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INSINUATIONS OF MULTIFACTORIAL AUTOIMMUNE DISORDERS AND THEIR INTERPLAY TO DEVELOP RHEUMATOID ARTHRITIS: FROM INFLAMMATION TO BONE DEFORMITY

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic and autoimmune disorder which leads to the disability, deformity of joints and even death. The particular reason of the disease is still unknown; but it has been confirmed that it is a multifactorial disease influenced by environmental and genetic factors. Destruction of the joint is associated with the immunological abnormalities and inflammatory mechanisms.

Objectives: The aim of this study is to determine the role of anti-oxidants, inflammatory cytokines and MMPs in the progression and aggregation of RA.

Methods: Blood samples of hundred male patients with rheumatoid arthritis were collected from University teaching hospital, The University of Lahore. Hundred age and sex matched blood samples from healthy volunteers were also collected as a control. Levels of MDA, NO, GSH, SOD and CAT were estimated spectrophotometrically while interleukins, TNF-α, MMP2,MMP3 and MMP9 were estimated by using a commercially available ELISA kit.

Results: The MDA levels in RA patients were elevated significantly as compared to control subjects (2.59±0.017 Vs 1.29±0.006 nmol/ml). The serum NO levels in these patients were recorded (18.58±4.160 µmol/L) as compared to normal subjects (9.28±1.22 µmol/L). However, the serum SOD, CAT, GSH and Vit E levels were measured in RA patients with the significant decrease values of 0.056±0.001 U/L, 0.99±0.015 U/L, 2.99±0.951 µmol/L and 1.95±0.019 µg/ml respectively. On the other hand, the levels of IL-1 (6.19±1.49 pg/ml), IL-6 (6.19±1.49 pg/ml), IL-15 (4.29±1.08 pg/ml) and TNF-α (31.25±1.99 pg/ml) were significantly increased in the patients with RA. Meanwhile, the increased serum MMP-2, MMP-9 and MMP-3 in these RA patients were recorded (96.58±6.59 ng/ml), (109.65±8.26 ng/ml) and (133.29±7.88 ng/ml) respectively against their control values 31.26±5.66 ng/ml, 36.29±4.16 ng/ml and 41.26±6.58 ng/ml. The levels of neutrophils were also increased in RA patients versus control (89.26±5.0 vs 51.66±3.66 µ/L). These values evidently points out the significant increase in oxidative stress and inflammation in bones, joints and cartilage that consequently leads to progression of RA.

Conclusions: Several lines of evidence suggest that decline in anti-oxidants activity triggers to enhance oxidative insult in RA patients. The macrophages in RA release wide range of inflammatory cytokines such as interleukins and tumor necrosis factor alpha. This enhances the

expression of inflammatory mediators potentiating damage of bones and cartilage by stimulating various proteolytic enzymes including MMPs. These MMPs triggers the degradation of bone, cartilage by degrading several extracellular components such as proteoglycans, collagen matrix protein and also regulating other MMPs in the patients with RA.

Keywords: Rheumatoid arthritis, Autoimmune disorder, Malondialdehyde, Superoxide dismutase, Matrix Metalloproteinases, Interleukins

Background

Rheumatoid arthritis (RA) is the chronic, inflammatory and autoimmune disease which is distinguished by the involvement of the joints that may lead to disability, deformity and even death. The etiology of the disease is still unknown, but it seems to be a multifactorial and inflammatory disease which is caused by genetics and environmental factors [1]. Basically, various immunological disorders and inflammation induce the destructive mechanism of joints. Synovial membrane consists of synovial fibroblasts, dendritic cells, T-lymphocytes and macrophages. These synovial macrophages have an important role during inflammatory processes and joint destruction [2]. According to different studies, it has reported that different cytokines have a major role in destructive mechanisms of rheumatoid arthritis and are also involved in systemic features [3]. These cytokines are soluble proteins which act as chemical messengers in cellular and immune system. Moreover, cytokines are also implicated in various biological activities such as cellular differentiation, tissue growth, repair, immune responses, cell proliferation and inflammation [4]. They have an important role in synovial cells that are responsible to synthesize hydrolytic enzymes, including cathepsin L and collagenases. In the pathological condition, these enzymes may trigger the degradation of bone and cartilage [5].

It has proved that TNF-α and IL-1 have a crucial role in the development of rheumatoid arthritis because they are located in the synovial fluid and synovial tissue. These cytokines trigger the formation of prostaglandin E2, COX-2, and nitric oxide (NO), increasing the development of adhesion molecules and regulate the expression of pro-inflammatory cytokines. Furthermore, these pro-inflammatory cytokines have a pivotal role in the pathogenesis of RA, as they are accountable for the regulation of enzymes which are present in synovial fluid and trigger bone damage. Other cytokines such as IL-2, IFN-ϒ, TNF-α and IL-6 are implicated in the progression of mineralization disturbances. Rheumatoid arthritis is one of the diseases that trigger oxidative insults. Synthesis of mitochondrial reactive oxygen species (ROS) in monocytes in the case of RA patient suggested that oxidative insult is one of the major factors for the disease progression. During oxidative stress, different free radicals are produced that are involved indirectly in the joint destruction because these free radicals act as a secondary messenger during immunological and inflammatory response in RA. Free radicals are also implicated in the degradation of joint cartilage that directly interacts with proteoglycans and hampering its synthesis [6]. Oxidation of low density lipoproteins (LDL), damaging of lipoperoxidation and hyaluronic acid products may trigger DNA damaging and protein oxidation. Moreover, according to different studies, it has summarized that, antioxidants which are enzymatic and non-enzymatic are relatively impaired in the patients with rheumatoid arthritis. There are decreased levels of glutathione, retinols, β-carotene, α-tocopherol, superoxide dismutase and glutathione reductase have also observed in these patients [7].

The ECM (extracellular matrix) has a major role in the structural support of tissues, cellular adhesion, cell migration, differentiation and proliferation. Usually the formation of ECM takes place slowly in the mature tissue, but become faster during joint destruction, wound healing and malignancy. The matrix metalloproteinases are considered to be an important enzyme that is involved in the degradation of many cellular components of ECM in the synovial joints [8]. MMP-3 is involved in the degradation of bone and cartilage through damaging several extracellular components such as proteoglycans, matrix protein, collagens and also regulating other MMPs [9]. Matrix metalloproteinases are synthesized in defective joints, then secreted into the circulatory

system of patients with rheumatoid arthritis [10]. Bone destruction is mainly the result of osteoclasts activation in rheumatoid arthritis patients. In RA patients, the synovial fluids formed a number of cytokines, including TNF-α, IL-1, IL-11 and IL-17 [11]. These inflammatory cytokines have the capacity to increase the osteoclastic activity and differentiation. Moreover, T-lymphocytes have the ability to express ODF (osteoclast differentiation factor) that is also known as receptor activator of nuclear factor kappa B ligand (RANKL). This ligand is capable of triggering cellular differentiation of macrophages and monocytes into osteoclasts. Additionally, RANKL is also involved in activating multi-nucleated osteoclasts which further lead towards the bone resorption at the mineral phase and consequently cause bone destruction [12].

MATERIALS AND METHOD

The present study was designed to evaluate the implications of extrapolative factors of medical importance and their interplay to develop rheumatoid arthritis. Hundred subjects diagnosed with rheumatoid arthritis were included. Hundred age and sex matched subjects were enrolled to serve as controls. Five ml of venous blood sample was taken from anticubital vain of each participant. The experimental protocols were approved by a research ethical committee of Institute of Molecular Biology and Biotechnology (IMBB), The University of Lahore. Within one hour of sample collection samples were centrifuged, serum were separated and stored at -70°C until assayed.

BIOCHEMICAL ANALYSIS

Lipid peroxidation was determined calorimetrically by using the method of Ohkawa et al [13] in test tubes 200µl of the sample was taken and 200µl of 8.1% SDS was added then 1.5ml of acetic acid (0.8%) TBA (20%) was added and after that heated for 60 min. 4 ml of butanol was added after cooling and centrifuged for 3000rpm for 10 min. Superoxide dismutase (SOD) was estimated by using the method of Kakkar [14]. Glutathione (GSH) was estimated by using the method of Moron et al [15]. GSH reacts with DTNB oxidized glutathione (GSSG) and TNB is produced and absorbance recorded at 412nm. Levels of NO were estimated by using a spectrophotometer. Catalase was estimated by using the method of Aebi's [16]. Interleukins and TNF-α were estimated by the standard protocols of ELISA (Bio Vendor). MMP2, 3 and 9 were also determined by using commercially available ELISA kit (Bio Vendor).While the neutrophils were measured by Sysmex 2001 Hematology analyzer.

RESULTS

The data represented in the figure 1 signifies the clear picture of various biomarkers which are measured from the patients with rheumatoid arthritis (RA). When the markers of oxidative stress were evaluated, raise in MDA levels was observed in the patients of RA as compared to healthy susbjects (2.59±0.017 vs. 1.29±0.006 nmol/ml). The levels of NO in RA patients were remarkably higher in RA patients (18.58±4.160 µmol/L) as compared to normal subjects (9.28±1.22 µmol/L). When the levels of antioxidants were measured, the serum level of GSH in RA patients lowered (2.99±0.951 µmol/L) in comparison with control group (7.59±2.16 µmol/L). SOD levels in RA patients were distinctly decreased (0.056±0.001 U/ml) as compared to control group (0.11±0.0013 U/ml). The serum catalase level was significantly lower in RA patients as compared to control groups (0.99±0.015U/L vs. 2.19±0.099U/L). Likewise, the decrease levels of vitamin E were observed in RA patients (1.95±0.019 µg/ml) in comparison with control individuals (5.17±1.56 µg/ml). On the other hand, the levels of IL-6 were raised in RA patients (6.19±1.49 pg/ml) as compared to healthy groups (3.19±0.0017 pg/ml). Increased levels of IL-1 were also measured in RA patients as compared to normal individuals (6.19±1.49 pg/ml vs. 3.19±0.0017 pg/ml). The serum IL-15 in the RA patients were significantly elevated (4.29±1.08 pg/ml) in comparison to healthy individuals (3.18±0.807 pg/ml). The levels of TNF-α in RA patient were evaluated as 31.25±1.99 pg/ml, while in control groups as 18.77±4.26 pg/ml. The biomarkers of matrix metalloproteinases (MMPs) were estimated, increased levels of MMP-2 were measured in RA

patients as compared to control (96.58±6.59ng/ml vs. 31.26±5.66 ng/ml). The serum MMP-9 levels were remarkably higher in RA patients (109.65±8.26 ng/ml) as compared to control individuals (36.29±4.16 ng/ml). The MMP-3 levels were estimated in RA patients, the value was significantly higher (133.29±7.88 ng/ml) than those measured in healthy groups (41.26±6.58 ng/ml). Meanwhile, the levels of neutrophils were also increased in RA patients (89.26±5.0 μ/L) as compared to control subjects (51.66±3.66 μ/L). The significant reduction in antioxidants and increased levels of interleukins results to enhance MMPs levels that trigger excessive ROS generation and involved in the destruction of synovial joints, bone and cartilage through damaging various extracellular components such as matrix protein, proteoglycans and collagens.

DISCUSSION

Rheumatoid arthritis (RA) is a progressive and chronic disorder that is distinguished by the joint involvement which leads to the disability and deformity of joints. The exact cause of the disease is still unclear, but it may caused by the association of genetic and environmental factors [1]. The synovial membrane is the site of initiation of joint destruction where the new blood vessels are formed along with the influx and local activation of mononuclear cells. This synovial membrane consists of macrophages, T lymphocytes, synovial fibroblasts and dendritic cells [2]. Different studies have suggested that reactive oxygen species (ROS) have a crucial role in the progression of various diseases, including rheumatoid arthritis [17]. These species are highly reactive and have the ability to damage DNA, proteins and lipids in the joint tissues. In the current study, the lipid peroxidation was estimated by measuring the level of MDA in the serum blood sample; this increased expression suggested to be a consequent biomarker of free radical causing tissue destruction in RA patients. The lipid peroxidation enhances due to the excessive ROS production, which leads to chronic inflammation and tissues damaging of the synovial membrane. According to the literature, it has suggested that increased levels of MDA were reported in the serum RA patients [18, 19]. In the present study, MDA shows a statistically strong positive significant correlation with IL-1 (MDA vs IL-1, r= 0.756) [Table 1]. Nitric oxide (NO) has a crucial function in inflammation and autoimmunity. The major source of NO production in RA patients is synovial fibroblast and chondrocytes. Moreover, the neutrophils, mast cells, macrophages and fibroblasts in inflamed joints are also involved in the formation of NO. Different findings suggested the increased expression of NO in rheumatoid arthritis patients and RNS was abundantly produced in synovial membrane [18]. The significant increase of NO level in the serum of RA patients is due to hyperactivity of nitric oxide synthase (NOS). Our findings of raise NO levels in RA patients are corroborated to subsist published data. Moreover, in the present study, NO shows a statistically strong positive significant correlation with IL-1 (NO vs IL-1, r= 0.635) as shown in table 1.

The study of Recklies *et al* [20] summarized the low levels of SOD in RA patients, which is basically the first line of defense against oxidative insults. SOD catalyzed the dismutation of superoxide anion into H_2O_2. Meanwhile, in the current study, the decrease level of SOD has reported in the serum of RA patients and this decrease activity indicated that SOD has degraded by ROS during the process of detoxification [21]. In the current study, SOD shows a statistically strong negative significant correlation with IL-15 (SOD vs IL-15, r= -0.857). Moreover, the levels of catalase enzyme also decline in the patients with RA which is similar to the work of Surapaneni and Venkataramana [22]. This decrease level of CAT in RA patients is due to its degradation by hydrogen peroxides which indicated that, this reduced level of enzyme has a crucial role to enhance oxidative stress and rheumatoid arthritis process. However, EL-Sohemy *et al* [23] documented the increased level of CAT has a protective role by limiting the synthesis of free radicals in RA patients. According to the present study, CAT shows a statistically strong negative significant correlation with MMP-3 (CAT vs MMP-3, r= -0.548).

In the pathological condition, IL-1 is involved in the blockage of tissue repair process in joint cartilage which aggravates the tissue destruction. It is accomplished by simultaneously decrease formation of proteoglycans and increase apoptosis of chondrocytes. The increase level of IL-1

hampers the formation of GAGs (sulfated glycosaminoglycans), that is an important mediator for synovium repair [24]. In the present study, there is increased level of IL-1 in the RA patients, which have the potential role to damage bone cartilage by stimulating the various proteolytic enzymes, including matrix metalloproteinases (MMPs). The study of Dinarello,summarized that IL-1 has the capability to activate the formation of other cytokines by macrophages and dendritic cells, including IL-15 and TNF-α [25]. Moreover, IL-1 is also implicated in the development of Th-17 cells, which triggers the pathogenic activity in RA. The separate study has also accomplished that IL-6 induce the synthesis of osteoclasts, that has a pivotal role in the bone tissue degradation [26]. Moreover, IL-6 triggers the expression of receptor RANK which has the RANK-ligand. This ligand combines with its receptor RANK and triggers the differentiation of myeloid cells into osteoclasts [27]. TNF-α is one of the major pro-inflammatory cytokine which has a major function to promote bone damaging, cartilage attrition and joint inflammation, that consequently cause the formation of pannus in the patients of RA [28]. Moreover, the involvement of TNF-α is to trigger and activate Stress-activated protein kinases (SAPK) that related to the family of JNK (c-Jun N-Terminal kinases) in the signaling pathway. This JNK protein belongs to the mitogen-activated protein kinases (ERKs) which are activated by tyrosine and threonine residues phosphorylation. Once activated, JNK kinases transfer into nucleus and contribute in the transcription of inflammatory transcriptional factor [29]. The study line of Rodriguez-Carreon [30] suggested the increase expression of TNF-α in RA patients which is similar to the present study.

In RA patients, the enhanced levels of destructive proteases are produced such as matrix metalloproteinases (MMPs). The MMPs are secreted from macrophages, fibroblasts, neutrophils and synoviocytes in inflamed joints. The increased production of MMPs in RA patients triggers arthritis by degrading matrix protein of joints. Enhanced level of MMP-9 has observed in SF with RA patients along several pro-inflammatory cytokines. There is the strong positive correlation has found between MMP-9 in SF of RA patients and the severity of the disease [31]. Moreover, MMP-9 is also involved in the migration of inflammatory cells through the degrading extracellular matrix (ECM). Therefore, there is statistically strong negative significant correlation is exist between with GSH and MMP-2 (MMP-2 vs GSH, r= -0.748) as shown in table 1. Because decreased level of antioxidants is responsible to enhance inflammatory markers in RA.

CONCLUSION

The present findings revealed that overproduction of ROS, LPO, DNA damage, protein oxidation and loss of antioxidants defense activity may lead to the formation of inflammatory cytokines in rheumatoid arthritis patients that induces oxidative insults. Increased oxidative stress in RA patient evidence by raise in MDA levels and reduction in antioxidants such Vit.E, SOD, CAT and GSH. The changes in these biomarkers may provide defense against lipid peroxidation. In the present study, the increased levels of IL-1 and TNF-α in RA patient have the potential role to damage bone cartilage by stimulating various proteolytic enzymes including MMPs. Meanwhile, MMP-3 triggers the degradation of bone and cartilage by damaging several extracellular components such as proteoglycans, matrix protein, collagens and also regulating other MMPs. In this regard, MMPS, inflammatory cytokines and profile of anti-inflammatory cytokines must be examined at the onset of disease to compensate the destructive effects.

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CONFLICT OF INTEREST

Authors declare no conflict of interest

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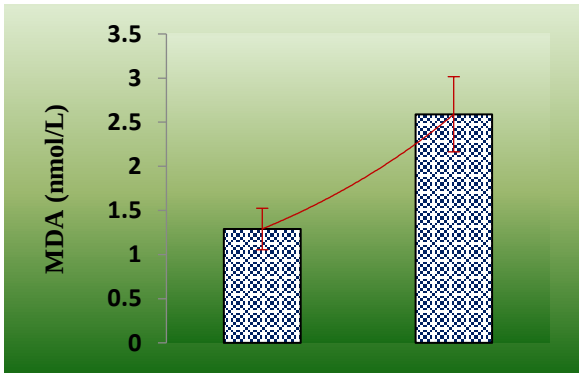
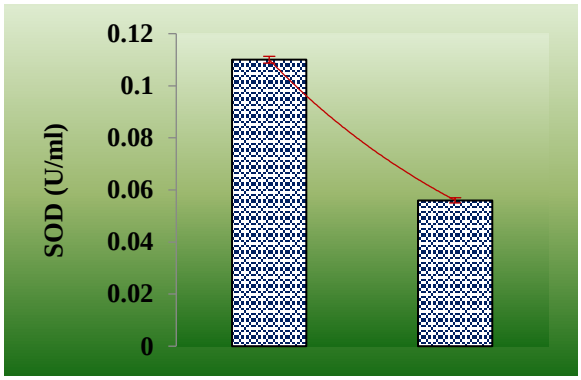


FIGURE (A)



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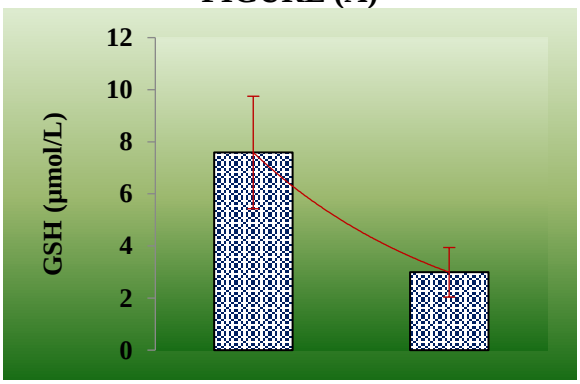

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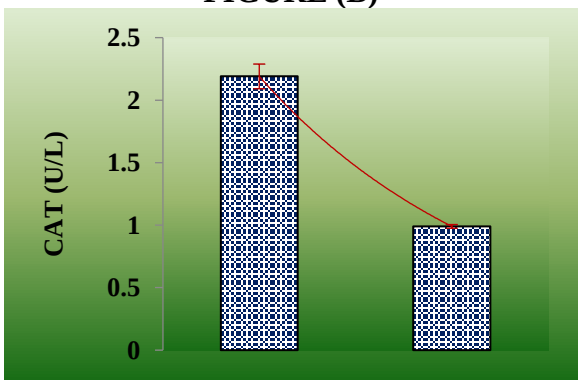

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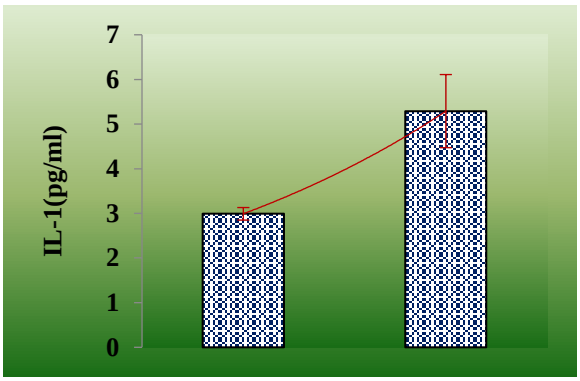

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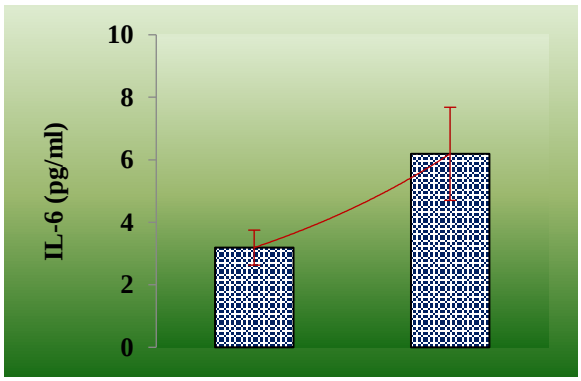

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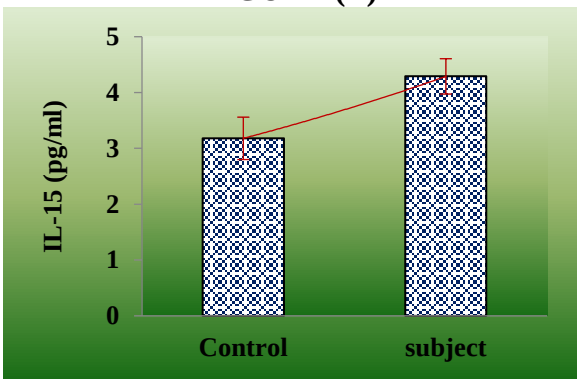

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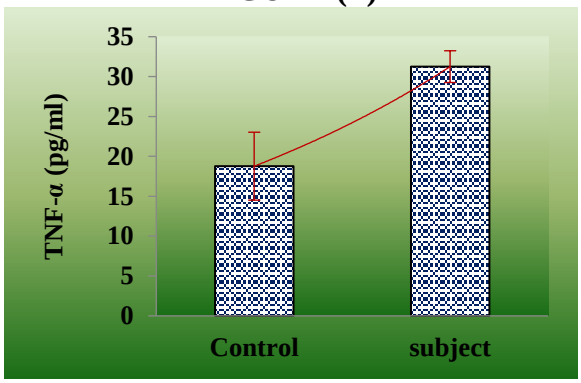

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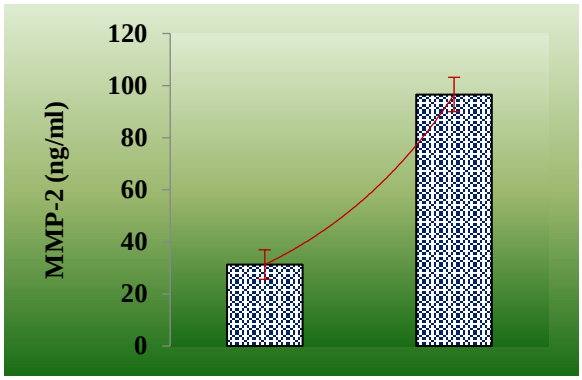

FIGURE (I)

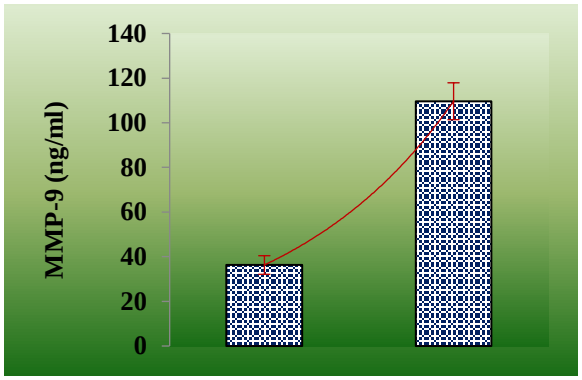

FIGURE (J)

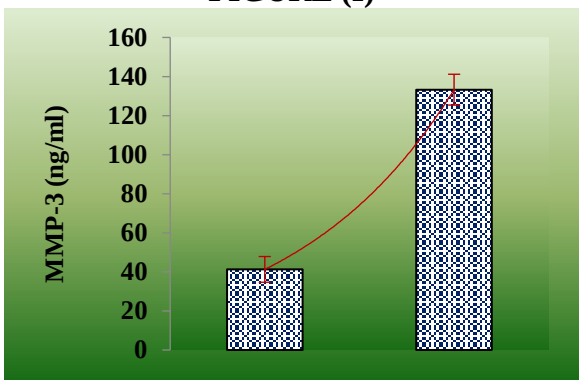

FIGURE (K)

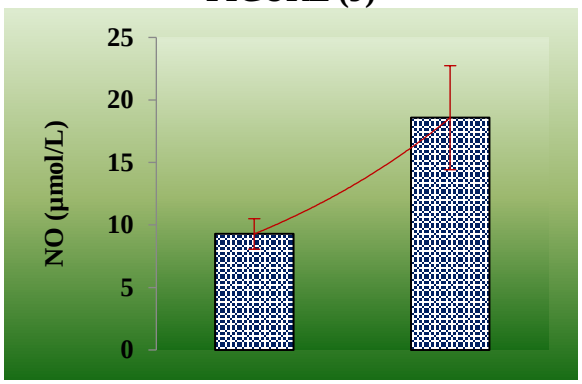

FIGURE (L)

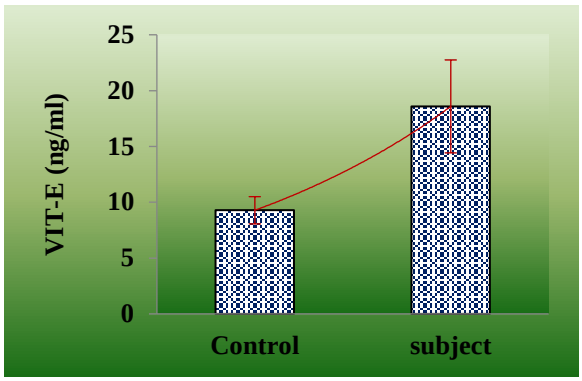

FIGURE (M)

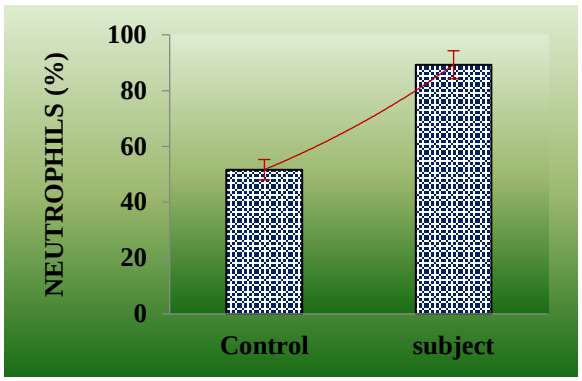

FIGURE (N)

FIGURE 1: LEVEL OF DIFFERENT VARIABLES AND THEIR INTERPLAY IN THE DEVELOPMENT OF RHEUMATOID ARTHRITIS

TABLE:01 PEARSON S' CORRELATION COEEFICIENT'S MATRIX OF DIFFERENT VARIABLES IN RHEUMATOID ARTHRITIS

VARIABLES		A	B	C	D	E	F	G	H	I	J	K	L	M	N
MDA (nmol/ml)	**A**	1	-0.535	-0.456	-0.623	**0.756**	0.165	0.489	0.654	.05548	0.145	0.325	0.348	-0.324	**0.596**
SOD (U/ml)	**B**		1	0.568	0.425	0.265	0.158	**-0.857**	.0685	0.745	0.235	0.2350	0.235	0.468	**-0.525**
GSH (µmol/L)	**C**			1	0.125	0.356	0.253	0.235	0.235	**-0.748**	0.125	0.252	0.236	0.235	-0.632
CAT (U/L)	**D**				1	0.458	0.065	0.552	0.326	0.125	0.326	**-0.548**	0.326	0.235	-0.635
IL-1 (pg/ml)	**E**					1	0.1256	0.1258	0.235	0.326	0.125	0.562	**0.635**	0.325	0.124
IL-6 (pg/ml)	**F**						1	0.5356	0.235	0.236	0.568	0.235	0.156	0.325	0.215
IL-15 (pg/ml)	**G**							1	**0.625**	0.235	0.125	0.235	0.235	0.325	0.532
TNF-α (pg/ml)	**H**								1	0.568	0.156	0.235	0.2356	0.125	0.425
MMP-2 (ng/ml)	**I**									1	0.125	0.2560	0.235	0.568	0.132
MMP-9 (ng/ml	**J**										1	0.425	0.165	0.123	0.235

)															
MMP-3 (ng/ml)	**K**											1	0.532	0.125	0.235
NO (µmol/L)	**L**												1	0.235	0.426
VIT-E	**M**													1	0.445
Neut. (%)	**N**														1

Significant at (0.05)