Estimation of some salivary variables and oral health status of patients with chronic myeloid leukemia aged 45-55 years

Nagham H. Al-Shaikh Radhi, B.D.S. [(1)]
Athraa M. Al-Waheb, B.D.S, M.Sc. [(2)]

ABSTRACT

Background: Chronic myeloid leukemia is a cancer of the white blood cells characterized by the increased and unregulated growth of predominantly myeloid cells in the bone marrow. This study aimed to determine the effect of chronic myeloid leukemia on Dental caries and Oral health status including Gingivitis, Loss of attachment, Plaque index and Calculus index as well as evaluation of salivary flow rate and salivary interleukins-6 and tumor necrosis factor-α.

Material and methods: Study group consisted of (75) subjects, (25) were newly diagnosed with chronic myeloid leukemia, (25) were taking medications (Glevic), and (25) were control subjects, all aged 45-55 years old. Collection of stimulated salivary samples was performed under standard conditions, then salivary flow rate and salivary cytokines estimation was done. Clinical examination and oral health assessment were carried out under the standardized conditions of oral health surveys of World Health organization. dental plaque was scored according to the criteria of plaque Index by Silness and Loe(1964), Dental calculus was scored following the criteria of calculus component of the periodontal Index (Ramfjord, 1959), assessment of gingival health done according to the criteria of gingival Index for Loe and Silness (1963) and loss of attachment done following the criteria of WHO (1997). Caries assessment was done according to the WHO modified Decayed-Missing-Filled Index (DMF) and examination was done with a plane mouth mirror and CPI probe.

Results: DMFS index were higher in the newly diagnosed group followed by the control group and then the treated group but the LSD test showed that differences were statistically not significant between each two groups, Plaque index was higher in the newly diagnosed group, and the differences were statistically significant only between the newly and the control group ($p<0.05$), Calculus index was higher in the newly diagnosed group and the difference was statistically significant between the newly diagnosed group and the treated group. Gingival index was higher in the control group and the difference was statistically highly significant between the new and control groups ($p<0.01$) and also highly significant between control group and the treated group. Loss of attachment index was higher in the control group the LSD test show that the difference was statistically significant between the control group and each one of the other two groups. In regard to saliva, salivary flow rate was higher in the control group; the difference was significant between the control and the newly diagnosed group and highly significant between control and the treated group. Interleukin-6 level was higher in the newly diagnosed group then the treated group then the control group. LSD test show that the difference was statistically significant between the new and the treated group ($p<0.05$) and it was highly significant between the new and the control group ($p<0.01$) but it was not significant between the treated and control group. TNF-α level was higher in newly diagnosed group followed by the treated group then the control group and the difference was statistically significant with the treated group and highly significant with the control group, but the difference was not significant between the treated and the control group.

Conclusion: Salivary Interluekine-6 and Tumor necrosis factor- α levels were higher in the newly diagnosed group. Saliva provides an ideal tool for the detection of pro-inflammatory markers. Salivary IL-6and TNF-α may play an important role as biomarkers for CMLand IL-6 is more predictable for the response to the treatment than TNF-α.

Key words: chronic myeloid leukemia, myeloid cells, Glevic, salivary cytokines. (J Bagh Coll Dentistry 2013; 25(Special Issue 1):140-145).

الخلاصة

المقدمة:مرض ابيضاض الدم النقياني ، هو سرطان خلايا الدم البيضاء ، يتميز بزيادة و عدم انتظام نمو أغلب الخلايا النخاعية في نخاع العظم .الأهداف من الدراسة :تحديد تأثير ابيضاض الدم النقياني على تسوس الأسنان و صحة الفم بما في ذلك التهاب اللثة، فقدان التصاق الأسنان باللثة ، مؤشر الصفيحة الجرثومية و مؤشر الترسبات الكلسية ، و تقييم معدل تدفق اللعاب والعوامل المناعية (الأنترلوكين- 6 و عامل النخر الورمي- ألفا) .

المواد و الطرائق :شملت الدراسة (**75** مشاركا) ، 25 منهم كانوا مشخصين حديثا بمرض ابيضاض الدم النقياني و 25 منهم كان يتم علاجهم بالمستحضر (Glivec) ،و25مشارك سليم. تتراوح أعمارهم ما بين 45 و 55 سنة. تم جمع عينات من اللعاب المحفز ، حسب الظروف القياسية ، بأتباع الإرشادات المذكورة من قبل (Tenovuo & Lagerlof, 1996) ، و بعدها تم تقييم معدل تدفق اللعاب و تركيز الانترلوكين في اللعاب . كما و تم أجراء الفحص السريري و تقييم صحة الفم حسب الظروف القياسية الخاصة بمسح صحة الفم (منظمة الصحة العالمية 1997) . تم قياس الصفيحة الجرثومية تبعا لموصفات مؤشر الصفيحة الجرثومية حسب طريقة (Silness and Loe, 1964) . تم قياس الترسبات الكلسية الفموية حسب مواصفات مؤشر أمراض ما حول اللثة (Ramfjord, 1959) .تم تقييم صحة اللثة حسب مواصفات مؤشر اللثة (Loe and Silness, 1963) ، كما و تم تقييم فقدان الالتصاق حسب مواصفات منظمة الصحة العالمية 1997 ، كما و تم تقييم تسوس الأسنان حسب مواصفات منظمة الصحة العالمية (دالة تسوس الأسنان الدائمية المعدل) .

النتائج:مؤشر تسوس سطوح الأسنان الدائمية كان أعلى في مجموعة المرضى المشخصين حديثا (27.20±5.02) و تليهم المجموعة الضابطة (25.96±2.27) وتليهم مجموعة المرضى المعالجين (22.20±4.29) و كانت الفروقات غير معنويه بين المجموعات. مؤشر الترسبات الكلسية كان أعلى في مجموعة المرضى المشخصين حديثا (1.56±0.11) و الفروقات كانت ذات دلالة إحصائية بين مجموعتي المرضى المشخصين حديثا و مجموعة الضابطة ($P< 0.05$) . مؤشر الصفيحات الجرثومية كان أعلى في مجموعة المرضى المشخصين حديثا (0.32±0.06) و الفروقات كانت ذات دلالة إحصائية بين مجموعتي المرضى المشخصين حديثا و مجموعة المرضى المعالجين . التهاب اللثة كان أعلى في المجموعة الضابطة (0.49±0.06) و الفرو قات كانت ذات دلالة إحصائية عالية بين مجموعة المرضى المشخصين حديثا و المجموعة الضابطة ($P< 0.01$) و الفروقات كانت ذات دلالة إحصائية عالية بين مجموعة المرضى المعالجين و المجموعة الضابطة ($P< 0.01$). مؤشر فقدان الالتصاق كان أعلى في المجموعة الضابطة و الفرو قات كانت ذات دلالة إحصائية بين المجموعة الضابطة (0.56±0.10) و كل من مجموعتي المرضى المشخصين حديثا و مجموعة المرضى المعالجين . بخصوص اللعاب ، كان معدل تدفق اللعاب أعلى في المجموعة الضابطة (1.96±0.11) و الفروقات كانت ذات دلالة إحصائية بين مجموعة المرضى المشخصين حديثا و المجموعة الضابطة ، و الفرو قات كانت ذات دلالة إحصائية عالية بين مجموعتي المرضى المعالجين و المجموعة الضابطة . كان تركيز البروتين المناعي الأنترليوكين 6 أعلى في مجموعة المرضى المشخصين حديثا (134.20±60) و من ثم مجموعة المرضى المعالجين (76.86±18.25) و المجموعة الضابطة (56.0±8.33) و الفرو قات كانت ذات دلالة إحصائية بين مجموعة المرضى المشخصين حديثا و مجموعة المرضى المعالجين ($P < 0.05$) ، و الفرو قات كانت ذات دلالة إحصائية عالية بين مجموعة المرضى المشخصين حديثا و المجموعة الضابطة ($P < 0.01$) و لكن الفرو قات كانت غير ملحوظة بين كل من مجموعتي المرضى المعالجين و المجموعة الضابطة . تركيز البروتين المناعي (عامل النخر الورمي الفا) أعلى في مجموعة المرضى المشخصين حديثا (135.20±13.28) و من ثم مجموعة المرضى المعالجين (99.40±6.72) و المجموعة الضابطة (88.60±7.82) و كانت الفرو قات ذات دلالة إحصائية بين مجموعة المرضى المعالجين و مجموعة المرضى المشخصين حديثا ($P < 0.05$) ، والفرو قات كانت ذات دلالة إحصائية عالية بين مجموعة المرضى المشخصين حديثا و المجموعة الضابطة ، و لكن الفروقات كانت غير ملحوظة بين المجموعة الضابطة و مجموعة المرضى المعالجين .

الاستنتاجات :لا توجد فروقات إحصائية في حالة تسوس الأسنان بين المجاميع الثلاثة . الصفيحة الجرثومية و الترسبات الكلسية كانت أعلى في مجموعة المرضى المشخصين حديثا ، بينما ألتهاب اللثة و فقدان الالتصاق كانا أعلى في المجموعة الضابطة . بالنسبة لمعدل تدفق اللعاب فقد كان أعلى في المجموعة الضابطة ، و مستوى تركيز البروتين المناعي الأنترليوكين 6 والبروتين المناعي (عامل النخر الورمي الفا) فقد كانا أعلى بصورة ملحوظة في مجموعة المرضى المشخصين حديثا. لا توجد فروقات معنويه بين الرجال و النساء في جميع المتغيرات ما عدا العامل المناعي (الانترلوكين-6) في مجموعة المشخصين حديثا والمجموعه الضابطه. و كذلك مؤشر الصفيحه الجرثوميه في المجموعه المعالجه.

INTRODUCTION

Leukemia is a slowly progressing cancer that starts in blood-forming cells of the bone marrow.

Leukemia cells are the result of an abnormal development of leukocytes (white blood cells) and their precursors. These cells look different than normal cells and do not function properly[(1)]. There are four main types of leukemia, which can be further divided into subtypes. For classifying

(1)M.Sc. Student, Department of Pedodontic and Preventive Dentistry, Dental College, University of Baghdad.
(2)Professor, Department of Pedodontic and Preventive Dentistry, Dental College, University of Baghdad.

leukemia, the first steps are to determine whether the cancer is lymphocytic or myelogenous, (cancer can occur in either the lymphoid or myeloid white blood cells) and whether it is acute or chronic (rapidly or slowly progressing) [2]. Chronic leukemia cells live much longer than normal white blood cells, resulting in an accumulation of too many mature granulocytes or lymphocytes.

Chronic leukemia progresses slowly but can develop into an acute form. Major types include chronic lymphocytic leukemia (CLL) and chronic myelocytic leukemia (CML) [3].

Chronic myelomonocytic leukemia is a chronic, slowly progressing form characterized by malignant monocytes and myeloblasts, splenomegaly, and thrombocytopenia. Based on clinical characteristics and laboratory findings

CML is divided in to three phases: chronic phase, accelerated phase and blast crises phase [4].CML patients usually have a tendency to bleed and high risk of getting infection. Regarding to oral health, a number of scientific studies were carried out to determine the relation between CML and oral health status (dental caries and periodontitis) [5, 6].

MATERIAL AND METHODS

In this study the sample was consisting of study group (50 patients) with confirmed diagnosis of the disease (CML), 25 of them were newly diagnosed and 25 of them were taking medications which were derivative of 2-phenylaminopyrimidine, (Glevic), for more than one year; and they were examined in Baghdad teaching hospital.

In comparison with control group consisting of (25 subject). The samples (both study and control) were aged (45-55 years), (14) males and (11) females. Collection of stimulated salivary samples was performed under standard conditions following the instructions cited by (Tenovuo &Lagerlof) [7].

Salivary flow rate was expressed as milliliter per minute (ml\min). The salivary samples were then taken to the laboratory for biochemical analyses. Samples then centrifuged at 4000 rpm for 30 min; the clear supernatant was separated by micropipette and divided into 2 portions, stored at (-20 C) in a deep freeze till being assessed in the laboratory. Clinical examination and oral health assessment were carried out under the standardized conditions of oral health surveys of WHO [8]**. For dental plaque**, selected teeth were examined which was Ramfjord teeth [9].The four surfaces of each tooth were examined and scored following the criteria of plaque Index (PlI) by Silness and Loe [10]; this assessment done before saliva sample collection. **For Dental calculus**, the four surfaces of Ramfjord teeth were examined and scored following the criteria of calculus component of the periodontal Index. **Gingival health status,** The four surfaces of Ramfjord teeth were examined and scored following the criteria of gingival Index (GI) for Loe and Silness. **Loss of attachment (LOA)** was done after the Patient's teeth were divided into six sextants, a selected tooth from each sextant was examined by using community periodontal probe (CPI probe), and the maximum score of all the examined teeth were recorded as LOA score of that patient[8]. **Dental examination** was done after collection of salivary sample. According to the WHO modified Decayed-Missing-Filled Index (DMF) Examination was done with a plane mouth mirror and CPI probe. A systematic approach of examination was performed starting from upper right second molar and proceeding in an orderly manner from one tooth or space to the adjacent tooth or space reaching upper left second molar passing to the lower left second molar and then to the lower right second molar[8].

Salivary cytokines assessment: (R and D) system, Quantikine Enzyme-Linked Immuno Sorbent Assay (ELISA) (Sandwich technique). Before starting the procedure, all reagents were brought to room temperature and mix gently until the crystals completely dissolved and then the procedure was done according to the manufacturer insetructions for both IL-6 and TNF-α.

RESULTS

Caries experience: The mean values of DMFS index were higher in the newly diagnosed group followed by the control group and then the treated group but the LSD test showed that differences were statistically not significant between each two groups($p>0.05$). Mean value of the decayed surfaces (DS) was higher in the newly diagnosed group. However; the differences were statistically not significant among the three groups (P 0.05).On the contrary the mean value of missing surfaces (MS) was higher in the control group and the differences were statistically not significant among the three groups. .Control group showed a higher value of filled surfaces (FS) and statistically the differences were proved to be significant only between the treated and control groups ($P<0.05$) (table 1).

Plaque index (PlI) was higher in the newly diagnosed group, and ANOVA test show that the difference was significant among the three groups ($p<0.05$). The LSD test show that the differences

were statistically significant only between the newly and the control group (P 0.05) (table 2).

Calculus index (CalI) was higher in the newly diagnosed group. ANOVA test show that the difference was not significant among the three groups and the LSD test shows that the difference was statistically significant between the newly diagnosed group and the treated group but not significant between the newly diagnosed and the control group (P> 0.05) (table 2).

Gingival index (GI) was higher in the control group followed by newly diagnosed group then the treated group. ANOVA test show that the difference was highly significant among the three groups (p<0.01) and the LSD test showed that the difference was statistically highly significant between the new and control groups and also highly significant between control group and the treated group (P<0.01) (table2).

Loss of attachment index (LOA) was higher in the control group. ANOVA test show that the difference was not significant among the three groups (p>0.05) but LSD test show that the difference was statistically significant between the control group and each one of the other two groups (p<0.05) (table 2).

Salivary flow rate (SFR) was higher in the control group. ANOVA test show that the difference was significant among the three groups, and the LSD test show that the difference was significant between the control and the newly diagnosed group (P<0.05) and highly significant between control and the treated group (p<0.01) (table 2).

Cytokines level:

Interleukin- 6 levels was higher in the newly diagnosed group. ANOVA test show that the difference among the three groups was significant (p<0.05), LSD test show that the difference was statistically significant between the new and the treated group (P< 0.05) and it was highly significant between the new and the control group (P< 0.01) but it was not significant between the treated and control group (P>0.05) as shown in (table 3).

Regarding TNFα, ANOVA test show that the difference was highly significant among the three groups (p<0.01). It s level was higher in newly diagnosed group and the difference was statistically significant with the treated group (P 0.05) and highly significant with the control group, but the difference was not significant between the treated and the control group (P>0.05) (table 3).

The Cut off value test: show the sensitivity and the specificity of the ELIZA cytokines test done in this study which was acceptable for both IL-6 and TNF-α since the percent of both is near 70% (table 4).

DISCUSSION

In this study all participants was found to have dental caries and the difference in DMFS index was statistically not significant among the three groups and this finding was also reported by other studies [5] and it was higher in the newly diagnosed group as those patients had painful mucositis and bleeding tendency leading to alteration in their oral hygiene measures and food type. Saliva may affect caries- experience through its physical and chemical constituent [11].In this study the significant difference in salivary flow rate between the control and the newly diagnosed group may give an explanation for the increase in caries experience in this group, and for the treated group DMFS index was less than the other two groups may be because patients usually give more attention for their oral health to prevent the need for more aggressive dental procedure.

Plaque index was higher in the newly diagnosed group with a statistically significant difference with the control group and this result is in consistent with [6] which may explained by the decreased salivary flow rate, neglected hygienic measures and the type of diet of those patients as leukemia cause a burning mucositis that made tooth brushing painful and also made the patients have a tendency toward the soft food [12]In the treated group plaque index become less, this may be because treatment made the patients oral mucosa better so brushing became possible and may because the instructions given for the CML patients regarding the importance of good oral hygiene to prevent the need for any procedure that could cause bleeding or infection [13].

Differences in calculus index was significant only between the newly and the treated group, this result can be explained only by the fact that there are many factors effect dental calculus including the amount of dental plaque, which was higher in the newly diagnosed group, salivary flow rate which was lower in the treated group, and salivary composition [14].

Gingival index, was higher in the control group with a statistically highly significant difference with both the newly diagnosed and the treated group, and that was a confusing result as plaque index was the least in the control group and many previous studies reported a positive correlation between plaque and gingival indices [15], this result can be explained by the immune disturbances of those patients comparing to the normal subjects that lead to impaired inflammatory response.

Data of the current study show no impact of the CML on the loss of attachment since it was higher in the control group than in the other two affected groups with a significant difference; this result was expected since gingival index was higher in the control group and can be explained by the difference in the immune factors of the three studied groups. In the newly diagnosed group, IL-6 and TNF-α were highly increased comparing to the control group this may cause decrease in gingivitis and loss of attachment.

The mean value of the salivary flow rate was higher in the control group then the newly diagnosed group and the treated group and the differences was significant with the newly diagnosed ($p<0.05$) and highly significant with the treated group ($p<0.01$) and the lower value in the newly diagnosed group could be explained by the effect of medications such as analgesics because CML patients usually have abdominal pain before the diagnoses [16].

The mean value of IL-6 was higher in the newly diagnosed group than the treated group and the control group and the difference was highly significant with the control ($p<0.01$) and significant with the treated group ($p<0.05$), this results could be compared with Anand et al[17] ,who found that the level of IL-6 was significantly higher in the serum of newly diagnosed CML patients because of the fact that saliva is the mirror of the serum [18]. This increase in the salivary IL-6 in the newly diagnosed group may explain why gingival index and loss of attachment was higher in the control group comparing to the newly diagnosed one since IL-6 act as pro-inflammatory and anti-inflammatory mediators [19].

TNF-α level in the saliva of the newly diagnosed CML patients was the higher with a significant deference with the treated group and highly significant difference with the control group; this result is agreed with the fact that Dysregulation of TNF-α production is involved in many types of cancer and autoimmune diseases [20].

Table 1: Comparison of the mean (DMFS) and its component in the three groups enrolled in the present study

Variables	Descriptive statistic			Comparative statistic			
					LSD		
	Newly diagnosed group (mean±SE)	Treated group (mean±SE)	Control group (mean±SE)	F-value	P1 New + treated	P2 New + control	P3 Treated + control
DMFS	27.44±5.02	22.20±4.29	25.96±2.72	0.652	0.372	0.800	0.521
DS	11.80±2.79	9.64±3.28	5.20±0.99	0.183	0.551	0.071	0.222
MS	13.76±3.73	11.28±2.60	16.92±2.66	0.426	0.566	0.465	0.194
FS	1.92±0.83	1.28±0.57	3.84±0.90	0.059	0.562	0.085	0.023*

Table 2: Comparison of mean plaque index, gingival index, calculus index, loss of attachment and salivary flow rate among the three groups.

Variables	Descriptive statistic			Comparative statistic			
					LSD		
	Newly diagnosed group (mean±SE)	Treated group (mean±SE)	Control group (mean±SE)	F-value	P1 New + treated	P2 New + control	P3 Treated + Control
PlI	1.56±0.11	1.29±0.11	1.19±0.09	0.034*	0.061	0.012*	0.508
GI	0.71±0.07	0.63±0.06	0.94±0.06	0.002**	0.387	0.009**	0.001**
CalI	0.32±0.06	0.18±0.03	0.22±0.04	0.085	0.033*	0.108	0.591
LOA	0.28±0.09	0.28±0.09	0.56±0.10	0.062	1.000	0.041*	0.041*
SalFR	1.62±0.12	1.47±0.13	1.96±0.11	0.016*	0.383	0.048*	0.005**

Table 3: Comparison of mean Interleukin-6 and Tumor necroses factor-α among the three groups

Variables	Descriptive statistic			Comparative statistic			
				F-value	LSD		
	Newly diagnosed group(mean±SE)	Treated group (mean±SE)	Control group (mean±SE)		P1 New+ treated	P2 New+ control	P3 Treated+ control
IL6	134.60±25.51	76.86±18.25	56.00±8.33	0.012*	0.033*	0.004**	0.434
TNFα	135.20±13.28	99.40±6.72	88.60±7.82	0.001**	0.011*	0.001**	0.434

Table 4: The Cutoff value for IL6 and TNFα

	IL-6 Cutoff value = 57.5	TNF Cutoff value = 87.5
Sensitivity	64 %	76 %
Specificity	68 %	78 %
Area UC	0.730	0.775
P-value	0.005	0.001

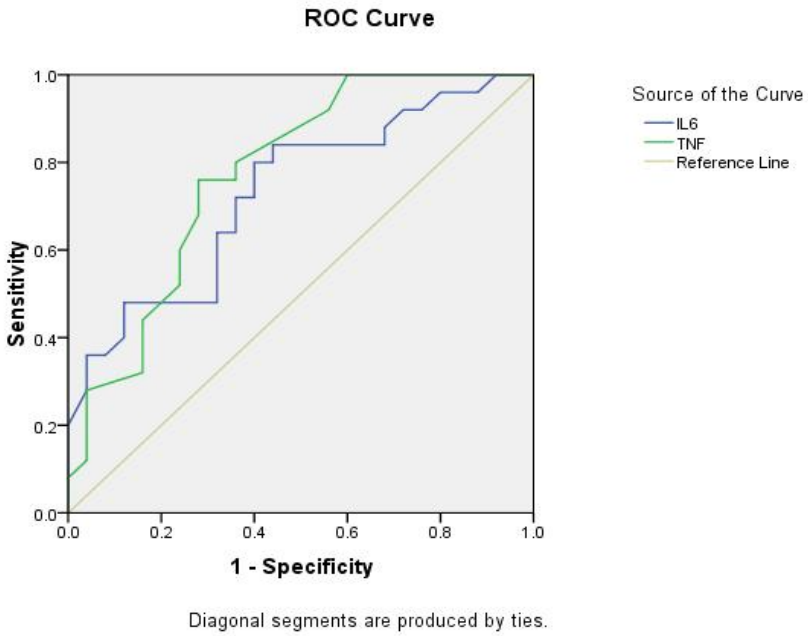

Figure 1: Receiver operator characteristic curve (ROC) to determine the cutoff values for both IL6 and TNFα

Table 5: Number of positive and negative cases in the newly diagnosed and the treated groups, calculated according to above mentioned cutoff value of IL-6

	Negative		Positive	
Groups	No.	%	No.	%
New	9	36%	16	64%
Glivic	16	64%	9	36%

Table 6: Number of positive and negative cases in the newly diagnosed and the treated groups, calculated according to above mentioned cutoff value of TNF-α

	Negative		Positive	
Groups	No.	%	No.	%
New	6	24%	19	76%
Glivic	12	48%	13	52%

REFERENCES

1. Greaves MF. Biological models for leukaemia and lymphoma. 2nd ed. London: IARC Sci Publ; 2004. p. 351-72.
2. Bullock L Henze L. Focus on pathophsiology. 3rd ed. Philadelphia: Lippincott Williams and Wilkins; 2000. p. 42-50.
3. Karbasian M, Morris E, Dutcher J, Wiernik P. Blastic phase of chronic myelogenous leukemia. Current Treatment Options in Oncology. 3rd ed. Copenhagen: Copenhagen; 2006.p**.** 189–199.
4. Hoffbrand A, Moss P, Pettit J. Essential Haematology. 4thed. Oxford: Blackwell science; 2006. p. 15-20.
5. Dens F, Boute P, Otten J, Vinckier F, Declerck D. Dental caries, gingival health, and oral hygiene of long term survivors of paediatric malignant diseases. J Arch Dis Child 1995; 72:129–32.
6. Patrícia D, Danilo A, Carlos C, Karla Z. Gingival inflammation and platelet count in patients with leukemia. J Periodontal Rec 2011; 25(6): 544-9.
7. Tenovuo J, Legerlof F. Saliva In: Thylstrup A, Fejerskov O. (eds). Textbook of clinical Cariology. 2nd ed. Copenhagen: Munksgaard; 1996. p.43.
8. WHO: Oral health surveys. Basic methods. 4th. Genora 1997.
9. Ramfjord S. Indices for prevalence and incidence of periodontal disease. J periodontal 1959; 30: 51-9.
10. Silness J, Loe H. periodontal disease in pregnancy II. J Acta Odontal Scand 1964; 24: 747-759.
11. Harris N, Godoy F. Primary preventive dentistry .6th ed. New Jersey: Upper Saddle River; 2004. p.88.
12. Ross J, Kasum C, Davies S, Jacobs D, Folsom A, Potter J. Diet and risk of leukemia in the Iowa Women's Health Study. J Cancer Epidemiology Biomarkers 2002;11(8):777-81.
13. Emidio T, Maeda Y, Caldo-Teixeira A, Puppin-Rontani R. Oral manifestations of leukemia and antineoplastic treatment - a literature review (part II). Braz J Health 2010; 1:136-49.
14. Alnsudar J, kingman A, Brown L. Gingival inflammation and subgingival calculus a 5 determenauts of disease progression in early-onset periodontitis. J Clin Periodontal 1998; 25: 231.
15. Tefferi A. Classification, diagnosis and management of myeloproliferative disorders. Hematology Educ Program; 2006. p. 240–5.
16. Faguet, B. The War on Cancer. Springer ISBN; 2005. p. 1020-1083.
17. Anand M, Chodda SK, Parikh PM, Nadkarni JS .Abnormal levels of proinflammatory cytokines in serum and monocyte cultures from patients with chronic myeloid leukemia in different stages, and their role in prognosis. J Hematol Oncol 1998; 16(4): 143-54.
18. VanBruggen D, Hackney C, McMurray G, Ondrak S. The relationship between serum and salivary cortisol levels in response to different intensities of exercise, saliva as a mirror of serum. J Sports Physiol and performance 2011; 6(3): 396-407.
19. Song M, Kellum J. Interleukin-6. J Crit Care Med 2005; 33(12): 463-5.
20. Cronstein B. Interleukin-6: A key mediator of systemic and local symptoms in rheumatoid arthritis. J Bull NYU Hosp Joint Dis 2007; 65(1): 11-15.