



Research Article

Assessment of Serum Level of Protein Carbonyl as a Marker of Protein Oxidation in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

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Background: Diabetes mellitus is a chronic disease with an increasing prevalence worldwide and characterized by an increase in oxidative stress and inflammation. The most important factor that is responsible for oxidative stress and production of reactive oxygen species (ROS) is hyperglycemia. The major targets of ROS are proteins. The most common and widely used biomarker of severe oxidative protein damage is protein carbonyl content.

The study was designed to assess the serum level of protein carbonyl as a marker of protein oxidation in patients with type 2 diabetes mellitus and to evaluate the effect of age, body weight, waist circumference, diabetic control and disease duration on the level of protein carbonyl.

Subjects and Methods: This is a case-control study that included 91 patients with type 2 diabetes mellitus Eighty-five non-diabetic apparently healthy subjects matched for both age and sex with cases were enrolled as controls. Fasting blood samples were collected after an overnight fasting to measure protein carbonyl, fasting blood sugar, lipid profile, and glycated hemoglobin.

Results: The level of serum protein carbonyl was significantly higher in diabetic patients than in controls and positively correlated with glycated hemoglobin, age of participant and disease duration as well as with body mass index and waist circumference.

Conclusion: Diabetes mellitus is associated with an increase in protein oxidation in term of increase in the level of serum protein carbonyl with significant association in those who had poor glycemic control, obesity, higher age, and prolonged disease duration suggest that the carbonyl content of protein may be useful in evaluating the disease progression. Significant positive correlation of protein carbonyl together with waist circumference suggest that individual with central obesity are more susceptible to protein oxidation.

Introduction

Diabetes Mellitus (DM) refers to a group of diverse metabolic disorders characterized by elevated blood glucose levels caused by insufficient insulin release, resistance to action of insulin, or both

(1). The prevalence of DM in Iraq had significantly raised from 19.58/1000 in the year 2000 to 42.27/1000 in 2016 (2). In Basrah, the age-adjusted prevalence of diabetes in individuals aged 19-94 years is 19.7 percent (3). The high prevalence of DM in Basrah, Iraq,

which affect one in every five adults, will put a strain on the financial resources of health care systems (3), therefore several studies have been conducted in Basrah to study diabetes from various aspects (4,5). Protein oxidation is a major class of post-translational modifications that affects proteins, caused by reactions between protein amino acid residues and reactive oxygen species (ROS) or reactive nitrogen species (RNS) (6). Protein oxidative changes are classified into two types: irreversible oxidation and reversible oxidation, both of which can be produced selectively by ROS and RNS (6). According to several studies, DM has been linked to an increase in the formation of ROS or RNS as well as a decrease in anti-oxidant potential (7). Oxidative stress plays a crucial role in the development of diabetes complications, both microvascular and macrovascular (8). Generally, reactive species can generate damage to all cellular components, including proteins, carbohydrates, lipids, and DNA (9). Proteins are the most common targets for oxidation reactions due to their high abundance in cells, extracellular tissues, and body fluids as well as their rapid reaction rates with oxidants. Additionally, oxidative stress is able to degrade lipids and carbohydrates to highly reactive intermediates, which eventually attack proteins at various functional sites (9). It has been estimated that proteins can scavenge a majority (50%–75%) of generated reactive species (10). The variety of reaction sites leads to a wide range of post-translational protein modifications which change protein composition and folding as well as their net charge and hydrophobicity/hydrophilicity. This has an impact on their functions as receptors, enzymes, carrier and structural proteins (11). The attack of ROS modifies amino acid residues resulting in generation of protein carbonyl (PC) groups, while chloraminated oxidants, primarily hypochlorous acid and chloramines, which are produced in activated neutrophils by myeloperoxidase, form dityrosine-containing cross-linked protein products called advanced oxidation protein products (AOPPs). Both have been identified as early markers for oxidative stress and are used as a measure of protein oxidative damage (12).

There are four major pathways for the production of PC: (i) backbone fragmentation via the α -amidation pathway and β -scission, (ii) binding of non-protein carbonyl compounds derived from lipid peroxidation by Michael addition of 4-hydroxy-2-nonenal (HNE) and malondialdehyde (MDA) to amino acid side chains of protein including histidine imidazole, cysteine sulfhydryl, and lysine amino groups, (iii) direct oxidation of amino acid side chains including arginine, lysine, proline, and threonine, (iv) addition of reactive carbonyl derivatives (ketoaldehydes, ketoamines, and deoxyosones) generated by reaction of reducing sugars and their oxidation products with lysine (13).

As PC groups occur on multiple amino acid residues on selected protein targets, its magnitude is much greater than any other modifications that occur only on a specific amino acid residue, and thus is more readily detectable (6). Because of their relative early formation and relative stability, the usage of PC as a biomarker of oxidative protein damage has some advantages in comparisons with the measurements of other oxidation products (14). The aim of this study is to assess the serum level of PC in patients with type 2 diabetes mellitus (T2DM) and to evaluate the effect of age, body

mass index (BMI), waist circumference (WC), diabetic control and disease duration on the level of PC.

Subjects and methods

Study population:

This is a case-control study done in Basrah governorate, southern Iraq, from December 2020 to December 2021, on 176 participants categorized into two main categories; 91 patients with T2DM as cases, and 85 apparently healthy individuals matched for both age and sex. Each participant in this study signed an informed written permission form. A detailed questionnaire contains demographic data include (Age, Gender, Residency, Duration of disease, Type of treatment whether dietary, oral, insulin or mixed therapy, and Family history of diabetes) were obtained from each participant. Blood pressure, body weight, height and WC were measured for each participant, and body mass index (BMI) was calculated as (kg/m²) (13).

Blood collection:

After an overnight fast for at least 8 h, five ml venous blood samples were obtained from each participant by venipuncture and divided into two parts: 2ml was dispensed in a tube contains 1.5mg/ml Ethylenediaminetetraacetic acid (K3EDTA) for the determination of Glycated hemoglobin (HbA1c%). The rest of blood was placed in a serum separator tube (SST) that contains gel and clot activator without anticoagulants and was left at room temperature (20-25) °C for 30 minutes, and centrifuged at 3000 rpm for 5 minutes to collect serum. Then a part of the serum was used to estimate the routine biochemical tests promptly. The other part of serum was frozen in tightly closed eppendorf tubes and stored at -20°C for subsequent analysis of PC.

Laboratory investigation:

Fasting blood sugar (FBS), serum creatinine, total cholesterol (TC), triglyceride (TG), high density lipoprotein-cholesterol (HDL-C) and low density lipoprotein-cholesterol (LDL-C), were measured by automated colimetric methods using kits provided by Roche diagnostics GmbH, Germany. Glycated hemoglobin was measured by ion exchange high performance liquid chromatography (HPLC) using VARIANT II TURBO HbA1c Kit-2.0 provided by Bio-Rad, USA. The estimation of PC was done by sandwich enzyme-linked immunosorbent assay (ELISA) kit, according to instruction of manufacturer (My Biosource, USA, REF MBS161516). Absorbance was measured at 450 nm and standard curve constructed from the known dilution of PC. Results were compared with standard curve and the lower detection limit was 2ng/ml. The inter-assay precision was <10%, while intra-assay precisions was <8%.

Statistical analysis:

The data of this study were analyzed by a computer program Statistical Package for Social Science (SPSS) version 23 and the results were expressed as Mean±Standard Deviation (SD) and percentage. For analysis of continuous data Independent t-test was used, while categorical data; were analyzed using Chi-square test (χ^2)

test). Bivariate Pearson correlation was used to find out the correlation coefficient (r-value) between the parameters. P-value<0.05 was considered the lowest limit for significance.

Results

The demographic, clinical and biochemical data of the patients and controls were shown in (Table 1). There were no significant differences between the patients and the controls regarding the age, gender, WC, TC, LDL and creatinine (p>0.05). More than half of the individuals were females (54.9% for patients and 55.3% for controls respectively). The mean of BMI was significantly higher in diabetes than the controls (p<0.05). Hypertension was significantly more frequent in diabetic patients than controls (p<0.05), in addition to that the majority of diabetes (76.9%) with family history of DM. There were statistically significant differences between the diabetic patients and the controls in FBS, HbA1c, TG, VLDLC (P<0.001) and HDL-C (P<0.05). Regarding the marker of protein oxidation, the mean value of serum PC was significantly higher in diabetic patients than in controls (3.93± 0.18 vs. 3.36± 0.13 ng/ml; P <0.05).

To investigate the effect of age on the serum level of PC, participants were categorized in to five age groups (Table 2). The mean value of PC levels increased with the age of participants with significant difference only in control group (P<0.05). Furthermore, the study showed that the mean value of PC levels in the diabetes patients was higher in comparison with apparently healthy controls with respect to their similar age groups, the difference was significant between the age of 36-65 years (P <0.05).

Comparison of PC among the studied groups according to BMI categories revealed that the mean of PC levels was higher but not significant in overweight and obese participants when compared to those with normal weight (P>0.05), in addition to that, the mean of PC was higher in diabetic patients than in control group, the difference was significant in those with overweight and obesity (P<0.05). Regarding WC, the study found that the mean of PC was higher in individuals with central obesity than those with normal WC with significant differences in control groups (P<0.05). Moreover, the mean of PC was higher in diabetic patients than controls across the studied groups with significant differences in females (P <0.05) (Table 3).

With respect to disease duration, the mean of PC levels was higher but not significant in patients with disease duration more than 5 years than those with a duration ≤5 years (p>0.05). Comparison of PC among the studied groups according to glycemic control found that the level of PC was higher in patients with poor glycemic control than those with good glycemic control and fair control (P<0.001) (Table 4). There was significant positive correlation of PC level with HbA1c and duration of disease in patients with known disease as well as with age, BMI and WC in all studied population (Table 5):

Table 1: Demographic, clinical and biochemical data of the participants.

Variables	Cases (n=91)	Controls (n=85)	P value*
Age (years)	50.29±10.32	49.59±10.18	NS‡
Gender	Male	41(45.1%)	38(44.7%)
	Female	50(54.9%)	47(55.3%)
BMI (kg/m ²)	31.81±5.57	30.19±4.89	<0.05‡
Waist circumference (cm)	103.59±13.30	99.92±11.64	NS‡
Hypertension (n, %)	49(53.8%)	25(29.4%)	<0.05*
Family medical history of DM (n, %)	70 (76.9%)	47 (55.3%)	<0.05*
Duration of disease (years)	----	6.80±4.93	----
Fasting blood sugar (mg/dL)	210.51±76.13	89.45±11.20	<0.001‡
HbA1c (%)	9.07±2.21	5.13±0.46	<0.001‡
Serum total cholesterol (mg/dL)	175.46±40.67	173.31±38.17	NS‡
Triglyceride (mg/dL)	168.80±90.93	119.71±44.50	<0.001‡
HDL-C (mg/dL)	44.20±9.80	49.02±9.43	<0.05‡
LDL-C (mg/dL)	120.70±36.37	118.02±35.70	NS‡
VLDL-C (mg/dL)	33.75±18.09	24.06±8.90	<0.001‡
Creatinine (mg/dL)	0.73±0.19	0.77±0.19	NS‡
PC (ng/ml)	3.48±0.27	3.36±0.13	<0.05‡

Data were represented as mean ± SD or percent
 * P Level of significance between cases and controls
 ‡ Student t-test
 * Chi-square test

Table 2: Distribution of PC of the study population according to age groups

Age (Years)	PC (Mean±SD) (ng/ml)		P value*
	Cases n=91	Controls n=85	
26-35 year	3.82±0.25#	3.76±0.15##	NS
36-45 year	3.89±0.15#	3.77±0.12##	<0.05
46-55 year	3.94±0.17#	3.86±0.11##	<0.05
56-65 year	3.97±0.17#	3.87±0.11##	<0.05
≥66 year	4.04±0.24#	3.93±0.16##	NS

Data were represented as mean ± SD
 * Level of significance between cases and controls
 # Level of significance between age categories
 # P> 0.05
 ## P< 0.05
 Student t-test

Table 3: Distribution of PC of the study population according to BMI and WC

BMI (Kg/m2)	PC (Mean±SD)(ng/ml)		P value*
	Cases n=91	Controls n=85	
Normal weight 18.5-24.9	3.85±0.12 #	3.79±0.17 #	NS
Over weight 25-29.9	3.93±0.18 #	3.80±0.14 #	<0.05
Obese ≥30	3.95±0.19 #	3.88±0.09 #	<0.05

Waist circumference (cm)		PC (Mean±SD)(ng/ml)		P value*
		Cases n=91	Controls n=85	
Male	≤102	3.87±0.18£	3.79±0.14££	NS
	>102	3.90±0.14£	3.88±0.11££	NS
Female	≤88	3.96±0.18£	3.73±0.16££	<0.05
	>88	4.01±0.20£	3.86±0.11££	<0.05

Data were represented as mean ± SD

* Level of significance between cases and controls

Level of significance between normal weight, overweight and obese

P> 0.05

£ Level of significance between normal waist and central obesity

£ P> 0.05

££P<0.05

Student t-test

Table 4: Distribution of PC according to duration of DM and glycaemic control

Parameter		PC (Mean±SD) (ng/ml)	P value*
Duration of DM	≤5 years (n=46)	3.41±0.28	<0.05
	> 5 years (n=45)	3.55±0.24	
HbA1c%	Good control <7% (n=14)	3.30±0.19	<0.001
	Fair control 7-8% (n=24)	3.32±0.26	
	Poor control >8% (n=53)	3.58±0.23	

Data were represented as mean ± SD

* Level of significance

P<0.05 statistically significant

P<0.001 highly significant

Student t-test

Table 5: Correlation of the study variables with PC levels in the study population

Variables		PC (ng/ml)
Age (years)	Correlation Coefficient	0.283**
	P-value	0.001
BMI (Kg/m2)	Correlation Coefficient	0.196**
	P-value	0.009
Waist Circumference(cm)	Correlation Coefficient	0.150*
	P-value	0.046
Duration of DM	Correlation Coefficient	0.213*
	P-value	0.043
HbA1c%	Correlation Coefficient	0.465 **
	P-value	0.001

** Correlation is significant at the 0.01 level (2-tailed)

* Correlation is significant at the 0.05 level (2-tailed)

Discussion

Diabetes mellitus type 2 is the most common type of diabetes, which is a multifactorial chronic metabolic disorder with a rising global prevalence (14). It has been stated that, PC groups are the most common and reliable biomarker of oxidative/nitrosative stress (15). The role of protein oxidation in diabetes has received a lot of attention over the last years (16). The results of present study showed that the mean value of PC levels was significantly higher in diabetic patients as compared with controls (P <0.05). Similar finding results were reported by several other studies (17, 18, 19), while Odetti p et al. (20) reported no significant difference in plasma PC levels between diabetic and non-diabetic individuals. Increased oxidative stress is the most likely cause of protein oxidation in diabetic patients (21). Several studies which support the presence of accelerated oxidative stress in DM reported that there was an increased level of lipoperoxidation markers as well as an excess of antioxidant consumption (22). Furthermore, glycation, a nonenzymatic reaction, that is highly activated by chronic hyperglycaemia, catalyzes the release of free radicals during the formation of early and late glycation products, which contributes to the enhancement of oxidative stress (23). Increased ROS levels can interact with proteins, resulting in oxidative protein modifications (24). The current study revealed that the mean value of PC levels increased with age of participants with significant difference in control group. In addition to that, there was significant positive association between the level of PC and age of the study population. These finding were in agreement with the results of several other studies (17, 25, 26, 27). However, Odetti p et al. (20) found no correlation between age and PC in both diabetic patients and controls. Aging causes an oxidative and nitrosative redox imbalance in plasma, and the reactive products of oxidative and nitrosative damage tend to accumulate during the aging process (28). Disruption of redox regulation is likely to contribute to the significant rise in oxidized protein levels with age and the development of disease (29). In this study a significant positive correlation was reported between the level of serum PC and BMI (r=0.196, p=0.009). These findings were in agreement with the results of Bollineni RC et al (30). Furthermore, there was significant positive correlation between PC level and WC of the study population. These findings were consistent with the results of Caimi G et al (31). The elevation of PC could be due to several causes; the first of which is that, despite the fact that the mitochondrion is the primary source of ROS and the major regulatory node for ROS synthesis, adipocytes contain a variety of enzyme systems that produce ROS (32). Secondly: individuals with overweight and obesity with metabolic syndrome have lower activities of superoxide dismutase (SOD) and glutathione peroxidase (GPX) (33). Goyal R et al have reported that there was suppression of GPX activity in diabetic patients compared to non-diabetic control subjects, with the magnitude of the suppression being greater in the presence of obesity (34). Thirdly: presence of high percentage of unsaturated fatty acid in adipose tissue which are a significant target of oxidation by hydroxyl radical (.OH-)(35). Peroxidation of poly unsaturated fatty acid (PUFAs) result in release of lipid aldehydes (36) which are highly diffusible electrophilic and prone to nucleophilic attack by the side chain of amino acids: histidine, cysteine and lysine residue of protein resulting in protein carbonylation (37). The present study showed that there was significant positive correlation between the level of PC and the

duration of DM ($r=0.213$, $p=0.043$). These findings were in accordance with the results of other studies (17, 38). oxidative stress may be increased with chronicity of DM and provide a strong evidence of the involvement of it in progression of the disease and development of diabetic complication (17). In the present study a positive significant correlation was found between the level of PC and glycaemic control of the patients with DM. These findings are going with the results of several other studies (17, 20, 27, 39). Patients with poor glycaemic controls have a higher level of lipids, which are a largely peroxidizable substrate, and more activation of glycation cascade, which produces an excess of free radicals, resulting in an increase formation of carbonyl groups (20).

Conclusion

The main finding of the current study was that the serum concentration PC was significantly higher in patients with T2DM than in apparently healthy controls. The results demonstrate that there was an increase in the oxidation of protein in diabetic patients in terms of an elevation in content of PC which might play an active role in progression of disease. The significant positive correlation of PC levels observed in the present study together with age, glycaemic control and the duration of DM may provide an evidence of the involvement of oxidative stress and protein oxidation in the development of DM and its complication as well as, suggest that the carbonyl content of protein may be useful in evaluating the disease progression and illustrating the mechanism of disease pathogenesis. There was a significant positive association of PC levels with WC suggest that individual with central obesity are more susceptible to protein oxidation even if BMI was normal.

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Conflict of Interest

No conflict of interest

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