Original Research Article

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Studies on the Effect of Serum Prolidase Enzyme Activity and Certain Oxidative Stress Markers in Uncontrolled Diabetic Patients of North West Indian Population

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Abstract

Background: Diabetes is a worldwide metabolic disease with high morbidity and mortality rates resulting from a number of factors in which an absolute or relative deficiency of insulin or its function occurs. It has emerged as a major public health problem in developing countries like India. The association of oxidative stress and serum prolidase activity has been reported in many chronic diseases.

Aim: A study was performed to evaluate serum prolidase enzyme activity and certain oxidative stress markers in young uncontrolled diabetic patients.

Materials & Methods: 100 Type-2 diabetic confirmed patients with duration of diabetes ranged from 6–9 years and equal number (n = 100) of healthy subjects of Punjab origin were recruited in the present study. Fasting blood samples from both study and healthy control subjects were collected for the evaluation of serum prolidase activity and oxidative stress marks like total antioxidant status, total oxidative status, and oxidative stress index levels.

Results: A significant fall in serum prolidase and total antioxidant status was observed in type-2 diabetic patients while a significant increased in total oxidative status, oxidative stress index levels were recorded in diabetic patient's w.r.t. healthy control subjects. Serum prolidase activity was negatively correlated with serum total oxidative status and oxidative stress index levels.

Conclusion: Aforementioned observations of significantly increase in total oxidant status ($P < 0.01$) and oxidative stress index levels ($P < 0.001$) while a significant ($P < 0.05$) fall in total antioxidant status levels suggested a continuous increase in oxidative stress with increase in duration of the disease. Moreover, a significant ($P < 0.05$) decrease in prolidase activity in uncontrolled diabetic patients could be due to decreased collagen turnover, might be used as biomarkers for the prediction and diagnosis of diabetes.

Keywords: Uncontrolled diabetes, prolidase, Oxidative Status (OS), Body Mass Index (BMI), Total Antioxidant Status (TAS), Total Oxidative Status (TOS)

Introduction

Diabetes is a worldwide metabolic disorder, characterized by chronic hyperglycemia, a relative or absolute lack of insulin action. It is well established that hyperglycemia is the main cause of diabetic complication. Hyperglycemia leads to altered level of non enzymatic protein glycation and glucotoxicity and increased activity of aldose reductase. These events enhance the production of collagen as well as oxygen free radicals such as superoxide (O^{2-}) radicals, hydroxide radicals (HO^{-}), and hydrogen peroxide (H_2O_2), and/or inadequacy of antioxidant defense systems.[1–3] The cumulative effect of all oxidants is defined as total oxidative stress (TOS). Cells have developed antioxidant defense mechanisms to remove these harmful oxidative reactions. These mechanisms consist of enzymes such as catalase, superoxide dismutase, paraoxonase, and glutathione peroxidase and vitamins such as ascorbic acid, β-carotene, and tocopherols. Total antioxidant status (TAS) measures all these serum antioxidants. The ratio of TOS to TAS levels is indicated as the oxidative stress index (OSI). The oxidative stress resulting in the development and progression of complications of diabetes, which induces chronic inflammation and prolidase, considered as a target enzyme for this.[4–6]

Prolidase (EC. 3.4.13.9), a member of the matrix metallopeptidases (MMP) family plays a very important role in the recycling of proline for collagen synthesis and matrix remodeling, is reported as a marker for oxidative stress for many diseases, like chronic liver diseases, erectile dysfunction, osteoporosis, diabetes etc.[3,7–11] Prolidase is involved in cell growth, collagen metabolism, and matrix remodeling.[12–14]

High glucose level in diabetes may delay the proliferation of cell and degree of collagen production and increased breakdown of collagen, which impair their structural integrity and functions.[11–13] So, the present was designed to evaluate prolidase activity in uncontrolled diabetic patients along with total antioxidant status (TAS), total oxidative status (TOS) and oxidative stress index (OSI).

Materials and Methods

The present cross-sectional study was carried out in the Department of Biochemistry, Govt. Medical College Patiala in collaboration with medicine department; Rajindra hospital Patiala on uncontrolled Type-2 diabetic patients (Group-2) and who were diagnosed 6 to 9 years ago and on 100 healthy subjects (Group-1). The subjects of both groups were taken from rural and urban area of general community of both genders (male and female) in the age ranging of 45–51 years.

Inclusion Criteria: Type 2 diabetes patients with time duration of 6–9 years of diabetes/diabetic nephropathy attending medicine outpatient department, Rajindra Hospital Patiala who agreed to participate in the study were included. Medical history, standard physical examination, and biochemical tests such as blood glucose and HbA1c were used for selection of cases and controls.

Exclusion Criteria: Patients suffering from major infections like tuberculosis, HIV, and so forth, chronic heart failure, pregnant females, taking potent antioxidant, and history of alcohol intake were excluded from present study.

Diabetic complications like coronary artery disease, peripheral vascular disease, and stroke and acute myocardial infarction in diabetic groups were also excluded.

Study Design: The present study was a case control cross-sectional prospective study. The study protocol was approved by the Institution Ethical Committee. A detailed history, physical, and systemic examination, including measurement of Body Mass Index (BMI), was carried out in every subject who entered the study as per a predesigned performa for assessing the

signs of chronic heart failure, diabetes and also the presence of any exclusion criteria.

Data Collection

Measurements of Anthropometric Parameters: The examination of body weight was done by taking weight in kilogram (kg) and height was measured in centimeters. The BMI was calculated from the formula: BMI = weight in kg/ (height in meters).

Blood sampling Collection and sample preparations for Biochemical Assays: A volume of approximately 8–9 ml of peripheral venous blood was collected by vein puncture using a dry, disposable syringe between 8 and 9 AM after an overnight fast from both groups in a plan vial (5 ml) for serum preparation and in potassium oxalate: sodium fluoride vial (3:1 ratio) (2 ml) and in EDTA vial (1 ml).

a. **Serum Preparation:** Blood samples collected in plain vial was kept at 37°C temperature for 15–25 minutes then centrifuged at 4000 rpm at 4°C and a clear supernatant (Serum) was stored at –20°C for the analysis of TAS, TOS, OSI and prolidase levels.

b. **Plasma Preparation:** Blood samples collected in potassium oxalate: sodium fluoride vial was immediately centrifuged at 4000 rpm at 4°C and a clear supernatant (plasma) was stored at –20°C for the determination of HbA1C.

c. Whole Blood collected in EDTA vial (1 ml) was used for evaluation of HbA1C levels.

1. **Measurements of Anthropometric Parameters:** The examination of body weight was done by taking weight in kilogram (kg) and height was measured in centimeters. The BMI was calculated from the formula: BMI = weight in kg/(height in meters)^2.

2. **Estimation of Fasting Blood Glucose (FBS) & Postprandial Blood glucose (PPBS) and HbA1C:** Fasting and post-prandial blood glucose levels were estimated using ortho-toluidine method of Hyvavria and Nikkila, 1962.[15] HbA1c was analyzed by using kit supplied by Transasia Biomedical Private Limited, Mumbai (India) based on ion-exchange resin method in which a hemolyzed preparation of the whole blood is mixed continuously for 5 min with a weak binding cation exchanges resin. During this time, non-HbA1c binds to the resin. After the mixing period a filter is used to separate the supernatant containing the glycohemoglobin from the resin. The glycohemoglobin percent is determined by measuring the absorption at 415 nm of the glycohemoglobin fraction and the total hemoglobin fraction. The ratio of the two absorbances gives the percentage glycohemoglobin.

3. ***Estimation of Total Antioxidant Status (TAS):*** TAS of serum was determined using a novel automated measurement method, developed by Erel, 2004.[16] This method produces hydroxyl radicals, which are the most potent biological radical. The sequentially produced radicals, such as brown-colored dianisidinyl radical cations produced by the hydroxyl radical, are also potent. This method measures the antioxidant effect of the sample against the potent free radical reactions, which is initiated by the produced hydroxyl radical. The assay has excellent precision values of lower than 3%. The results are expressed as μmol Trolox equivalent (equiv.)/L.

4. ***Estimation of Total oxidative status (TOS):*** Serum TOS was determined using a novel automated measurement method developed by Erel, 2005.[17] Oxidants present in the sample oxidize the ferrous ionodianisidine complex to ferric ion. The oxidation reaction is enhanced by glycerol molecules, which are abundantly present in the reaction medium. The ferric ion forms a colored complex with xylenol orange in an acidic medium. The color intensity, which can be measured spectrophotometrically, is related to the total amount of oxidant molecules present in

the sample. The assay is calibrated with hydrogen peroxide, and the results are expressed in µmol H_2O_2 equiv./L).

5. ***Estimation of Oxidative Status Index (OSI):*** The percent ratio of TOS level to TAS level was considered as the OSI, which indicates the degree of oxidative stress.[18,19] OSI was calculated according to the following formula:

OSI (arbitrary unit) = TOS (µmol H_2O_2 equiv./L)/ TAS (µmol Trolox equiv./L).

6. ***Estimation of Serum Prolidase:*** Serum prolidase levels were estimated by Chinard's, 1952[20] method modified by Myara et al., 1982[21] by using a spectrophotometrically method that measures the levels of proline produced by prolidase. The supernatant was diluted two-fold with physiologic saline (0.9% NaCl). Next, 25 µl of the mixture was preincubated with 75 µl preincubation solution (50 mmol/l Tris–HCl buffer (pH 7.0) containing 1 mmol/l glutathione and 50 mmol/l $MnCl_2$) at 37°C for 30 minutes. A total of 100 µl reaction mixture, which was composed of 144 mmol/l gly–pro (pH 7.8), was incubated with 100 µl preincubated sample at 37°C for 5 minutes. To stop the incubation reaction, 1 ml glacial acetic acid was added. After adding 300 µl Tris–HCl buffer (pH 7.8) and 1 ml ninhydrin solution (3 g/dL ninhydrin was dissolved in 0.5 mol/L orthophosphoric acid), the mixture was incubated at 90°C for 20 minutes and then cooled with ice. Absorbance was then measured at a 515-nm wavelength to determine proline content. The intra- and interassay coefficients of variation were both lower than 7%.

Statistical Analysis: The data were analyzed using a SPSS-17 program and expressed as mean ± standard deviation continuous variables with normal distribution. The student's *t*-test was used to test the significance of differences between the mean values uncontrolled diabetic patients (study group) and healthy control subjects (control groups). The differences were considered significant at $P < 0.05$.

Results

1. ***Demographic Parameter:*** The age, BMI Blood pressure (systolic & diasystolic) and haemoglobin in healthy control subjects (Group-1) and Type-2 diabetic patients (Group-2) recruited in the present study were in the normal range. The young healthy subjects and Type-2 diabetic patients in the age range of age from 45.00 ± 8.00 to 51.00 ± 11.00 years were recruited. The BMI levels were ranged from 23.80 ± 4.05 Kg/m^2 to 24.16 ± 3.97 Kg/m^2. A systolic blood pressure and diastolic blood pressure from 125.59 ± 9.77 mmHg to 127.61 ± 5.46 mmHg and 83.15 ± 5.18 to 85.93 mmHg ± 6.76 mmHg was recorded. All the Demographic Parameter: was within the normal range [Figure 1].

2. ***Fasting glucose, Postprandial glucose and glycosylated haemoglobin levels***: A significant increase (($P < 0.001$) in fasting glucose (from 75.19 ± 8.25 mg/dL to 174.78 ± 9.02 mg/dL) and postprandial glucose levels (from to 128.22 ± 9.29 mg/dL to 215.26 ± 21.10 mg/dL) was observed in healthy control subjects (Group-1) and Type-2 Diabetic Patients respectively. The percent increase by 132.45% and 67.88% in fasting glucose and postprandial glucose levels were recorded was in Type-2 Diabetic Patients (Group-2) w.r.t healthy control group [Figure 2]. The levels of HbA_1C were significantly ($P < 0.01$) increased from 5.90 ± 0.52% in control subjects) to 9.00 ± 1.80% to 9.00 ± 1.80% (Type-2 Diabetic patients) by 52.54% increase in Type-2 diabetic patients (Group-2) w.r.t. Group-1 [Figure 3].

3. **Total antioxidant status (TAS), Total oxidant status (TOS), Oxidative status index (OSI) and prolidase levels:** A significant increase ($P < 0.001$) in TOS and OSI from 20.69 ± 4.56 µmol H_2O_2 Equiv./L to 29.13 ± 4.38 µmol H_2O_2 Equiv./L, 13.79 ± 1.71 to 36.82 ± 3.11 respectively was observed in Type-2 diabetic patients (Group-2) w.r.t healthy

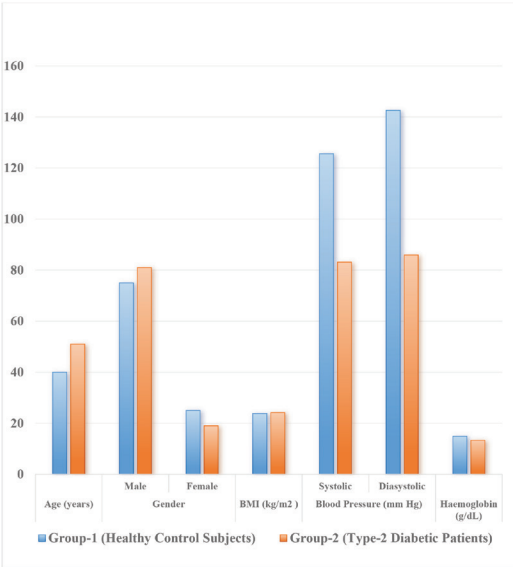

Figure 1: Anthropometric parameter status of healthy control subjects (Group-1) and Type-2 Diabetic patients (Group-2).

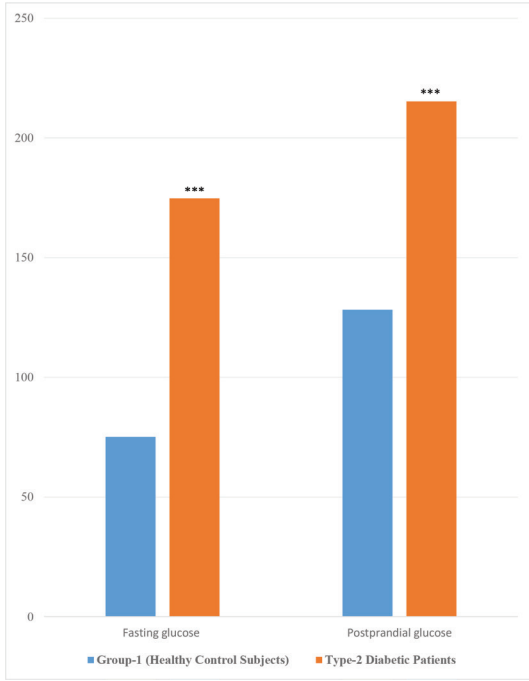

Figure 2: Alterations in fasting glucose and postprandial glucose levels. The values in figure represents the mean values 100 observations obtained in healthy control subjects (Group-1) and Type-2 Diabetic patients (Group-2). ***$P < 0.001$.

control group [Figure 4], while the levels of TAS and prolidase activities were significantly reduced ($P < 0.001$) from 1.50 ± 0.12 µmol Trolox equiv./L to 0.791 ± 0.10 mol Trolox equiv./L and and 42.18 ± 3.98 mmol/min/L to 55.72 ± 7.90 mmol/min/L ($P < 0.05$) respectively in Type-2 diabetic patients respectively [Figure 3]. The percent increase in TOS, and OSI by 40.79%, 167% was recorded in Type-2 diabetic patients (Group-2) w.r.t healthy control group. The 47.26% decrease in TAS levels [Figure 3] and 24.30% fall in prolidase activities [Figure 4] were found in Type-2 diabetic patients w.r.t. healthy control group.

Discussion

The present cross-sectional study was conducted to evaluate the prolidase, TAS, TOS and OSI levels in uncontrolled Type-2 diabetics patients (duration of diabetes was 7–9 years) with respect to equal number of healthy control subjects to elucidate their role. It was aimed to show whether serum prolidase levels can be regarded as a marker of inflammation in diabetes and to determine the relationship between prolidase and oxidative - antioxidant status. Oxidative stress, a well established marker for the pathophysiology of numerous health disease such as cancer, cardiovascular disease, arthritis pulmonary disorders diabetes etc.[22–25] In patients with T2DM, oxygen free radicals increase with continuous elevation of glucose and this leads to increased oxidative stress.[26,27] Free radical-mediated pathologies are often influenced by the imbalance between oxidant and antioxidant system.[28] A significant ($P < 0.001$) increase in serum TOS and OSI was observed in uncontrolled Type-2 diabetics patients (Group-2) w. r. t healthy control subjects [Figure 4] while a significant ($P < 0.001$) fall in serum TAS levels and prolidase activity ($P < 0.05$) was recorded in uncontrolled Type-2 diabetics

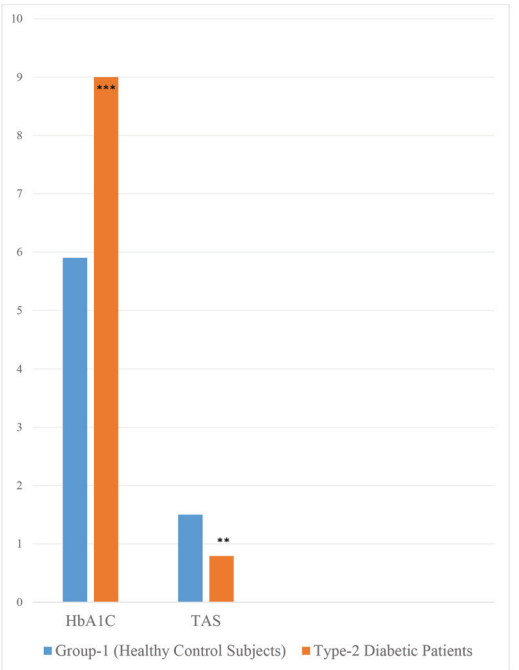

Figure 3: Alterations in glycosylated haemoglobin (HbA1C) and total antioxidant status (TAS) levels. The values in figure represents the mean values 100 observations obtained in healthy control subjects (Group-1) and Type-2 Diabetic patients (Group-2). $^{**}P < 0.01$.

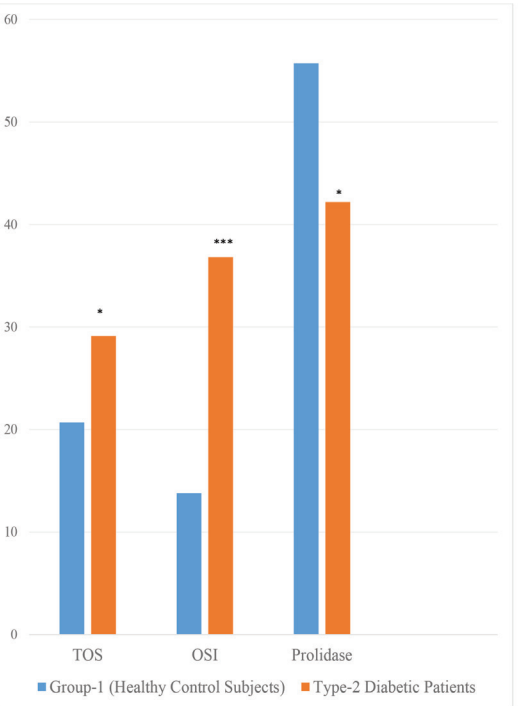

Figure 4: Alterations in total oxidative stress (TOS), oxidative stress index (OSI) and prolidase levels. The values in figure represents the mean values 100 observations obtained in healthy control subjects (Group-1) and Type-2 Diabetic patients (Group-2). $^{*}P < 0.05$, $^{***}P < 0.001$.

patients (Group-2) w. r. t. healthy control subjects [Figure 3] further a fall in prolidase activity was seen in uncontrolled Type-2 diabetics patients (Group-2) w. r. t. healthy control subjects, which was statistically non significant [Figure 4]. Thus it seems that with increase in duration of the disease, continuously increased the oxidative stress.

Our findings of significant alterations in TAS, TOS OSI and prolidase, levels in present study are with consistent with various literature reports[29–31] who observed that prolidase and TAS values in diabetes were significantly lower w. r. t. control healthy subjects. Prolidase, a MMP family member, is essential for the remodeling of the ECM and the metabolism of collagen and proline recycling is crucial for collagen synthesis. Collagen is an important component of cellular tissues and disruption of the collagen cycle can impair their structural integrity and functions.[32–34] However, certain studies[2,6] reported elevation in prolidase activity in diabetic patients. A significant ($P < 0.05$) fall in prolidase activity in present study suggests a potential alteration in collagen recycling and ECM remodeling processes in uncontrolled diabetic patients, which may contribute to the pathogenesis of late complications of diabetes. Despite several studies, there are many conflicting data on prolidase levels in diabetes.

Conclusion

Aforementioned observation of significantly increase in total oxidant status & oxidative stress

index levels while a fall in total antioxidant status levels suggested a continuous increase in oxidative stress with increase in duration of the disease. Moreover, a decrease in prolidase activity in uncontrolled diabetic patients could be due to decreased collagen turnover and can be used as biomarkers for the prediction and diagnosis of diabetes. Further studies with large sample size suggested to clarify the effects on prolidase activity in diabetic patients.

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Conflict of Interest

The authors have declared that no conflict of interests exists.

Abbreviation

T2DM: Type-2 Diabetes Mellitus
OSI: Oxidative Stress Index
BMI: Basal Metabolic Index
TAS: Total Antioxidant Status
TOS: Total Oxidant Status
PSA: Prolidase Activity
MMP: Matrix Metallopeptidases

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