

Low Serum Zinc and Increased Acid Phosphatase Activity in Type 2 Diabetes Mellitus with Periodontitis Subjects

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Abstract

Micronutrient zinc plays a major role in influencing the periodontal conditions in Type 2 diabetes mellitus (T2DM) subjects. In the developed countries nearly 40% of the people are zinc deficient among the T2DM. Now it is estimated that nearly 2 billion subjects in the developing world may be zinc deficient. The periodontal diseases are highly prevalent and can affect up to 90% of the world wide population. Many chronic diseases have been associated with periodontal disease which results in adverse pregnancy outcomes, cardiovascular disease, stroke, pulmonary disease, and diabetes, but the causal relations have not been established. Zinc in human play an important role in cell mediated immunity and was also an antioxidant and anti-inflammatory agent. Zinc helps in the stabilization of lysosomal membranes. The increased acid phosphatase activity might be a result of destructive processes in alveolar bone in advanced stages of periodontal disease. In light of the available data, the study aimed to show how low serum zinc and increased level of lysosomal enzyme, acid phosphatase affect the subjects of Type 2 diabetes mellitus with periodontitis.

Keywords: Acid phosphatase; Inflammation; Periodontitis; Type 2 diabetes mellitus; Zinc

Introduction

Type 2 diabetes mellitus (T2DM) is one of the most challenging health concerns of the 21st century. It is a chronic disease reaching epidemic levels in both developed and developing countries. According to International Diabetes Federation (IDF), Diabetes Atlas, sixth edition, the prevalence of T2DM is increasing at an alarming rate, affecting 382 million people worldwide in 2013 and this would rise to 592 million in 2035 [1]. The West Pacific Region is home to one quarter of the world's population, and China now has the largest patient population with diabetes as well as Pacific Islands countries with the highest prevalence rates. The incidence of periodontitis is rapidly increasing worldwide and is still a significant problem for many patients with T2DM [2]. The expression of a range of immune mediators, such as C-reactive protein (CRP) and the inflammatory cytokines interleukin (IL)-1, IL-6 and tumour necrosis factor (TNF)- α , are often reported in T2DM [3]. The possible for the dietary components to modulate inflammatory processes are found to be a new approach in the management of T2DM [4].

Periodontitis is considered as one of the main, oral health problems encountered in patients with diabetes mellitus. Periodontitis affects approximately 50% of adults and over 60% of over 65 year olds, with severe periodontitis impacting 10–15% of populations [5,6]. Periodontal disease is a microbially initiated chronic inflammatory disease, in which dysregulated immune-inflammatory processes are responsible for the majority of host tissue destruction, and ultimately tooth loss [7]. Periodontal disease is associated with increased incident diabetes risk, poor glycemic control, and diabetic complications, probably due to the higher levels of systemic proinflammatory mediators that exacerbate insulin resistance [8,9].

Polymorphonuclear leukocytes (PMNLs) are the primary defence cells of the periodontium. In uncontrolled diabetes, reduced PMNL function and defective chemotaxis can give rise to impaired host defences and development of disease [10]. Plenty of microbial antigens stimulate both humoral antibody-mediated and cell mediated immune responses are usually safety, but a continual microbial task in the use of the fore mentioned risks results in the malfunction of both soft and hard tissues, mediated by cytokine and prostanoid flows. Both the host and bacteria in the periodontal biofilm liberate proteolytic

enzymes that damage tissue [11]. They release chemotactic factors that hire polymorphonuclear leucocytes into the tissues; if continual, these cells discharge various enzymes that break down tissues. Once a periodontal pocket forms and becomes packed with bacteria, the situation becomes mostly permanent and produce pro-inflammatory cytokines and mediators [12,13]. Peripheral blood monocytes from diabetic subjects produce elevated levels of tumor necrosis factor-alpha (TNF- α) in response to antigens from *Porphyromonas gingivalis* compared to monocytes from non-diabetic controls [14]. During phagocytosis, the granular (lysosomal) enzymes are released from polymorphonuclear cells into the extracellular medium.

Gingival epithelial cells function as an innate host defense system to prevent intrusion by periodontal bacteria. However, persistent contact of sub-gingival bacterial biofilm with gingival crevices induces bacterial penetration into periodontal tissues. Immunofluorescence and immunohistochemical techniques have revealed the existence of *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, *Prevotella intermedia*, and *Actinomyces naeslundii* in gingival tissues [15]. In addition, intra cellular localization of several periodontal bacteria, including *P. gingivalis*, *A. actinomycetemcomitans*, *Tannerella forsythia*, and *Treponema denticola* has been identified.

Acid phosphatases (EC 3.1.3.2) are generally classified as non-specific enzymes and often occur in multiple molecular forms [16]. It is one among the hydrolytic enzymes associated with lysosomes of cells from a variety of tissues. They differ in molecular size and cellular localisation, as well as in substrate specificity and susceptibility to

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Received: January 02, 2015; Accepted: January 31, 2015; Published February 07, 2015

Citation: Pushparani DS (2015) Low Serum Zinc and Increased Acid Phosphatase Activity in Type 2 Diabetes Mellitus with Periodontitis Subjects. Biochem Pharmacol (Los Angel) 4: 162. doi:10.4172/2167-0501.1000162

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inhibitors. There is also a particular class of ACPs that require metal ions for activity [17]. The Zn²⁺ dependent ACP has been detected in several animal tissues and species [18]; two main molecular forms, differing in tissue distribution, have been found. Brain, heart, skeletal muscle, erythrocytes, lung, spleen, and stomach contain a 62 kDa molecular form of the Zn²⁺ dependent ACP, whereas liver contains a higher molecular weight form of the enzyme. The small intestine and kidney contain both high and low molecular weight forms [19].

Zinc is required by all cell types, playing crucial catalytic, structural and regulatory roles, by binding to a zinc proteome estimated in humans to contain approximately 3000 members [20]. Crystallographic studies have demonstrated the presence of zinc in the crystal of insulin. There are several reasons to suspect, that abnormal zinc metabolism could play a role in the pathogenesis of diabetes mellitus and some of its complications. Several human studies confirmed that diabetes had an effect on disrupting Zn homeostasis. A defect in Zn homeostasis may affect the signal transduction response to insulin and by reducing the production of cytokines, which lead to beta-cell death during the inflammatory process in the pancreas [21]. Under normal conditions Zn is found throughout the pancreas, where it forms an integral component of the insulin crystalline structure [22], serving to stabilize the insulin granule by rendering it less soluble [23].

Zinc interacts with general metabolism of protein, carbohydrate and lipid, as well as on taste, smell, appetite regulation and food consumption. This micronutrient participates both in the synthesis and actions of these hormones, which are intimately linked to bone metabolism. In vitro studies have shown that Zn stimulates osteoblastic bone formation [24]. The basic mechanisms of action of this trace element are intimately linked to the structure and action of countless enzymes involved in many different metabolic processes. In this respect, when Zn specifically acts on cartilage growth it is involved in multiple enzymatic reactions which make this a multi factorial event. Zn could decrease the extent of oxidative damage by decreasing free radical production at the ligand-binding site; and through its role in the Cu-Zn superoxide dismutase enzyme [25,26]. In animals, Zn supplementation lowers elevated blood glucose in genetically obese mice [27] and reduces the extent of lipid peroxidation and atherosclerotic plaques in rabbits on a high-cholesterol diet even though these animals are not Zn deficient [28]. The interaction between glycemic markers and serum zinc levels in humans is unclear. Therefore, with the available data, the present study aimed to study the relationship between serum zinc and acid phosphatase level in type 2 diabetes mellitus with periodontitis.

Material and Methods

Study participants

The study consisted of a total of 600 subjects in the age group of 25 to 56 years. The subjects were divided into four groups, consisting of 150 participants in each group as:

- Group I: Control healthy subjects
- Group II: T2DM without periodontitis
- Group III: T2DM with periodontitis
- Group IV: Non-DM with periodontitis

Group I subjects were selected from a generalised population. Group II subjects for the studies were enrolled from the SRM Speciality Hospital, India and group III and group IV subjects were selected from the outpatients attending the Department of Periodontology and Oral Implantology, SRM Dental College, India. The study plan was approved

by the Institutional Ethical Committee of Medical and Health Sciences, SRM University, India and an informed written consent was obtained from all the participants.

Clinical assessments

Relevant clinical history and physical examination were recorded for all the subjects. Six milliliters of fasting blood sample was withdrawn from ante-cubital vein under aseptic precautions and collected into the vials for assessment of various parameters. All subjects were submitted blood collection, number of teeth present and missing, pathological migration, and probing depth (PPD) and clinical attachment level (CAL) evaluation.

Patients with diabetes mellitus were under diabetic diet and did not take nutritional supplements and any drugs that are known to interfere with the serum levels of studied metals during the period of study. The healthy controls were not on any kind of prescribed medication or dietary restrictions.

Inclusion and exclusion criteria

All periodontitis individuals included under the category of periodontitis should have more than 30% of the sites with Clinical attachment level (CAL) \geq 3mm and pocket depth (PD) \geq 5 mm, at least 2 teeth in each quadrant with the condition of 20 teeth in all the subjects. Diabetic subjects should have T2DM, diagnosed by a physician by means of the oral glucose tolerance test, for at least the past 5 years.

Type 2 diabetic patients having vascular complications as diabetic nephropathy, neuropathy and retinopathy were excluded from the study. Smokers, alcoholics, drug abused, patients who had periodontal therapy six months prior to the study, patients under antibiotics and having systemic disease other than diabetics, taking hormone drugs, lipid lowering drugs, hypotensive diuretics, oral contraceptives, and pregnant women, were excluded from the study.

Basic measurements and assays

BMI was calculated based on measures of body weight and height as weight in kilograms divided by height in meters squared. The systolic and diastolic blood pressure was determined as the mean of two measurements. Blood samples were collected after an overnight fast for each subject. Serum was obtained by centrifuging the blood at 1500 rpm for 10 minutes. HbA1c was analyzed by the high-performance liquid chromatography method (Biosystems S.A, Costa Brava, Spain) and results are expressed in percentage, with a reference value of 5 to 7%. Serum glucose was measured by the glucose oxidase-peroxidase (GOD-POD) method, using the reagent kit purchased from Merck Specialities Private Limited, India.

Serum zinc was estimated, using the Nitro-PAPS (pyridylazo-N-propyl-N-sulfopropylamino-Phenol) method, and the values expressed in $\mu\text{g/dl}$. Acid phosphatase (ACP) was analysed by the technique described by Gutman and Gutman [29], using di sodium phenyl phosphate as the substrate. The incubations were performed at 37°C for 1 hour, and the reaction was stopped by adding 10% trichloroacetic acid. After removal of the precipitate, the concentration of ACP was determined by the differences in extinction at 620 nm against the reagent blank in a spectrophotometer. This difference in extinction was used as a measure of enzyme activity. The enzyme activity was expressed as micromoles of substrate hydrolysed/ min/ L.

Statistical analysis

Data were presented as mean \pm SD (standard deviation). An

unpaired Student's t test and Newman-Keuls multiple comparison test were used to evaluate the differences between groups. Correlations between various variables are done using Pearson's correlation equations. The statistical significance was taken as $p < 0.05$. All statistical analysis was performed, using the statistical software package, Winks SDA 7.0.5 (Windows Kwik Stat).

Results

The demographic characteristics within group I (healthy controls), group II (T2DM without periodontitis), group III (T2DM with periodontitis) and group IV (Non-DM with periodontitis) are shown in Table 1. There were no statistical differences in the mean of the systolic blood pressure, and diastolic blood pressure among the four groups. The mean (\pm SD) percentages of HbA1c levels was found to be 7.74 ± 1.31 in group II and 8.38 ± 1.17 in group III and are statistically significant when compared to control. However, T2DM patients with periodontitis had significantly higher HbA1c than T2DM patients without periodontitis and there was no significant difference between the Group IV and Group I (control) subjects.

The clinical parameters descriptive statistics are shown in Table 2. The mean FBG level was significantly elevated in the group II and group III subjects, when compared to group I and group IV. As expected the mean levels of periodontal probing depth (PPD) and clinical attachment level (CAL), were significantly greater than 4 mm in T2DM with periodontitis and in Non-DM with periodontitis, when compared to healthy subjects.

The serum concentration of zinc in groups I, II, III and IV is shown in Figure 1. According to the Newman-Keuls Multiple Comparison test, the means levels of the serum zinc of group III was lesser than the means of all other groups. At $p < 0.05$, the means of group III was significantly different when compared to other groups. Our data show that T2DM with periodontitis (106.8 ± 31.83) individuals have lower zinc than those without this disease. The serum zinc level in T2DM without periodontitis (157.2 ± 45.8 , group II) and Non-DM with periodontitis (135.7 ± 51.39 , group IV) which are found to be significantly higher when compared to control (113.4 ± 12.65 , group I).

The expression of Acid phosphatase was found to be ten times

Parameters	Control Group I	T2DM without periodontitis Group II	T2DM with periodontitis Group III	Non-DM with periodontitis Group IV
No of subjects	150	150	150	150
Gender (M/F)	80/70	78/72	77/73	75/75
Age, years	35.46 \pm 10.74	46.26 \pm 10.02 ^{***}	44.42 \pm 10.37 ^{***}	41.66 \pm 10.45 ^{***}
Duration of diabetes, years	-	8.39 \pm 5.35	8.70 \pm 4.82	-
HbA1c %	5.20 \pm 0.51	7.74 \pm 1.31 ^{***}	8.38 \pm 1.17 ^{***}	5.14 \pm 0.56 ^{NS}
BMI, kg/m ²	22.72 \pm 1.5	23.32 \pm 1.49 [*]	24.07 \pm 1.51 ^{**}	23.93 \pm 1.12 ^{**}
Systolic blood pressure(mm Hg)	119.5 \pm 4.65	126.4 \pm 5.70 ^{NS}	128.8 \pm 5.09 ^{NS}	126.7 \pm 8.39 ^{NS}
Diastolic blood pressure(mm Hg)	72.93 \pm 2.10	75.14 \pm 1.78 ^{NS}	79.05 \pm 3.03 ^{NS}	76.47 \pm 4.52 ^{NS}

Values are expressed as Mean \pm SD; except for gender (Male, M / Female, F). Glycosylated hemoglobin, HbA1c; Body mass index, BMI. Differences were considered significant at ^{***} $p < 0.0001$; ^{**} $p < 0.001$ for parameters of group II, III, IV vs group I and NS, non-significant

Table 1: Demographic characteristics of the study population within the four groups.

Parameters	Control Group I	T2DM without periodontitis Group II	T2DM with periodontitis Group III	Non-DM with periodontitis Group IV
No of subjects	150	150	150	150
Gender (M/F)	80/70	78/72	77/73	75/75
FBG, mg/dl	95.28 \pm 12.51	183.7 \pm 57.16 ^{***}	176.7 \pm 59.12 ^{***}	96.88 \pm 12.67 ^{NS}
PPD, mm	1.45 \pm 0.13	1.42 \pm 0.17 ^{NS}	4.61 \pm 0.51 ^{***}	4.67 \pm 0.46 ^{***}
CAL, mm	0.708 \pm 0.27	0.64 \pm 0.49 ^{NS}	4.91 \pm 0.37 ^{***}	4.62 \pm 0.58 ^{***}

Values are expressed as Mean \pm SD; except for gender (Male, M / Female, F). Fasting blood glucose, FBG; Periodontal probing depth, PPD; Clinical attachment level, CAL. Differences were considered significant at ^{***} $p < 0.0001$; ^{**} $p < 0.001$; ^{*} $p < 0.05$ for parameters of group II, III, IV vs group I and NS, non-significant.

Table 2: Clinical characteristics of the study population.

Parameters	Control Group I		T2DM without periodontitis Group II		T2DM with periodontitis Group III		Non-DM with periodontitis Group IV	
	r	p	r	p	r	p	r	P
Zinc								
HbA1c	0.024	0.809	0.000	0.100	0.024	0.813	0.0816	0.420
FBG	-0.107	0.390	0.006	0.446	0.216	0.002 [*]	0.133	0.333
PPD	0.266	0.437	0.030	0.766	-0.123	0.445	-0.112	0.266
CAL	-0.033	0.331	0.039	0.693	0.065	0.257	0.125	0.214
Acid phosphatase								
HbA1c	-0.139	0.167	-0.045	0.655	0.009	0.924	-0.129	0.199
FBG	-0.141	0.160	0.170	0.049 [*]	-0.023	0.813	0.039	0.696
PPD	-0.008	0.936	-0.003	0.976	0.193	0.054	-0.028	0.777
CAL	-0.038	0.702	0.032	0.746	-0.327	0.000 [*]	-0.062	0.537

Pearson coefficient ratio, r; Glycosylated hemoglobin, HbA1c; Fasting blood glucose, FBG; Periodontal probing depth, PPD; Clinical attachment level, CAL, ^{*}significant p value.

Table 3: Pearson correlation between Zinc and Acid phosphatase with other independent variables in the 4 groups.

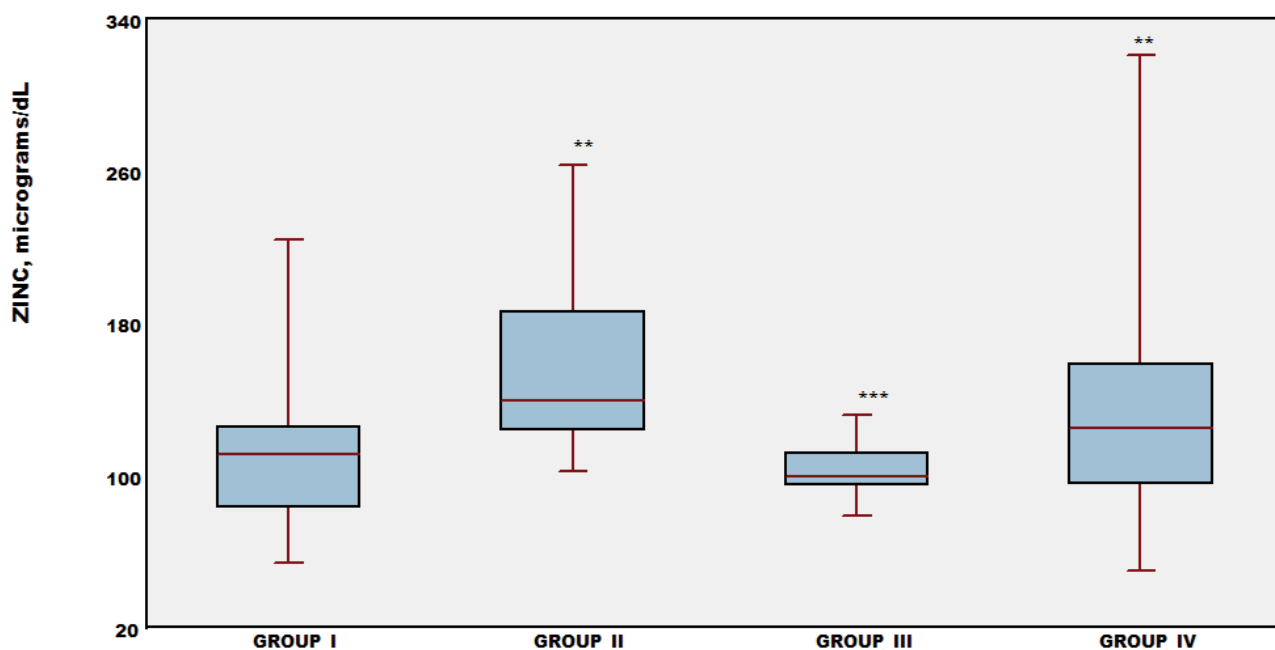


Figure 1: Serum zinc level in the healthy control (group I), T2DM without periodontitis (group II), T2DM with periodontitis (group III) and Non-DM with periodontitis (group IV). The box represents the mean, mean \pm SD and the range. Differences were considered significant at *** $p < 0.0001$; ** $p < 0.001$ when compared to control.

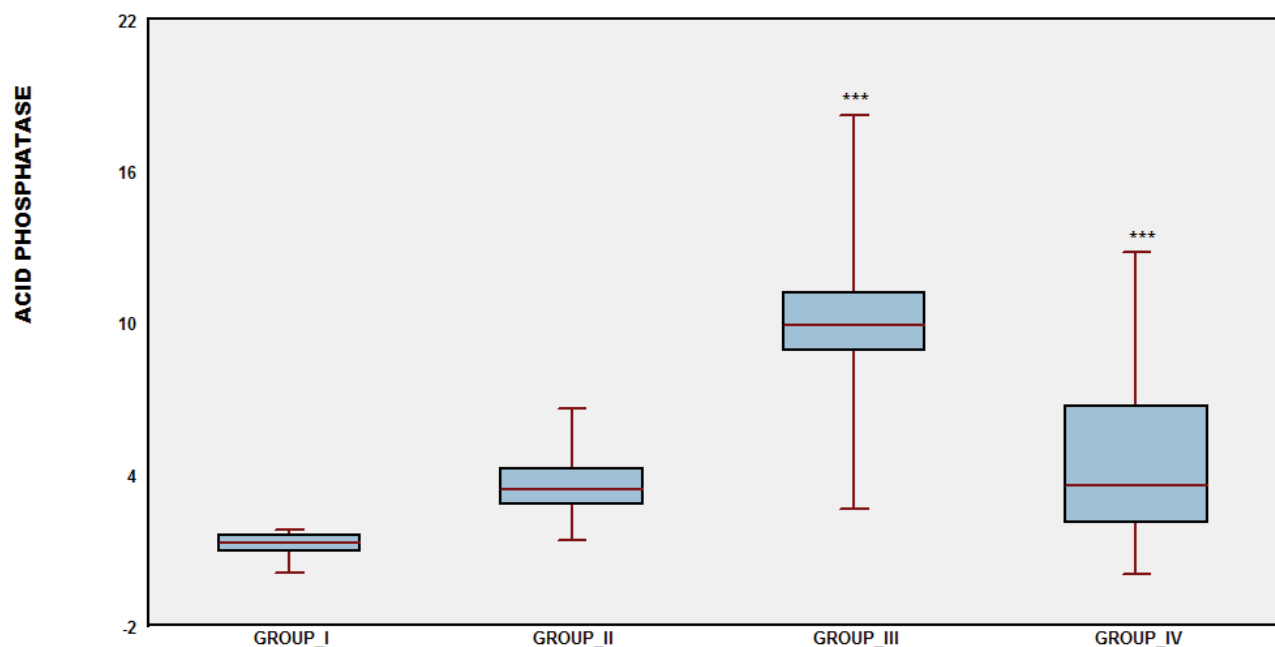


Figure 2: Serum Acid phosphatase (micromoles/min/L) in the healthy control (group I), T2DM without periodontitis (group II), T2DM with periodontitis (group III) and Non-DM with periodontitis (group IV). Differences were considered significant at *** $p < 0.0001$ when compared to control.

increased in group III whereas the levels were found to be elevated three times in group II, and four times in the group IV subjects (Figure 2). We found a significant positive correlation between serum zinc and acid phosphatase among the group II (T2DM without periodontitis),

and group IV (Non-diabetes with periodontitis) but no correlation with group I and group III (T2DM with periodontitis) (Figure 3a-3d). In T2DM without periodontitis (group II), ACP showed positive correlation with FBG. Among the T2DM with periodontitis (group

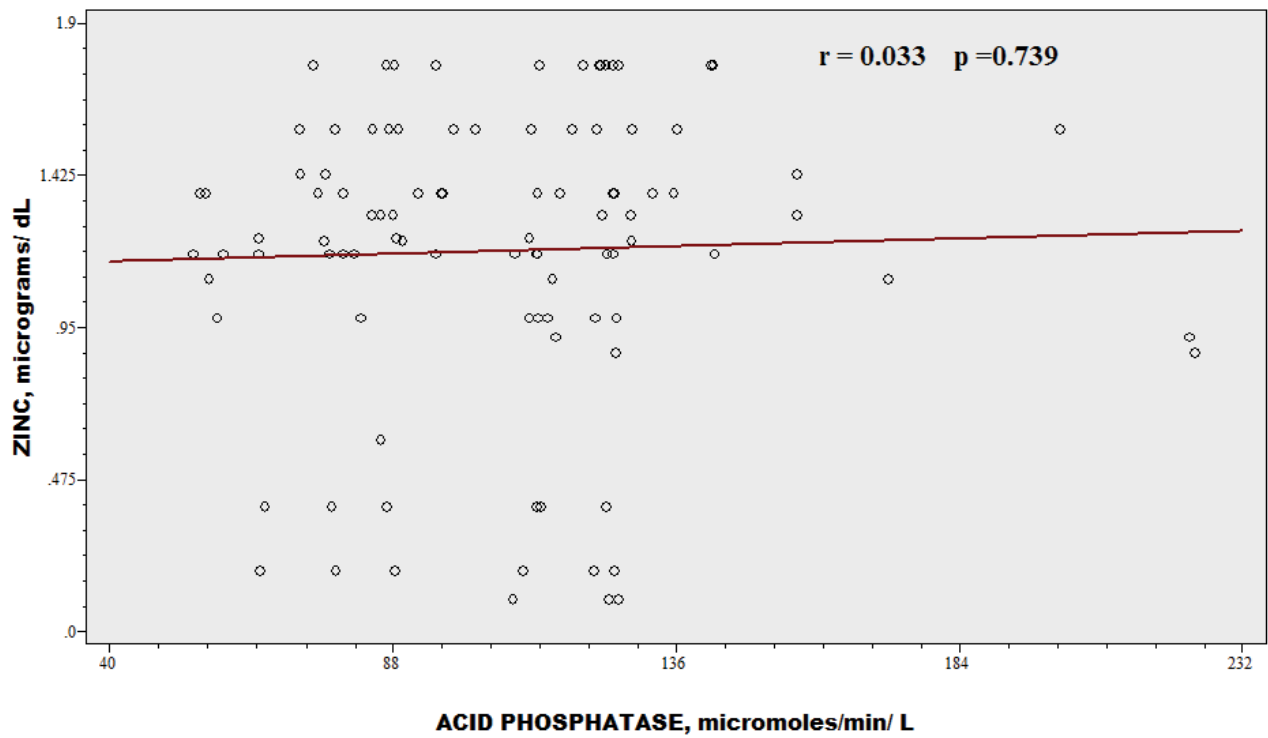


Figure 3a: Pearson's correlation plots showing the relationship between serum Zinc and Acid phosphatase in Control healthy individuals.

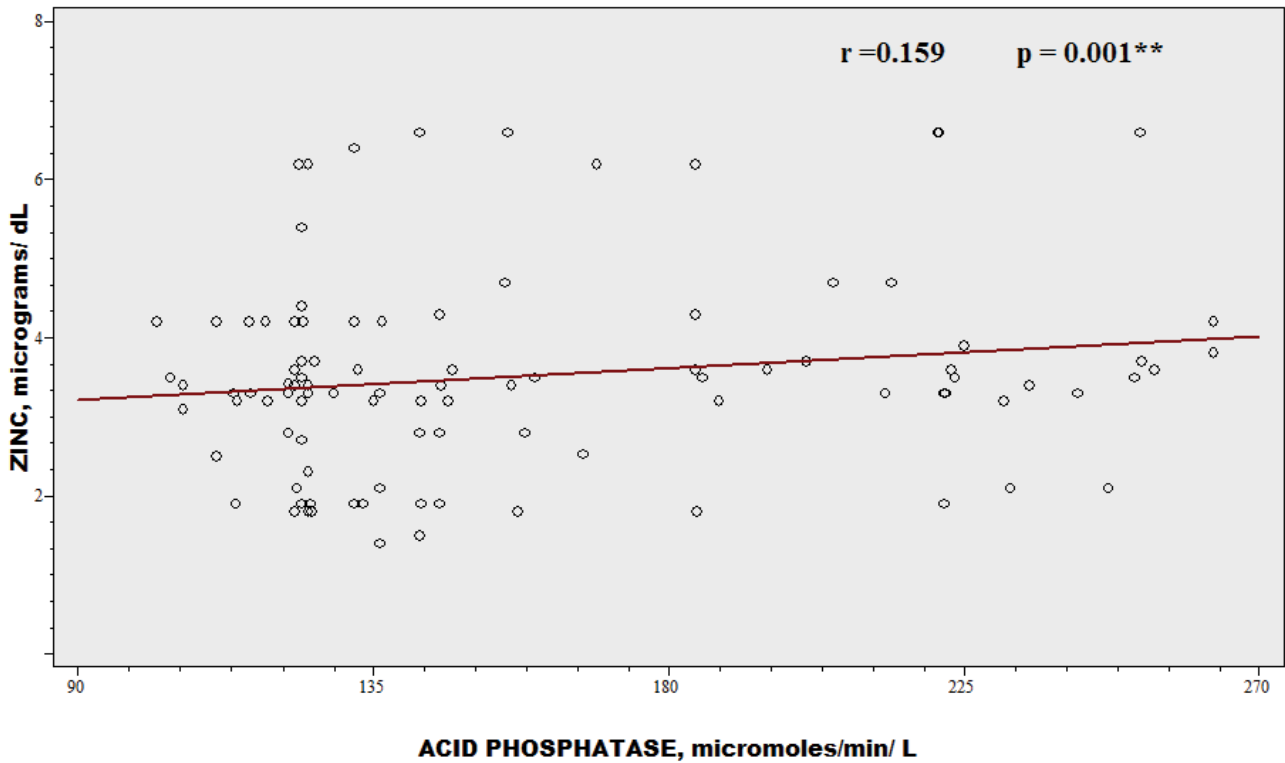
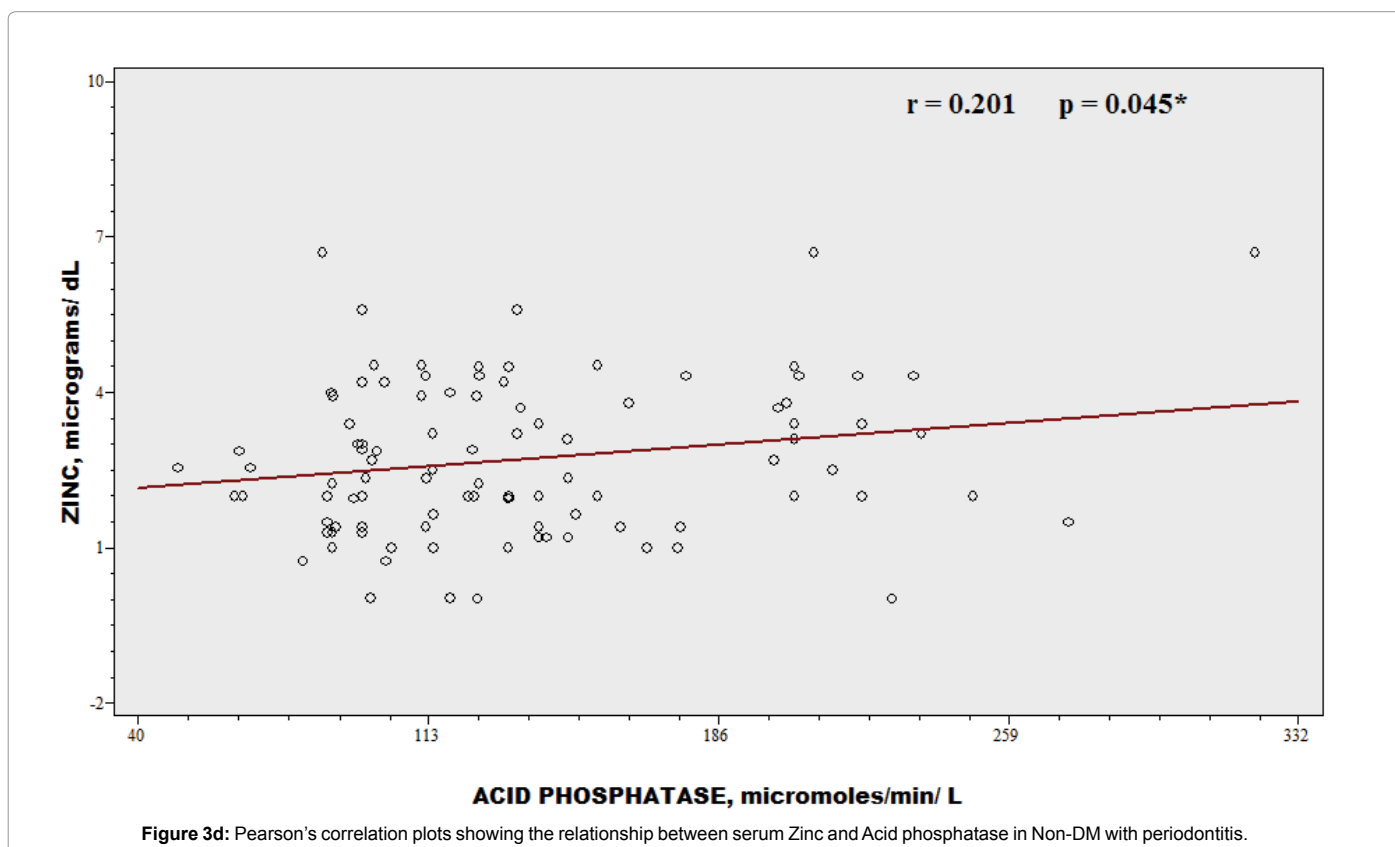
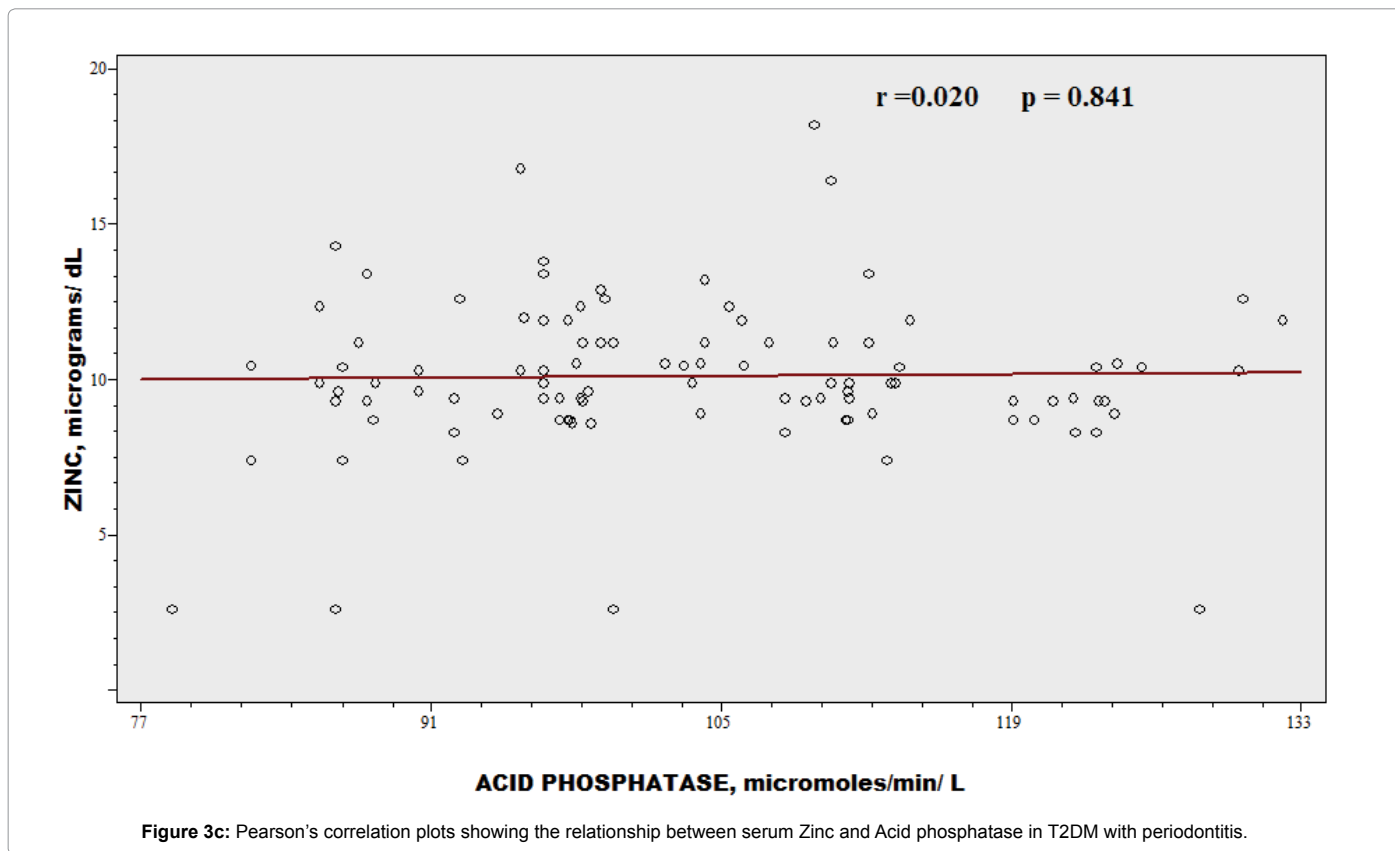


Figure 3b: Pearson's correlation plots showing the relationship between serum Zinc and Acid phosphatase in T2DM without periodontitis.



III), ACP showed positive correlation with PPD and it showed negative correlation with CAL, and zinc correlated positively with fasting blood glucose (Table 3).

Discussion

Antioxidants play a role as defenders against occurred damages by metal-mediated free radicals. Zinc acts as an antioxidant for the decrease of oxidative stress [30]. Usually the serum Zn concentration is used to determine the Zn status, but the serum Zn concentration is not only decreased in real Zn deficiency, but also in stress [31]. During stress, serum Zn is redistributed from the serum into the liver. The protective effects of zinc against increased rates of lipid peroxidation could be due to its capability to combine and strengthen cellular membranes against lipid peroxidation and disintegration. Another probable protective mechanism of metallothionein is its ability to release Zn for binding at sites on membrane surfaces, displacing adventitious iron thereby inhibiting lipid peroxidation. A substitute protective mechanism of Zn may be its capacity to induce metallothionein synthesis. The high sulfhydryl content enables metallothionein to efficiently scavenge oxy-radicals [32]. Furthermore, the suggested outcome of Zn in causing the SH-rich metallothionein synthesis may preserve the SH-residue in many functional proteins. Therefore, Zn may protect the structural and functional integrity of the SH dependent enzymes including those regulating glucose metabolism.

Acid phosphatase (ACP) activity is widespread throughout nature. It has been widely investigated amongst the lysosomal enzymes, and has often been used as a lysosomal marker. Enzyme reactions are inhibited by metals which may form a complex with the substrate, combine with the protein-active groups of the enzymes, or react with the enzyme-substrate complex. This ACP is transported to lysosomes as an integral protein with the lysosomal targeting signal contained in the cytoplasmic tail [33]. Metals play a central role in life processes of living organisms. Essential metals are catalysts in biochemical reactions function as stabilizers of protein structures and serve in maintaining an osmotic balance. High concentrations of most metals essential and non-essential are toxic for living cells. Zinc can act as co-factors for several enzymes. At pH 5.5, the Zn ion is an essential activator, since the enzyme shows no activity in the absence of this ion. Metal treatment may affect cell and/or mitochondrial membrane permeability, lysosome membrane stability, protein unfolding and/or precipitation, enzyme inhibition, irreversible conformational changes and mutations in nucleic acids [34].

In our study, the ACP level was found to be increased significantly to about ten times (10.09 ± 2.46) among the T2DM with periodontitis (group III) when compared to control (1.18 ± 0.47). We also observed that the ACP level was increased in to about three times in group II (3.50 ± 1.27) and four times (4.38 ± 3.15) in group IV subjects. This finding is in agreement to the findings of Agoda and Glew [35] who found elevated activity of ACP in diabetes mellitus. When comparison was done between diabetes with and without periodontitis, a statistically significant increase was found in diabetes with periodontitis group. But the level of enzyme concentration is increased three times in group II and four times in group IV. This gives for the evidence that, the increased activity of this enzyme in diabetes with periodontitis may be as a result of decreased serum Zn in group III.

ACP was found to be elevated in diabetes mellitus. We found higher activity of acid phosphatase in T2DM with periodontitis [36] which would indicate that in these patients the activation process is not restricted to the enzymes capable of degrading mucopolysaccharides

and glycoproteins and the levels of ACP correlate with measurements of disease severity or activity. Hydrolysis of a variety of orthophosphate esters as well as transphosphorylation reactions is catalyzed by enzymes from many sources. One of the possible explanations for this relation could be that the insufficient influx of glucose into cells owing to the lack of insulin led to the decreased synthesis of adenosine triphosphate (ATP).

The presence of acid phosphatase in serum arises from various sources, including erythrocytes, leukocytes, platelets, kidneys, spleen and liver, each of which contribute molecular variants (isoenzymes) of ACP that are specific to the organ or cells of origin. It was observed that zinc correlated positively with ACP among the group II and group IV subjects. The correlation between ACP activity and zinc concentration may reflect a common origin of these two substances, or binding of Zn by acid phosphatase [37]. Various studies have shown that ACP, which is an important marker of phagocytic activity in phagocytes (activated macrophages and neutrophils).

Results obtained in the present study indicate a close and complex relationship between lysosomal and antioxidant responses to metals. These elements in fact could exert their toxicity both through a direct and indirect pathway, the effects of which are not easy to distinguish. The direct effect of zinc could be related to the binding of these elements to the lysosomal membrane, to the increased loading of metal-binding proteins within the lysosomal compartment, as well as to the removal of antioxidant compounds (through oxidation or mixed complexes formation) and inhibition of antioxidant enzymes. Further, metals could have an indirect effect mediated by the formation of oxy radicals. These reactive species could enhance lysosomal damage by promoting the peroxidation of membranes and in the meantime would further reduce the antioxidant cellular defenses. In this respect, it could be speculated that lysosomal damage is at least in part dependent on the efficiency of antioxidant mechanisms. In fact, as more of these defenses are depleted, the more severe will be the indirect effects of zinc metal on lysosomal membranes.

ACP is among the enzymes associated with bone metabolism. It is present in neutrophils and considered a lysosomal marker. Desquamated epithelial cells, macrophages and several bacteria, including *Actinobacillus*, *Capnocytophaga* and *Veillonella*, also produce this enzyme. The increased activity might be a consequence of destructive processes in alveolar bone in advanced stages of development of periodontal disease [38]. The demise associated with tissue can cause a discharge of lysosomal enzymes, with a destruction of the nearby tissue. The extracellular ACP found in gingival fluid could represent an accumulation of lysosomal enzyme from the rapidly desquamating epithelial cells of the crevicular epithelium or from connective tissue cells. It may have a bacterial origin and for that reason they play a role in the formation of pathological pocket [39]. Among its isozymes circulating L-tartrate-resistant acid phosphatase has been shown to be a sensitive marker for evaluation of osteoclastic function. Bone histology and biochemical markers of bone formation and resorption in the diabetic animal models indicated a decreased osteoblast activity combined with normal or decreased osteoclast activity [40].

Human ACP is normally found at low concentrations. However, pronounced changes in their synthesis occur in particular diseases, where unusually high or low enzyme expression is seen as part of the patho-physiological process [41]. In our study, the result of ACP is highly increased in T2DM with periodontitis when compared to other groups. Different forms of ACP are found in different organs, and their serum levels are used as a diagnostic tool for many diseases. Therefore,

decreased zinc and elevated level of ACP may be a contributing factor for the progression of T2DM with periodontitis. Pro- and anti-inflammatory processes are crucial in the different phases of wound healing and their disturbances interfere with tissue homeostasis and wound healing.

Acknowledgement

The author would like to thank the Management, Dean and Vice-Principal of SRM Dental College, SRM University, Ramapuram, Chennai, for supporting and providing all the laboratory facilities to carry out the experimental work.

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