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Serum Zinc and Iron Level in Type 2 Diabetes Mellitus with Periodontitis

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Abstract: Aim of the study: Zinc and iron are essential nutrients necessary for the growth, development, and long-term survival of most organisms. The disturbance in micronutrient status and increased oxidative stress in diabetes mellitus may contribute to insulin resistance and the development of diabetic complications. Therefore, the aim of the study was to investigate the association between serum zinc and iron levels among the type 2 diabetes mellitus (T2DM) with and without periodontitis.
Materials and methods: This study was performed among the three groups as healthy individuals (group I, n=150), T2DM with periodontitis (group II, n=150) and T2DM without periodontitis (group III, n=150). Zinc was estimated, using the Nitro-PAPS (pyridylazo-N-propyl-N-sulfopropylamino-Phenol) method, and the values expressed in µg/dl. Serum iron was determined, using Ramsay's dipyridyl method. The readings were measured using a SL 159-UV visible spectrophotometer (ELICO) at the wavelength of 520 nm.
Results: The serum Zn level in T2DM without periodontitis (group II) was found to be significantly higher when compared to other groups. The level of iron in the group II subjects is greater than group III, but lesser than in group I subjects. Increased level of serum Fe in T2DM with periodontitis can act as a strong pro-oxidant, which catalyze several reactions leading to the formation of reactive oxygen species.
Conclusion: High level of iron increases the iron store thereby depleting the concentration of serum zinc in T2DM with periodontitis, causing oxidative stress and increased cytokines production, all these might leads to insulin resistance and decreased insulin secretion in T2DM with periodontitis.
Key Words: Iron, Type 2 diabetes mellitus, Oxidative stress, Periodontitis, Zinc.

Introduction

Type 2 diabetes mellitus (T2DM) is a highly prevalent metabolic disorder and accounts for about 85-90% of all cases of diabetes in the world and could be an overwhelming health pressure on society in both the developed and developing countries. [1] The global prevalence of T2DM has reached 382 million people in 2013 and by 2035 this will rise to 592 million's adult inhabitants. Diabetes has caused 5.1 million deaths in 2013. Every six seconds a person dies from diabetes [2]. Lifestyle changes, especially in urban areas, obesity, dietary patterns and decreased physical activity, are the main recognized factors in the occurrence of T2DM across the country [3].

Periodontal disease is postulated to place individuals at an increased risk of T2DM. It is an inflammatory response to bacteria that exist in the gum tissue (periodontal ligament) adjoining the teeth that, if left untreated, may result in the recession of the gums, resorption of bone, tooth loosening and eventual loss of teeth [4]. Inflammatory periodontal diseases are the most common chronic inflammatory conditions of humans worldwide. The destructive form of periodontal disease, periodontitis, affects approximately 50% of adults and over 60% of over 65 year olds, with severe periodontitis impacting 10–15% of populations.

Zinc (Zn) is considered to be comparatively non-toxic to humans and the human body contains a total amount of 2–4 g zinc. This micronutrient is important for several different intracellular processes of more than 400 different enzymes and is part of more than 3000 Zn-dependent gene transcription factors and other protein

domains such as zinc metaloenzymes [5]. Zinc is known to be insulin mimetic and now a number of experiments have added new information and improved our knowledge [6]. Insulin is packaged with Zn in secretory granules in β-cells and the local concentration of Zn in those granules has been estimated to be as high as 10–20 mM [7].

In pancreatic islets, Zn is involved in insulin synthesis, storage, and secretion. Insulin exists in monomeric form in Zn-free conditions; insulin in the presence of Zn is thought to exist primarily as a hexamer binding two moles of Zn per mole of hexamer [8]. When pancreatic cells are stimulated by elevated glucose concentration, insulin is coreleased with Zn through exocytosis. The dissociation of the insulin- Zn complex occurs as a result of exposure to the extracellular pH. The dissociation results in the formation of insulin monomers, the biologically active form of insulin. The role of Zn ions in insulin secretion and in the pathology of diabetes is not entirely understood; however, disturbances in Zn homeostasis that may contribute to, or exacerbate, pathology have been observed in many chronic conditions including Alzheimer's disease, cardiovascular disease, cancer, autoimmunity, and diabetes [9]. Low serum levels of Zn, which is typically associated with poor renal Zn re-intake, have been found in many diabetes patients [10].

Iron (Fe) serves as a cofactor for several enzymes involved in oxidation-reduction reactions due to its ability to exist in two ionic forms - ferrous (Fe^{2+}) and ferric (Fe^{3+}). It is essential for all eukaryotes and most prokaryotes, where it is used in the synthesis of heme, iron-sulfur (Fe-S) [11] and other cofactors. Fe-S proteins are involved in catalysis, redox reactions, respiration, DNA replication, and transcription. Iron homeostasis is tightly regulated to avoid iron toxicity or iron deficiency. In human systemic Fe metabolism, Fe uptake, trafficking, export, and utilization are highly regulated [12]. Metal Fe has a significant function in the development of diabetes and its complications [13]. Studies suggest that increased Fe stores tend to be firmly associated with the growth of diabetes and coronary heart disease. Iron is a strong prooxidant that catalyzes several cellular reactions resulting in the production of ROS with a consequent increase in the level of oxidative stress [14].

Minerals play a vital role in metabolic pathways in human body. The progression of diabetes mellitus may also lead to perturbation in micronutrient metabolism and status. Several studies have reported an association between diabetes mellitus and alterations in the metabolism of micronutrients. Therefore, the present study focused on the levels of serum zinc and iron, which can be a useful tool in assessing T2DM with periodontitis.

Materials and Methods

The study consisted of a total of 450 subjects in the age group of 25 to 56 years among the three groups as healthy individuals (group I, n=150), T2DM with periodontitis (group II, n=150) and T2DM without periodontitis (group III, n=150). 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 subjects were selected from the outpatients attending the Department of Periodontology & 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 Assessment of study subjects

Information about the age, gender, blood pressure, body mass index (BMI), duration of diabetes mellitus, current medications (insulin supplementation, and oral hypoglycemic agents), diet and diabetes mellitus complications, were obtained by a standardized questionnaire. For all the subjects, the basic clinical history and demographic data were recorded. The clinical assessment for periodontitis subjects included examination of the gingiva, intra oral examination- number of teeth present and missing, pathological migration, and probing depth.

The mean pocket probing depth (PPD), and clinical attachment loss (CAL) were measured using mouth mirror and William's periodontal probe to assess the periodontal status. Pocket probing depth was measured as the distance from the gingival margin to the bottom of the probed pocket. Probing depths were recorded at six sites per tooth, rounded up to the nearest millimetre. Periodontitis was confirmed by bone loss evident on radiographic examination. The periodontal status was examined by a trained Periodontist of SRM Dental College, Department of Periodontology, Chennai -600 089.

Patients with DM 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) ≥ 3mm and pocket depth (PD) ≥ 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

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, analyzed by the high-performance liquid chromatography method (Biosystems S.A, Costa Brava, Spain) was 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.

Estimation of serum zinc, and iron

Serum zinc was estimated, using the kits purchased from Crest Biosystems (a division of Coral Clinical Systems), Goa, India by Nitro-PAPS (pyridylazo-N-propyl-N-sulfopropylamino-Phenol) method, and the values expressed in µg/dl. Serum iron was determined, using Ramsay's [15] dipyridyl method. Equal volumes of serum, 0.1 M sodium sulphite and dipyridyl reagent were mixed in a glass stoppered tube and centrifuged. The supernatant is heated in boiling water for 5 minutes. It is cooled, 1ml. of chloroform added, stoppered and shaken vigorously for 30 seconds. It is then centrifuged for five minutes at 300 rpm to get a clear supernatant fluid. The readings were measured using a SL 159-UV visible spectrophotometer (ELICO) at the wavelength of 520 nm.

Results and Discussion

The demographic characteristics within group I (healthy controls), group II (T2DM without periodontitis), and group III (T2DM 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 percentage of the HbA1c levels was found to be 7.74 ± 1.31 in group II and 8.38 ± 1.17 in group III when compared to control. The mean FBG level was significantly elevated in the group II and group III subjects, when compared to group I. As expected the mean levels of periodontal probing depth (PPD) and clinical attachment level (CAL), were significantly greater than 4mm in T2DM with periodontitis when compared to healthy subjects, Table 2.

Table 1 Demographic characteristics of the study population within the three groups

Parameters	Control Group I	T2DM without periodontitis Group II	T2DM with periodontitis Group III
No of subjects	150	150	150
Gender (M/F)	80/70	78/72	77/73
Age, years	35.46 ± 10.74	46.26 ± 10.02***	44.42 ± 10.37***
Duration of diabetes, years	-	8.39 ± 5.35	8.70 ± 4.82
HbA1c %	5.20 ± 0.51	7.74 ± 1.31***	8.38 ± 1.17***

BMI, kg/m^2	22.72 ± 1.5	23.32 ± 1.49 **	24.07 ± 1.51**
Systolic blood pressure(mm Hg)	119.5 ± 4.65	126.4 ± 5.70 ^{NS}	128.8 ± 5.09 ^{NS}
Diastolic blood pressure(mm Hg)	72.93 ± 2.10	75.14 ± 1.78 ^{NS}	79.05 ± 3.03 ^{NS}

Values are expressed as Mean ± SD; except for gender (Male, M / Female, F). Glycosylated hemoglobin, HbA1c; Body mass index, BMI. Differences were considered significant at *** p <0.0001; ** p <0.001for parameters of group II, III, 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
No of subjects	150	150	150
Gender (M/F)	80/70	78/72	77/73
FBG, mg/dl	95.28± 12.51	183.7 ± 57.16***	176.7 ± 59.12***
Zinc, µg/dl	113.4 ±12.65 1	157.2±45.8**	106.8±31.83**
Iron, µg/dl	82.46 ± 14.42	76.53 ± 20.23*	114.9 ± 40.91***
PPD, mm	1.45 ± 0.13	1.42 ± 0.17^{NS}	4.61 ± 0.51***
CAL, mm	0.708 ± 0.27	0.64 ± 0.49^{NS}	4.91± 0.37***

Values are expressed as Mean ± 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, vs group I and NS, non-significant.

Serum Zinc and iron levels in the three groups of studied population

The serum concentration of zinc and iron in groups I, II, and III are shown in Table 2. The mean levels of the serum Zn of group III were lesser than the means of all other groups. Our data shows that T2DM with periodontitis individuals have lesser Zn than those without this disease. The serum Zn level in T2DM without periodontitis (group II) was found to be significantly higher when compared to other groups. The level of iron in the group II subjects is greater than group III, but lesser than in group I subjects.

Diabetes mellitus is global problem associated with increased formation of free radicals and decrease in antioxidant potential, which results in disturbed balance between radical formation and antioxidant protection in normal cell. Both insulin dependent (type 1) and non-insulin-dependent diabetes (type 2) are associated with increased oxidative stress. Hyperglycemia can also stimulates ROS formation from a variety of sources like oxidative phosphorylation, glucose autooxidation, NAD(P)H oxidase, lipooxygenase, cytochrome P450 monooxygenases, and nitric oxide synthase (NOS). The serum zinc level was found to be increased in T2DM without periodontitis (group II) subjects and it was observed that, the iron levels are reduced in these subjects. The results of the study are in agreement with other studies.

Zinc and iron are essential trace elements responsible for the function of many cellular enzymes and proteins; however, the same elements become toxic whenever excessive intracellular accumulation occurs [16]. Several studies are reported about the depletion of antioxidant nutrient levels in patients with diabetes. Oxidative stress has also implicated in the pathogenesis of cardiovascular disease, retinopathy, neuropathy, nephropathy, and erectile dysfunction in diabetes [17]. The redox activity seems to play a driving role in addressing the main effects of these trace metals. Iron may contribute to the production of free radicals and, therefore, are likely to play a relevant role in regulation and induction of apoptosis. On the contrary, Zn, either directly or through the induction of metallothionein, is agreed to have protective roles against oxidative damage.

In particular, it has been shown that Zn supplementation in hepatoma cells can alter the Fe transporter expression, and functionally decrease Fe absorption, reflecting a homeostatic control in response to high Fe accumulation [18]. The ingestion of excess Zn depresses the apparent absorption of iron. Supplements containing Fe and multiple trace elements and minerals are used by millions of people world-wide. It is also a common practice to take iron supplements during pregnancy in the developing countries. There are indications that

simultaneous iron and zinc supplementation could be effective in correction of iron depletion and reduction of oxidative damages induced by iron [19]. This shows that Zn also plays a role in Fe homeostasis.

Iron and zinc are thought to compete for absorptive pathways, and evidence from cell culture studies has shown that iron may inhibit zinc absorption at high ratios of iron to zinc. The absorption of zinc is diminished in the presence of high doses of iron [20]. In T2DM with periodontitis subjects (group III), the level of zinc is lower and iron is found to be increased. The increased iron levels in specific tissues may increase type 2 diabetes risk through other mechanisms. For example, high iron stores in the liver may induce insulin resistance by impeding its capacity for insulin extraction, thereby resulting in impaired suppression of hepatic glucose production [21]. Similarly, iron may also impair insulin action and interfere with glucose uptake in adipocytes. Further, increased muscle iron stores may enhance free fatty acid oxidation and thereby could interfere with glucose disposal. Thus, both increased glucose production and decreased glucose utilization may occur with increasing levels of body iron. Excess body iron may also cause iron deposition in the pancreatic β-cells resulting in impaired insulin secretion [22].

In terms of toxicity, chronic iron toxicity is a condition that can be associated with: (a) primary hemochromatosis, a genetic disorder related to increased intestinal absorption of iron; (b) high dietary iron intake; and (c) frequent blood transfusions (often required for the treatment of certain refractory anemias). Cases of acute iron toxicity are rare and mostly related to hepatoxicity[23]. Many immune dysfunctions and diseases set along with reduced serum zinc levels, including T2DM with periodontitis indicating potential co-effects of IL-6 overproduction and enhanced susceptibility of B cells due to zinc deficiency. During the past four decades, a spectrum of clinical deficiency of zinc in human subjects has emerged. Besides PMN, monocytes/macrophages and DCs, B cells represent a main modulator population of humoral immunity. From the study, it was observed that the serum Fe level are elevated and the Zn levels are very low in group III subjects (T2DM with periodontitis), compared to other groups. Here zinc deficiency causes an excess loss of lymphoid tissue compared to other tissues, and thus B cell development, is impaired. The results of Joanna Kaluza et.al [24] indicated that combined iron and zinc supplementation may contribute to lower HDL-C and higher non-HDL-C concentrations.

The serum zinc in T2DM with or without periodontitis, has multi-directional effects on cellular physiology and can activate multiple death pathways within neurons, since Zn modulates both necrosis and apoptosis. Once thought to be mutually exclusive, the two death pathways are nowadays agreed to actually co-exist, with the affected status of cellular energy levels determining which process prevails in a given cell. Zinc can potently disrupt mitochondrial functions by triggering the release of ROS, modulating the opening of the mPTP, and promoting the release of pro-apoptotic factors. The mobilization of intracellular Zn under conditions of oxidative stress may provide the link between necrotic and apoptotic pathways. In fact, it has been observed in intact neurons that [Zn]i mobilization by cellular oxidants affects the mitochondrial membrane potential; whereas, in isolated mitochondria, comparable [Zn] rises trigger the mPTP opening [25]. Conversely, Zn-induced mitochondrial ROS generation is expected to promote further Zn release.

A few investigators have reported that inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and IL-1β, generated by activated monocytes–macrophages, are also known to produce increased amounts of ROS. Increases in these cytokines are associated with decreased Zn status in patients with T2DM with periodontitis. It is, therefore, clear that even a mild deficiency of Zn in humans affects clinical, biochemical, and immunological functions adversely.

Iron is particularly damaging when it exists in the loosely free state. Free iron in the greater levels, accelerates the production of toxic radicals. It is a transitional metal and a strong pro-oxidant that catalyses several cellular reactions that result in the production of reactive oxygen species (ROS), with a consequent increase in the level of oxidative stress. This contributes to tissue damage that may potentially elevate the risk of T2DM [26]. Regarding the effect of blood donation on risk of type 2 diabetes, the Health Professionals Follow-up Study reported that increased number of lifetime blood donations was associated with decreased prevalence of type 2 diabetes in men (4.1% among non donors and 2.7% among those with ≥30 lifetime donations). Lowering total iron has increased the life span of fruit flies and houseflies [27].

It may also be important in elucidating the link of iron to diabetes that in turn is linked to inflammation [28]. The relationships among diabetes, inflammation, and ferritin, therefore, could be complex, with ferritin reflecting excess iron stores that cause diabetes, reflecting inflammation that causes diabetes, or both.

Furthermore, if iron causes diabetes, one of the mechanisms could be through its ability to cause oxidant stress that may be linked to inflammation.

Zinc can interact with iron in biological systems, and this interaction can have beneficial effects preventing undesirable iron mediated damage. One of the several mechanisms that have been shown to be involved in the antioxidant action of zinc, a metal that does not have redox activity, is the capacity of zinc to compete with iron for multiple cellular binding sites. The replacement of iron with zinc can prevent the redox-cycling of iron, thus minimizing the rate of oxidising chemical groups in the close vicinity of the metal binding site. In this context, zinc can reduce the iron-mediated oxidation of lipids, proteins, and DNA [29].

The competition of zinc for iron binding sites is particularly relevant taking into account that one consequence of zinc deficiency can be a marked increase in membrane and intracellular iron concentration [30]. The concentration of the needed metal may be too low or too high and metal export or its sequestering will be required. Even essential metal ions like zinc or iron could be highly toxic when badly managed. Cells very efficiently exploit speciation in the metal–protein systems and reach a very strict control over the metal acquisition, distribution and regulation processes.

Conclusion

Zinc and iron, are essential for all living organisms and participate in a wide diversity of metabolic processes in the cells. However, their concentrations in the body tissues must be strictly and tightly regulated because increased Fe activity contribute to the production of toxic free radicals that can react with various biomolecules. Excess level of iron increases the iron store thereby depleting the concentration of serum zinc in T2DM with periodontitis, causing oxidative stress and increased cytokines production, all these might leads to insulin resistance and decreased insulin secretion in T2DM with periodontitis. The molecular understanding basis of the metal homeostasis and regulations in the cells are critical in identifying the underlying causes for diseases pathophysiology, providing proper diagnosis and treatments. It is also necessary for the development of new therapeutic agents able to treat and prevent their occurrence.

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