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ADIPONECTIN AND MYELOPEROXYDASE IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

Hussein Abd El Maksoud [a,*], **Yaser M. Abdel-Nabi** [a] and **Raafat R. Gindi** [b]

[a] *Biochemistry Department, Faculty of Veterinary Medicine, Benha University,* [b] *Clinical Pathology Department, Faculty of Medicine, Benha University*

[*] *Corresponding author: E-mail: Abdel-maksoud @ yahoo.com, Fax: +2013-2463074.*

A B S T R A C T

To evaluate the relationship between plasma adiponectin levels, myeloperoxidase (MPO), lipid profile and serum nitrite/nitrate in patients with acute myocardial infarction (AMI), thirty AMI patients and 10 clinically healthy subjects (control), aged 35 - >70 years, were used. The results of the present study showed the association between Adiponectin and MPO concentration, Nitrite and Nitrate levels, in addition to serum lipid profile including (total cholesterol, Triacylglycerol (TG), Low density lipoprotein – cholesterol (LDL-ch) and High density lipoprotein-cholesterol (HDL-ch) and acute phase of myocardial infarction in patients. These parameters may be regarded as predictors or risk factors for AMI and suggesting that, hyperlipidemia and vascular inflammation, and oxidative stress are primary interacting mediators in the pathogenesis of AMI.

KEY WORDS: Acute myocardial infarction, Adiponectin, Hyperlipidemia, Myeloperoxidase, Vascular inflammation

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1. I N T R O D U C T I O N

Acute myocardial infarction (AMI) is a serious medical emergency syndrome resulting in most cases from complete thrombotic occlusion of infarct related coronary artery and in a substantial proportion of patients with suspected myocardial infraction, biochemical markers are needed for clinical decision making at the time of admission, because electrocardiograph (ECG) recordings may be inconclusive [8].

The role of adipose tissue as an endocrinal organ capable of secreting a number of adipose tissue-specific or enriched hormones, known as adipokines, which is an adipose tissue-specific protein accounts for 0.01% of the total plasma proteins concentration . Increasing attention has been paid to the vascular effects of adiponectin, where adiponectin was hypothesized to play a role in AMI [18].

Myeloperoxidase (MPO) is a member of heme peroxidase superfamily, abundant in neutrophils, monocytes, and macrophages. This enzyme plays a critical role as host defenses and inflammatory tissue injury. It also played a pathophysiologic role in AMI [1].

Nitric oxide (NO) is a signaling molecule involved in the regulation of many biological processes including activities in the cardiovascular, nervous, and immune systems .It also had a role in both acute and chronic inflammation. Moreover, NO was proposed to play a role in AMI atherogenesis [14].

The aim of the present study was to assess the changes in adiponectin and MPO following AMI and to evaluate the correlation between Adiponectin, Myeloperoxidase activity, Nitric oxide metabolites (nitrite/nitrate) and Lipid

profile in patients with acute Myocardial infarction patients.

2. MATERIAL AND METHODS

2.1. *Subjects and design*

This study was performed on 30 male - patients in Emergency Center at Hospital, Faculty of Medicine Alexandria University with complaining of acute chest pain and 10- healthy subjects with normal coronary arteries served as a control healthy group after application of the inclusion and exclusion criteria for diagnosis of AMI patients according to Alpert et al. [3]. AMI was confirmed at coronary care unit (CCU) by a cardiologist guided by the world health organization (WHO) criteria. Patients were classified according to their age into four equal groups as follow:

Group I: Control healthy individuals (n=10) with ages ranged from 35-70 years.

Group II: AMI patients (n=10) with an age ranged from 30 to 50 years old.

Group III: AMI patients (n=10) with an age ranged from 51 to 70 years old.

Group IV: AMI patients (n=10) over 70 years old.

2.2. *Blood Sampling*

Blood samples (10 ml) were collected after overnight fasting together during cardiac catheter and coronary angiography for every patient as well as control healthy subjects. The samples were divided into 2 portions, the first one was drown into evacuated tubes containing EDTA as anti-coagulant ant Plasma were separated after centrifugation and processed directly for determination of Adiponectin concentration [16]. The resulting granulocyte/ erythrocyte pellets were further processed for isolation of Neutrophils to assess myeloperoxidase level [17]. The remained blood portion was drawn into tubes without anti-coagulants and allowed to clot then, after centrifugation at 3500 rpm for 3 minutes the serum was separated and used freshly for determination of nitric oxide metabolites (Nitrate/Nitrite) [11], total cholesterol [2], Triacylglycerols [13], HDL-ch, LDL-ch concentrations [5], and VLDL-ch [10].

2.3. *Statistical analysis*:

Statistical analysis was done by SAS [28].

3. RESULTS AND DISCUSSION

Millions of patients present in hospitals annually with chest pain, but only 10-15% has myocardial infarction which is the major killer in the western industrialized countries. Sensitive biochemical assays are essential for identification of novel markers associated with the extent or severity of AMI allowing better insight into the pathobiology of coronary atherosclerosis and may facilitate the development of preventive and therapeutic measures for this disease [27]. The presented data revealed that AMI is accompanied by significant decreased in the mean values of plasma adiponectin level, serum nitrite , nitrate and HDL-cholesterol with significant increase in the myeloperoxidase level, serum total cholesterol, triacylglycerol, LDL-cholesterol and VLDL-cholesterol in comparison with the control healthy subjects group.

The present study showed that plasma adiponectin level was significantly lowered in AMI patient groups when compared to the control group (table 1) which was in agreement with those recorded by Tsukinoki et al. [31] and Lim et al. [21] who reported that, the link between hypoadiponectinemia and AMI events which might be mediated by angiographically for quantified the disease severity. The recorded low adiponectin concentration in AMI patients could be attributed to adiponectin gene mutations in AMI patients. Such mutations were associated with low adiponectin concentration [24]. Moreover, the recorded decreased values of adiponectin in AMI may be related to accumulation of

adiponectin in atherosclerotic vascular walls through its binding to collagens that are abundant in the vascular intimae. Such accumulation may suppress adiponectin elimination half-life from plasma [15].

The present study showed a significant negative correlation between adiponectin level and age in AMI patients. This result could be due to a possible disturbed adipokines synthesis or secretion in old age individuals, an explanation that might support the concept of old age being a risk factor [29].

On the other hand, a significant positive correlation was observed between adiponectin and nitric oxide metabolites (nitrite/nitrate) levels which could be explained by the assumption that adiponectin increases NO production by promoting the activity of eNOS or by ameliorating the suppression of eNOS activity by ox-LDL [22].

The Myeloperoxidase levels serve as a strong and independent predictor of endothelial dysfunction in human subjects, giving a mechanistic link between oxidation, inflammation and cardiovascular disease [7].

The obtained results showed a significant increase in MPO level in AMI patient groups (group I, II and III) when compared to the control normal healthy subjects. This might be related to MPO secretion from activated leukocytes under inflammatory conditions which promote numerous pathological events [33]. In this respect, MPO has been shown to active metalloproteinase and to promote destabilization and rupture of atherosclerotic plaque surface, thus MPO could be related to the future risk of AMI events [7].

A significant negative correlation between MPO activity and nitric oxide metabolites (nitrite/nitrate) levels was observed due to its uptake by endothelial cells through transcytotic process, to accumulate within the sub-endothelial space, and to consume NO thus interfering with its athero-protective effect [6].

The obtained results revealed that, serum levels of both nitric oxide metabolites (nitrite and nitrate) were significantly lowered in AMI patient groups as compared to the control healthy ones .The degree of decrease in nitrite level was correlated with the increasing number of cardiovascular risk factors, and high level of NO metabolites was observed in both acute and chronic inflammatory conditions including atherosclerosis [32].

Reduced NO bioavailability is the hallmark of endothelial dysfunction occurring early in cardiac diseases. It has potentially anti atherosclerotic as it inhibits platelet aggregation and adherence to endothelial cells, monocyte adherence to endothelial cells, expression of monocyte chemo-attractant proteins, vascular smooth muscle proliferation, and in vivo intimae proliferative response to cardiac injury [9]. The detected decreased values of NO could be related to the hypercholesterolemia was found to be accompanied by increased superoxide production which accounts for significant proportion of NO deficit [26]. Moreover, it was reported that dyslipidemia decreases basal activity and protein expression of cGMP-dependent protein kinase, and increases activity of cGMP-phosphodiesterase. The latter effect results in interference with NO signaling pathway [4].

Also, the significantly decreased NO metabolites in AMI patients may be due to the hypertension followed AMI as stated by Taniyama [30] Who reported that, hypertensive patients showed oxidation of BH_4 which results in loss of NOS demyelization and generation of significant amounts of superoxide besides reduction of endothelial NO production. Meanwhile L-arginine, a NO precursor, acutely improves endothelial-dependent dilatation of brachial artery in hypertensive patients.

The present study showed a significant positive correlation between levels of NO metabolites and adiponectin and a

significant negative correlation between levels of NO metabolites and MPO activity. The low level of NO metabolites in the current study could be collectively due to hypoadiponectinemia, which results in decreased production of NO and the increased MPO activity which results in increased NO scavenging, and MPO-derived oxidants (e.g. HOCL, chlorinated arginine) on NOS as observed by Barbato [9].

The recorded low level HDL-ch in AMI patients (table 2) could be due to HDL has a protective effect against the inflammation followed AMI which has been attributed to its role in reverse cholesterol transport. This is beside the possible anti - inflammatory and antioxidant actions of HDL It can prevent LDL oxidation by hydrolyzing lipid peroxides, hydro-peroxides and hydrogen peroxide and Paraxonase can also maintain the capacity of HDL to induce reverse cholesterol transport [19]. In addition, HDL-associated enzyme, lecithin cholesterol acyl transferase (LCAT), can prevent the accumulation of oxidized lipids in LDL and increases lipoprotein oxidation and endothelial dysfunction [12].

The recorded high serum cholesterol level might be due to induction of thrombosis through stimulating platelet adhesion and aggregation, enhancing the procoagulant activity of endothelium, reducing the fibrinolytic activity of endothelium, contributes to the formation of atherosclerotic plaques in arteries [23]. Moreover, the hypertriacyle-glyceridemia causes an independent risk factor for AMI, since high circulating levels of TG-rich lipoproteins can inhibit the efflux of cholesterol from macrophages to apo-A1; they also directly influence endothelial function through modulating NO and endothelin-1 and may thereby inhibit the arterial reverse cholesterol transport and promote the formation of atherosclerotic lesion [25]. The present study showed a significant correlation between lipid profile and Adiponectin and MPO. In addition, a significant correlation was found between lipid profile and NO metabolites as mentioned before [20].

Table 1 Mean (±S.E.) of plasma adiponectin, myeloperoxidase, and serum nitrite (μmol/l) and nitrate in patients with acute muocardial infarction and control healthy subjects

Group	Adiponectin (ug/ml)	MPO activity (U/mg protein)	Serum Nitrite (μmol/L)	Serum Nitrate (μmol/L)
Group I: Healthy control	64.09± 0.80	2.35± 0.71	6.70±0.33	10.78±1.11
Group II: 30-50 years	27.31±0.96*	5.99±0.89*	4.25±0.29	6.84±0.97
Group III: 51-70 years	25.81±0.82*	9.13±0.77**	3.38±0.39*	6.01±0.89*
Group IV: >70 years	20.05±0.71**	14.57± 2.09**	2.17±0.91**	4.75±0.38*

Significant at ($P < 0.05$) and ** highly significant at ($P < 0.01$)

Table 2 Mean (±S.E.) of Serum lipid profile in patients with acute myocardial infarction and control healthy subjects in (mg/dl)

Groups	Total cholesterol	Triacylglycerol	HDL-Cholesterol	LDL-cholesterol	VLDL-cholesterol
Group I: Healthy control	138.60±3.40	97.25±2.11	49.81± 2.13	70.10±3.15	19.45±0.42
Group II: 30-50 years	198.75±3.91	174.28±3.09*	32.40±2.11	130.61±4.11*	34.86±0.62*
Group III: 51-70 years	236.66±5.01*	200.81±3.27**	33.92± 2.75	162.59±4.19**	40.03±0.66**
Group IV: >70 years	265.35±5.90**	250.13±4.17**	24.16±2.25*	191.31±4.89***	50.13±0.84**

Significant at ($P < 0.05$), highly significant at ($P < 0.01$) and *** Very high significant at ($P > 0.001$)

From the observed results it could be concluded that, patients with AMI accompanied by low levels of adiponectin, nitrite, nitrate, and HDL-ch, with high levels of MPO, total cholesterol, TG, LDL-ch. These may all be regarded as risk factors and could be used as diagnostic tools for AMI. The present study showed the importance of NO as a predictor of AMI severity, a common mediator for the action of adiponectin and MPO, besides its possible interaction with dyslipidemia, hypertension. These findings point revealed the importance of NO in diagnosis and treatment of AMI.

4. REFERENCES

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مجلة بنها للعلوم الطبية البيطرية
BENHA UNIVERSITY
FACULTY OF VETERINARY MEDICINE

الأديبونكتين و الميلوبيروكسيديز فى مرضى احتشاء عضلة القلب الحاد

حسين عبد المقصود على[1]، ياسر محمد عبد النبى محمد[1]، رأفت رمسيس جندى محمد[2]

[1] قسم الكيمياء الحيوية- كلية الطب البيطري-جامعة بنها، [2] قسم الباثولوجيا الإكلينيكية- كلية الطب- جامعة بنها

الملخص العربى

يعتبر مرض إحتشاء عضلة القلب أحد الأسباب الرئيسية للوفاة فى العالم والسبب السائد له هو التصلب الحاد بالشرايين التاجية. ويهدف هذا البحث إلى دراسة العلاقة بين الأديبونكتين ونشاط خميرة الميلوبيروأوكسيديز وأكسيد النيتريك و مستوى الدهون بالدم وشدة هذا المرض. ولإجراء هذه الدراسة تم اختيار 30 مريض باحتشاء عضلة القلب تم تقسيم هؤلاء المرضى بناءا على عامل السن إلى 3 مجموعات مرضية تتراوح اعمارهم بين 35 و اكثر من 70 سنة. وقد أثبتت نتائج تلك الدراسة أن هناك ارتباط بين حدوث هذا المرض وانخفاض مستوى كل من أديبونكتين والنترات والنيتريت والكوليستيرول عالى الكثافة. كذلك أثبتت نتائج هذه الدراسة وجود ارتباط بين حدوث هذا المرض وارتفاع مستوى كل من نشاط خميرة الميلوبيروأوكسيديز والكوليستيرول الكلى والدهون الثلاثية والكوليستيرول قليل الكثافة ونسبة الكوليستيرول قليل الكثافة الى الكوليستيرول عالى الكثافة. وتشير هذه النتائج إلى أن كل هذه العوامل يمكن اعتبارها من عوامل الخطر المصاحبة لمرض إحتشاء عضلة القلب. وقد دلت نتائج الدراسة على وجود علاقة ذات دلالة إحصائية بين انخفاض مستوى الأديبونكتين وزيادة نشاط خميرة الميلوبيروأوكسيديز من جهة وانخفاض مستوى نواتج هدم أكسيد النيتريك (نترات/نيتريت) من جهة أخرى وبالتالى يمكن إعتبارأكسيد النيترك كعامل ربط ووسيط مشترك فى أسلوب عمل كل من الأديبونكتين وخميرة الميلوبيرأوكسيديزز ومن خلال الدراسة الحالية نستطيع أن نستخلص ما يلى: يحدث مرض إحتشاء عضلة القلب نتيجة لعوامل عدة منها انخفاض مستوى كل من أديبونكتين، والنترات، والنيتريت، والكوليستيرول عالى الكثافة وخميرة الميلوبير وأوكسيديز والكوليستسرول الكلى والدهنيات الثلاثية والكوليستيرول قليل الكثافة ونسبة الكوليستيرول قليل الكثافة الى الكوليستيرول عالى الكثافة وهذا يشير إلى أن إصابة الغشاء المبطن للأوعية الدموية والعمليات الالتهابية بالأوعية الدموية وحالة الإجهاد التأكسدى وسائط أولية فى حدوث مرض إحتشاء عضلة القلب.

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