Relationship Between Dental Caries and YKL-40 Levels in Saliva

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Objective: *YKL-40, a new biomarker of localized inflammation, is secreted by macrophages and regulates inflammation and immune responses. The aim of this study was to investigate YKL-40 levels in saliva and compare the level of this mediator in healthy and unhealthy oral cavity.* ***Study design:*** *80 children (42-girl, 38-boy), aged 6-15 (mean±SD: 9.35±2.08) were included in this cross-sectional study. The children were divided into four groups: Group-I (control, n=20, dmft/DMFT=0), Group-II (n=20, exist of dental caries), Group-III (n=20, exist of advanced dental caries without pulp exposure), and Group-IV (n=20, exist of advanced dental caries with pulp exposure). The dmft/DMFT, dmfs/DMFS, and the number of advanced dental caries according to the ICDAS and pufa/PUFA index were recorded. Saliva was collected and YKL-40 concentrations were measured.* ***Results:*** *The highest level of YKL-40 was obtained in Group IV, followed by Groups III, II, and I, respectively ($p<0.01$). There was a positive correlation between YKL-40 and the number of caries There were no statistically significant difference in YKL-40 levels in terms of age and gender ($p>0.05$).* ***Conclusions:*** *The advanced dental caries with pulp exposure may play an important role in the increasing levels of YKL-40 in saliva.*

Keywords: *Dental caries, pulpit, saliva, YKL-40.*

INTRODUCTION

YKL-40 is a 40-kDa glycoprotein, which is produced by activated macrophages,[1] neutrophils,[2] and mast cells in the inflamed areas.[3] The plasma levels of YKL-40 are elevated in the patients with acute inflammation (e.g. pneumonia, endotoxemia, and hepatitis) or chronic inflammation (e.g. rheumatoid arthritis, inflammatory bowel disease, asthma, chronic obstructive pulmonary disease, type I and II diabetes, and coronary artery disease) and in the patients with liver fibrosis and cancer.[4-8]

The relationship between the proinflammatory cytokines and the oral pathogenic bacteria has been determined in previous studies.[9-12] Some of these studies also determined the correlation between these proinflammatory markers and YKL-40 in body fluids.[13,14]

Of all the studies on YKL-40, only one of them was performed to investigate the possible role of YKL-40 in oral cavity.[15] It was related to periodontal diseases and investigated in GCF and serum. Our hypothesis is that YKL-40 may be an important causative factor, related to the density of localized inflammation in the oral cavity by oral bacteria and may play a pathophysiological role in this entity.

A new biomarker will partially help the clinician to determine the level of caries and the type of treatment. It is important to determine whether the caries are deep or shallow and whether there is inflammation in advanced caries with a pulpal involvement. For example, in children with dental anxiety or in individuals with special needs, which is indicated for dental treatment under general anesthesia or sedation, it will be beneficial for the dentist to acquire prior knowledge about the health status of the oral cavity from saliva samples. At least the dentist can make a prediction about whether it may be a

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deeply decayed tooth and know what awaits him / her during treatment. According to the anamnesis of the patients who can not be examined (whether there are dental pain at night, asymmetry on the face, etc.), YKL-40 can help physicians to strengthen his / her estimation. It is an advantage for the physician and the patient / patient's caregivers to predict that the tooth will be endodontically treated or extracted instead of being filled, before the dental treatment.

Thus, the goal of this study was to investigate YKL-40 levels in saliva to be able to compare the level of this mediator in a healthy oral cavity and an unhealthy oral cavity, which had dental caries at different stages.

MATERIAL AND METHODS

Patient selection

This study was performed in the Faculty of Dentistry, Department of Pedodontics, at Inönü University. According to the previous power analysis clarifying the changes of YKL-40 in saliva, the estimated number of participants was 15 per group, with an alpha level of 0.05 and a power of 0.80.[15]

This cross-sectional study was conducted in accordance with the Declaration of Helsinki after obtaining ethical approval. It was approved by a Clinical Research Ethics Committee in Inönü University School of Medicine (ethic number: 2017/67). The written informed consent was obtained from the parents before the examination.

A total of 80 subjects, aged 6-15 (9.35 ± 2.08 years; 42 girls, 38 boys) participated in this study. The participants were divided into four groups: Group I (control, n=20, mean age=8.15 ± 1.14), Group II (n=20, with dental caries, mean age=8.90 ± 1.92), Group III (n=20, with advanced dental caries without pulp exposure, mean age=10.10 ± 2.32), and Group IV (n=20, with advanced dental caries with pulp exposure, mean age=10.25 ± 2.10). The children were excluded from the study if they had any systemic and/or periodontal diseases, and if they had taken antibiotics or anti-inflammatory drugs in the last 30 days.

Calibration of the examiners

All clinical examinations were performed by an experienced pediatric dentist (GD). On the other hand, biochemical analysis was performed by another experienced biochemist (EL).

The examiners were trained and calibrated prior to the study. The examiner (GD) was calibrated to measure clinical parameters (dmft/DMFT, ICDAS, and pufa/PUFA) and radiological parameters (periapical x-ray evaluation). The intraclass correlation coefficient (ICC) was 99.1 (ICC>0.90, excellent). On the other hand, one of the examiners (GD) was trained in saliva collection and the other (EL) was trained in YKL-40 extraction from saliva samples and the measurement of its amount (ng/mL).

Clinical measurements

The decayed-missing-filled teeth (dmft/DMFT) and decayed-missing-filled teeth surfaces (dmfs/DMFS) were recorded. The extraction of the primary teeth due to the physiological root resorption was not recorded as a missing tooth. The teeth were scored using International Caries Detection and Assessment System (ICDAS)[16] and pufa/PUFA index (Exposed pulp, Ulceration, Fistula, Abscess)[17] (*Table 1*). The diagnosis was based on two factors: clinical and radiographic features.

Group I; control. ICDAS code=0, dmft/DMFT=0

Group II; shallow caries; caries in dentin and cavitation was not exaggerated. ICDAS code=1-4. All children had caries lesions with ICDAS code 3 and 4 in their oral cavity.

Group III; deep caries; caries lesion was close to the dentin-pulp interface, the dentin thickness was less than 1mm, without *pulp exposure*. ICDAS code=5-6. Group III had at least one tooth with ICDAS code-5 or 6.

Group IV; deep caries; caries lesion with pulp exposure. ICDAS code=5-6. Group IV had at least one tooth with ICDAS code-5 or 6 and pulp exposure. The caries lesions extending into the pulp tissue were classified according to the pufa/PUFA index. They were children with or without pulpal pain.

Radiological examination

The radiographic examination was made to confirm caries lesion depth and whether a pulpal involvement of caries lesions, especially in groups II, III, and IV.

Saliva collection

All the saliva samples were obtained in the morning and the participants were asked to avoid eating or drinking 1 h before the collection of samples. All the unstimulated saliva samples were collected by the spitting method and transferred into a 2-ml polypropylene tube. All the saliva samples were homogenized on a Vortex mixer (1 min) and centrifuged (10,000× *g*, 10 min) to remove cellular debris. The resultant supernatants of the samples were stored at −80 °C for further analyses.

Table 1. ICDAS code and pufa/PUFA index

	ICDAS code
0	Sound tooth surface, no evidence of caries after prolonged air drying (5 seconds)
1	First visual change in enamel: opacity or discolouration (white or brown) is visible at the entrance to the pit or fissure after prolonged air drying, which is not or hardly seen on a wet surface
2	Distinct visual change in enamel: Opacity or discolouration distinctly visible at the entrance to the pit and fissure when wet, the lesion must still be visible when dry
3	Localized enamel breakdown due to caries with no visible dentine or underlying shadow: opacity or discolouration wider than the natural fissure/fossa when wet and after prolonged air drying
4	Underlying dark shadow from dentin, +/− Localised enamel breakdown
5	Distinct cavity with visible dentine: visual evidence of demineralisation and dentine exposed
6	Extensive distinct cavity with visible dentine and more than half of the surface involved
	pufa/PUFA index
p/P	Pulpal involvement
u/U	Ulceration
f/F	Fistula
a/A	Abscess

YKL-40 assay

The level of YKL-40 in saliva was measured by ELISA (R&D Systems, Minneapolis, MN) and the analysis was performed according to the manufacturer's instructions using human recombinant standards in Biochemistry Laboratory. All samples were run in duplicate and the results were averaged for the analysis. The results were reported in pg/mL. The detection limit was 3.5 pg/mL for YKL-40. The samples with YKL-40 levels below the limits of the assay's detectability were scored 0. The results recorded in pg/mL were converted to ng/mL.

Statistical analysis

Data analysis was performed using the statistical package IBM SPSS 21 (SPSS Inc., Chicago Illinois, USA). The results were expressed as means ± standard deviations. The data were firstly analyzed for the normal distribution using Shapiro-Wilk test. The parameters among the groups were compared with one another using One-way ANOVA, Tukey post hoc and Kruskal-Wallis tests. Multiple linear regression analysis was used to determine the explanatory power of the variables causing the increasing of YKL-40 level in saliva. Pearson and Spearman rank correlation test was used to verify the correlations between the parameters.

RESULTS

The dmft/DMFT, dmfs/DMFS, ICDAS, and pufa/PUFA, were used in this study. For each participant, it was recorded the followings: YKL-40 levels in saliva, the number of decayed, missing, and filled teeth. The decayed teeth were categorized according to the ICDAS, while advanced dental caries were categorized according to both ICDAS and pufa/PUFA.

The mean±SD of YKL-40 levels in saliva and clinical parameters (dmft/DMFT, dmfs/DMFS, the number of missing / filling / caries teeth) were presented in *Table 2*. There were statistically significant differences among the groups for YKL-40, dmft/DMFT, dmfs/DMFS, the number of missing teeth, and the number of shallow /advanced caries ($p<0.01$) (*Table 2*). The distribution of the advanced caries teeth (n) according to the pufa/PUFA index and the mean values of YKL-40 in group IV were shown in *Table 3.*

YKL-40 was positively correlated with the number of caries (*Table 4*).

In addition, there was no statistically significant difference in YKL-40 levels in terms of age and gender ($p>0.05$).

The variables (the number of shallow caries, the number of advanced caries without pulp exposure, and the number of advanced caries with pulp exposure) determined in the regression model explain 80% of the variances in the YKL-40 level in saliva. In the regression model 4, the "advanced caries with pulp exposure" variable had the most explanatory power ($\beta=0.855$; $p<0.001$) (*Table 5*).

Table 2. The mean±SD of YKL-40 levels in saliva and clinical parameters

	Group I	Group II	Group III	Group IV	p value
YKL-40 (ng/mL)	26.27 ± 9.67[a]	41.16 ± 15.37[b]	60.71 ± 13.59[c]	102.63 ± 25.85[d]	<0.001*
dmft/ DMFT	-	16.00 ± 5.32[a]	15.50 ± 5.44[a]	8.75 ± 2.86[b]	<0.001*
dmfs/ DMFS	-	46.35 ± 13.93[a]	46.80 ± 17.25[a]	23.3 ± 7.93[b]	<0.001**
Filling teeth	-	4.35 ± 4.57	3.25 ± 3.02	2.80 ± 1.99	0.803**
Missing teeth	-	4.05 ± 2.37[a]	4.20 ± 2.46[a]	1.30 ± 1.42[b]	0.001**
Caries teeth (shallow & advanced)	-	7.6 ± 3.93[a]	8.05 ± 4.22[a]	4.65 ± 1.90[b]	0.004**
Advanced caries teeth (pulpal exposure-/+)	-	-	2.45 ± 1.19[a]	3.55 ± 1.43[b]	0.015***

	Caries		Mean±SD
Group II	Shallow caries n=152 teeth		7.6 ± 3.9
Group III	Shallow caries n=112 teeth		5.6±3.0
	Advanced caries	*pulpal exposure* - n=49 teeth	2.5±1.2
Group IV	Shallow caries n=27 teeth		1.4±2.7
	Advanced caries	*pulpal exposure*– n=20 teeth	1.0±0.97
		pulpal exposure + n=51 teeth	2.6±0.8

The difference **letters** in the **same row** indicate **significant** differences (*p<0.01*)

*One-Way ANOVA, **Kruskal Wallis test, ***Independent Sample *t*-test

Caries teeth: Caries in dentin and cavitation was not exaggerated. ICDAS code=1-4

Advanced caries teeth: Caries lesion was close to the dentin-pulp interface, the dentin thickness was less than 1mm, with or without **pulpal exposure.** ICDAS code=5-6.

Table 3. The distribution of the advanced caries teeth (n) according to the pufa/PUFA index and the mean values of YKL-40 in group IV

The number of patients (n)	Advanced caries teeth (n) *(pulpal exposure -,+)*	pufa/PUFA	YKL-40 Mean± SD
1	1 (0,1)	A	132.88
1	4 (2,2)	NNFF	130.12
1	5 (3,2)	NNNPP	106.31
1	4 (2,2)	NNPP	113.42
1	5 (2,3)	NNPPF	121.21
2	5 (2,3)*2	NNPPP	113.76±10.54
1	6 (2,4)	NNPPPF	115.93
1	4 (1,3)	NPFA	130.12
1	4 (1,3)	NPPP	88.81
3	4 (1,3)*3	NPPU	97.01±14.21
1	3 (0,3)	PFA	132.88
1	2 (0,2)	PP	76.21
1	4 (0,4)	PPPF	130.12
3	2 (0,2)*3	PU	64.48±10.93
1	1 (0,1)	U	62.68
20	71 teeth (20,51)	2.55 ± 0.83	102.63 ± 25.85

N: None- **pulpal exposure**, SD: Standard deviation

Table 4. The correlation between YKL-40 and dental caries

	Group I	Group II	Group III	Group IV	Total (n=80)
YKL-40–The number of shallow caries		r; 0.642** p; 0.002	r; 0.633** p; 0.003	r; -0.427 p; 0.061	r; 0.130 p; 0.251
YKL-40–The number of advanced caries (pulpal exposure-)			r; 0.686** p; 0.001	r; 0.270 p; 0.250	r; 0.573** p; <0.001
YKL-40–The number of advanced caries (pulpal exposure+)				r; 0.359 p; 0.120	r; 0.699** p; <0.001

Pearson & Spearman rank correlation tests. *p<0.05, **p<0.01.

Shallow **caries:** Caries in dentin and cavitation was not exaggerated. ICDAS code=1-4

Advanced caries: Caries lesion was close to the dentin-pulp interface, the dentin thickness was less than 1mm, with or without **pulpal exposure.** ICDAS code=5-6.

Table 5. Explanation of salivary YKL-40 level with multiple linear regression analysis

		Multiple linear regression analysis					
Group		**B**	**SE B**	**β**	**t**	**(95% CI) B**	***p*-value**
II	(Constant)	22.113	6.001		3.685	(9.507–34.720)	0.002
	Shallow caries	2.507	0.705	0.642	3.557	(1.026–3.987)	0.002
III	(Constant)	38.561	5.427		7.105	(27.110–50.011)	<0.001
	Shallow caries	1.655	0.936	0.361	1.769	(-0.319–3.630)	0.095
	Advanced caries (pulpal exposure-)	5.257	2.329	0.461	2.257	(0.344–10.170)	0.037
IV	(Constant)	49.418	22.934		2.155	(0.800–98.036)	0.047
	Shallow caries	3.252	2.452	0.340	1.326	(-1.946–8.451)	0.203
	Advanced caries (pulp exposure-)	10.425	5.826	0.393	1.790	(-1.924–22.775)	0.092
	Advanced caries (pulp exposure+)	15.059	7.814	0.481	1.927	(-1.507–31.624)	0.072
Total	(Constant)	27.321	2.782		9.820	(21.780–32.862)	<0.001
	Shallow caries	2.188	0.445	0.272	4.912	(1.301–3.075)	<0.001
	Advanced caries (pulpal exposure-)	8.133	1.373	0.307	5.924	(5.399–10.868)	<0.001
	Advanced caries (pulpal exposure+)	24.156	1.545	0.855	15.633	(21.078–27.233)	<0.001

Model		R	R^2	Adjusted R^2	SEE	p-value
Model 1	Group II	0.642	**0.413**	0.380	12.09993	0.002
Model 2	Group III	0.734	0.539	**0.485**	9.75493	0.001
Model 3	Group IV	0.570	0.325	**0.198**	23.14448	0.091
Model 4	Total	0.899	0.809	**0.801**	14.91246	<0.001

Dependent variable: YKL-40

SE: Standard Error, SEE: Standard Error of Estimate, CI: Confidence Interval

Shallow caries: Caries in dentin and cavitation was not exaggerated. ICDAS code=1-4

Advanced caries: Caries lesion was close to the dentin-pulp interface, the dentin thickness was less than 1mm, with or without pulpal exposure. ICDAS code=5-6.

For Group II, Linear regression analysis was used because of one variable (R^2 **=**0.413).

DISCUSSION

In this study, we found that YKL-40 levels of saliva were significantly higher in an unhealthy oral cavity with caries-deep&shallow caries than in a healthy oral cavity, and these levels were correlated with dental caries. Dental caries and periodontal diseases are the most common chronic diseases.[18] Of the more than 300 species of bacteria in the oral cavity, only some of them, known as *S. mutans*, are caries-causing (cariogenic) organisms. S. mutans is the first bacteria growing in dental plaques. Dental plaque may cause tooth decay, periodontal diseases, or the both at the same time.[18]

In this study, periodontal examinations for all the patients were performed. Periodontal problems were not detected in the children. Gingivitis due to plaque accumulation around the gingival margin of some carious teeth was detected. However, in this study, since the effectiveness of decayed teeth on YKL-40 was evaluated, these mild gingival problems were ignored. This situation can be examined as the subject of future studies.

In this study, it was found out that the deep dentinal caries led to an important increase in the level of YKL-40 in saliva. This result shows that intense inflammatory properties of caries lesions in oral cavity had a major effect on YKL-40 level. Therefore, it can be concluded that the size of caries are more important than the number of caries. Similarly, whether the caries lesion reaches the pulp also has a significant effect on the level of YKL-40 in saliva. Gram-positive and negative bacteria can be detected in dental caries. There are different responses of odontoblasts to gram-positive and gram-negative bacteria. In the studies on the relationship between dental caries and cytokines, it was reported that dental caries could lead to inflammation of the dental pulp, resulting in aggregation of inflammatory cells that in turn release inflammatory cytokines.[9-11]

In this study, YKL-40 was considered being associated with severity of caries. All of the shallow and advanced dental caries indicate YKL-40 level in saliva, but the explanatory power of the advanced dental caries (β=0.307;pulp- and β=0.855;pulp+) on the increasing of YKL-40 in saliva was higher than that of the shallow dental caries (β=0.272). The inflammation level of advanced dental caries with pulp exposure was measured by using pufa/PUFA index. The highest level of YKL-40 in saliva was found in the individuals with advanced dental caries with pulp exposure. This shows that YKL-40 could be used as a biomarker of inflammation. The pulp disease can be the most important cause influencing the YKL-40 (multiple linear regression analysis; β=0.855). But increased YKL-40 in group II and III indicate that it is not the only reason. Because in these two groups, there was no pulpal involvement in carious teeth.

Data in this field indicate that inflammatory process is responsible for enhancing YKL-40 production.[13,14] Many inflammation markers have been correlated with YKL-40. This study showed that YKL-40, the indicator of many disease, could also be an indicator of dental caries, especially extending into the pulp tissue. In this study, the different levels of caries lesions were seen in the individuals. However, it will be more clear to answer the question whether YKL-40 can be a caries biomarker to evaluate YKL-40 separately in individuals, who have only shallow dental caries, who have only deep dental caries without pulp exposure, and who have only deep dental caries with pulp exposure. This study will lead such studies in this sense. YKL-40, which we think is an important biomarker, should be investigated in detail in dentistry.

Limitation

- No previous studies in this region were available for comparison.
- Serum levels could not be evaluated because it was difficult to take blood from the children.
- The mean age of the participants in the control group was smaller than in test groups. The number of individuals without dental caries is quite few in Turkey. We detected the individuals in the control group during our dental screening in kindergartens for this study. The individuals in the test groups were mostly in mixed dentition period, and the period of teeth eruption may have affected the YKL-40 levels somewhat, which had to be ignored, though. This, however, can be evaluated in future studies.
- Because of its high cost, YKL-40 is not convenient to use very often but can be used when necessary.
- This research is a cross-sectional study. It cannot allow causative relationship to be established.

CONCLUSIONS

Dental caries and an infected pulp could increase YKL-40 release in saliva. Additional studies should be conducted to explain the role of YKL-40 in hard and soft tissue pathogenesis in oral cavity, and longitudinal prospective studies with a larger population are needed to confirm the findings of the present study. The

authors of this study suggest that further studies will determine the relationship between the amount of bacteria causing dental caries and periodontal diseases and YKL-40 level in saliva. Also, there is a need for studies in which YKL 40 levels are obtained, directly from caries cavity, gingival crevicular fluid as well as saliva.

Abbreviations

DMFT/dmft: Decayed-missing-filled teeth
DMFS/dmfs: Decayed-missing-filled teeth surfaces
ICDAS: International Caries Detection and Assessment System
PUFA/pufa: Exposed pulp, Ulceration, Fistula, Absess
S. mutans: Streptococcus mutans
pg/mL: Picogram/milliliter
ng/mL: Nanogram/milliliter
min: minute

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Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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REFERENCES

1. Rehli M, Krause SW, Andreesen R. Molecular characterization of the gene for human cartilage gp-39 (CHI3L1), a member of the chitinase protein family and marker for late stages of macrophage differentiation. Genomics 43(2): 221-225, 1997.
2. Volck B, Price PA, Johansen JS, et al. YKL-40, a mammalian member of the chitinase family, is a matrix protein of specific granules in human neutrophils. Proc Assoc Am Physicians 110(4): 351-360, 1998.
3. Ringsholt M, Hogdall EV, Johansen JS, Price PA, Christensen LH. YKL-40 protein expression in normal adult human tissues--an immunohistochemical study. J Mol Histol 38(1): 33-43, 2007.
4. Fontana RJ, Dienstag JL, Bonkovsky HL, et al. Serum fibrosis markers are associated with liver disease progression in non-responder patients with chronic hepatitis C. Gut 59(10): 1401-1409, 2010.
5. Johansen JS, Jensen BV, Roslind A, Nielsen D, Price PA. Serum YKL-40, a new prognostic biomarker in cancer patients? Cancer Epidemiol Biomarkers Prev 15(2): 194-202, 2006.
6. Letuve S, Kozhich A, Arouche N, et al. YKL-40 is elevated in patients with chronic obstructive pulmonary disease and activates alveolar macrophages. J Immunol 181(7): 5167-5173, 2008.
7. Nielsen AR, Erikstrup C, Johansen JS, et al. Plasma YKL-40: a BMI-independent marker of type 2 diabetes. Diabetes 57(11): 3078-3082, 2008.
8. Turkyilmaz AK, Devrimsel G, Kirbas A, et al. Relationship between pulse wave velocity and serum YKL-40 level in patients with early rheumatoid arthritis. Rheumatol Int 33(11): 2751-2756, 2013.
9. Pezelj-Ribaric S, Anic I, Brekalo I, Miletic I, Hasan M, Simunovic-Soskic M. Detection of tumor necrosis factor alpha in normal and inflamed human dental pulps. Arch Med Res 33(5): 482-484, 2002.
10. D'Souza R, Brown LR, Newland JR, Levy BM, Lachman LB. Detection and characterization of interleukin-1 in human dental pulps. Arch Oral Biol 34(5): 307-313, 1989.
11. Duruk G, Gurbuz T, Aksoy H. Effect of interproximal caries in primary molars on clinical parameters and levels of some biochemical markers in gingival crevicular fluid. J Interferon Cytokine Res 40(2): 75-81, 2020.
12. Duruk G, Aksoy H, Gurbuz T, Laloglu E, Tan H. Oral hygiene in children with epilepsy: Effect of interleukin-1 beta and VEGF levels in gingival crevicular fluid. Dent Med Probl 54(1): 67-71, 2017.
13. Nielsen AR, Plomgaard P, Krabbe KS, Johansen JS, Pedersen BK. IL-6, but not TNF-alpha, increases plasma YKL-40 in human subjects. Cytokine 55(1): 152-155, 2011.
14. Vaananen T, Koskinen A, Paukkeri EL, et al. YKL-40 as a novel factor associated with inflammation and catabolic mechanisms in osteoarthritic joints. Mediators Inflamm 2014: 215140, 2014.
15. Keles ZP, Keles GC, Avci B, Cetinkaya BO, Emingil G. Analysis of YKL-40 acute-phase protein and interleukin-6 levels in periodontal disease. J Periodontol 85(9): 1240-1246, 2014.
16. Pitts NB, Ekstrand KR, Foundation I. International Caries Detection and Assessment System (ICDAS) and its International Caries Classification and Management System (ICCMS) - methods for staging of the caries process and enabling dentists to manage caries. Community Dent Oral Epidemiol 41(1): e41-52, 2013.
17. Monse B, Heinrich-Weltzien R, Benzian H, Holmgren C, van Palenstein Helderman W. PUFA--an index of clinical consequences of untreated dental caries. Community Dent Oral Epidemiol 38(1): 77-82, 2010.
18. Forssten SD, Bjorklund M, Ouwehand AC. Streptococcus mutans, caries and simulation models. Nutrients 2(3): 290-298, 2010.