Brazilian Dental Science

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UNIVERSIDADE ESTADUAL PAULISTA
"JÚLIO DE MESQUITA FILHO"
Instituto de Ciência e Tecnologia
Campus de São José dos Campos

ORIGINAL ARTICLE

DOI: https://doi.org/10.4322/bds.2022.e2837

Evaluation of alkaline phosphatase as a biomarker in the healing progression following tooth extraction

Avaliação da fosfatase alcalina como um biomarcador na progressão da cicatrização após extração dentária

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ABSTRACT

Objective: The progression of a healing socket following an extraction is usually analysed through clinical examination and radiographic investigation. Whilst soft tissue healing is usually maintained well, healing progression of hard tissue is more challenging to predict and manage, with issues such as a dry socket or mal-union of the underlying bone. Serum biomarkers for bone healing progression, such as alkaline phosphatase (ALP), could prove helpful as a diagnostic tool for early intervention. **Material and Methods:** Twenty healthy 18-30-year-old individuals who were to extract lower impacted wisdom teeth were included. 2ml of blood was collected before treatment, 48 hours after then following samples were collected 1 month, 2 months and 3 months after the procedure. Intra-oral radiographs were taken at the end of the three months. **Results:** There was a significant correlation elicited with the healing and ALP levels at 1,2 & 3 months' time intervals ($p<0.05$), where 17 patients who had a substantial increase in the levels of ALP also had satisfactory healing after three months. Three individuals who did not show any increase in ALP level did not have satisfactory healing. **Conclusion:** ALP is a useful supplementary biomarker for bone healing.

KEYWORDS

Alkaline phosphatase; Tooth extraction; Bone healing; Oral surgery.

RESUMO

Objetivo: A progressão da cicatrização de um alvéolo após uma extração é geralmente analisada por meio de exame clínico e investigação radiográfica. Embora a cicatrização do tecido mole geralmente seja mantida bem, a progressão da cicatrização do tecido duro é mais difícil de prever e gerenciar, com problemas como alvéolo seco ou má união do osso subjacente. Biomarcadores séricos para progressão da cicatrização óssea, como a Fosfatase Alcalina (FAL), podem ser úteis como ferramenta diagnóstica para intervenção precoce. **Material e Métodos:** Vinte indivíduos saudáveis de 18-30 anos de idade que deveriam extrair dentes do siso inferiores impactados foram incluídos. Foram coletados 2 ml de sangue, antes do tratamento e 48 horas depois, as amostras seguintes foram coletadas 1 mês, 2 meses e 3 meses após o procedimento. As radiografias intraorais foram realizadas no final dos três meses. **Resultados:** Houve uma correlação obtida com a cura e os níveis de FAL em intervalos de tempo de 1, 2 e 3 meses ($p <0,05$), onde 17 pacientes que tiveram um aumento substancial nos níveis de FAL também tiveram cura satisfatória após três meses. Três indivíduos que não apresentaram aumento no nível de FAL não tiveram cura satisfatória. **Conclusão:** FAL é um biomarcador suplementar útil para a consolidação óssea.

PALAVRAS-CHAVE

Fosfatase alcalina; Extração dentária; Cicatrização óssea; Cirurgia oral.

INTRODUCTION

Bone healing is a proliferative physiological process that can take substantially longer than soft tissue healing [1]. This is due to the multi-step process involving new organic matrices and differentiation into mature osteocytes [2].

Whilst soft tissue healing can be predicted and closely monitored clinically, the progression of bone healing requires a clinico-radiographic approach [3]. Suppose there are complications during the process of bone healing. In that case, they may present at later stages, which could have detrimental health effects on the patient and compromise treatment for implants or prostheses [4].

Hence, early diagnosis is essential to decrease morbidity in these patients who may suffer from the complications of delayed bone healing [5]. The serum enzyme alkaline phosphatase is a well-documented biomarker for the healing of bone [6]. There have been studies confirming its role and how its serum levels fluctuate during the healing of long bone fractures with humans as well as various animals such as dogs [7].

Other studies have also confirmed the role of ALP enzyme in dental treatment. Tooth extraction causes morphological changes to the socket, which elicits a change in the serum ALP levels of rats [8]. Hence the present study aimed at evaluating the association between the healing and alkaline phosphatase enzyme levels in patients undergoing dental extraction.

MATERIALS & METHODS

Sample size calculation

The sample size using the G power 3.1 version. This was conducted as a pilot study, where estimated power was adjusted to 95% with 5% margin of error. The total sample size was estimated to be 20.

Twenty systemically healthy patients under 18-30 years we selected for the present study. In the present study, both the operator and patients were blinded and unaware of the assessment criteria from the start to the end of the study. The patients were randomly screened before the recruitment, and only the eligible group of participants were included in the study.

Inclusion criteria

Twenty normal, healthy patients of age group 18-30 years who have advised extraction of lower impacted wisdom teeth were chosen for the study.

Exclusion criteria

1. Patients with physiologically altered serum ALP levels
2. Pregnant woman
3. Immunocompromised patients
4. Patients with signs of acute inflammation or infection and/or Toxaemia symptoms
5. Patients on oral contraceptives and immunosuppressive drugs,
6. Patients with conditions such as uncontrolled diabetes mellitus, Inflammatory bowel disease, Hepatobiliary diseases
7. Patients who were not willing/able to give consent for inclusion in the study

The objective of the study:

Primary objective: The present study aimed at correlating the clinical and radiographic healing in patients undergoing dental extraction.

Secondary objective: To evaluate the Serum alkaline phosphatase levels at different experimental time periods in patients undergoing extraction.

Patients who fulfilled the inclusion criteria were chosen at random to take part in the investigation. The purpose of the study was briefly explained, and written consent was obtained before the commencement of the study.

Before the surgical extraction, a trained nurse collected 2ml of peripheral venous blood in standard EDTA vials. This sample was given a designated serial number for identification purposes and anonymity of the patient. The samples collected were sent to the Biochemistry lab at Sri Ramchandra University for analysis. Quantitative estimation was done through the International Feral Clinical Chemistry Method.

Further samples from the patient were collected 48 hours after the procedure and one, two and three months following the procedure.

Intra-oral periapical radiographs (IOPAR) were taken at the end of the three months to

Table 1 - Table depicting the serum level of ALP at different follow up periods

No.	Serum level of ALP in Sample collected (U/L)					Healing
	Pre-op	48 hrs post-op	1-month post-op	2 months post-op	3 months post-op	
1	74	68	74	80	76	Satisfactory
2	87	82	92	95	90	Satisfactory
3	85	78	86	99	84	Satisfactory
4	56	52	55	59	56	Unsatisfactory
5	68	64	72	80	75	Satisfactory
6	72	64	75	82	76	Satisfactory
7	81	75	80	92	86	Satisfactory
8	67	52	66	95	74	Satisfactory
9	90	86	91	98	95	Satisfactory
10	58	53	59	79	64	Satisfactory
11	63	59	64	83	75	Satisfactory
12	74	68	74	86	83	Satisfactory
13	82	72	80	93	87	Satisfactory
14	66	58	65	78	75	Unsatisfactory
15	62	54	60	78	75	Satisfactory
16	72	65	70	83	78	Satisfactory
17	71	66	71	86	80	Satisfactory
18	62	57	64	81	76	Satisfactory
19	64	56	60	79	75	Unsatisfactory
20	71	67	71	82	77	Satisfactory

Table 2 - Table of results

	Mean	Std. Deviation	N
Pre-OP	71.25	9.657	20
48 hrs	64.80	10.014	20
1 Month	71.45	10.415	20
2 Months	84.40	9.208	20
3 Months	77.85	8.573	20

Std. Deviation-Standard Deviation, N- Sample Size

assess bone health. The healing progression was categorised into two groups, satisfactory and unsatisfactory, based on the amount of healing that had occurred (Table 1). The IOPARs were compared with the levels of ALP found to find a correlation. The collected data was then tabulated, and the mean ALP values obtained were plotted graphically.

Statistical analysis

The collected data were analysed with IBM.SPSS statistics software 23.0 Version. To describe the data descriptive statistics frequency analysis, percentage analysis was used for categorical variables. The mean & S.D were used for continuous variables as enlisted in Table 2 and Figure 1. To find the significant difference in repeated measures, the repeated measures of ANOVA was used with Bonferroni correction to control the type I error on multiple comparisons (Table 3).

RESULTS

Of the 20-people sampled, 3 were found to have unsatisfactory healing, and 17 were found to have satisfactory healing. Table 1 highlights a correlation found between the amount of healing that occurred and the extent to which serum levels of ALP fluctuated. Individuals, who did not show any significant increase in serum levels at the time of the 2-month sample, had unsatisfactory healing. On the contrary, those who had a significant increase in the serum levels of ALP were found to have satisfactory healing at the end of the 3 months.

Table 2 shows a trend that was also appreciated in the pattern in which the ALP levels fluctuate, initially decreasing 48 hours after the procedure and then gradually increasing, peaking during the second month postoperative sample. The present study results proved that there was a statistical

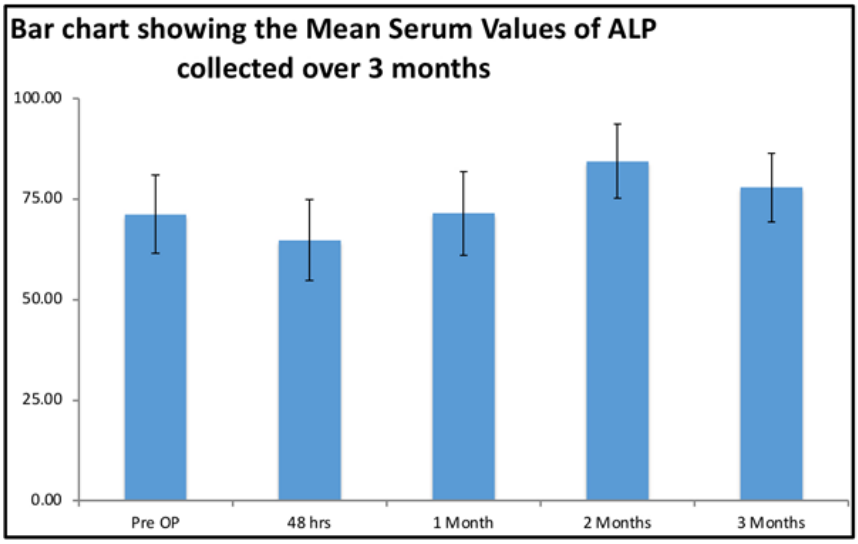

Figure 1 - Bar Chart Depicting the Mean Serum ALP values at Different Time Intervals

Table 3 - Table comparing the statistical significance at different follow-up periods

(I) Followup		Mean Difference (I-J)	Std. Error	Sig.[b]	95% Confidence Interval for Difference	
					Lower Bound	Upper Bound
1	2	6.450*	.596	0.001	4.559	8.341
	3	-.200	.484	1.000	-1.738	1.338
	4	-13.150*	1.276	0.001	-17.199	-9.101
	5	-6.600*	.907	0.001	-9.479	-3.721
2	1	-6.450*	.596	0.000	-8.341	-4.559
	3	-6.650*	.591	0.001	-8.524	-4.776
	4	-19.600*	1.645	0.001	-24.822	-14.378
	5	-13.050*	1.111	0.001	-16.576	-9.524
3	1	.200	.484	1.000	-1.338	1.738
	2	6.650*	.591	0.000	4.776	8.524
	4	-12.950*	1.410	0.001	-17.423	-8.477
	5	-6.400*	1.113	0.001	-9.933	-2.867
4	1	13.150*	1.276	0.000	9.101	17.199
	2	19.600*	1.645	0.000	14.378	24.822
	3	12.950*	1.410	0.000	8.477	17.423
	5	6.550*	1.080	0.001	3.123	9.977
5	1	6.600*	.907	0.000	3.721	9.479
	2	13.050*	1.111	0.000	9.524	16.576
	3	6.400*	1.113	0.000	2.867	9.933
	4	-6.550*	1.080	0.000	-9.977	-3.123

*The mean difference is significant at the .05 level; b. Adjustment for multiple comparisons: Bonferroni

correlation between the healing and the ALP at different follow-up periods assessed ($p<0.05$).

DISCUSSION

The increased osteoblastic activity generates bone healing. These osteoblasts secrete large quantities of ALP involved in bone matrix formation and mineralization [1]. Hence, following the extraction, ALP levels increase.

The ideology in conducting the present study was to correlate the ALP levels with the clinical and radiographic healing in patients after dental extractions. Our main motto was to assess its efficiency of ALP as a biomarker in the healing of

dental extraction sockets. In day to day practice, patients report to us with impaired healing after dental extraction. If we detect and analyze the healing by a biomarker at the diagnostic phase, we could control, intertwine or anticipate the outcome at an initial stage.

Previous literature was concentrated on assessing Alkaline phosphatase as a biomarker in the assessment of various oro-dental diseases [9]. Especially after dental extraction, a clinician cannot always anticipate the healing or untoward sequences in due course of healing. So, ALP levels before the procedure could be a biomarker for estimating the future healing process. So, when clinical applicability of the Alkaline Phosphatase is considered, it could be helpful both as a diagnostic and prognostic marker in patients after dental extraction for assessing the healing.

Ideally, when the study importance to a surgeon has to be analyzed, our study was not replacing the clinical and radiographic healing assessments criteria with the assessment of ALP as a biomarker. Ideally, our biomarker would serve as an adjunctive assessment tool for healing assessment. There are certain situations where surgeons need to have precise detail on the healing activity or in patients with impaired bone healing. Our assessment criteria would give a more prognostic value on the assessment of healing after dental extraction. We were trying to explore this marker as an additional aid in assessing the outcome of healing. When the present study has to be considered, third molar impactions present a challenging scenario, sometimes leading to delayed or poor healing. A surgeon cannot always interpret the healing outcome. Hence, the present study was unique in analyzing the healing after removal of impacted third molars.

In previous studies, the serum ALP levels reached over 300 U/L. The present study revealed the serum levels to a maximum of 110 U/L. However, since the normal serum levels of ALP is 40 – 129 U/L, it may be argued that the ALP levels do no increase significantly enough to be recorded. Various factors may have influenced the results of our study.

In the other studies conducted, healing of long bone fractures was investigated, which is a much more significant trauma to the body, requiring a more significant proliferative response than a tooth extraction [5,7]. The time frame in which the samples were collected may have shown a different picture between the 2nd and 3rd-month samples. The ALP levels seem to increase sharply at the 2-month sample but decrease towards the 3rd-month sample. Further investigation would be required to confirm the time duration in which the ALP levels peak. At this true peak, the serum ALP levels may have breached the upper normal limit of 129 U/L.

When the clinical implication of the present study to a dental surgeon is considered, Alkaline phosphatase can not only be used as a marker for diagnosis and detection, they can also serve as a biomarker for prognostic prediction of healing of extracted socket, and future adverse effects of the healed socket can be assessed and analyzed before the start of the procedure. So the future prediction of the success and healing of dental sockets can be assessed. The other trend changing assessment of healing using a biomarker can be used as a quantifying factor for healing. Ideally, healing based surgical studies use various assessment criteria; this biomarker could be used as a trend changing assessment factor for surgical recovery. It could help a surgeon assess the healing in patients, modify the treatment protocols accordingly, and take adequate precautions to prevent future untoward sequences.

When future implications of the present study have to be considered, ideally, studies should concentrate more on healing after third molar impactions. This preliminary study would give more precise, detailed assessments and provide a pavement pathway for novel ways of evaluations in the field of surgery. Especially when third molar impactions and various other types of impactions are considered, there is extensive trauma involved during the surgical procedure. The procedure is also complicated in a few cases, leading to untoward outcomes. So, when surgeons take-home message has to be considered, the present study laid a unique pathway assessment for future studies in assessing the healing outcomes in various other complex surgeries, which require a prior check on healing to prevent future untoward consequences.

CONCLUSION

ALP remains an accurate biomarker for the progression of bone healing. Patients who displayed a more significant increase in serum ALP levels did have satisfactory healing when checked radiographically. ALP could be used as a

supplementary diagnostic aid in the early detection of delayed or insufficient bone healing, provided the ALP levels are known before commencement.

Author Contributions

Sekaran Senthoor Pandian: Concept and design of the study, Data acquisition.

Sabari Nathan Rajamoorth: Data acquisition, analysis, Revising the manuscript critically for intellectual content.

Tharunya Gowthaman: Data acquisition, analysis, Revising the manuscript critically for intellectual content.

Chinnaswamy Ravindran: Data acquisition, analysis, Revising the manuscript critically for intellectual content.

Kavalipurapu Venkata Teja: Analysis and interpretation of data, Revising the manuscript critically for intellectual content.

Krishnamachari Janani: Analysis and interpretation of data, Revising the manuscript critically for intellectual content

Conflict of Interest

The author declares no conflict of interest.

Funding

There is no external source of funding.

Regulatory Statement

Nil.

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Date submitted: 2021 Feb 27
Accept submission: 2021 May 13