Advances in Biological Research 8 (1): 18-22, 2014
ISSN 1992-006

DOI: 10.5829/idosi.abr.2014.8.1.8151

The Relationship between Ischemia Modified Albumin and Lipids in Type 2 Egyptian Diabetic Patients

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Abstract: The most important reason for risk increase in diabetic patients is endothelial dysfunction and subclinical low grade systemic inflammation. Ischemia modified albumin (IMA) is produced as a result of serum albumin flowing through ischemic tissues and is a marker of oxidative stress and ischemia, as serum level of modified albumin rise in many diseases accompanied by ischemia. In this study we evaluated the relationship between serum IMA and lipid profile in type 2 Egyptian diabetic patients. Forty subjects participated in this study; 20 of them were type 2 diabetic patients with normal lipid profile; 20 patients were type 2 diabetic patients with dyslipidemia; and 10 subjects as a control group. The study revealed a significant positive correlation of serum IMA to glycosylated hemoglobin of type 2 diabetic patients without dyslipidemia and a non significant correlation of serum IMA to all lipids of the patients of the same group. The study also revealed a significant positive correlation of serum IMA to serum triglycerides, total cholesterol, low density lipoprotein cholesterol, very low density cholesterol, glycosylated hemoglobin and high density lipoprotein of type 2 diabetic patients with dyslipidemia. The present study indicates that measuring serum IMA in diabetic patients with dyslipidemia would provide an index of ischemia due to structural modification of circulating albumin in serum. This will aid better prognosis and management of diabetes mellitus.

Key words: Dyslipidemia · Ischemia · Oxidative Stress

INTRODUCTION

Macro vascular diseases are the most common frequent complications of type 2 diabetes and this process starts before the diagnosis of onset diabetes [1]. The most important reason for risk increase in diabetic patients is endothelial dysfunction and subclinical low grade systemic inflammation [2].

The information obtained as a result of studies showed that type 2 diabetes and atherosclerosis share common pathogenic mechanisms [1]. Coexistence of insulin resistance, vascular inflammation and high blood pressure risk factors, causes endothelial dysfunction and damage and this forms the first step of atherosclerosis [3].

The development of diabetic complications such as cardiovascular complications and nephropathy is responsible for significant proportion of the increased death rates in patients with diabetes [4]. The mechanism by which diabetes leads to those complications is complex and not yet fully understood, but involves the direct toxic effects of high glucose levels, along with the impact of elevated blood pressure, abnormal lipid levels, hypoxia and ischemia [5].

Lots of markers such as high sensitivity C-reactive protein (hsCRP), micro-albuminuria and hyperhomocysteinemia which clinically show the start of endothelial dysfunction, and it's intensity and extensity and also are powerful and predicting factors for macro vascular diseases that may develop, have been determined [3].

Ischemia modified albumin (IMA), also called cobalt binding albumin, is produced as a result of serum albumin flowing through ischemic tissues and is a marker of oxidative stress and ischemia, as serum levels of modified

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albumin rise in many diseases accompanied by ischemia [6]. Emerging investigations suggest that in both cases, diabetic and hypercholesterolemic patients, IMA levels are higher than in healthy subjects and that the albumin molecule in the plasma of diabetic patients is modified in the chronic hypoxic conditions provoked mainly by hyperglycemia and oxidative stress in diabetes [7].

During ischemia, the generation of reactive oxygen species (ROS) influences the metal binding capacity of albumin for transition metals [7]. Ischemia modified albumin has shown to be a rapidly rising and sensitive biochemical marker especially for the diagnosis of myocardial ischemia [8].

The aim of this work was to assess the serum levels of ischemia modified albumin in type 2 Egyptian diabetic patients and evaluate its relationship to the all parameters of lipid profile in those patients.

MATERIALS AND METHODS

Forty subjects were chosen from outpatient clinics of Research Institute of Ophthalmology to participate in this study; 20 of them were type 2 diabetic patients with normal lipid profile; 20 patients were type 2 diabetic patients with dyslipidemia; and 10 apparently healthy subjects as a control group. A written consent was obtained from every patient in the study and approval of the ethical committee is also obtained. Subjects with hypertension, gout, renal or hepatic diseases were contraindicated.

Four ml of fasting (12-16 hours) venous blood samples were drawn from each subject participating in the study. 1.5 ml of blood was added into tube containing EDTA for determination of HbA_1c by cation exchange resin [9]. The rest of blood (3.5 ml) was left to clot and the serum was separated by centrifugation at 3000 xg for 5 minutes and high density lipoprotein (HDL) was determined immediately using phosphotungestic and magnesium ions for precipitation of all lipoproteins except the HDL fraction which was present in the supernatant and measured by Hitachi 736 auto analyzer.

The rest of the serum was stored at -20°C for determination of total cholesterol, triglyceride and IMA. The determination of total cholesterol and triglyceride was carried out on Hitachi auto analyzer 736 using colorimetric techniques. Low density lipoprotein (LDL) was calculated according to Friedwald formula [10].

Serum IMA was determined manually using a spectrophotometric CO (II)-albumin biding assay described by Bar-Or *et al*. [11]. This method consists of adding an excess of a known amount of exogenous CO^2 to serum sample and measuring the unbound Co^2 calorimetrically using dithiothreitiol (DTT). The results are given in absorbance units (ABSU).

Statistical software package (SPSS, version 15, Chicago, USA) for data analysis were used. While comparing between two independent mean groups for parametric data, the Students *t*-test was used. Mann-Whitney test was used when comparing between two independent mean groups for nonparametric data. To find the relation between two continuous variables, Pearson's correlation test was used. A P value <5 was considered significant.

RESULTS

Table 1 shows the clinical features of all subjects participating in the study.

Tables 2 and 3 show the laboratory findings of all the subjects participating in the study.

Table 4 shows the correlation of the serum levels of IMA to other parameters of group (A). The table revealed that there is no significant correlation of serum IMA to age, sex, all lipid profile of group (A) patients, but there is

Table 1: The clinical features of different studied groups

	Groups		
Parameters	Group (A)	Group(B)	Group(C)
Age (years) (mean ± S.D)	52± 4.0	53 ± 6.0	55 ± 3.0
Sex			
Female	12	11	5
Male	8	9	5
Duration of DM(years) (mean ± S.D)	10 ± 3.0	11± 2.6	-

Group A: Type 2 DM without dyslipidemia. Group B: Type 2 DM with dyslipidemia.

Group C: Control group.

Table 2: Different laboratory parameters of Group (A) and Group (C) (mean ± S.D)

	Groups		
Parameters	Group A	Group C	P-value
HbA_1c (%)	7.8 ± 1.9	4.2 ± 1.6	< 0.05
Serum triglyceride (mg/dl)	145± 5.2	140 ± 12.1	> 0.05
Serum total Cholesterol (mg/dl)	148 ± 12.3	150 ± 19.0	> 0.05
Serum VLDL (mg/dl)	31± 1.7	29 ± 2.6	> 0.05
Serum LDL (mg/dl)	90 ± 9.8	89 ± 1.0	> 0.05
Serum HDL (mg/dl)	49± 6.3	55 ± 4.0	> 0.05
Serum IMA(ABSU)	0.513±0.215	0.392 ± 0.10	< 0.05

P< 0.05: significant. P>0.05: Non significant.

Table 3: Different laboratory parameters among group (B) and group (C) (mean ± S.D)

	Groups		
Parameters	Group (B)	Group (C)	P-value
HbA_1c (%)	8.1 ±1.2	4.2 ± 1.6	< 0.001
Serum triglyceride (mg/dl)	253 ± 18	140 ±12.1	< 0.001
Serum total Cholesterol(mg/dl)	262 ± 19.1	150 ± 19	< 0.001
Serum VLDL(mg/dl)	46 ± 5.1	29± 2.6	< 0.05
Serum LDL (mg/dl)	159 ±22.3	89 ± 7.4	< 0.001
Serum HDL (mg/dl)	29 ± 3.9	55± 4.5	< 0.001
Serum IMA (ABSU)	0.654 ± 0.092	0.392±0.101	< 0.001

P<0.05: Significant. P<0.001: Highly significant.

a significant positive correlation of it to duration of diabetes and glycosylated hemoglobin levels of this group.

Table 5 shows the correlation of serum IMA to other parameters of group (B). The table revealed that there is a significant positive correlation of serum IMA to age, duration of diabetes, serum triglycerides, cholesterol, very low density lipoprotein (VLDL) of group (B), glycosylated hemoglobin levels, serum LDL-cholesterol and HDL-cholesterol and no significant correlation of IMA to sex of the same group.

Table 4: Correlation of serum IMA to other parameters of group (A)

	Serum IMA	
	r	P
Age	0.26	> 0.05
Sex	0.32	> 0.05
Duration of disease	0.58	<0,05
HbA_1c	0.59	<0,05
Serum triglyceride	0.26	> 0.05
Serum total cholesterol	0.31	> 0.05
Serum VLDL	0.19	> 0.05
Serum LDL	0.32	> 0.05
Serum HDL	0.29	> 0.05

Table 5: Correlation of serum IMA to other parameters of group (B)

	Serum IMA	
	r	P
Age	0.52	<0.05
Sex	0.28	> 0.05
Duration of disease	0.62	<0,05
HbA_1c	0.81	<0.001
Serum triglyceride	0.68	<0.05
Serum Cholesterol	0.69	<0.05
Serum VLDL	0.58	<0.05
Serum LDL	0.82	<0.001
Serum HDL	0.80	<0.001

DISCUSSION

Diabetes mellitus is characterized by chronic hyperglycemia and this condition is now recognized as a major factor in the pathogenesis of diabetes complications. Hyperglycemia increases oxidative stress through several pathways [12]. An important way appears to be the overproduction of the superoxide anion by the mitochondrial electron transport chain [13].

Really, diabetes is commonly accompanied by extended production of free radicals and /or impaired antioxidant defense mechanisms, indicating a central

contribution to reactive oxygen species (ROS) in the onset progression and pathological complications of diabetes [13]. Furthermore, overproduction of free radicals may produce a chemical modification of human serum albumin (HSA), resulting in an increased IMA, which in turn, seems to play a role as an oxidative stress biomarker [7].

There have been several studies on IMA and type 2 diabetic patients that suggest that IMA molecule in the plasma of diabetic patients is modified by the chronic hypoxic conditions provoked by hyperglycemia and oxidative stress (14). Beside, oxidative stress may be also a determinant of increased C-reactive protein (CRP) levels and promote proatherosclerotic inflammatory at coronary heart diseases and acute myocardial infarction [15].

In this study we evaluated the relationship between serum IMA and lipid profile in type 2 Egyptian diabetic patients. The study revealed a significant positive correlation of serum IMA to glycosylated hemoglobin of type 2 diabetic patients without dyslipidemia and a non significant correlation of serum IMA to all lipids of the patients of the same group. The study revealed also a significant positive correlation of serum IMA to serum triglycerides, total cholesterol, LDL, VLDL, glycosylated hemoglobin, LDL and HDL of type 2 diabetic patients with dyslipidemia.

Our results agree with Ukinc *et al*. [16] who reported that plasma IMA increases significantly in type 2 diabetic patients compared to healthy controls and that IMA increases in type 2 diabetic patients, either with or without cardiovascular diseases. Also agree with Kaefer *et al.,* [17], revealed that the levels of triglycerides and IMA are higher in type 2 diabetic patients with a significant correlation IMA to triglycerides in those patients.

Valle Gottlieb *et al.,* [18] detected higher levels of IMA in patients with metabolic syndrome. Ma *et al.,* [6] stated that total cholesterol, LDL and IMA levels are higher in type 2 diabetic patients with peripheral arterial diseases than those without peripheral arterial diseases.

Our results revealed, higher level of serum IMA in diabetic patients which confirms that it may be of non-cardiac origin.

CONCLUSION

The present study indicates that measuring serum IMA in diabetic patients with dyslipidemia would provide an index of ischemia due to structural modification of circulating albumin in serum. This will aid better prognosis and management of diabetes mellitus.

REFERENCES

1. Hu, F.B., M.J. Stampfer, S.M. Hoffiner, C.G. Solomon, W.C. Willett and J.E. Manson, 2002. Elevated risk of cardiovascular disease prior to clinical diagnosis of type 2 diabetes. Diabetes Care, 25: 1129-1134.
2. De Jager, J., J.M. Dekker, A. Kooy, P.J. Kostense, G. Nijpels, R.J. Heine, L.M. Houter and C.D.A. Stehouwer, 2006. Endothelial dysfunction and low-grade inflammation explain much of the excess cardiovascular mortality in individuals with type 2 diabetes: The Hoorn Study. Arteriosclerosis Thrombosis Vascular Biology, 26: 1086-1093.
3. Rafai, N. and P.M. Ridker, 2001. High-Sensitivity C- reactive protein: A Novel and Promising Marker of Coronary Heart Disease. Clinical Chemistry, 41: 403-411.
4. American Diabetes Association, 2009. Standards of medical care in diabetes. Diabetes Care, 32: S13-S61.
5. Lebeche, D., A.J. Danidoff and R.J. Hajjar, 2008. Interplay between impaired calcium regulation and insulin signaling abnormalities in diabetic cardiomyopathy. Nat Clin Pract Cardiovas Med., 5: 715-724.
6. Ma, S.G., C.L. Wei, B. Hong and W.N. Yu, 2011. Ischemia modified albumin in type 2 diabetic patients with and without peripheral arterial disease. Clinics (Sao Paulo), 66(10): 1677-1680.
7. Durate, M.M., J.B. Rocha, R.N. Moresco, T. Duarte, I.B. Da Crug, V.L. Lara and M.R. Schetinger, 2009. Association between ischemia modified albumin, lipids and inflammation biomarkers in patients with hypercholesterolemia. Clin. Biochem., 42: 666-671.
8. Sinha, M.K., D. Ray, D.C. Goza, P. Collinson and J. Kaski, 2004. Role of ischemia modified albumin, a new biomarker of myocardial ischemia, in the early diagnosis of acute coronary syndrome. Emerg Med J., 21: 29-34.
9. Maquart, F., P. Giller and J. Bernard, 1980. Method for specifically measuring of hemoglobin A_1C with disposable commercial ion exchange column. Clin Chem Acta, 108: 329.
10. Friedwald, W.T., R.I. Levy and D.S. Frederickson, 1972. Estimation of the concentration of low density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. Clin Chem., 18: 499.
11. Bar-Or, D., E. Lau and J. Winkler, 2000. A novel assay for cobalt albumin binding and its potential as a marker of myocardial ischemia-a preliminary report. J. Emerg Med., 19: 311-315.

12. Arenscon, D., 2008. Hyperglycemia and pathology of diabetes complications. Adv Cardiol., 45: 1-16.
13. Rolo, A.P. and C.M. Plamia, 2006. Diabetes and mitochondrial function: role of hyperglycemia and oxidative stress. Toxicol Appl Pharmacol., 212: 167-178.
14. Dahiya, K., K. Aggrwal and K. Seths, 2010. Type 2 diabetes mellitus without vascular complications and ischemia modified albumin. Clin Lab., 56: 187-190.
15. Kamezaki, F., K. Yamashika, T. Kubara, Y. Suzuki, S. Tanaka, R. Rkouzuma, M. Okazaki, H. Tasaki and Y. Otuji, 2008. Derivatives of reactive oxygen metabolities correlates with high sensitivity c-reactive protein. J. Atheroscl Thrombo, 15: 206-212.
16. Ukinc, K., S. Eminagaoglu, H.O. Ersoz, C. Erem, C. Karahan, A.B. Hacihasanoglu and M. Kocak, 2009. A novel indicator of widespread endothelial damage and ischemia in diabetic patients. Endoc, 36: 425-432.
17. Kaefer, M., S.J. Piva, J.A. De Carvalho, D.B. Da Silva, A.M. Becker, A.C. Coelho, M.M. Duarte and R.N. Moresco, 2010. Association between ischemia modified albumin, inflammation and hyperglycemia in type 2 diabetes mellitus. Clinic Bioch., 43: 450-454.
18. Valle Gottlieb, M.G., I.B.M. da Cruz, M.M.F. Duarte, R.N. Moresco, M. Wiehe, C.H.A. Schwanke and L.C. Bodanese, 2010. Associations among metabolic syndrome, ischemia, inflammatory, oxidative and lipids biomarkers. J. Clin Endoc Metab, 95(2): 586-591.