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Correlation between Salivary Enzymes Levels CK and LDH with Severity of Chronic Periodontitis among Type 2 Diabetic Patients

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Abstract:
Background*: Diabetes mellitus (DM) is a systemic condition that has been long associated with an increased risk and severity of periodontal disease(PD).Host responses to PD include the production of many intracellular enzymes, that are released outside cells after destruction of periodontal tissue .*
Aims of the study: *To determine theperiodontal health condition and the salivary levels of creatin kinase (CK) and lactate dehydrogenase (LDH) enzymes among chronic periodontitis (CP) patients with or without controlled or uncontrolled type2 diabetes mellitus (T2DM) and the correlations of these enzymes with the severity of CP.*
Materials and Methods: *The salivary levels of (CK & LDH) enzymes and clinical periodontal parameters (plaque index PLI, gingival index GI, bleeding on probing BOP, probing pocket depth PPD and clinical attachment level CAL) were measured from 75 males divided into four groups,the study groups are(GroupI:(20) CP patients with controlled T2DM, GroupII:(20) CP patients with uncontrolled T2DM, GroupIII:(20)CP patients without DM)andGroupIV:(15)systemically healthy subjects with healthy periodontium as control group.*
Results: *Uncontrolled T2DM with CP patients showed the highest mean values of (CK & LDH) enzymes, PLI, GI and percentages of(B0P sites, CAL (≥6mm) and PPD(≥6-8mm)&(≥9mm)). Inter groups comparisons revealed significant differences for CK & LDH enzymes levels as well as all clinical periodontal parameters except between groups I with III regarding PPD, CAL and BOP sites which demonstrated non-significant differences.Strong positive correlations were demonstrated between (CK & LDH) enzymes levels with clinical periodontal parameters in all study groups, except the correlations between BOP sites with both CK & LDH enzymes at groups II and III respectively and LDH enzyme with PPD(≥4-5mm) at group I, which werenon significant positive.*
Conclusion: *The present study generally demonstrated strong positive correlations between salivary enzymes (CK & LDH) levels with the severity of CP patients with T2DM and measuring these biomarkers can use to evaluate the effect of T2 DM and glycemic control on periodontal health status.*
Keywords: *Salivary enzymes, periodontitis, Diabetes mellitus.*

I. Introduction

Periodontal diseases are a group of inflammatory disorders with complex etiology and multifactorial in origin. The most common form of PD is called CP which is irreversible and cumulative condition that damages tissue through the complex interactions between periopathic bacteria and the host defense system[(1)].

Systemic diseases are among risk factors of PD. DM and PD are thought to be associated biologically. A model for two way relationships between PD and DM has been proposed based on the evidence that periodontal infections contribute to glycemic control and DM is believed to promote periodontitis through an exaggerated inflammatory response to the periodontal microflora and hyperglycemia induced vascular changes[(2)]. T2DM is the most common form of diabetes and it is characterized by disorders of insulin action and insulin secretion and usually has an adult onset[(3)].

A response of the subject to the periodontal infection includes production of intracellular enzymes such as CK &LDH from the damaged cells of periodontal tissues into the gingival crevicular fluid(GCF) and saliva. The analysis of these enzymes in salivary secretion(which is an important biological diagnostic material)can contribute to clarification of pathogenesis and improvement of making a prompt diagnosis of the PD[(4)].

The purpose of the present study was to correlate between the salivary enzymes levels(CK and LDH) and severity of CP disease among controlled and uncontrolled T2 DM patients.

II. Materials And Methods

The human sample consisted of 75 males with age range of (35-50) years, attending the specialized center for Endocrinology and Diabetes, as well as, patients from department of Periodontics, College of Dentistry, University of Baghdad. They were divided into fourgroups,the study groups are: GroupI (20) males with CP and well controlled T2DM, the glycated hemoglobin A1c test (HbA1c) were <7%[(5)], GroupII (20)

males suffer from CP and uncontrolled T2DM, the HbA1c were >7.5%[5], GroupIII (20) males with only CP and the controlGroupIV (15) systemically healthy males and have healthy periodontium (GI scores <0.5[6] , without periodontal pocket or clinical attachment loss) .

All subjects have at least 20 teeth,with normal weight(body mass index level ranges between (18.5-24.9 Kg/m^2))[7] and patients with CP must have at least 4sites with PPD ≥ 4mm with clinical attachment loss of 1-2mm or greater[8], the duration of T2DM (≥ 5years) on oral hypoglycemic medication (Glibenclamide tab. 5mg/ once a day with Metformin tab. 500mg/ twice daily).

Subjects with Type1 and T2DM taking insulin therapy, suffer from other systemic diseases or retinopathy, nephropathy, diabetic foot, undergone periodontal treatment in the last 6 months, a course of anti-inflammatory or antimicrobial therapy during the last 3 months, smoking or alcohol drinking were excluded from the study.

All the individuals were informed about the purpose of the investigation and consented to its protocol then 5ml of unstimulated salivary samples were collected from all participants under standard condition following the instructions documented[9], then the samples were centrifuged at 4000 rpm for 15min, the clear supernatant were collected and kept frozen (-20º C) until biochemical analysis of salivary enzymes (CK and LDH) to be performed.The kits used for CK analysis was manufactured by (Randox/ UK) and for LDH analysis by (Spin react/ Spain) and these reagents were used for quantitative determination of CK&LDH activity in human serum and a modification was done by a specialist (biochemist) in the labrotaries of the poison center of the specialized surgeries hospital to measure the levels of these enzymes in saliva spectrophotometrically.

The clinical periodontal parameters by using Michigan O periodontal probe were recorded for each subject at four sites (mesial, buccal/labial, distal and lingual/palatal) for all teeth except 3rd molar, which includes:

Assessment of PLI[10], GI[6].

BOP[1]: The periodontal probe inserted to the bottom of the periodontal pocket. If bleeding is provoked within 30 seconds after probing, the site was given (score1) and for non-bleeding site (score 0).

PPD: The distance from the gingival margin to the bottom of the periodontal pocket was measured. A scale was designed for ease of estimation and as follows:

Score 1: ≥ 4-5 mm.

Score 2: ≥ 6-8 mm.

Score 3: ≥ 9 mm.

CAL: The distance from the cemento- enamel junction to the location of the inserted probe tip (bottom of gingival crevice or pocket). A scale was designed for ease of assessment and as follows:

Score 1: ≥ 1-3 mm.

Score 2: ≥ 4-5 mm.

Score 3: ≥ 6 mm.

Statistical analysis was done using mean, standard deviation(SD), percentages, paired t-test, chi -square, ANOVA test and correlation coefficient (r). Level of significance at $0.05 \geq P > 0.01$, highly significance at $0.01 \geq P > 0.001$ and non-significance at $P > 0.05$.

III. Results

As observed in table(1), the study group II showed the highest mean values of PLI and GI amongthefourgroups.Table (2), illustrates that the percentage of BOP sites (55.2%) for group II, was the highest with highly significant differences among the study groups, as well as, the highest percentages of score 3 PPD&CAL demonstrated in group II which were (5.2%) & (71.3%) respectively with highly significant differences among the study groups.

From table (3), it was demonstrated that the levels of LDH & CK enzymes were highest in the study group II, the mean ±SD were (1119.14±27.85) and (57.12±1.428) respectively, with highly significant differences were found among the four groups.

Inter groups comparisons of the mean values of PLI & GI between all pairs of the study groups demonstrated significant differences. Regarding the mean values of PPD & CAL, the results were highly significant differences between group II with groups I and III, while non-significant differences were shown between groups I and III. By Chi-Square test, significant differences were presented between group II with groups I and III about percentages of BOP sites, but a non-significant difference between groups I and III was demonstrated, as shown in table(4).

The results from inter groups comparisons of mean values of LDH and CK enzymes revealed significant differences between group I with groups II and III, as well as between group II with group III, while highly significant differences were observed between group IV with groups I,II and III, as shown in table(5).

Strong positive correlations were revealed between clinical periodontal parameters (PLI, GI, BOP, all scores of PPD & CAL) with the levels of LDH & CK enzymes in all study groups except, thenon-significant

positive correlations between BOP sites with CK & LDH enzymes at groups II & III respectively as well as between LDH enzyme with score1 for PPD at group I, as shown in table(6).

IV. Discussion

Comparisons between all pairs of the study groups regarding PLI demonstrated significant differences with highest mean value present in uncontrolled T2DM with CP patients, these results agree with other results[11-15]and disagree with some studies[16-18].Plaque is the major etiological factor in periodontitis and it is expected to be accumulating more in CP patients because the presence of dental plaque is the main clinical finding for CP.In addition, diabetic patients suffer from the reduction in the buffering capacity, volume of their saliva and increased salivary viscosity, so increase in cariogenic bacteria occur with higher numbers of decayed, missing and filled teeth, also increased level of glucose in GCF and saliva, all these factors lead to higher accumulation of plaque and calculus[19].However, diabetic patients had poorer oral health related behaviors because they might perceive as unrelated to diabetes or even disregard the importance as they need to engage into control their diabetes[20].

The increased gingival inflammatory reactions in response to bacterial plaque are intensified during poor metabolic control.However, more plaque accumulation in uncontrolled T2 DM with CP group leads to more gingival inflammation than in the controlled T2 DM, these results are in accordance with other findings[11,14,16,21-23] but disagree with Khader YS et al[24].

Microvascular disease complication originate from complex abnormalities on the host side through chronic hyperglycemia[14],thus the same amount of plaque cause more gingival bleeding in uncontrolled compared to well controlled diabetic subjects, these results are in consistent with Bridge RB et al[25], although other studies[15,17,18,26,27] disagree with this result.

Poorly controlled DM with extensive calculus deposition and subsequent plaque accumulation had increased prevalence and severity of periodontal destruction and tooth loss than well controlled or non- diabetics with CP, suggests that the host bacterial interactions normally seen in CP are altered, result in more aggressive periodontal breakdown[28], in addition to that patients with diabetes duration more than five years showed higher means of PLI, PPD and CAL scores than in diabetics with disease duration five or less years[29].The reduction in defense mechanisms and the increased susceptibility to infection in diabetic patients especially those with poor glycemic control through accumulation of high levels of advanced glycation end products (AGEs) in periodontium which increase the intensity of the immune inflammatory response to periodontal pathogens and the interaction between AGEs and their receptors on inflammatory cells (monocytes & macrophages) increased production of proinflammatory cytokines such as (Interleukin 1beta), tumor necrosis factor alpha[3], hence AGEs when deposited on polymorphonuclear leukocytes (PMNs), they inhibit their chemotactic, phagocytic capacities and adherence so permitting the advance gram negative anaerobic bacteria which are more pathogenic in nature (PorphyromonasGingivalis, Campylobacter species and AggregatibacterActinomycetemComitans) will become dominate[30].Diabetes with defective neutrophil apoptosis result in increased retention of PMNs within the periodontal tissues which contribute to tissue destruction by non-specific increased release of matrix metalloproteinases (MMPs) and reactive oxygen species providing a further mechanism for increased susceptibility to PD progression[1], also the collagen that is produced by fibroblast in high glucose environment is susceptible to rapid degradation by MMPs enzymes with decreased collagen turn over[3].A variety of changes have been described in periodontium of diabetic patients, including a tendency toward enlarged gingiva, polypoid gingival proliferations and periodontitis[1], thus they have greater prevalence and extent of periodontal pockets[31] and twice as likely to exhibit clinical attachment loss as non-diabetic patients[1]. Previous studies[32-34]had shown similar results with this study but Serrano C et al disagree[13].

Numerous markers have been proposed as a diagnostic test for PD such as intracellular enzymes (CK&LDH), which are released into systemic circulation from stromal, epithelial, inflammatory or bacterial cells and degenerating gingival tissue[35]. From the present study, highly significant differences were demonstrated among the four groups regarding (CK & LDH) with highest levels present in uncontrolled T2 DM with CP patients, these results are in agreement partly with Ikekpeazu EJ et al[36].The cooccurrence of the two conditions (CP&DM) probably led to higher salivary enzymes activities, in addition, the negative effect of T2DM on periodontal tissue especially the soft tissue since these enzymes are intracellular included in the metabolic processes of cells and their increased concentration in GCF and saliva as a consequence of their increased release indicate a higher level of cellular damage in soft tissue of periodontium and reflect metabolic changes in the inflamed gingiva[4].Leading rules in this sense, LDH is an enzyme in the cytoplasm of almost every cell of human body, increased extracellular presence of LDH in saliva is the indication to cell necrosis or tissue breakdown and provide information on cellular glycolitic capacity thus, measurement of LDH leakage is an important test for destruction of cellular membrane permeability and sever irreversible cell damage.However, CK enzyme useful in interpreting the cellular necrosis usually caused by ischemia and toxins[35].

This study showed that the value of the increased activities of certain enzymes during PD can be proved in saliva and reflect the depth of pathological changes in cells, damages of periodontal tissues and sever periodontal destruction represented in deep pockets & clinical attachment loss especially in diabetes i.e. can show whether it is the matter of inflammation only or the destructive changes in soft tissues and bones have already commenced and can indicate the prognosis of the course of this disease[(4)]. That is to say, this study generally showed strong positive correlations between the levels of CK & LDH enzymes in saliva and the clinical periodontal parameters at all study groups.

V. Conclusion

The greatly increased levels of CK & LDH enzymes in CP and T2DM patients in comparison with the control, shows destruction of periodontal tissues as primary cause of increased salivary enzyme levels however, the presence of T2DM leads to higher enzymes levels in the CP patients. Poor glycemic control has deteriorating effect on health and can consider as a risk factor for PD.

It is strongly recommended that salivary enzymes be considered as biochemical markers for the assessment of periodontal tissues destruction which will provide better opportunities in diagnosis, monitoring and efficient management of periodontal disease and T2 diabetic patients.

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Table(1) Descriptive statistics of PLI &GI for the study and control groups

Periodontal parameters	Group 1		Group ll		Group lll		Group IV	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
PLI	2.02	0.058	2.87	0.071	1.71	0.042	0.2	0.005
GI	2.12	0.053	2.91	0.072	1.73	0.043	0.1	0.0025

Table(2) Statistical analysis of scores of PPD,CAL & BOP for the study groups

	PPD scale						CAL scale						BOP scale			
	Score 1		Score 2		Score 3		Score 1		Score 2		Score 3		Score 0		Score 1	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
GROUP I	690	87.8	75	9.5	21	2.7	262	47.9	90	16.5	194	35.6	1742	60.1	1094	22.1
GROUP II	1047	65.7	462	29.1	84	5.2	231	19.6	107	9.1	842	71.3	51	1.8	2725	55.2
GROUP III	977	84.1	178	15.3	8	0.70	257	35.3	139	19.1	332	45.6	1110	38.1	1121	22.7
Chi-square	1.915		2.029		11.36		1.988		2.114		8.92		13.62		12.03	
P-value	0.082		0.049		P<0.01		0.072		0.047		P<0.01		P<0.01		P<0.01	
Sig	NS		S		HS		NS		S		HS		HS		HS	

Table(3) Statistical analysis of LDH & CK enzymes concentrations (U/l) for the study and control groups

Enzymes	GROUP I		GROUP II		GROUP III		GROUP IV		ANOVA	P-value	Sig
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD			
LDH	1107.61	27.69	1119.14	27.85	1039.32	25.98	96.50	2.41	17.88	P<0.01	HS
CK	50.61	1.159	57.12	1.428	45.62	1.140	4.32	0.108	36.34	P<0.01	HS

Table(4)Inter groups comparisons of mean values of PLI, GI, PPD ,CAL & BOP between all pairs of the study groups

Groups		PLI		GI		PPD		CAL		BOP	
		p-value	Sig	p-value	Sig	p-value	Sig	p-value	Sig	p-value	Sig
Groupl	Groupll	0.049	S	0.048	S	0.000	HS	0.000	HS	0.032	S
	Groupllll	0.032	S	0.041	S	0.091	NS	0.222	NS	0.965	NS
Groupll	Groupllll	0.042	S	0.042	S	0.000	HS	0.006	HS	0.048	S

Table(5) Inter groups comparisons of the mean concentrations of LDH&CK enzymes between all pairs of the study and control Groups

Groups		LDH enzyme		CK enzyme	
		P-value	Sig	P-value	Sig
GroupI	GroupII	0.049	S	0.049	S
	GroupIII	0.047	S	0.048	S
	GroupIV	0.000	HS	0.000	HS
GroupII	GroupIII	0.048	S	0.048	S
	GroupIV	0.000	HS	0.000	HS
GroupIII	GroupIV	0.000	HS	0.000	HS

Table(6) Person correlation coefficient (r) between PLI ,GI ,BOP , scores of PPD& CAL with the levels of LDH,CK enzymes for the study groups

Study groups	PPD scale						CAL scale						PLI		GI		BOP	
	Score1		Score2		Score3		Score1		Score2		Score3							
LDH	R	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p
GroupI	0.403	0.102	0.62	0.042	0.713	0.032	0.621	0.04	0.72	0.043	0.46	0.05	0.62	0.041	0.489	0.168	0.662	0.03
GRoupII	0.562	0.09	0.63	0.046	0.79	0.031	0.603	0.042	0.73	0.042	0.52	0.047	0.482	0.098	0.607	0.109	0.493	0.102
GroupIII	0.596	0.08	0.686	0.042	0.74	0.032	0.633	0.043	0.69	0.09	0.56	0.052	0.591	0.29	0.704	0.192	0.422	0.126
CK	R	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p
GroupI	0.662	0.042	0.603	0.039	0.69	0.043	0.652	0.046	0.602	0.08	0.62	0.042	0.73	0.039	0.506	0.098	0. 682	0.04
GRoupII	0.703	0.039	0.592	0.042	0.593	0.046	0.692	0.046	0.63	0.07	0.63	0.043	0.495	0.105	0.633	0.116	0.395	0.166
GroupIII	0.719	0.038	0.593	0.056	0.503	0.052	0.663	0.04	0.65	0.072	0.65	0.046	0.546	0.24	0.598	0.186	0.482	0.186