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Proanthocyanidines a boon in treatment of periodontitis and diabetes - A two-way relation

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Abstract

Introduction: Although periodontal bacteria are causative agents in periodontitis, subsequent progression and disease severity are thought to be determined by host immune response. Increasing evidence of pharmacological effects of a new plant flavonoid, with variation in chemical structure and related derivatives have been vastly studied for its antioxidant, free radical scavenging and ant carcinogenic property. Since oxidative stress is encountered in periodontitis, the effect of proanthocyanidins, a potent antioxidant on periodontal inflammation is worth studying.

Aim and Objectives: To estimate the HbAIc levels, ROS in serum and antioxidant levels in patients with and without periodontitis and type 2 diabetes mellitus. Before administration of proanthocyanidines, after 3 months of administration and after discontinuation of proanthocyanidines at six months

Material and Methods: Total number of 80 known Type 2 diabetic patients in the age group 30 – 60 years (both males and females) was selected from the outpatient department of endocrinology, A.J. institute of medical sciences and outpatient department of periodontology A.J. institute of dental sciences, Mangalore. Informed consent was taken from all the participants. Blood samples were collected from all patients. After centrifugation the collected serum was stored at -70"c and analysed for HbA1c, ROS and anti-oxidants vitamin C and E using HPLC (high pressure liquid chromatography) and spectrometry respectively. All the patients were prescribed proanthocyanidine capsules (500mg) once daily for the first three months.

Results: There is significant difference in the mean values of vitamin C and E levels at baseline and the 3 months as well as baseline and 6 months in both the groups. Vitamin C and E levels increased from baseline

to 3 months during grape seed extract consumption, and decreased after discontinuation of the treatment from 3rd month to 6th month. Significant difference in the mean values of Superoxide dismutase levels at baseline and the 3 month as well as baseline and 6 months in both the groups. The levels decreased from baseline to 3 months during grape seed extract consumption, and increased after discontinuation of the treatment from 3rd month to 6th month. No significant difference in the mean values of HbA1c levels was seen.

Conclusion: Periodontal diseases (Gingivitis and Periodontitis) are among the most widespread chronic conditions affecting populations worldwide. The incidence and progression of periodontal disease is related casually to periodontal pathogens as well as to various host and environmental factors. The aberrant response is characterized by exaggerated inflammation involving the release of excess of proteolytic enzymes and reactive oxygen species. Persons with diabetes mellitus (DM) are at greater risk of developing periodontal disease (PD), in fact PD is considered the sixth complication of diabetes. Antioxidant effects of grape seed extract i.e., proanthocyanidins on the reactive oxygen species, antioxidant mechanisms and HbA1c levels signifying the glycaemic index in diabetic individuals with or without periodontitis

Keywords: Proanthocyanidins, ROS (reactive oxygen species), diabetes mellitus (DM), Superoxide dismutase (SOD), antioxidants

Introduction

Periodontitis is a bacterially induced chronic inflammatory disease that destroys the connective tissue and bone that support teeth. This disease can also be involved in altering systemic physiology. In diabetic patients chronic form of periodontal disease can result in systemic response to the bacteria and bacterial products which can destroy periodontal apparatus (ligament attachment around the teeth and bone). Chronic hyperglycaemia has been associated with an inflammatory response that has been associated with an inflammatory response that has been linked to complications in diabetes.[1,2] The presence of periodontal disease provides a unique opportunity for oral pathogens and their products to gain access to systemic circulation. Bacterial toxins are known to elicit immune response that can disrupt homeostasis of the system. Inflammation involves the release of excess chemical mediators and reactive oxygen species. A growing body of evidence implicates oxidative stress in patho-biology of many human diseases and recently in periodontitis. There is strong evidence linking Reactive Oxygen Species (ROS), Interleukins (1 and 6), tumour necrosis factor α, Matrix metalloproteinase (mmp-2,8 and 9), macrophages, monocytes, T-lymphocytes, prostaglandins, acute phase reactins etc to the pathological destruction of connective tissue during periodontal disease. Reactive oxygen molecules (ROS) include molecules such as hydrogen peroxide (H2O2), hypochlorous acid (HOCL) and singlet oxygen (O2). ROS may cause damage to various cellular and extracellular tissues by causing protein damage, lipid peroxidation and DNA damage.[1]

Diabetes is a metabolic disorder characterised by impaired metabolism of glucose, lipids and proteins. Delayed wound healing and altered host defence in diabetes further complicates the disease. Diabetes and periodontitis are thus polygenic disorders with some degree of immune regulatory dysfunction. The interaction between the two diseases has been proposed based on binding of advanced glycation end products (AGE) that are present in diabetic patients to the receptors of macrophages. Accumulation of AGE

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products in periodontium causes cross linking of collagen fibres which causes loss of integrity and breakdown of fibres.[1]

Oxidative stress results from an imbalance from an imbalance between radical generating and radical scavenging systems that is increased free radical production or reduced activity of antioxidant defences or both. In recent years more attention has been focused on the role of ROS, lipid peroxidation products and antioxidant systems in the pathology of periodontitis. Total antioxidant activity is reduced in saliva of patients with periodontits relative to that in non-periodontitis subjects. The aberrant response is characterized by exaggerated inflammation involving the release of excess of proteolytic enzymes and ROS.[1]

An antioxidant is a molecule capable of slowing or preventing the oxidation of other molecules. In a biological system they may protect cells from damage caused by unstable molecules known as free radicals. They are believed to play a role in preventing the development of such chronic diseases like periodontitis. Vitamin C and E are the ones responsible for maintaining the collagen regulation and antioxidant regulation, respectively in the body. Vitamin C is a water-soluble whereas vitamin E is a fat-soluble vitamin. Deficiency of vitamin C is known to cause aberrations in connective tissues throughout the body including that of the oral cavity and periodontium which might result in un favorable and unhealthy gingival consistency and delayed post-surgical healing. Deficiency of vitamin E will result in increased oxidative stress resulting in destruction of the tissues by toxic radicals resulting in destruction and attachment loss in periodontium.[1] Grape seed extract (GSE) is the richest source of PC. It has potent antioxidant, free radical scavenging, anticarcinigenic and anti-inflammatory properties. Since oxidative stress is encountered in periodontitis, knowing the effect of PC on periodontal inflammation is an important breakthrough in periodontal therapeutics [2-7]. With the above background the aim of the study was to compare the effect of proanthocyanidins on HbA1c vitamin C, E and ROS in diabetic patients with and without periodontitis a clinic-biochemical study.

Materials and methods

Total number of 80 known Type 2 diabetic patients in the age group 30 – 60 years (both males and females) was selected from the outpatient department of endocrinology, A.J. institute of medical sciences and outpatient department of periodontology A.J. institute of dental sciences, Mangalore. Informed consent was taken from all the participants. Medical examination included body mass index (BMI) blood pressure recording, fasting blood glucose level. Parameters such as gingival index (Loe and Sillness) plaque index (O'Leary) probing pocket depth and clinical attachment level was measured in periodontal examination. Blood samples were collected from all patients at 8:00 am; 10ml of blood will be taken in each case from cephalic vein. After centrifugation the collected serum was stored at -70"c and analysed for HbA_1c, ROS and anti-oxidants vitamin C and E using HPLC (high pressure liquid chromatography) and spectrometry respectively. All the patients were prescribed proanthocyanidine capsules (500mg) once daily for the first three months. Blood samples were collected from all the patients at the end of three months and the parameters were estimated. Proanthocyanidine capsules were discontinued and the subjects were recalled at the end of six months for the estimation of all the above-mentioned parameters.

Results

A total number of 80 known Type 2 diabetic patients in the age group 30 – 60 years (both males and females)

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were selected from the outpatient department of endocrinology, A.J. institute of medical sciences and outpatient department of periodontology to participate in the study. Statistical analysis was carried out using paired 't'test for estimating the mean values and standard deviation of vitamin C and E levels, superoxide dismutase and HbA1c levels in both the groups.

Figure 1 and Figure 2 shows a very high significant difference in the mean values of vitamin C and E levels at baseline and the 3 month as well as at the baseline and 6 months in both the groups. Vitamin C and E levels increased from baseline to 3 months during grape seed extract consumption, and decreased after discontinuation of the treatment from 3rd month to 6th month. (p value < 0.001)

Figure 3 shows very high significant difference in the mean values of superoxide dismutase levels at baseline and the 3 month as well as the baseline and 6 months in both the groups. The levels decreased from baseline to 3 months during grape seed extract consumption, and increased after discontinuation of the treatment from 3rd month to 6th month. (p value < 0.001)

Figure 4 suggests no significant difference in the mean values of HbA1c levels at baseline and at 3 month, as well as baseline and 6 months in both the groups. (p value < 0.05)

Discussion

Periodontitis may be a risk factor for worsening glycaemic control among patients with diabetes. The first clear evidence to support this hypothesis came from investigations of individuals in the Gilia River Indian Community.[8] Severe periodontitis was associated with an increased risk of poor glycaemic control (HbA1c > 9.0%) at follow up of minimum 2 years, suggesting that severe periodontitis was a risk factor for compromised diabetes management. Diabetes is known to increase oxidative stress in the body. Vitamin C and E both act as antioxidants to control ROS levels in the body. The present study is aimed at comparing the antioxidant effects of proanthocyanidins on HbA1c, vitamin C, E and ROS in 2 groups of diabetic patients i.e. with and without periodontitis. On administration of proanthocyanidin for 3 months, significant difference was noted in vitamin C and E levels and SOD levels, from baseline to 3 months, as well as from baseline to 6 months. Later the difference is reversed indicating a decrease in their levels. This may be attributed to the higher proanthocyanidin levels in the blood in the first 3 months. From 3-6 months, the levels of PC declined leading to decreased effect on the antioxidant mechanisms. Similar findings on vitamin C and E levels were found studies done by H. Staudte[9]. Irving and Milton[10]. Amaliya et al[11] Kuzmanova[12]. Giuseppe paousso[13] Contradictory results to the present study was noted by Joel h. Parrish[14], who suggested that deficiency of vitamin E does not cause increased destruction of the periodontium in the presence of periodontitis. Moreover, no beneficial effects from the therapeutic use of vitamin E to combat periodontitis were found.

Superoxide dismutase (SOD) is the enzymatic antioxidant in the body which helps control the oxidative stress in the body. Levels of Superoxide dismutase increase on increasing oxidative stress. Thus Superoxide dismutase is taken as a measure of oxidative stress in the body. In the present study, the Superoxide dismutase levels decreased from baseline to 3 months after administration of proanthocyanidin both the groups. But a reverse action was noted after the drug was discontinued, but remained significantly higher than at baseline.

Similar effects of proanthocyanidins on efficacy of antioxidant mechanism, as in the present study, were

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noted by Zuo-hui shao et al.[15] Vanessa et al[16] Yusuke Katsuda et al[17] HbA1c gives the amount of glycated hemoglobin in the blood. In diabetes patients, HbA1c levels are raised. Proanthocyanidins have shown marginal reduction in HbA1c levels in diabetics in many previously conducted studies[18,19]. In this study Hba1c levels decreased in 3 months under the action of proanthocyanidins, and then increased again in 3- 6 months, after the discontinuation of the drug after 3 months. However the values were not statistically significant suggesting that antioxidant supplementation has limited effect in reducing glycated hemoglobin levels. Pure form of grape seed extracts has shown to be a good nutritional supplementation. On long term use there could be beneficial effects in reducing systemic inflammation by reducing total bacterial burden.

Whenever a free radical interacts with another molecule, secondary radicals may be generated that can then react with other targets to produce yet more radical species. The classic example of such a chain reaction is lipid peroxidation, and the reaction will continue to propagate until two radicals combine to form a stable product or the radicals are neutralised by a chain breaking antioxidant. Chain breaking antioxidants are small molecules that can receive an electron from a radical or donate an electron to a radical with the formation of stable byproducts. Lipid phase chain breaking antioxidants scavenge radicals in membranes and lipoprotein particles and are crucial in preventing lipid peroxidation. The most important lipid phase antioxidant is probably vitamin E. Vitamin E occurs in nature in eight different forms, which differ greatly in their degree of biological activity. The tocopherols (α, β, γ and δ) have a chromanol ring and a phytyl tail, and differ in the number and position of the methyl groups on the ring. The tocotrienols (α, β, γ and δ) are structurally similar but have unsaturated tails. Both classes of compounds are lipid soluble and have pronounced antioxidant properties. They react more rapidly than polyunsaturated fatty acids with peroxyl radicals and hence act to break the chain reaction of lipid peroxidation. In addition to its antioxidant role, vitamin E might also have a structural role in stabilizing membranes.

Conclusion

Periodontal diseases (Gingivitis and Periodontitis) are among the most widespread chronic conditions affecting populations worldwide. The incidence and progression of periodontal disease is related casually to periodontal pathogens as well as to various host and environmental factors. The aberrant response is characterized by exaggerated inflammation involving the release of excess of proteolytic enzymes and reactive oxygen species. Persons with diabetes mellitus (DM) are at greater risk of developing periodontal disease (PD), in fact PD is considered the sixth complication of diabetes. Antioxidant effects of grape seed extract i.e. proanthocyanidins on the reactive oxygen species, antioxidant mechanisms and HbA1c levels signifying the glycaemic index in diabetic individuals with or without periodontitis. Results revealed

1. There is very high significant difference in the mean values of vit C and E levels at baseline and the 3 month as well as baseline and 6 months in both the groups. Vitamin C and E levels increased from baseline to 3 months during grape seed extract consumption, and decreased after discontinuation of the treatment from 3rd month to 6th month.
2. There is very high significant difference in the mean values of Superoxide dismutase levels at baseline and the 3 month as well as baseline and 6 months in both the groups. The levels decreased from baseline to 3 months during grape seed extract consumption, and increased

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after discontinuation of the treatment from 3rd month to 6th month.

3. No significant difference in the mean values of HbA1c levels at baseline and the 3 month, as well as baseline and 6 months in both the groups.

Long term clinical trials need to be carried out to analyse the efficacy of pc in chronic systemic inflammation.

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Legend Figures

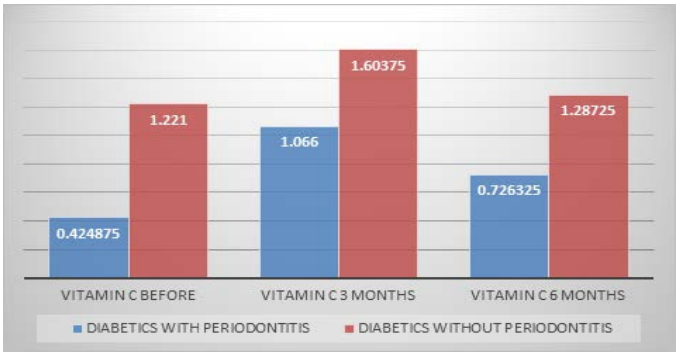

Figure 1: Levels of vitamin C in diabetics with periodontitis (blue bar) and without periodontitis (red bar) at baseline, 3 months and 6 months.

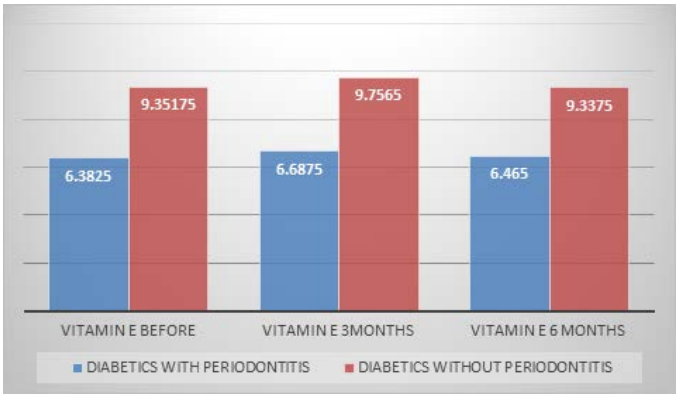

Figure 2: Levels of vitamin E in diabetics with periodontitis (blue bar) and without periodontitis (red bar) at baseline (0 months), 3 months and 6 months.

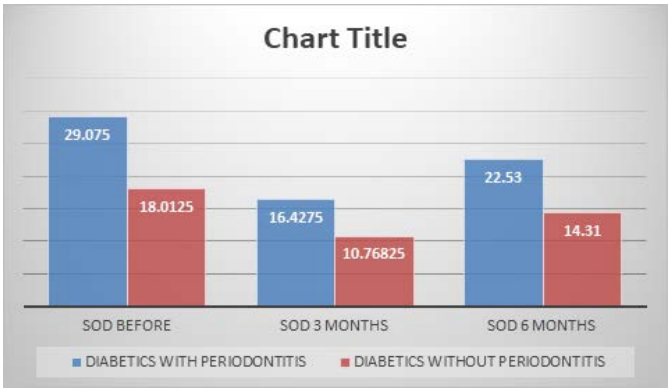

Figure 3: Levels of SOD in diabetics with periodontitis (blue bar) and without periodontitis (red bar) at baseline (0 months), 3 months and 6 month.

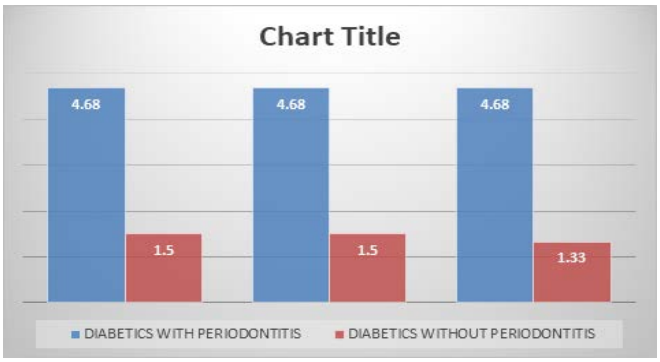

Figure 4: Levels of HbA1c in diabetics with periodontitis (blue bar) and without periodontitis (red bar) at baseline (0 months), 3 months and 6 month.

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