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HAEMOSTATIC VARIATIONS IN MALE SMOKERS WITH RHEUMATOID ARTHRITIS

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ABSTRACT

The present work aims to assess the impact of cigarette smoking on haemostatic equilibria versus the magnitude of vascular endothelial damage in male subjects with and without rheumatoid arthritis.

For this purpose, thirty male smokers (age range 30-45 years) were classified into two equal groups (GI and GII). Cases in GI were with rheumatoid arthritis and cases in GII were without rheumatoid arthritis. Thirty age-matched non-smokers were similarly classified into cases with rheumatoid arthritis (GIII) and healthy normal controls (GIV). Biochemical assessments involved: serum cotinine levels, percent of total antioxidant capacity (AOC%); glutathione peroxidase (GSH-Px) enzyme activity; indices of vascular endothelial damage [fibronectin (FN) and E-selectin], and interleukin-1β (IL-β); trace elements (copper, zinc, and selenium); indices of inflammation [ceruloplasmin (CP), C-reactive protein (CRP), and sialic acid]; and indices of haemostatic equilibria {lipoprotein (a) [Lp(a)], antithrombin III (AT III), tissue plasminogen activator (t-PA), and plasminogen activator inhibitor-1 (PAI-1)}.

The results showed significant variations in serum cotinine levels in smokers coordinated with increased levels of FN, E-selectin, IL-1β, Copper, Cp, CRP, sialic acid, Lp (a) and PAI-1 versus decreased AOC%, GSH-Px, zinc, selenium, AT III and t-PA. Greater

magnitude of change in assessed data was potentiated by the dual impact of smoking and rheumatoid arthritis.

With respect to the abovementioned findings, it could be concluded that a synergistic interaction occurred between products of cigarette smoke inhaled and mediators of inflammatory response to rheumatoid arthritis. Their impact on magnitude of oxidative stress-induced vascular endothelial damage was equivocal to variations in indices of haemostatic equilibria.

Key words: Cigarette smoking, haemostatic equilibria, rheumatoid arthritis, vascular endothelial damage.

INTRODUCTION

Rheumatoid arthritis (RA) has a worldwide distribution and involves all racial and ethnic groups, occurring at any age and generally an increase in incidence appears with advancing age (Feldman et al., 1996). The disease is characterized by a non-suppurative proliferative synovitis which in time leads to the destruction of articular cartilage and progressive disabling arthritis (Panayi, 1993). Many of the early findings in RA suggest that the responsible etiological factor(s) may be carried to the joint by the circulation (von Mühlen & Tan, 1995).

The importance of genetic factors in the genesis of RA is supported by the increased frequency of this disease among first degree relatives (Akil & Amos, 1995). Furthermore, even the expression of inherited disorders can be influenced by environmental factors and life style (Seashore & Wappner, 1996). Air pollution has been a continuing problem in many communities with hazardous health consequences (Kumar et al., 1997). Adverse health outcomes of cigarette smoke inhalation which is a powerful oxidative stressor is attributable to subjection to different population of free radicals (Hulea et al. 1995). Their damage to DNA by reactive oxygen and nitrogen species and their role in inflammatory diseases and progression to cancer has been documented (Halliwell, 1995). Rheumatoid arthritis (RA) and increased risk of developing coronary disease are amongst the conditions in which oxidative stress and depletion of antioxidant defenses are prominent features (Knight, 1995).

The chronic inflammatory systemic status in RA involves certain cytokines that cause joint inflammation and acts as a powerful modulator of immune response. It also causes proliferation of synovial cells and fibroblasts and potentiates the secretion of a variety of proinflammatory and tissue degrading factors (Callard & Gearing, 1994; Seymour et al., 1995). These could be

associated with activation of cell adhesion molecules (e.g. E-selectin) and alterations in cell matrix proteins, acute phase reactants and hemostatic equilibria (Aplin et al., 1998; Osama et al., 1998).

The present study aims to assess in cases with RA the influence of cigarette smoke intensity viz products absorbed from cigarette smoke as sources of endothelial injury. Their impact on hemostatic equilibria involving antithrombin III (AT III), tissue plasminogen activator (t-PA), plasminogen activator inhibitor-1 (PAI-1), lipoprotein (a) [Lp (a)] will be assessed in view of vascular endothelial damage monitored by fibronectin (FN) and E-selectin relative to monitoring changes in the inflammatory response by determining levels of C-reactive protein (CRP), sialic acid, rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), and serum cotinine.

MATERIAL AND METHODS

Thirty male heavy smokers (age range 30-45 years) were classified into two equal groups, group I (GI) and group II (GII). Cases in GI involved those with active rheumatoid arthritis (RA) and cases in GII were without RA. Thirty age-matched non-smokers were similarly classified into cases with active RA (GIII) and normal healthy controls (GIV).

Smoking index was calculated according to Brinkman Index based on the product of the number of cigarettes smoked each day and the number of smoking years. Those who had smoking index > 400 (smoke 30 ± 8 cigarettes/day for a duration > 10 years) were considered heavy smokers (Abdel Meguid et al., 1999).

Based on the revised criteria of the American Rheumatism Association (Arenett et al., 1988), the diagnosis of RA was based on the criteria of disease activity (Rhind et al., 1980) involving Ritchie Articular Index score more than 20, a morning stiffness > 45 minutes, number of tender joints not less than 6, number of swollen joints not less than 3 and erythrocyte sedimentation rate > 28 mm/1st hour (Ritchie et al., 1986).

All subjects under study fulfilled the following clinical and biochemical analyses:

1- Complete history taking and thorough clinical examination including the diagnostic criteria of RA.
2- Monitoring of liver and kidney function tests to exclude cases with hepatic or renal disorders.
3- Biochemical assessment of serum cotinine (Pichini et al., 1992); total antioxidant capacity (AOC%) (Bonnetont et al., 1989); glutathione peroxidase (GSH-Px) enzyme activity, plasma fibronectin by radial immuno diffusion

(Mancini et al., 1965); soluble E-selectin in serum (Blann et al., 1995); IL-1 , trace elements in serum by atomic absorption spectrosmetry included the following: copper (Cu), zinc (Zn) (Kilholma et al., 1984) and selenium (Se) (Gardiner et al., 1995); ceruloplasmin (Cp) which was determined by using non-partigen plates and standards provided by Behring Hoechst Inst., Germany (Buffone et al., 1979); C-reactive protein (CRP) (Deodhar, 1994); erythrocyte sedimentation rate (ESR), serum sialic acid (Crook, 1993); rheumatoid factor (RF) by the Rose Waaler test (Laurence & Nacham, 1987); lipoprotein (a) [Lp (a)] (Walton et al., 1974); plasma antithrombin III (AT III) (Shrader et al., 1981); tissue plasminogen activator (t-PA) (Bergedorf et al., 1983); and plasminogen activator inhibitor-1 (PAI-1) (Declerck et al., 1988).

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Table (1): Values of Serum Cotinine, Indices of Vascular Endothelial Damage and Inflammatory Response in Selected Groups. Data are Mean ± SD.

Biochemical Parameters	Smokers (n=30)		Non-Smokers (n=30)	
	With RA GI (n=15)	Without RA GII (n=15)	With RA GIII (n=15)	Control GIV (n=15)
Serum Cotinine (ng/ml)	394 ± 80.2	373 ± 71.5	ND	ND
AOC%	48.5 ± 12.6***	63.4 ± 16.5**	73.9 ± 18.1	89.2 ± 22.0
GSH-P_X (U/gHb)	10.7 ± 3.1***	12.8 ± 3.6**	14.1 ± 3.9*	18.3 ± 4.8
Fibronectin (mg/L)	654 ± 194***	415 ± 99***	528 ± 172***	86.8 ± 21.5
E-selectin (µg/L)	112 ± 25.3***	74.5 ± 17.8**	89.7 ± 22.5***	58.8 ± 11.9
IL - 1β (pg/mL)	15.0 ± 4.7***	11.2 ± 2.8	12.4 ± 3.1**	8.9 ± 2.5

Statistically Significant Values at

* ($P < 0.05$), ** ($P < 0.01$), and *** ($P < 0.001$).

RA = rheumatoid arthritis.

ND = non-detectable value.

AOC% = Percent of total antioxidant capacity.

GSH – P_X = glutathione peroxidase enzyme.

IL - 1β = intorleukin - 1β.

Table (2): Values of Trace Elements, acute Phase Reactants, and Sialic Acid in Selected Groups.

Data are Mean ± SD.

Biochemical Parameters	Smokers (n=30)		Non-Smokers (n=30)	
	With RA GI (n=15)	Without RA GII (n=15)	With RA GIII (n=15)	Control GIV (n=15)
Copper (μg/dL)	177 ± 46.2***	131 ± 32.5*	145 ± 37.1**	109 ± 27.3
Zinc (μg/dL)	59.8 ± 13.2***	91.3 ± 19.1**	71.3 ± 16.4***	115 ± 21.7
Selenium (μg/dL)	51.4 ± 10.2***	91.6 ± 19.3**	75.8 ± 17.3***	123 ± 30.7
Ceruloplasmin (mg/dL)	47.2 ± 11.4***	27.2 ± 8.1**	38.7 ± 9.8***	19.3 ± 5.3
CRP (μg/mL)	68.4 ± 17.6***	22.5 ± 6.8**	49.1 ± 14.4***	15.2 ± 4.1
Sialic acid (mg/dL)	127 ± 38.9***	72.6 ± 18.2**	89.4 ± 23.1***	52.7 ± 14.8

Statistically Significant Values at

* ($P < 0.05$), ** ($P < 0.01$), and *** ($P < 0.001$).

RA = rheumatoid arthritis.

CRP = C – reactive protein

Table (3): Indices of Hemostatic Equilibria in Selected Groups.

Data are Mean ± SD.

Biochemical Parameters	Smokers (n=30)		Non-Smokers (n=30)	
	With RA GI (n=15)	Without RA GII (n=15)	With RA GIII (n=15)	Control GIV (n=15)
Lp (a) (mg/dL)	20.1 ± 5.8***	10.8 ± 3.0*	12.8 ± 3.6**	8.7 ± 2.4
AT III %	65.1 ± 17.3***	81.7 ± 22.6*	74.3 ± 20.1**	107 ± 28.1
t – PA (ng/mL)	4.76 ± 1.9***	7.62 ± 2.2*	6.31 ± 2.0**	9.61 ± 3.0
PAI –1 (ng/mL)	23.4 ± 5.9***	15.2 ± 4.7*	18.4 ± 5.7**	12.1 ± 3.5

Statistically Significant Values at

* ($P < 0.05$), ** ($P < 0.01$), and *** ($P < 0.001$).

RA = rheumatoid arthritis.

Lp (a) = lipoprotein (a)

AT III % = percent of antithrombin III

t-PA = tissue plasminogen activator

PAI –1 = palsminogen activator inhibitor –1

RESULTS

Cases with RA exhibited values for ESR>28 mm/1st hour and RF>30 U/mL. In table (1), the serum cotinine levels in smokers were 394±80.2 ng/mL in GI and 373±71.5 ng/mL in GII, while non-detectable values were recorded for non-smokers with RA (GIII), and without RA (GIV). The cigarette smoke inhalation products induced oxidative stress presenting lower levels of AOC% and GSH-Px was evident in GI>GII when values were compared to non-smokers GIII relative to controls (GIV). The Increased magnitude of vascular endothelial damage and the inflammatory response (viz increased levels of FN, E-selectin, and IL-1β) showed higher values in GI>GIII>GII relative to GIV.

Table (2) presented assessed levels of selected trace elements and acute phase reactants in groups under study. Increased levels of copper, ceruloplasmin, CRP and sialic acid were paralleled with decreased levels of zinc and selenium with significant variations from controls. The values expressed higher magnitude of change in GI>GIII>GII relative to GIV.

In table (3), the alterations in haemostatic equilibria presented lowering in AT III and t-PA versus increased Lp (a) and PAI-1 which elaborate thrombotic tendencies. The statistical variation was noted in assessed values in table (1), table (2), and table (3) denoting the influence of RA and products of cigarette smoke inhalation.

DISCUSSION

Of all pollutants, cigarette smoke inhalation is the one associated with the highest prevalence of disease relative to intensity and duration of exposure to the extraordinary number of noxious chemicals generating free radicals (Miller et al., 1997). The present findings of raised levels of serum cotinine (the metabolite of nicotine) (Abdel-Aziz et al., 1998) versus a relative reduction in total antioxidant capacity in smokers and more pronouncedly in rheumatoid arthritis (RA) cases elaborate the culminative effect of reactive oxygen species (ROS). Its impact on the magnitude of endothelial damage in RA smokers was verified herewith by the assessed increments in values of plasma fibronectin (FN) and E-selectin in serum. Both favor the formation of hemostatic plugs after endothelial injury (Cotran & Briscoe, 1997). Also, the paralleled changes in levels of antithrombin III (AT III), tissue plasminogen activator (t-PA), plasminogen activator inhibitor-1 (PAI-1), and lipoprotein (a) [Lp (a)] exhibit prothrombotic response to injury implicating the influence of smoking and RA.

In compliance, upregulation of endothelial adhesion molecules (e.g. E-selectin) accompanied by the release of their soluble fractions into the blood stream verifies the consequent response to endothelial cell damage and chronic inflammatory response noted elsewhere (El-Dardiry et al. 1999). Conceivably, in RA the subsynovial connective tissue is heavily infiltrated by lymphocytes and new vascularization is prominent with plump endothelial cells that expressed high levels of adhesion molecules (Akil & Amos, 1995).

The selectin-carbohydrate interactions in extracellular matrix mediate leukocyte trafficking and movement of immune cells through the capillary wall from blood to tissues at sites of inflammation to initiate the immune attack (Lasky, 1995; McEver et al., 1995). It could elicit changes in the expression of acute phase reactants (APRs) known to be mediated by a complex network of cytokines (Colten, 1992). Of these, the IL-1 increments noted herein is to be clearly involved in triggering the transcription and synthesis of acute phase reactants (APRs) in addition to its cooperative interaction with IL-6 and tumor necrosis factor alpha (TNF-) in this context (Dinarello, 1984).

It is suggested that IL-1 causes both changes of copper increment and zinc decrement as observed herewith. This may occur via the increase of metallothionein-mediated hepatic uptake of serum Zn as well as upregulation of the acute phase reactant ceruloplasmin gene and its synthesis in liver which subsequently influences the level of ceruloplasmin-copper complexes in the blood (Mulder et al., 1991). The decreased selenium could be associated with decreased plasma antioxidant enzyme GSH-Px activity with the RA state (Honkanen et al., 1991).

The reactive oxygen species (ROS)-mediated inflammatory response to RA and cigarette smoking was evaluated herein by increments in C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), and sialic acid. The CRP which is the most sensitive index of inflammation among APRs represents a measure of disease activity (Doedhar, 1994; Schivick & Haupt, 1996). However, ESR expresses the general severity of inflammatory status. This occurs via its relationship to immunoglobulins and RF autoantibodies which are deposited as complexes in the superficial layers of articular cartilage (Wolfe, 1997). Reports denoted in cases with RA a relationship between increments in serum RF and increments in RF in joints involving either polyclonal B cell activation or defective T cell regulation of rheumatoid B lymphocytes that are genetically programmed to produce RF (Firestein et al., 1987; Zvaifler, 1988).

The present findings of increments in serum levels of Lp (a), APRPs, sialic acid, and CRP relate the dual influence of smoking and rheumatoid arthritis to the

magnitude of damage to vascular endothelium and cardiovascular risk (Watts et al., 1995). Hence, reports indicated the association of increased CRP to angina and progressive coronary atherosclerosis and increased sialic acid to cardiovascular mortality (Lindberg et al., 1991; Liuzzo et al., 1994). Concordantly, the relationship between high Lp (a) and myocardial infarction has been attributable to the involvement of Lp (a) in atherogenesis, reduced blood flow and thrombogenesis (Quyyumi, 1998; El-Dardiry et al., 2000).

Verifiably, thrombotic tendencies induced by cigarette smoking and RA was assessed by lower AT III, t-PA and higher PAI-1 as elaborated herein. Evidence of vascular damage with impaired t-PA release is reported (Lau et al., 1993) and coincides with the present findings. Consequently, it may confer haemostatic disequilibria in view of procoagulant state elicited by the paralleled increase in PAIs and decrease in AT III (Handin, 1998a). This may occur in consequence to increased hepatic synthesis of coagulation proteins, reduced synthesis of anticoagulants as AT III or its increased consumption. As well, it could event from activation of endothelial cells secreting inhibitors of plasminogen activators as PAI-1 which depresses fibrinolysis and confers an overall procoagulant effect (Collen & Lijnen, 1991; Handin, 1998b).

In conclusion, based on intensity of cigarette smoke inhalation (CSI) (viz serum cotinine), in patients with RA, the magnitude of depressed AOC% represents ROS induced injury. This modulates the regulation of immune and inflammatory reactions in rheumatoid synovium and extra-articular sites. It poses a high risk of CHD, ischemia, and thrombotic manifestations. Exposure of subendothelial collagen and matrix proteins is evidenced with increments of serum levels of cotinine, E-selectin, CRP, sialic acid, Lp (a), and plasma levels of FN and ESR. Haemostatic disequilibria were affected by lower AT III, t-PA and higher PAI-1 values. As the prognosis and eventual outcome of RA is largely dependent on the associated vascular affections (Osama et al., 1998), the present findings confirm the aggravating impact of CSI on such aspects. Therefore, cigarette smoking should be discontinued and antioxidants should be supplemented alongside the therapeutic regimen to RA patients.

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التغير فى عوامل وقف النزف فى الذكور المدخنين المصابين بالتهاب المفاصل

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يهدف هذا البحث إلى تقدير تأثير التدخين على توازن وقف النزف ومدى تلف الغشـــاء الطلائـــى الوعائى فى الذكور المدخنين المصابين وغير المصابين بالتهاب المفاصل.

ولتحقيق هذا الغرض تم اختيار ثلاثين من الذكور المدخنين تتراوح أعمارهم بين ٣٠ و٤٥ عاما. ثم تقسيم هؤلاء المدخنين إلى مجموعتين متساويتين هما : مجموعة (١) من المصـــابين بالتـــهاب المفـــاصل ومجموعة (٢) من غير المصابين بالتهاب المفاصل ، كما شمل البحث ثلاثين ذكرا من غير المدخنين ومـــن نفس المرحلة السنية قسموا أيضا بالتساوى إلى مجموعتين : مجموعة (٣) من المصابين بالتهاب المفـــاصل ومجموعة (٤) من الذكور الأصحاء يمثلون المجموعة الضابطة.

تم فى هذا البحث تقدير بعض القياسات الكيميوحيوية هى : الكوتينين فى مصل الدم (وهو أحد نواتج أيض النيكوتين) ، النسبة المئوية للقدرة الكلية لمضادات الأكسدة ، نشاط إنزيم الجلوتاثيون بيروكســـيديز ، مؤشرات تلف الغشاء الطلائى الوعائى (الفيرونكتين والسلكتين-هـــ) ، الانـــترلوكين-١ بيتـــا ، بعـــض العناصر النادرة (النحاس، الزنك والسيلينيوم) ، مؤشرات حدوث الالتهاب (السريولوبلازمين ، البروتين-ج التفاعلى وحمض السياليك) ، مؤشرات توازن وقف النزف [البروتين الدهنى(أ) ، مضاد الـــثرومبين-٣ ، منشط البلازمينوجين النسيجى ومثبط منشط البلازمينوجين-١].

أظهرت النتائج عن تغير فى مستوى الكوتينين فى مصل دم المدخنين مع زيادة ذات دلالة إحصائية فى مستوى كل من الفيرونكتين ، السلكتين - هـ ، الانترلوكين-١ بيتا ، النحـــاس ، المـــريولوبلازمين ، البروتين - ج التفاعلى ، حمض السياليك ، البروتين الدهنى (أ) ومثبط منشط البلازمينوجين-١. وذلك فـــى مقابل نقص ذو دلالة إحصائية فى مستوى كل من النسبة المئوية للقدرة الكلية لمضادات الأكســـدة ، نشـــاط إنزيم الجلوتاثيون بيروكسيديز ، الزنك ، السيلينيوم ، مضاد الثرومبين-٣ ومنشط البلازمينوجين النســـيجى. وكان معدل التغير أقوى وأوضح فى مجموعة المدخنين المصابين بالتهاب المفاصل.

بالنظر إلى النتائج المذكورة ، يمكن استنتاج أنه قد حدث تداخل تآزرى بين نواتج استنشاق دخـــان السجائر مع وسائط الالتهاب لمرضى التهاب المفاصل. وقد أثرت هذه الوسائط على مـــدى تلـــف الغشـــاء الطلائى الوعائى المتأثر بالضغط المؤكسد وبالتغير فى مؤشرات توازن وقف النزف.