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Research Article

Correlation between Advanced Oxidation Protein Products (AOPP) and Antioxidant status in Type 2 diabetics in Southern Asian Region

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Abstract: Incidence & prevalence of type 2 DM is increasing in worldwide but greatest prevalence in Asian population as also its chronic complications. Oxidative stress is believed to be a common pathogenic factor for these grave consequences. Advanced oxidation protein product (AOPP) is a marker of protein damage whereas total oxidant status(TOS) reflects the severity of oxidative stress. Different results were found by different authors about correlations between these markers and antioxidant status. It was a cross sectional study. 50 patients of clinically diagnosed type 2 DM & 47 age and sex matched controls were selected for the study, according to inclusion and exclusion criteria. We analysed HbA1C, AOPP, TOS and Trolox Equivalent Antioxidant Capacity (TEAC) in diabetes patients and compared them with controls. (HbA1C was estimated by boronate affinity chromatography, and others were estimated spectrophotometrically). We also tried to find out any correlation between oxidants (AOPP and TOS) and antioxidant (TEAC). Significant increase in mean HbA1C, AOPP ($p<0.0001$) and increase in mean TOS level ($p<0.184$) were found in diabetes patients in comparison to controls. We also observed significant decrease in mean TEAC levels ($p<0.0001$). Significant negative correlations were observed between TEAC& AOPP ($r=-0.99, p<0.0001, y=1.607-0.004x$) AOPP accumulation is correlated with increased antioxidant consumption in type 2 diabetes. Estimation of AOPP is very much beneficial for prediction of chronic and grave complications of type 2 diabetes.
Keywords: Type 2 diabetes, AOPP, TEAC

INTRODUCTION

The incidence and prevalence of type 2 diabetes mellitus (T2DM) is increasing in developing countries as well as worldwide and the number is expected to be 333 million over the next 20 years [1, 2]. The greatest increase in prevalence is expected to occur in Asia and Africa, where most of the patients will probably be found by 2030 [3]. With rapid development of therapy, the mortality from acute complications of diabetes has decreased, but mortality from chronic complications like diabetic nephropathy has increased [4]. A currently favoured hypothesis is that oxidative stress, is the common pathogenic factor leading to insulin resistance which turn ultimately into T2DM as well as its macrovascular and microvascular complications [5, 6].The vicious circle mechanism between glycation and oxidation ('glyco-oxidation') display a disturbance of oxidative–antioxidative balance, and creates molecular damage [7, 8]. The majority of the glyco-oxidation products, accumulated in biological systems and brings about tissue degeneration and takes part in the origin of the diabetic vascular late complications e.g. nephropathy [9, 10].

Several studies suggested that, diabetes is associated with increased modification of proteins. In addition to the formation and accumulation of advanced glycation end products (AGEs), a family of oxidized protein compounds termed advanced oxidation protein products (AOPP), has emerged as a novel class of inflammatory mediators. AOPPs are the dityrosine containing and cross linked protein products, [11,12] first described by Witko-Sarasat *et al*. [13]. They are supposed to be structurally similar to AGE proteins and to exert similar biological activities as AGEs, i.e. induction of pro-inflammatory cytokines and adhesive molecules [11, 12]. AOPP are recognized as markers of oxidative damage to proteins, the intensity of oxidative stress and Inflammation [14], Proteins damaged by oxidative stress are especially albumin [15], but fibrinogen is also responsible for blood plasma AOPP levels [16].

Studies have already suggested that AOPP plays a major role in the development of diabetic nephropathy, [10, 12, 17] as well as diabetic retinopathy [18]. These structural and functional changes in diabetic

nephropathy take place in the kidney during the early phases of diabetes, prior to microalbuminuria [19, 20, 21].

Reactive oxygen species (ROS) by increasing oxidative stress are thought to play an important role in disease mechanisms and development of microvascular complications in patients with diabetes [22-27]. Studies have also suggested that oxidative stress, in terms of Total Oxidant Status (TOS) is increased in patients with diabetic nephropathy as well as in diabetics without nephropathy and increase is related to the severity of diabetes [23].

Human bodies are constantly protected against excessive oxidative stress by a complex set of enzymatic and non-enzymatic antioxidant systems. The enzymatic antioxidants superoxide dismutase (SOD) and glutathione peroxidase (GPx) are involved in the metabolism of superoxide and hydrogen peroxide respectively [28]. Albumin, uric acid, and ascorbic acid constitute >85% of the total antioxidant capacity (TAC) in human plasma [29]. however, overproduction and/or inadequate removal of ROS can result in oxidative stress, which is characterized as an imbalance between the formation of active oxygen metabolites and the rate at which they are scavenged antioxidants [22]. Rather than the individual antioxidants, measurement of the TAC is preferred to detect the antioxidant status of blood [29].

Many authors submitted different opinions about altered values of AOPP and TOS in diabetes [8, 17, 23, 30, 31]. Considering these facts we have tried to evaluate the values of those parameters in diabetes and to compare them with controls. Furthermore we tried to find out the total antioxidant status in those patients, and whether change of any individual oxidative stress marker in diabetes is correlated with alteration of antioxidant capacity.

This review will focus on identification of any oxidative stress factor to recognise and treat this devastating disease early in its progression and to postpone or even prevent the serious complications associated with it.

MATERIALS AND METHODS

Study design

This hospital based, cross sectional, non interventional study was conducted during the period of 2010-12 in the Biochemistry department of NRS Medical College and Hospital, Kolkata, West Bengal, India.

Selection of the case group

The case group (Group-II) primarily included 50 (fifty) patients of clinically diagnosed type 2 diabetes Mellitus (diagnosed from history and relevant biochemical tests), attending the Outpatient Department (OPD) and admitted in Medicine indoor ward of the institution on convenience basis. The patients were selected with the age group of 40-60 years following the inclusion and exclusion criteria.

Exclusion criteria for the case group

Hypertensive patients, T2DM patients with acute and chronic complications, severely ill, unconscious and disabled patients were not included in the study along with abnormal liver function tests. Patients with recent history of stroke, myocardial infarction or any disease which can cause oxidative stress were also excluded from the study.

Selection of the control group

47 age and sex matched healthy control subjects (Group I) were also selected for the study. All control subjects were considered from more or less similar geographical area with similar socioeconomic status with no significant difference in their food habit and drinking water quality.

Exclusion criteria for control subjects

Persons with chronic smoking habits, alcohol addiction or any drug addiction were excluded from the study.

Ethical considerations

Written consents (informed consents) were obtained from the participants (disease and control groups). The study protocol was approved by the ethics committee of N.R.S. Medical College. Control subjects are included in Group 1, type 2 diabetes patients are included in group II.

Sample Collection

The amount of blood collected in absolute fasting condition with all aseptic precautions in 2 parts was 5 ml. The first part collected in ethylene diamine tetraacetic acid (EDTA) vial for estimation of glycated haemoglobin (HbA_{1C}).The second part collected was allowed to clot and serum was separated for estimation of AOPP, TOS and Trolox Equivalent Antioxidant Capacity (TEAC).

Measurement of biochemical analytes

HbA_{1C}, the index of long term glycemic control,was determined with Micromat II(Biorad) instrument based on boronate affinity chromatography [32].

AOPP Assay

Determination of AOPP was based on spectrophotometric detection according to Witko-Sarsat *et al.* (1996) in our modification [33]. Concentration of AOPP is expressed in chloramine units (µmol/l).

TOS Assay

Serum TOS was measured using Erel's TOS method [34], which is based on the oxidation of ferrous Into ferric ion in the presence of various oxidative species in

acidic medium and the measurement of the ferric ion by xylenol orange. The results were expressed in µmol H_2O_2 equivalent/l (µmol H_2O_2 equiv./l).

TEAC Assay

Trolox equivalent antioxidant capacity which signifies the total antioxidant status of our body was determined according to ABTS+ decolourisation assay of Re R *et al*. [35], principle based on the inhibition of radical cation of ABTS, which has the characteristic of long wavelength absorbance maximum at 734 nm. The results were expressed in mmol Trolox equivalent/l.

Statistical methods used

Statistical analysis was done by student`s t test and correlation coefficient linear regression plot. P value was considered significant at the confidence level of 0.05. All statistical analyses were performed using SPSS software version 16.0 for windows.

Data collection and processing for statistical analysis

Statistical analysis was aimed

- To asses the significance of difference between the mean values of serum HbA1c, AOPP, TOS and TEAC between the Group I (controls) and Group II (cases).
- To find out any correlations between individual oxidative stress parameters(AOPP or TOS)s and TEAC between Group I(controls), and Group II(cases).

RESULTS

Table 1 shows that there is a significant increase in mean HbA1c ($p<0.0001$) and AOPP ($p<0.0001$) levels as well as significant decrease in mean TEAC ($p<0.0001$) level in diabetes patients in comparison to controls. The mean HbA1c level was found 9.8% in diabetics in comparison to 5.4% in controls. The mean AOPP level was also observed as 150.6 µmol/L in T2DM when compared to controls as 84.23 µmol/L ($p<0.0001$).The mean TEAC levels were found 0.96mmol/l in diabetics and 1.15mmol/l in control ($p<0.0001$). The TOS levels were increased in diabetes but not significantly.The mean TOS value was 10.96 µmol H_2O_2 equivalent/l in control subjects in comparison to 11.94 in diabetics ($p<0.184$).

Furthermore table 2 shows, significant negative correlation between AOPP and TEAC in diabetes patients ($p<0.0001$).

Figure 1 reveals significant negative correlations between AOPP and TEAC in disease population.($r=-0.99, p<0.0001, y=1.607-0.004x$)

No significant correlation was found between TOS and TEAC (TOS was not significantly increased in diabetes in comparison to controls).

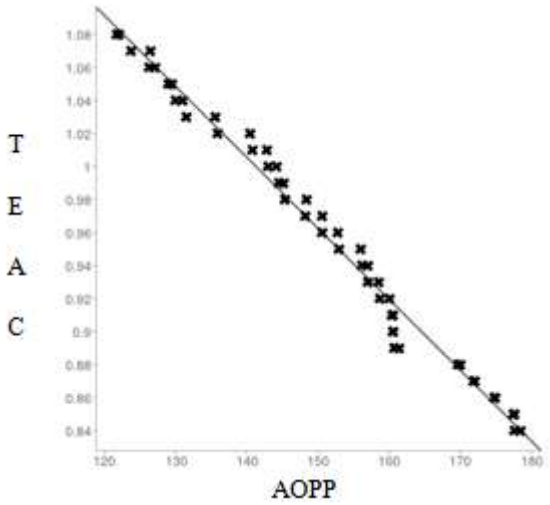

Fig. 1:Correlation between AOPP & TEAC in T2 DM patients. Correlation between AOPP & TEAC in DM-2 patients (r=-0.99,p<0.0001,y=1.607-0.004x)

Table 1: HbA_{1C} , AOPP, TOS & TAS value in control group and DM-2 patients

	HbA_{1C} %	**AOPP(µmol/l)**	**TOS(µmol/H_2O_2 equiv./l)**	**TEAC(mmol Trolox eqivalent/l)**
Control(n=47)	Mean- 5.45 SD- 0.27 SEM- 0.039 N=47	Mean- 84.23 SD- 12.39 SEM- 1.80 N=47	Mean- 10.96 SD- 3.4 SEM- 0.49 N=47	Mean- 1.15 SD- 0.12 SEM- 0.0170 N=47
DM-2 (n=50)	Mean- 9.8 SD- 1.301 SEM- 0.18 N= 50	Mean- 150.6 SD- 28.85 SEM- 4.08 N=50	Mean- 11.94 SD- 3.8 SEM- 0.54 N=50	Mean- 0.96 SD- 0.12 SEM- 0.0175 N=50
p-value	<0.0001	<0.0001	<0.184	<0.0001

Table 2: Correlation between AOPP & TEAC

	Control	**DM2**
AOPP &TEAC	Sample size= 47 Correlation coefficient (r)=(-0.97)	Sample size= 50 Correlation coefficient (r)=(-0.99)
P -value	<0.0001	<0.0001

DISCUSSION

The results of our study have shown that there is a significant increase in mean HbA_{1C} and AOPP & decrease in TEAC levels in diabetes in comparison to controls. Furthermore we also observed negative correlations between AOPP and TEAC. TOS level increased in diabetes but not significantly.

The findings in our study keep in tract with the observations found by Piwowar A [17], who described that AOPP formation is induced by intensified glyco-oxidation process, oxidant antioxidant imbalance and coexisting inflammation. Similar findings were also observed by Pan *et al*. [36] and Fathy *et al*. [37] Gil del valy [38] and Fathy *et al*. [39] found correlations between AOPP and HbA_{1C}. Furthermore Fathy *et al*. [37] found correlations of AOPP with microvascular complications of T2DM.

In agreement with previous studies we also observed significant increase of HbA1C and AOPP in diabetes than controls. Kalousova [31] found increase of AOPP is more pronounced in T2DM than T1DM and it is a better parameter than AGE. Previous studies also observed that AOPP is a good marker for progression of diabetic Nephropathy [10]. Sharada HM [39] observed that AOPP increased progressively and significantly with the growth of albuminuria ($p<0.01$).A significant positive correlation was also found by him between plasma level of AOPP and both of (S) creatinine and albumin creatinine ratio (ACR). Xhi Xiang Ng *et al*. [18] observed the increased AOPP level in patients with diabetic retinopathy. Baskol et al found the increased AOPP and decreased antioxidants in diabetes patients [40]. From our review we can assume that at our region, progress to diabetic retinopathy and nephropathy as well as decreased antioxidant level may appear earlier in diabetes patients with increased AOPP levels. In our study TOS level was not increased significantly in diabetes. Recently, numerous stable end products of oxidative stress have been identified and these include the AOPP [18]. From our result we can assume that AOPP is a better marker than TOS in diabetes.

Estimation of AOPP as well as HbA_{1C} may be useful to predict the risk of development of diabetic complications [8]. Diabetes Complications and Control Trial (DCCT) demonstrated in patients with type 1 diabetes that, despite having similar HbA_{1C}levels, participants in the intensive treatment group showed a marked reduction in the risk of development of diabetic retinopathy compared with their counterparts in the conventional treatment group [5]. Some have hypothesised that increased glycaemic variability generated more ROS, leading to vascular damage [6].

Some authors found significant decrease of GPx and SOD activity in diabetes retinopathy patients which provides further evidence on the imbalance of antioxidant system in subjects with DM complications [18]. Pandey *et al*. found the inverse relationship of AOPP and protein carbonyl with antioxidants **[**41]. Similar studies were observed by Lapola *et al*. [42] One study indicates a possible increase in the copper and iron-mediated generation of ROS leading to increased consumption of antioxidants in the body **[**43].

Negative correlations between protein carbonyl and TAS have been found by Fenkcl V *et al*. in his observations [44]. Similar type of findings was found in colorectal carcinoma [45]. Positive correlations were observed between AOPP and severity of decompensated liver cirrhosis [46].

In agreement with those studies we observed negative correlation between AOPP and TEAC in type 2 diabetes. Previously similar findings were observed in type 1 DM [47].

We found AOPP but not the TOS is correlated with TEAC in diabetes. So AOPP is more stable marker than TOS in diabetes in our study. Some authors found that metformin therapy decreases AOPP and increases antioxidant status in diabetes [48].

AOPP may be a therapeutic target. AOPP have their own particular biological proprieties, similar to those of AGEs, and also bind to the same receptor, i.e. RAGE [14]. Zi Ziang Ng [18], stated that, the soluble RAGE (sRAGE), is a recently discovered naturally occurring inhibitor of AGE-RAGE mediated pathological effects. AOPP shares common biological effect exerted by AGE, including interaction with RAGE which ultimately leads to neo-vascularisation that could result in DR [7].

AOPP accumulation may be a therapeutic target at least for the prevention and delaying the progression of renal complications in diabetics [14]. Furthermore, medications targeted to increase the sRAGE level in plasma can also prevent the binding the AOPP with RAGE, to reduce the microvacular complications of T2DM [18].

CONCLUSION

Oxidative stress has been implicated in the progression of long-term diabetes complications, including microvascular and macrovascular dysfunction.

We have measured HbA_{1C}, AOPP, TOS and TEAC in type 2 diabetes. We observed that AOPP has increased significantly in type 2diabetes but increase of TOS was not significant. TEAC decreased significantly in them. We also found negative correlations between AOPP and TEAC.

AOPP accumulation may be a therapeutic target of the physicians to challenge the chronic complications of diabetes. AOPP and TEAC may be included in diabetic

investigations. Moreover, in view of the socio-economical status of Asian developing countries, measurement of AOPP is beneficial as it is simple and not too costly.

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