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Role of serum allograft inflammatory factor-1 (AIF-1) in Egyptian type 2 diabetic patients

ABSTRACT

Background. Diabetes mellitus (DM) is a powerful and independent risk factor for cardiovascular disease. The atherosclerosis process in diabetes is indistinguishable from that of the nondiabetic population, but it begins earlier and is often more extensive and more severe. AIF-1 promotes chemotaxis, spreading and migration of macrophages and vascular smooth muscle cells (VSMCs) which suggest a role of AIF-1 in the atherosclerotic plaque formation. Thus, this study determines the role of AIF-1 in the Egyptian type 2 diabetic patients.

Results. The level of AIF-1 was significantly higher in the type 2 diabetic group when compared to the control group ($p = 0.000$). In type 2 diabetic patients group, there was a significant positive correlation between CIMT and AIF-1 ($r = 0.468$, $p = 0.000$). In addition to the positive correlation between CIMT and AIF-1, CIMT in regression model analysis was significantly positive contributing to the outcome variable (AIF-1) ($p < 0.05$), denoting the possible role of elevated serum AIF-1 level in atherosclerotic process with further studies on larger scale needed. (Clin Diabetol 2019; 8, 6: 271–276)

Key words: allograft inflammatory factor-1 (AIF-1), diabetes mellitus (DM), atherosclerosis, inflammation

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Introduction

Diabetes mellitus (DM) is a powerful and independent risk factor for cardiovascular disease which remains to be the major cause of death in type 2 diabetic patients [1, 2]. Low grade inflammation and activation of the immune system play a role in the common pathogenesis of both insulin resistance and endothelial dysfunction and subsequently the development of type 2 diabetes and atherosclerosis [2–4].

Subclinical vascular disease in type 2 diabetic patients was proved to be assessed by carotid intima media thickness (CIMT) [5–7] and the presence of plaques (calcified or not) [8] specially in patients with normal renal function by many researches. The dyslipidemic lipid profile (increased LDL and total cholesterol) usually associated with type 2 diabetes and adds more impact to the process of atherosclerosis process development in these patients [9–11].

AIF-1 (ionized calcium-binding adaptor molecule-1 (Iba1) is a 17 kDa conserved structural cytoplasmic, calcium-binding, inflammation-responsive scaffold protein [12, 13]. It is one of the EF hand proteins' family [14, 15].

AIF-1 was originally identified in rat cardiac allografts with chronic rejection. In humans, AIF-1 is involved in many pathological processes where it has been found to be expressed by activated T cells, vascular endothelial cells and blood vessel smooth muscle cells after a balloon injury ie: vascular trauma inducible cytokine [16, 17]. Thus AIF-1 may play a role in endothelial dysfunction, macrophages and VSMCs activation, migration, reorganization and tissue remodelling as a response to endothelial damage [3, 16, 18].

The in vivo expression of AIF-1 in human VSMCs in atherosclerotic plaques supported the in vitro studies

that have shown the role of AIF-1 in atherosclerotic plaque formation through promotion of chemotaxis, cell attachment, spreading and migration of macrophages and VSMCs [19].

This work aimed was to study serum AIF-1 in type 2 diabetic patients.

Materials and methods

One hundred subjects were included in the study after approval of the ethical committee of Medical Research Institute and informed consents was taken. The included subjects were divided into two groups; Forty apparently healthy volunteers as a control group (group 1), sixty type 2 diabetic patients (group 2). Subjects with obesity, urinary tract infections UTI and renal impairment or increased urinary proteins were excluded. The source of finance was supplied by authors.

To all studied subjects; thorough history taking was done including history of cardiovascular diseases, smoking habits, drinking habits, medications such as anti-diabetic, anti-hypertensive and anti-hyperlipemic drugs. Complete physical examination with special stress on BMI calculation, cardiovascular examination and measuring the carotid intima media thickness (CIMT) and presence of plaques (calcified or not) using a β mode ultrasound.

The following laboratory investigations were done to all participating subjects: quantitation of urinary albumin, urinary proteins, creatinine, calculation of urinary albumin and protein to creatinine ratio, estimation of serum fasting and postprandial glucose, urea, creatinine, calculation of estimated glomerular filtration rate (eGFR) [20], urine cultures and determination of hemoglobin A_{1c} [21]. In addition to estimation of serum lipid profile (total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), triglycerides with calculation of low density lipoprotein cholesterol (LDL-C). Also, serum C-reactive protein (CRP) [22] was estimated and serum AIF-1 by ELISA technique (Biocompare, South San Francisco, USA, catalog no. SEC288Hu) [23].

Data analysis was performed by using SPSS for Windows, version 20 (Statistical Package of social sciences, Chicago, USA) [24]. Normality of the quantitative variables was determined with the use of the Kolmogrov-Smirnov test. Where normally distributed data were presented as mean ± standard deviation and unpaired Student's t-test was used to compare a variable across two subgroups in addition to Pearson's correlation test was used to investigate the relationship between different quantitative variables. The non-normal distributed data were presented as median (minimum–maximum). Non parametric Mann-Whitney test was used to compare the variables across two groups. Stepwise multiple regression analysis was conducted to test the variables contributing in the AIF-1 marker.

Table 1. Statistical significance of clinical data of the studied groups

Item	Group 1 (n = 40)	Group 2 (n = 60)
Age (years)		
Mean	46.15	56.87
SD	± 8.41	± 8.00
p	0.000**	
Sex		
Males	19 (47.50%)	25 (41.79%)
Females	21 (52.50%)	35 (58.30%)
p	0,794	
Weight [kg]		
Mean	68.15	74.62
SD	± 4.38	± 5.45
p	0.000**	
Height [m]		
Mean	1.71	1.75
SD	± 0.05	± 0.04
p	0.001*	
BMI [kg/m^2]		
Mean	23.36	24.38
SD	± 1.39	± 0.75
p	0.000**	
Hypertension		
Yes	0 (0%)	19 (31.7%)
No	20 (100%)	41 (68.3)
p	0.004*	
CIMT [mm]		
Mean	0.285	1.235
SD	± 0.12	± 0.32
p	0.000**	
Plaques and calcification		
Yes	0 (0%)	15 (25%)
No	20 (100%)	45 (75%)
p	0.013*	

χ^2, Chi square test, Mann-Whitney test; p — p value for comparing between the two groups; *statistically significant at $p \leq 0.05$

Results

Blood pressure, CIMT and presence of plaques and calcification in type 2 diabetic patients was significantly increased comparing to controls ($p = 0.004$, $p = 0.000$, $p = 0.013$) respectively (Table 1).

Glycemic control measures showed significant increase in fasting, post prandial blood glucose and HbA_{1c} in type 2 diabetic patients than controls ($p = 0.000$, $p = 0.000$, $p = 0.000$) respectively (Table 2).

Table 2. Statistical significance of laboratory data in the studied groups

Item	Group 1 (n = 40)	Group 2 (n = 60)
Total cholesterol [mg/dL]		
Mean	152.85	189.25
SD	± 11.27	± 51.53
p	0.003*	
HDL-C [mg/dL]		
Mean	51.05	37.55
SD	± 6.70	± 9.71
p	0.000**	
TG [mg/dL]		
Mean	80.05	128.8
SD	± 25.81	± 47.29
p	0.000**	
LDL-C [mg/dL]		
Mean	85.79	125.94
SD	± 10.38	± 43.83
p	0.000**	
CRP [mg/L]		
Median	3.00	10.00
Min–Max	(2.00–4.50)	(2.00–650.00)
p	0.000**	
Fasting serum glucose [mg/dL]		
Mean	87.35	203.53
SD	± 9.4	± 72.13
p	0.000**	
Postprandial serum glucose [mg/dL]		
Mean	108.15	190.025
SD	± 15.39	± 76.33
p	0.000**	
HbA_{1c} (%)		
Mean	4.63	7.93
SD	± 0.37	± 2.49
p	0.000**	
Serum urea [mg/dL]		
Mean	27.6	29.47
SD	± 6.83	± 7.32
p	0.336	
Serum creatinine [mg/dL]		
Mean	0.78	0.78
SD	± 0.14	± 0.11
p	0.957	
eGFR [ml/min]		
Median	103.5	98.6
Min–Max	(91.70–134.7)	(90.10–157.60)
p	0.065	
Urine protein/creatinine ratio [mg/g]		
Mean	100.5	110.93
SD	± 23.74	± 25.17
p	0.108	
Urine albumin/creatinine ratio [mg/g]		
Mean	20.25	22.67
SD	± 4.13	± 4.6
p	0.04*	
Serum AIF1 [pg/mL]		
Median	90.00	1.235
Min–Max	(20.00–500.00)	± 0.32
p	0.000**	

χ^2, Chi square test, Mann-Whitney test; p — p value for comparing between the two groups; *statistically significant at $p \leq 0.05$

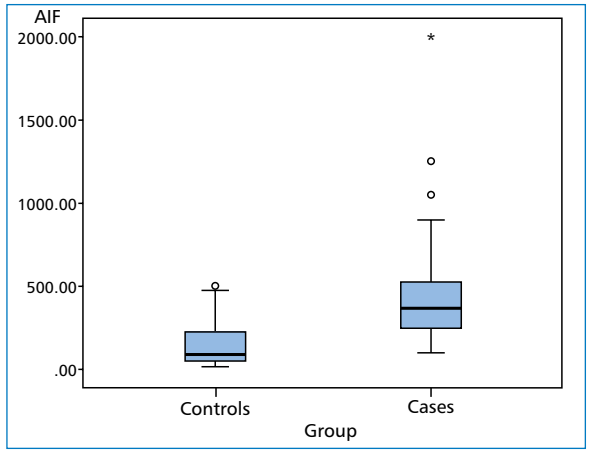


Figure 1. Box plot illustrates the median and range of serum AIF-1 readings [pg/mL] among the studied groups. Box plot represents the interquartile range 25^{th}–75^{th} percentile. The wiskers below and above represents 10–90 percentile. The line across each box represents the median value. Significant increase in AIF-1 in the group of diabetic atherosclerotic patients when compared to the control group (p = 0.000)

Table 3. Statistical significant correlations between the studied parameters in the type2 diabetic group (group 2)

Item	Correlation coefficient (r)	Significance (p-value)
AIF-1 and creatinine	0.338	0.008
AIF-1 and CIMT	0.468	0.000
BMI and HbA_{1c}	0.343	0.007
BMI and fasting serum glucose	0.376	0.003
HbA_{1c} and CIMT	0.257	0.047

Lipid profile and CRP levels showed significant increase in cholesterol, triglycerides, LDL and CRP in type 2 diabetic patients than control (p = 0.003, p = 0.000, p = 0.000, p = 0.000) respectively (Table 2).

Renal functions tests showed only a significant increase in albumin creatinine ratio in the type 2 diabetic patients than controls (p = 0.04) (Table 2).

AIF-1 showed significant increase in type 2 diabetic patients than control group (p = 0.000) (Table 2, Figure 1).

Pearson's correlation test showed positive significant correlations only between AIF-1 and creatinine level in addition to CIMT (r = 0.3380, r = 0.468) (p = 0.008, p = 0.000) respectively in type 2 diabetic patients (Table 3).

Multiple regression analysis showed the overall model was statistically significant (F = 3.309,

p = 0.001). Where, CIMT was significantly positive contributing to the outcome variable (AIF-1) ($p < 0.05$), while other predictors were not significantly contributing to the outcome ($p > 0.05$) (Table 4).

Discussion

Diabetes when accompanied by other major cardiovascular risk factors, such as hypertension, dyslipidemia, and smoking, show marked increase in the incidence of atherosclerosis. The atherosclerosis process begins earlier and more aggressive in diabetes and indistinguishable from nondiabetic population [2]. The atherogenic lipid profile characterized by elevated triglycerides and low levels of high-density lipoprotein (HDL) cholesterol are major modifiable risk factors contributing to progressive cardiovascular risk generally in addition to both type 2 diabetes and metabolic syndrome [25, 26].

Atherosclerosis is known to be an inflammatory disease as an overall process where inflammatory cells (pro-inflammatory cytokines secreting cells) such as neutrophils, lymphocytes and monocytes participate in the overall process of atheroscelerosis [27].

AIF-1 plays a role in endothelial cell, macrophage, T-lymphocyte, and VSMC activation, proliferation and migration which are known to play a role in inflammation [3, 16, 18].

It has been shown that serum AIF-1 was increased in patients with diabetic nephropathy [23], also it is considered as a human adipokine produced mainly by macrophages within the white adipose tissue in obese patients and might participate in the regulation of adipose tissue inflammation and, in turn, insulin resistance [28]. In the present study, all the studied groups were of normal e GFR and BMI.

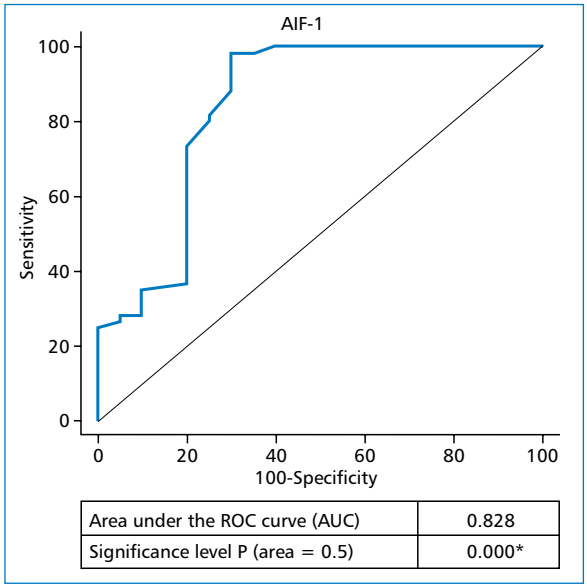
The level of AIF-1 was significantly higher in type 2 diabetic groups when compared to the control group (p = 0.000) (Figure 1). The statistical correlation in our study revealed that there was a significant positive correlation between CIMT and AIF-1 (r = 0.468, p = 0.000) in type 2 diabetic patients group, denoting the possible role of elevated serum AIF-1 level in atherosclerotic process. In addition the significant increase in the presence of plaques and calcification in the patients than controls (p = 0.013) has been seen. Although there is significant increase in dyslipidemic profile of type 2 diabetic patients than controls (cholesterol, triglycerides and LDL (p = 0.003, p = 0.000, p = 0.000) which add to the process of atherosclerosis development in these patients, there were no significant correlations between dyslipidemia and AIF-1 level in these patients thus a study on larger scale of type 2 diabetic patients is needed.

In multiple linear regression analysis, the overall model is statistically significant (F = 3.309, p = 0.001) and it is found that increased CIMT is significantly contributing to elevated serum AIF-1 level in type 2 diabetic patients ($p < 0.05$). Thus, elevated serum AIF-1 level in type 2 diabetic patients in addition to its positive significant correlation with CIMT add to the possible role of AIF1 in contribution to the process of atherosclerotic changes in type 2 diabetic patients. This was consistent with Berglund et al., 2012 [29] who stated that expression of AIF-1 mRNA in human carotid plaques

Table 4. Multiple regression analysis

Model	Regression coefficients		t	Sig.	95% confidence interval for B	
	B	S.E			Lower bound	Upper bound
(Constant)	1235.852	1068.189	1.157	0.251	–895.687	3367.39
Age	–6.52	5.094	–1.191	0.280	–16.687	3.648
BMI	–10.074	40.213	–0.251	0.803	–90.318	70.170
Hypertension	–139.901	94.727	–1.477	0.144	–328.554	49.124
Plaques and calcification	68.936	115.962	0.594	0.554	–162.462	300.334
CIMT	502.386	127.204	3.949	0.001*	248.554	756.217
Fasting blood sugar	–0.449	0.746	–0.602	0.549	–1.939	1.040
Post prandial blood sugar	0.118	0.703	0.168	0.867	–1.284	1.520
Albumin to creatinine ratio	0.467	0.897	0.134	0.890	–2.284	3.652
HbA_{1c}	–20.978	33.729	–0.622	0.536	–88.340	46.383
Cholesterol	0.421	1.264	0.333	0.740	–2.102	2.945
LDL	0.169	1.224	–1.581	0.138	–2.273	2.611
Triglycerides	–0.185	1.286	–0.144	0.886	–2.753	2.383
CRP	–0.353	0.479	–0.078	0.464	–1.640	0.603
e-GFR	–6.404	3.486	–1.837	0.071	–13.361	0.552

*Predictors are significantly contributing to the outcome variable if $p < 0.05$



Area under the ROC curve (AUC)	0.828
Significance level P (area = 0.5)	0.000*

Figure 2. ROC curve for serum AIF-1 in the studied groups at a cutoff value of 120 pg/mL. Receiver operating characteristic curve (ROC) for serum AIF-1 at cutoff value of 120 pg/mL, the area under the ROC curve denotes the diagnostic performance of the test (0.0828), significance p = 0.000*

associates with less extracellular matrix and a more pro-inflammatory plaque and plasma profile, features that may predispose to plaque rupture.

Zhao et al, 2013 [14] reported that AIF-1 is expressed by activated lipid-rich macrophages and VSMCs during the progression of atherosclerosis. In this regard, AIF-1 may be involved in the early stage of atherosclerosis and CAD. Kelemen et al, in 2005 [30] stated that increased AIF-1 expressed in activated T lymphocytes enhance activation of adjacent arterial vascular smooth muscle cells (VSMCs) and development of atherosclerosis. Expression of AIF-1 seems to be involved in vascular smooth muscle cells and macrophages migration, chemotaxis, proliferation and tissue remodeling as a response to endothelial damage which suggest a positive role of AIF-1 in the atherosclerotic plaque formation. These in vitro studies were supported by immunohistochemical analysis which has shown in vivo protein expression of AIF-1 in human smooth muscle cells in atherosclerotic plaques [19].

In the present work, by drawing receiver operating characteristic (ROC) curve of serum AIF-1 at a cutoff value of 120 pg/mL in the studied group (Figure 2), the area under the curve (AUC) for AIF-1 was 0.843, $p \leq 0.0001$. The sensitivity, specificity, positive predictive value, negative predictive value and overall accuracy of AIF-1 for detection of atherosclerosis were 98.33%, 70%, 91%, 93% and 91% respectively. Thus, the present study supported that AIF-1 can be a helpful marker for early detection of atherosclerosis and prediction of cardiovascular complications in type 2 diabetic patients.

Conclusion

In conclusion, AIF-1 was significantly higher in the type 2 diabetic patient group (group 2) when compared to the control group (group 1). In the group of type 2 diabetic patients AIF-1 showed positive correlation with CIMT denoting the possible relation between increased AIF-1 levels and subsequent vascular damage and the process of atherosclerosis in type 2 diabetes.

Recommendations: further work is needed on a larger number of type 2 diabetic patients with higher focus on the presence of vascular calcification and atherosclerosis.

Compliance with ethical standards

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study.

Conflicts of interest

ElDeeb MK, Khalil GI, Zaki MA, Mehana E, Omer S declare that they have no conflict of interest.

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