 (−0.13,0.56)	−0.08(−0.43,0.29)	0.11 (−0.26,0.46)	0.18 (−0.20,0.51)	0.35 (−0.01,0.64)	0.06 (−0.31, 0.42)

[a] Correlation coefficient for continuous variables and median (IQR) for binary and categorical variables. Spearman rank correlation was used for quantitative variables, the Man-Whitney test for binary variables, and Kruskal-Wallis for categorical variables.

[b] Other CFTR modulator therapy= ivacaftor, lumacaftor/ivacaftor, or tezacaftor/ ivacaftor.

* P-Value < 0.05

** P-Value <0.001

Table 5.6. Association between sociodemographic, mdeical, oral health behavior correlates and CFQ-R domains for adults with CF (N=32) (part 2) [a].

	Treatment burden	Health perception	Social	Body image	Role	Weight
Age	0.36 (0.003,0.64)*	0.35 (−0.01,0.63)	0.06 (−0.31,0.41)	0.43 (0.09,0.69)*	0.25 (−0.12,0.56)	0.23 (−0.09,0.60)
Sex						
Female	72.2 (44.4-88.9)	77.8 (58.3-88.9)	66.7 (52.8-83.3)	77.8 (55.6-97.2)	79.2 (66.7-91.7)	100 (33.3-100)
Male	55.6 (25.0-66.7)	72.2 (58.3-88.9)	69.4 (62.5-76.4)	66.7 (47.2-97.2)	75.0 (66.7-89.6)	66.7 (33.3-100)
Health insurance						
Public	44.4 (44.4-55.6)	66.7 (44.4-66.7)*	50.0 (27.8-72.2)*	55.6 (44.4-88.9)	58.3 (50.0-66.7)**	66.7 (33.3-100)
Private or dual	66.7 (38.9-88.9)	88.9 (66.7-88.9)	72.2 (61.1-83.3)	77.8 (55.6-100)	83.3 (75.0-95.8)	100 (33.3-100)
Household income						
<$70K	44.4 (25.0-63.9)*	61.1 (47.2-66.7)*	69.4 (45.8-76.4)	50.0 (44.4-55.6)*	66.7 (52.1-72.9)*	50.0 (33.3-91.7)
≥$70K	66.7 (50.0-88.9)	88.9 (66.7-88.9)	72.2 (61.1-83.3)	77.8 (61.1-94.4)	83.3 (70.8-100)	100 (33.3-100)
Dental insurance						
Yes	66.7 (38.9-88.9)	77.8 (66.7-88.9)*	66.7 (61.1-83.3)	77.8 (55.6-100)	75.0 (66.7-91.7)*	100 (33.3-100)
No	44.4 (44.4-50.0)	44.4 (33.3-55.6)	50.0 (38.9-63.9)	44.4 (44.4-66.7)	50.0 (50.0-54.2)	33.3 (33.3-66.7)
FEV_1% predicted	0.10 (−0.27,0.45)	0.45 (0.11,0.69)*	0.12 (−0.25,0.46)	0.18 (−0.19,0.51)	0.29 (−0.08,0.59)	0.16 (−0.21,0.49)
CF genotypes						
F508del homozygous	66.7 (38.9-72.2)	88.9 (50.0-88.9)	72.2 (61.1-80.6)	77.8 (50.0-94.4)	75.0 (66.7-91.7)	100 (33.3-100)
F508del heterozygous	55.6 (22.2-88.9)	77.8 (55.6-88.9)	66.7 (50.0-72.2)	77.8 (55.6-100)	75.0 (66.7-91.7)	100 (33.3-100)
Other mutations	77.8 (58.3-88.9)	83.3 (66.7-100)	75.0 (54.2-91.7)	88.9 (55.6-97.2)	87.5 (56.3-100)	100 (50.0-100)
CFTR modulator therapy						
Elexacaftor/tezacaftor/ivacaftor	50.0 (41.7-69.4)	72.2 (55.6-88.9)	69.4 (56.9-79.2)	66.7 (52.8-91.7)	75.0 (66.7-83.3)	33.3 (8.3-83.3)*

Other modulators [b]	88.9 (33.3-100)	83.3 (61.1-91.7)	69.4 (61.1-83.3)	88.9 (75.0-100)	91.7 (72.9-100)	100 (100-100)
None	66.7(55.6-86.1)	77.8 (66.7-97.2)	63.9 (52.8-87.5)	72.2 (47.2-97.2)	79.2 (54.2-97.9)	66.7 (33.3-100)
Antibiotic use						
Yes	55.6 (44.4-77.8)	77.8 (61.1-88.9)	66.7 (61.1-77.8)	77.8 (55.6 -100)	75.0 (66.7-91.7)	100 (33.3-100)
No	88.9 (44.4-100)	77.8 (55.6-88.9)	72.2 (63.9-91.7)	66.7 (55.6-83.3)	91.7 (66.7-100)	100 (50.0-100)
CF-related diabetes						
Yes	55.6 (44.4-77.8)	77.8 (55.6-88.9)	61.1 (50.0-83.3)	77.8 (44.4-100)	75.0 (58.3-91.7)	100 (33.3-100)
No	66.7 (38.9-94.4)	77.8 (66.7-88.9)	72.2 (63.9-80.6)	77.8 (55.6-88.9)	75.0 (66.7-95.8)	100 (50.0-100)
Anxiety						
Yes	44.4 (44.4-77.8)	66.7 (50.0-83.3)	61.1 (36.1-72.2)*	77.8 (55.6-88.9)	66.7 (54.2-79.2)*	100 (50.0-100)
No	66.7 (33.3-88.9)	88.9 (66.7-88.9)	72.2 (61.1-83.3)	77.8 (55.6-100)	83.3 (66.7-100)	100 (33.3-100)
Depression						
Yes	44.4 (38.9-77.8)	61.1 (52.8-80.6)*	66.7 (40.3-80.6)	66.7 (52.8-80.6)	66.7 (56.3-77.1)*	100 (58.3-100)
No	66.7 (41.7-88.9)	88.9 (66.7-88.9)	88.9 (66.7-91.7)	83.3 (55.6-100)	83.3 (66.7-100)	100 (33.3-100)
Unmet dental treatment needs						
Yes	44.4 (27.8-63.9)	61.1 (47.2-66.7)*	47.2 (31.9-75.0)*	55.6 (44.4-80.6)	62.5 (50.0-72.9)*	66.7 (33.3-100)
No	66.7 (44.4-88.9)	88.9 (66.7-88.9)	72.2 (61.1-83.3)	77.8 (58.3-100)	83.3 (68.8-97.9)	100 (33.3-100)
Dietary inflammatory index	0.18 (−0.2,0.51)	0.06 (−0.32,0.41)	−0.15(−0.49,0.23)	0.13 (−0.25,0.47)	−0.03(−0.39,0.34)	0.10 (−0.27,0.45)

[a] Correlation coefficient for continuous variables and median (IQR) for binary and categorical variables. Spearman rank correlation was used for quantitative variables, the Man-Whitney test for binary variables, and Kruskal-Wallis for categorical variables.

[b] Other CFTR modulator therapy= ivacaftor, lumacaftor/ivacaftor, or tezacaftor/ ivacaftor.

* P-Value < 0.05

** P-Value <0.001

Table 5.7. CFQ-R domain scores by Triple CFTR therapy use (N=32).

	Triple CFTR therapy use [a]		
	Yes (N=18)	**No (N=14)**	
CFQ-R domains	**Median (IQR)**	**Median (IQR)**	**P-value** [b]
Respiratory	77.8 (66.7-90.3)	63.9 (50.0-79.2)	0.19
Physical	81.3 (61.5-100)	75.0 (59.4-91.7)	0.63
Vitality	54.2 (41.7-66.7)	62.5 (50.0-75.0)	0.23
Emotion	70.0 (58.3-81.7)	86.7 (73.3-93.3)	**0.046**
Eating	100 (80.6-100)	100 (97.2-100)	0.26
Digestion	66.7 (55.6-88.9)	77.8 (55.6-91.7)	0.37
Treatment burden	50.0 (41.7-69.4)	83.3 (50.0-91.7)	0.078
Health perception	72.2 (55.6-88.9)	83.3 (66.7-91.7)	0.34
Social	69.4 (56.9-79.2)	66.7 (61.1-83.3)	0.73
Body image	66.7 (52.8-91.7)	88.9 (63.9-100)	0.18
Role	75.0 (66.7-83.3)	91.7 (66.7-100)	0.14
Weight	66.7 (52.8-91.7)	100 (33.3-100)	0.35

[a] Triple CFTR modulator therapy yes= Elexacaftor/tezacaftor/ivacaftor, no= other CFTR modulator therapy (ivacaftor, lumacaftor/ivacaftor, or tezacaftor/ ivacaftor), or no modulator therapy.

[b] Mann-Whitney test

P-Value < 0.05 is **bolded**

Supplementary Table 5.1. Description of correlates of HRQoL.

	Variable	Type	Unite/value	Instrument	References	
					OHRQoL	CFRQoL
Sociodemographic	Age	Continuous	- Years	Medical record	(Zucoloto ML et al., 2016)	(Cronly JA et al., 2019) (Habib a 2015)
	Sex	Binary	- Male - Female	Medical record	(Zucoloto ML et al., 2016)	(Cronly JA et al., 2019) (Habib A 2015)
	Income	Categorical	- Less than $20,000 - $20,000 to $29,999 - $30,000 to $49,999 - $50,000 to $69,999 - $70,000 to $89,999 - More than $90,000 - I don't know - I prefer not to answer	Questionnaire	(Divaris K et al., 2011)	(Kerem E, 2016)
	Health insurance	Categorical	- Public - Private - Dual (public and private)	Medical records	(Kamimura A, 2017)	(Kerem E, 2016), (Hassan M, 2018)
	Dental insurance	Binary	- Yes/ No	Questionnaire	(Kamimura A, 2017)	New hypothesis
Medical	CFTR genotype	Categorical	- F508del homozygous - F508del heterozygous - Other mutations	Medical records	New hypothesis	(Cronly JA et al., 2019)
	CF severity (FEV_1%-predicted)	Continuous	- Percent %	Medical records	New hypothesis	(Cronly JA et al., 2019) (Habib A 2015)
	CF-related diabetes	Binary	- Yes - No	Medical records	New hypothesis	(Kwong E et al., 2019)
	Anxiety	Binary	- Yes - No	Medical records	(Kisely S et al., 2016), (Su N et al., 2021)	(Cronly JA et al., 2019)
	Depression	Binary	- Yes - No	Medical records	(Kisely S et al., 2016)	(Cronly JA et al., 2019)
	CFTR modulators use	Categorical	- Elexacaftor/tezacaftor/ivacaftor - Other modulators - None	Medical records	New hypothesis	(Middleton PG et al, 2019) (Cronly JA et al., 2019) (Habib A 2015)
	Current use of antibiotic	Binary	- Yes - No	Medical records	New hypothesis	(Cronly JA et al., 2019) (Habib A 2015)
Oral health behaviors	Unmet dental treatment need	Binary	- Yes - No	Questionnaire	(Cunha-Cruz J, 2008) (Zucoloto ML et al., 2016)	New hypothesis
	Dietary inflammatory index	Continuous	- ASA24	Questionnaire	New hypothesis	New hypothesis

FEV_1%-predicted= forced expiratory volume in one second percent predicted
ASA-24= Automated Self-Administered 24-Hour
Other CFTR modulator therapy= ivacaftor, lumacaftor/ivacaftor, or tezacaftor/ ivacaftor.

Chapter 6. Conclusions

This study examined the associations between CF and periodontitis, with an emphases on the impact of CFRD on the periodontal health of adults with CF and the impact of periodontitis on the quality of life of adults with CF.

Among the study group with CF, differences in CF-related comorbidities and treatments were not associated with differences in periodontal health. However, adults with CF had significantly higher prevalence of periodontitis than matched healthy non-CF controls and similar prevalence of periodontitis to non-CF controls with diabetes. Our analyses did not show any association between periodontitis status and OHRQoL or CFRQoL. However, our analysis showed that markers of low socioeconomic status (public health insurance, annual income of less than $70K, lack of dental insurance, and inability to receive needed dental treatments due to financial limitations) were significantly associated with low OHRQoL and CFRQoL.

Together, our findings suggest that while the overall periodontal health of adults with CF was good and that periodontitis is not likely to be a determinant of quality of life for this population, CF is a potential risk factor for periodontitis. The increased risk of periodontitis associated with CF observed in our study might be explained by the collective impact of CF-related comorbidities and treatments, which we were not able to test due to small sample size. This increased risk is unlikely to be a result of behavioral factors given that our study population with CF had optimal oral hygiene and reported frequent utilization of preventive dental care.

Future research should address the limitations of this study by including larger and more diverse study samples of adults with CF, especially adults with advanced lung disease, adults with low socioeconomic status, adults with no dental insurance, and non-white adults with CF, as well as by including a concurrent non-CF control groups to verify whether the difference in periodontal health by CF status is typical for all adults with CF. Given that CF is a rare disease, large and diverse study samples with CF are more likely to be recruited through multicenter studies involving interdisciplinary and multicenter research teams collaborations. In terms of priorities of future oral health research, other dental diseases mainly dental caries is potentially a more significant oral health problem than periodontitis, especially for adults with CF with low socioeconomic status. In our study, all identified unmet dental treatment needs were related to dental caries, and unmet dental treatment need was significantly associated with poor OHRQoL and CFRQoL, especially in the pain and health perception domains. Finally, feasibility studies evaluating the practicality of integrating oral health assessment into routine CF care are needed, with the overall goal of increasing the promotion of oral health and access to oral health care for adults with CF.

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