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Effects of Switching from Conventional Cigarettes to Combustion-Free Nicotine Delivery Systems (C-FNDS) on Salivary TNF-alpha Levels and Gingival Conditions: A Randomized Controlled Trial

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Abstract

Background: Tobacco smoking is an independent risk factor for periodontitis. Smokers may show impaired inflammatory responses, altered gingival vascular function, and increased salivary tumor necrosis factor-alpha (TNF-alpha). This study evaluated changes in salivary TNF-alpha levels and gingival conditions among smokers who switched from combustible tobacco cigarettes to combustion-free nicotine delivery systems (C-FNDS). **Methods:** This single-blind, open-label randomized controlled trial with 6-month follow-up was conducted at the Department of Periodontics, Dental and Oral Hospital, Faculty of Dentistry, Universitas Padjadjaran, Bandung, Indonesia. Forty smokers were randomized into a C-FNDS switching group and a control group that continued combustible tobacco use. Gingival inflammation was assessed using the Modified Gingival Index (MGI), saliva samples were collected to measure TNF-alpha at baseline, 3 months, and 6 months, and exhaled carbon monoxide (CO) was assessed as a secondary outcome. **Results:** A total of 40 participants were analyzed. Switching to C-FNDS was associated with a reduction in salivary TNF-alpha levels over 6 months and lower MGI scores compared with continued combustible tobacco smoking. Exhaled CO decreased in the switching group, supporting reduced exposure to combustible tobacco products. **Conclusion:** Switching from conventional cigarettes to C-FNDS for 6 months was associated with reduced salivary TNF-alpha levels, lower gingival inflammation, and lower exhaled CO levels compared with continued combustible cigarette use.

Keywords: *combustion-free nicotine delivery system; gingiva; Modified Gingival Index; periodontitis; TNF-alpha.*

Background

Periodontal tissue comprises the gingiva, alveolar bone, cementum, and periodontal ligament. Periodontal disease is a multifactorial inflammatory condition that begins as gingivitis and may progress to chronic destructive periodontitis with attachment loss and alveolar bone loss.[1]Smoking is one of the most important lifestyle-related risk factors for periodontal destruction, with smokers having a substantially higher risk of periodontal disease than never-smokers.[2]

In smokers, clinical signs of gingival inflammation may be less pronounced despite deeper probing depth, greater attachment loss, and increased tooth loss. Cigarette smoke may impair gingival vascular function, increase oxidative stress, and alter inflammatory mediator production, including interleukin-1, interleukin-6, interleukin-8, transforming growth factor-beta, and TNF-alpha.[3-5] Although smoking cessation remains the preferred approach, many smokers are unwilling or unable to quit despite repeated attempts. Nicotine replacement therapy and alternative nicotine products have been used as harm-reduction strategies.[6-9] However, the periodontal and inflammatory effects of switching from combustible tobacco to C-FNDS remain controversial and require clinical evaluation.[10-12] This study aimed to evaluate salivary TNF-alpha levels and gingival conditions in smokers switching to C-FNDS during a 6-month period.

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Methods

Study design and ethical approval

This was a single-blind, open-label randomized controlled trial with a 6-month follow-up conducted at the Department of Periodontics, Dental and Oral Hospital, Faculty of Dentistry, Universitas Padjadjaran, Bandung, Indonesia, from October 2023 to May 2024. The study complied with the Declaration of Helsinki and received ethical approval from the Research Ethics Commission of Universitas Padjadjaran (643/UN6.KEP/EC/2021). The study was registered in the UMIN Clinical Trial Registry (UMIN000051684). All participants provided written informed consent.

Participants

Participants were recruited from May to September 2023 through advertising channels including social networking sites. Inclusion criteria were age 18-59 years, tobacco smoking for at least 5 consecutive years, at least 10 natural teeth, exhaled CO level above 7 ppm, good general health or gingivitis/mild periodontitis, and willingness to join either the switching or control group. Exclusion criteria included pregnancy or lactation, systemic diseases such as diabetes mellitus, HIV infection, tuberculosis, hypertension, cardiovascular disease, fixed orthodontic appliances or tooth prostheses, use of antibiotics or anti-inflammatory drugs within 14 days before the first visit, and tooth loss due to periodontitis.

Sample size and randomization

The sample size was calculated using the Federer formula, with an anticipated 10% dropout rate, resulting in a minimum requirement of 17 participants per group. Subjects were randomized using digital randomization software into a C-FNDS switching group and a control group that continued combustible tobacco smoking.

Intervention and clinical assessment

Before enrollment, smokers received brief smoking cessation education and were reminded of the risks associated with smoking and nicotine consumption. The switching group received heated tobacco products or vape devices, with education on use and refills provided every 2 weeks until 6 months. All subjects received full-mouth scaling or dental cleaning using an ultrasonic scaler at enrollment. Gingival conditions were measured using the Modified Gingival Index described by Lobene et al.[21] at baseline, 3 months, and 6 months.

Salivary TNF-alpha and exhaled CO

Ten milliliters of unstimulated whole saliva were collected by the spitting method at baseline, 3 months, and 6 months. Samples were stored at -70°C and salivary TNF-alpha levels were analyzed using an enzyme-linked immunosorbent assay. Exhaled CO was measured as a secondary outcome to assess recent combustible tobacco exposure.[22-24]

Statistical analysis

Data completeness was checked before analysis. Normality was assessed with the Shapiro-Wilk test and transformation was performed when necessary. Levene test was used for homogeneity of variance when normality was confirmed. Independent t-test compared differences between groups, and Spearman rank correlation coefficient assessed correlations between parameters. A two-tailed p-value <0.05 was considered statistically significant. Analyses were performed using SPSS version 26.

Results

Forty participants were included in the final analysis: 23 in the C-FNDS switching group and 17 in the control group. Baseline characteristics were generally comparable between groups. Most participants were male and consumed 11-20 cigarettes per day. Most subjects had gingivitis, with a smaller proportion having mild periodontitis.

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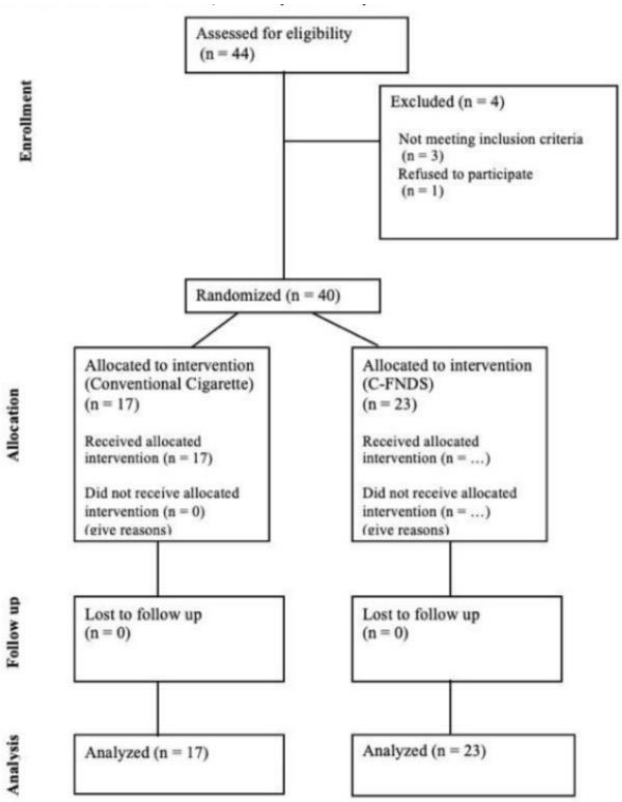

Figure 1. Consort Flow Diagram

Table 1. Baseline characteristics of participants

Characteristic	C-FNDS group (n=23)	Control group (n=17)
Age 20-30 years	14 (60%)	9 (55.55%)
Age 31-40 years	8 (35%)	8 (44.45%)
Age 41-50 years	1 (5%)	0
Male	20 (85%)	15 (88.89%)
Female	3 (15%)	2 (11.11%)
Cigarette consumption 11-20 sticks/day	18 (80%)	15 (83.33%)
Cigarette consumption >20 sticks/day	5 (20%)	2 (16.67%)
Gingivitis	19 (80%)	13 (88.89%)
Mild periodontitis	4 (20%)	4 (11.11%)

MGI values increased in both groups during follow-up; however, the increase was lower in the C-FNDS group than in the control group. Salivary TNF-alpha levels showed significant intra-group changes over 6 months. Exhaled CO decreased in the switching group, whereas the control group maintained higher CO levels.

Table 2. Mean TNF-alpha, MGI, and exhaled CO levels during follow-up

Variable	Group	Baseline	Day 90	Day 180	p-value
TNF-alpha	C-FNDS	0.47 +/- 0.27	2.92 +/- 1.72	6.72 +/- 8.65	0.026*
TNF-alpha	Control	0.57 +/- 0.27	2.73 +/- 1.55	9.54 +/- 9.52	0.003*
MGI	C-FNDS	0.49 +/- 0.23	0.19 +/- 0.17	0.78 +/- 0.23	0.000*
MGI	Control	0.56 +/- 0.32	0.58 +/- 0.48	1.13 +/- 0.55	0.000*

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CO (ppm)	C-FNDS	12.48 +/- 6.49	5.35 +/- 4.73	4.43 +/- 2.76	0.000*
CO (ppm)	Control	12.53 +/- 5.99	10.53 +/- 5.86	10.35 +/- 8.05	0.373

Table 3. Intergroup comparison of changes between baseline and day 180

Variable	**C-FNDS group**	**Control group**	**p-value**
TNF-alpha change	6.44 +/- 0.268	9.55 +/- 0.25	0.05*
MGI change	0.42 +/- 0.24	0.68 +/- 0.26	0.01*
CO change (ppm)	-8.04 +/- 5.51	-3.00 +/- 4.58	0.002*

*Statistically significant difference; C-FNDS: combustion-free nicotine delivery systems; CO: carbon monoxide; MGI: Modified Gingival Index; TNF-alpha: tumor necrosis factor-alpha.

Discussion

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This randomized controlled trial showed that smokers who switched from combustible tobacco products to C-FNDS had lower salivary TNF-alpha levels, less severe gingival inflammation, and lower exhaled CO levels over 6 months compared with smokers who continued combustible tobacco use. These findings support the hypothesis that eliminating or reducing exposure to combustible cigarette smoke may reduce selected inflammatory markers relevant to periodontal health.

Smoking increases the risk of periodontal disease and may compromise the effectiveness of periodontal therapy through inflammatory dysregulation, oxidative stress, impaired vascular response, and altered host defense.[2,3,11,12] TNF-alpha is a key pro-inflammatory cytokine involved in periodontal tissue destruction and bone resorption.[16] The reduction of salivary TNF-alpha in the switching group suggests a potential reduction in inflammatory burden after changing from combustible cigarettes to non-combustible nicotine products.

Clinical changes were consistent with biomarker findings. Participants who continued combustible tobacco use showed greater MGI scores, whereas those who switched to C-FNDS demonstrated lower gingival inflammation. These findings differ from some observational studies reporting worse oral conditions among e-cigarette users.[18-20] A possible explanation is that all participants received dental cleaning before baseline assessment, and participants with more severe periodontitis were excluded.

This study has limitations. The sample size was small, the follow-up was limited to 6 months, and the intervention involved different non-combustible products. In addition, TNF-alpha is only one biomarker and cannot fully characterize the

inflammatory or toxicological effects of switching. Longer studies with broader biomarker panels, larger sample sizes, and clinically meaningful periodontal endpoints are needed.

Conclusion

Switching from combustible tobacco cigarettes to C-FNDS for 6 months was associated with reduced salivary TNF-alpha levels, lower Modified Gingival Index scores, and lower exhaled CO levels compared with continued combustible cigarette smoking. Under the limitations of this study, C-FNDS switching may reduce selected markers of periodontal inflammation among smokers who are unwilling or unable to quit combustible tobacco use.

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Conflict of Interest

The authors declare no conflict of interest.

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Author Contributions

All authors contributed to study conception and design, data collection, data analysis, interpretation of findings, manuscript drafting, and critical revision. All authors approved the final manuscript.

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