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ORIGINAL ARTICLE

IMMUNOLOGICAL PROFILES, OXIDATIVE STRESS BIOMARKERS AND PLASMA CHOLINESTERASE ACTIVITIES IN PATIENTS WITH IMMUNE-MEDIATED INFLAMMATORY DISEASES TREATED IN A CLINIC IN DUHOK, IRAQ

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Abstract. Aim: *The purpose of the present study was to measure the levels of selected plasma biochemical variables among cases of immune-mediated inflammatory diseases (IMIDs), other than rheumatoid arthritis, treated in a clinic in the city of Duhok, Iraq, since such information is scarce in the region.* ***Materials and Methods:*** *A case-control study on IMIDs patients treated in a clinic in Duhok, Iraq, was performed from February 2022 to June 2023. A total of 29 patients of both genders with IMIDs and 61 healthy controls were recruited at the Duhok Center for Rheumatic Diseases and Medical Rehabilitation, Duhok, Iraq. The laboratory tests conducted on plasma samples from IMIDs patients and healthy controls included measurements of interleukin-6 (IL-6), tumor necrosis factor (TNF)-alpha, malondialdehyde (MDA), total antioxidant status (TAS) and cholinesterase (ChE) activity.* ***Results:*** *No significant differences were found in gender distribution, age, and body mass index between the IMIDs patients and healthy controls. The majority of patients (69%) received conventional therapy combined with biologic agents, whereas the remaining patients (31%) received only conventional medications. The IMIDs identified among the 29 patients were Behcet's disease (27.6%), ankylosing spondylitis (24.1%), inflammatory bowel diseases (24.1%), psoriatic arthritis (10.3%), systemic lupus erythematosus (6.9%) and psoriasis (6.9%). Conventional therapy used was mostly azathioprine (44.8%) and methotrexate (17.2%), whereas biological therapy included mostly etanercept (27.6%) and adalimumab (24.1%). The values of CRP, IL-6 and TNF-α among the IMIDs patients were not significantly different from those of the controls. The oxidative stress biomarker MDA was elevated in IMID patients (2.93 ± 1.106 μmol/L vs. 2.52 ± 0.478) at a p value of 0.064 (though not significant). The TAS level (1.21 ± 0.422 mmol Trolox Equiv./L vs. 1.00 ± 0.338, p = 0.022) and plasma ChE activity (1.18 ± 0.50 ∆ pH/20 min vs. 0.83 ± 0.30, p = 0.001) were significantly higher in IMIDs patients compared to controls.* ***Conclusions:*** *The data suggest that oxidative stress and changes in plasma ChE activity might be a part of the pathophysiological alterations among IMIDs patients. Therapeutic drug monitoring and its clinical outcome as well as response of IMIDs patients to anti-ChE agents are worth of further in depth exploration and pursuing. They are essential for better diagnosis, treatment, and management of IMIDs.*

Key words: *chronic inflammatory diseases, Behcet's disease, ankylosing spondylitis, inflammatory bowel diseases, psoriatic arthritis, systemic lupus erythematosus, psoriasis*

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INTRODUCTION

Immune-mediated inflammatory diseases (IMIDs) are progressive and chronic inflammatory conditions that are characterized by a persistent and progressive self-inflicting antigenic immune system dysregulation [1-4]. IMIDs generally affect the quality of life and productivity of the patients [3, 4]. Common IMIDs with different clinical manifestations include, but are not limited to, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), psoriasis, psoriatic arthritis, inflammatory bowel disease, ankylosing spondylitis and Behcet's disease [4-6]. Predisposing factors are mainly genetic susceptibility in the form of gene polymorphism in association with immunological abnormality/autoimmunity and environmental factors such as smoking, unbalanced diet and stressful conditions [7, 14]. Pharmaco-therapeutic agents used against IMIDs are remarkably different due to the diverse nature of the conditions and their clinical manifestations. Accordingly, the therapeutic options for IMIDs include non-steroidal anti-inflammatory medications, corticosteroids, disease modifying anti-rheumatic drugs and biologic agents [5, 8-11].

Adverse immunological findings among the IMIDs cases include changes in cellular immunity (e.g. T and B cells), the central pathogenic mediator Type I interferons such as type α, and production of pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6, which can be secreted via fibroblasts in response to localized tissue signals [4, 12-14]. Because of the chronicity of inflammation in IMIDs, modulation of cholinergic anti-inflammatory pathway and increments in blood cholinesterase (ChE) activities would be implicated in the pathophysiological changes of IMIDs [1, 4, 15-17]. A recent study reported an increase in plasma ChE activity in RA patients in a manner that could be a risk factor in patients subjected to conventional anti-rheumatic therapy [18]. Nevertheless, no consensus exists on complete and unified clinical biochemical picture of IMIDs, because of the diverse clinical outcomes, often with comorbidity, in the patients [10, 19-21].

To this end, because of the scarce information about IMIDs in our region [22, 23] and in order to better understand the complex metabolic syndrome of IMIDs, the purpose of the present study was to assess selected plasma biochemical measurements (interleukin-6 (IL-6), tumor necrosis factor (TNF)-alpha, malondialdehyde (MDA), total antioxidant status (TAS) and ChE activity among cases of IMIDs, other than RA, treated in a clinic in the city of Duhok, Kurdistan Region, Iraq.

MATERIALS AND METHODS

Patients

A case-control study to recruit IMIDs patients treated in the facilities of the Duhok Center for Rheumatic Diseases and Medical Rehabilitation in Duhok, Kurdistan Region, Iraq, was performed from February 2022 to June 2023. The conditions of IMIDs were diagnosed by specialized physicians of the center after careful clinical examination, serological tests, imaging tests, and tissue biopsy, as needed. A total of 29 patients of both genders with IMIDs were eventually recruited, regardless of concurrent therapy with medications. Volunteered healthy participants (n = 61) were also included in the study.

Inclusion and Exclusion Criteria

The inclusion criteria for the IMIDs patients were Iraqis (age < 70 years) registered at the Duhok Center for Rheumatic Diseases and Medical Rehabilitation, diagnosed with IMIDs, regardless of the duration of the illness or concurrent IMIDs therapy. The exclusion criteria included patients with IMIDs having moderate comorbidities (such as uncontrolled diabetes,

heart diseases, respiratory diseases), or severe ones (such as cancer, COVID-19, severe pneumonia, kidney failure and heart failure), those on antipsychotic, dementia, antioxidant and hormonal therapy. Patients with previous joints surgeries and pregnant women were excluded from the study, as well. We recorded the demographic characteristics of all patients and healthy controls who participated in the study.

Ethical Approval

The approval of the Research Ethics Committee, Duhok Directorate General of Health, Duhok, Kurdistan Region, Iraq, was obtained with a reference number of 15092021-9-14 R1 following the consent of the College of Pharmacy, University of Duhok, Kurdistan Region, Iraq (No. 320, August 4th, 2021). The present study complied with the guidelines of the Declaration of Helsinki. Written consents were obtained from patients and healthy participants recruited for the study. They were informed about the purpose of the study, blood sampling procedure and the nature of data collection. Participants' information was kept confidential.

Blood Sampling

On the day of confirming the diagnosis of IMIDs, heparinized blood samples (about 5 mL) were obtained from the patients and control individuals by a certified nurse under aseptic conditions. Plasma was separated from the blood by centrifugation at 1000 g for 15 min and aliquots were kept at -20°C for later assays to be conducted within one month.

Laboratory Tests

The laboratory tests conducted on plasma samples from IMIDs patients and healthy controls included measurements of IL-6 level using Enzyme-Linked Immunosorbent Assay (ELISA) kit (Catalogue No. E0090Hu, BT LAB Co., Shanghai, China), TNF-alpha level using an EKISA kit (Catalogue No. E0082Hu, BT LAB Co., Shanghai, China), total antioxidant status (TAS) using a TAS colorimetric assay kit (Elabscience Biotechnology, based in Houston, Texas, USA), MDA level (a product of lipid peroxidation) spectrophotometrically at 535 nm as outlined earlier [24] and ChE activity by an electrometric method using 0.2 mL plasma aliquot and 0.1 mL of the substrate acetylcholine iodide (7.1%) in a sodium chloride-barbital-phosphate buffer (pH 8.1)-distilled water reaction mixture with an incubation time of 20 min [24, 25].

Statistical Analysis

The data were statistically analyzed using the software package PAST4.13 [26]. Parametric data are presented as mean ± SD. Independent t-test was used to compare results of laboratory assay findings between IMIDs and control groups. Chi-squared test was used to analyze categorical variables. Descriptive statistics were also used to characterize the demographic and drug usage data of the IMIDs patients. Pearson's correlations among the laboratory test variables of the IMIDs patients were also assessed [27]. The level of statistical significance was at $p \leq 0.05$.

RESULTS

Characteristics of the IMIDs patients

Table 1 presents the demographic characteristics of 29 IMIDs patients participating in the present study performed from February 2022 to June 2023. No significant differences were found in gender distribution, age, and body mass index (BMI) between the IMIDs patients and healthy controls. The duration of the illness was (mean ± SD) 9.28 ± 7.28 years and the duration of therapy was 39.76 ± 50.78 months. More than two-thirds of these patients (n = 20, 69%) received conventional therapy combined with biologic agents (combination therapy), whereas the remaining patients (n = 9, 31%) received only conventional medications. The result was statistically significant (Chi squared 8.345, df = 1, $p < 0.00387$). The frequency of occurrence of each IMID among the patients of the present study is shown in Table 1. Eight of the IMIDs patients had

Table 1. Demographic characteristics of immune-mediated inflammatory diseases (IMIDs) patients and healthy controls

Variable	IMIDs patients (n = 29)	Healthy controls (n = 61)	p-value
Males, n (%)	18 (31.6%)	39 (68.4%)	0.864
Females, n (%)	11 (33.3%)	22 (66.7%)	
Age, years, mean ± SD	40.62 ± 13.57	37.21 ± 9.91	0.234
BMI, kg/m^2, mean ± SD	27.72 ± 6.40	27.88 ± 4.54	0.907
Duration of illness (years)	9.28 ± 7.28	-	-
Duration of therapy (months)	39.76 ± 50.78	-	-
IMIDs: conventional therapy, n (%)	9 (31%)	-	0.00387*
IMIDs: combination therapy, n (%)	20 (69%)	-	

P-value was estimated utilizing independent t-test for continuous variables and Chi-squared test for categorical variables.
BMI: body mass index; SD: standard deviation; combination therapy= conventional + biologic therapy.
*Chi squared 8.345, df = 1.

Table 2. Frequency of immune-mediated inflammatory diseases (IMIDs) among the patients

IMIDs	n	%
Behcet's disease	8	27.6
Ankylosing spondylitis	7	24.1
Inflammatory bowel diseases	7	24.1
Psoriatic arthritis	3	10.3
Systemic lupus erythematosus	2	6.9
Psoriasis	2	6.9
Total	29	100

Table 3. Conventional and biologic therapy received by 29 patients with immune-mediated inflammatory diseases

Therapy	n	%
Conventional therapy		
Azathioprine	13	44.8
Methotrexate	5	17.2
Prednisolone	4	13.8
Non-steroidal anti-inflammatory drugs	3	10.3
Colchicine	3	10.3
Hydroxychloroquine	3	10.3
Biologic therapy		
Etanercept	8	27.6
Adalimumab	7	24.1
Infliximab	5	17.2

Behcet's disease (27.6%), whereas seven patients (24.1%) were diagnosed with each of ankylosing spondylitis and inflammatory bowel diseases. The least common conditions were psoriatic arthritis (n = 3, 10.3%), systemic lupus erythematosus (n = 2, 6.9%) and psoriasis (n = 2, 6.9%). As shown in Table 3, IMIDs patients received therapy with various conventional drugs, with azathioprine being the most frequently used (n = 13, 44.8%) followed by methotrexate (n = 5, 17.2%). Among biological therapies, etanercept was the most frequently prescribed (n = 8, 27.6%), followed by adalimumab (n = 7, 24.1%).

Immunological profile, OS biomarkers, and plasma ChE activity

Table 4 presents comparisons of the measured quantitative variables between IMIDs patients and healthy controls. Although the IMIDs patients had higher levels of CRP, the observed difference did not reach statistical significance (9.58 ± 29.437 mg/L vs. 3.33 ± 6.565, p = 0.268). Likewise, statistical analyses of the levels of IL-6 (88.65 ± 108.465 ng/L vs. 66.71 ± 116.055, p = 0.384) and TNF-α (136.82 ± 127.153 ng/L vs. 156.77 ± 222.176, p = 0.591) did not reveal statistical significant differences. The oxidative stress biomarker MDA was elevated in IMID patients (2.93 ± 1.106 µmol/L vs. 2.52 ± 0.478) at a p value of 0.064 (though not significant). However, the TAS level (1.21 ± 0.422 mmol Trolox Equiv./L vs. 1.00 ± 0.338, p = 0.022) and plasma ChE activity (1.18 ± 0.50 Δ pH/20 min vs. 0.83 ± 0.30, p=0.001) were significantly higher in IMIDs patients compared to control counterparts (Table 4).

In patients with IMIDs, a significant moderate positive correlation was observed between plasma levels of IL-6 and TNF-alpha (r = 0.681, p = 0.001) (Figure 1), whereas those of MDA vs IL-6 levels and MDA level vs BMI were low positive ones with r values of 0.342 (p = 0.069) and 0.329 (p = 0.081), respectively. All other correlations were not-significant and negligible (r < 0.3).

DISCUSSION

In the present study we report several IMIDs (excluding RA) among the 29 recruited patients; they were mostly with Behcet's disease (n = 8), followed by ankylosing spondylitis and inflammatory bowel dis-

Table 4. Impact of immune-mediated inflammatory diseases (IMIDs) under various therapeutic agents on selected laboratory tests

Plasma variables	IMIDs patients (n = 29), mean ± SD	Healthy controls (n = 61), mean ± SD	p-value
CRP (mg/L)	9.58 ± 29.437	3.33 ± 6.565	0.268
IL-6 (ng/L)	88.65 ± 108.465	66.71 ± 116.055	0.384
TNF-α (ng/L)	136.82 ± 127.153	156.77 ± 222.176	0.591
MDA (µmol/L)	2.93 ± 1.106	2.52 ± 0.478	0.064
TAS (mmol Trolox Equiv./L)	1.21 ± 0.422	1.00 ± 0.338	0.022
ChE activity (Δ pH/20 min)	1.18 ± 0.50	0.83 ± 0.30	0.001

P-value was estimated using independent t-test

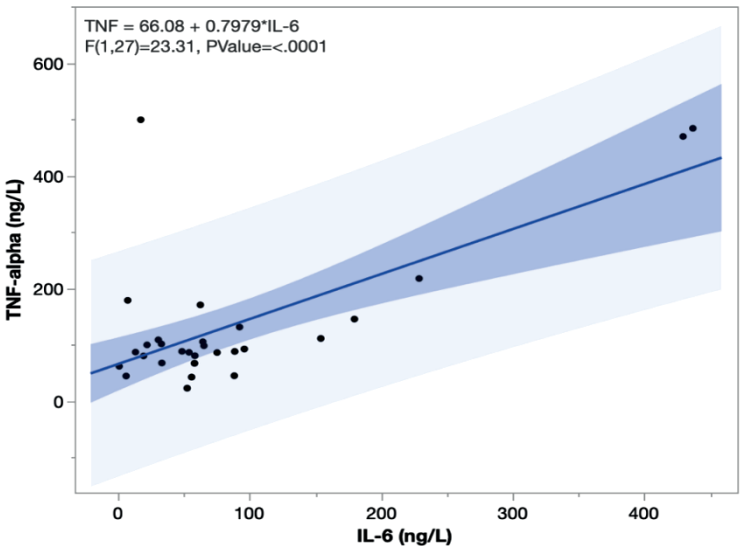

Fig. 1. Correlation between plasma TNF-alpha level (ng/L) and plasma IL-6 levels (ng/L) in patients with immune-mediated inflammatory diseases, r = 0.681, p < 0.001

eases (n = 7) and, to a lesser extent, psoriatic arthritis, systemic lupus erythematosus and psoriasis (n = 2-3). We recruited the patients for a period of 17 months according to our inclusion and exclusion criteria. Similarly, low prevalence of IMIDs has been reported in clinics in Duhok city, Iraq [22, 23]. These findings coincide with those reported globally, too [28]. It should be stressed herewith that the incidence rate of IMIDs could potentially increase as a result of several factors that include, among other things, ageing, diet style, the interaction of genetic and environmental factors and the pattern of socioeconomic development [7, 14, 28]. The diversity of clinical manifestations of IMIDs compromises, albeit in a unified manner, the underlying immune system in the form of dysregulation and tissue damage as a result of their progressive chronicity nature [1-4]. IMIDs are potentially disabling conditions that adversely affect the quality of life of the patients, with socioeconomic impact and loss of productivity [3, 4]. It is, therefore, a continuously challenging dilemma to assess the clinic-biochemical and immunological variables of IMIDs for better management and long-lasting therapy [5, 6, 8-12, 22]. To this end, the IMIDs patients of the study were subjected to either conventional therapy, with azathioprine being the most frequently used (44.8%) followed by methotrexate (17.2%), or biologic therapy (combined with conventional ones), where etanercept was the most frequently used (27.8%), followed by adalimumab (24.1%). The long term outcome of IMIDs therapy, immunological and blood biochemical profiles should be continuously monitored considering the challenging chronicity nature of the diseases and the need for drug therapy with persistent immune imbalance, which subject the patients to comorbidities [10, 19, 21, 28].

The selected immunological profile of the IMIDs patients, CRP, IL-6 and TNF-α were not significantly affected when compared to control values. Perhaps frequent blood examinations could have revealed a different outcome. However, an interesting finding of the present study was the potential oxidative stress that could have impacted the IMDIs patients. This is in the light of the increase in plasma lipid-peroxidative biomarker MDA in IMIDs patients (2.93 ± 1.106 μmol/L vs. 2.52 ± 0.478, p=0.064) and the elevated TAS (1.21 ± 0.422 mmol Trolox Equiv./L vs. 1.00 ± 0.338, p = 0.022). It is possible that pathophysiological and immunological impacts [4, 12-14] of IMIDs and even their therapies predispose the patients to oxidative stress [29, 30].

A unique feature of the present study is the significant elevation of plasma ChE activity in IMIDs patients compared to control values (1.18 ± 0.500 Δ pH/20 min vs. 0.83 ± 0.300, p = 0.001). Similarly, it has been recently reported that increased plasma ChE activity could be a risk factor in RA patients [18]. This effect on plasma ChE, which is mainly released by the liver [15], might reflect pathophysiological changes in the cholinergic anti-inflammatory pathway as a part of the impact of chronicity nature of IMIDs [1, 4,15-17]. However, the response of such an alteration in enzyme activity to anti-ChE therapeutic agents or toxicants is unknown [18]. Additionally, in the IMIDs patients, the impacts of concurrent drug therapy on these plasma variables are not clear at present. Overall, based on the present blood biochemical findings and therapeutic applications among IMIDs patients, developmental and metabolomics studies are continuously warranted.

Limitations of the study

The progress and long-term follow-up of the present IMIDs patients as well as their therapeutic outcome were out of the scope of the study. We did not analyze the response of blood ChE activity of IMIDs patients to anti-ChE agents that could be used clinically, or the response to ChE-inhibiting pesticides.

CONCLUSIONS

The body of evidence presented in the present study suggests that oxidative stress and changes in plasma ChE activity might be a part of the pathophysiological alterations among IMIDs patients and the impact of

their therapies. It is imperative to evaluate ChE activity before subjecting IMIDs patients to cholinergic manipulation. Therapeutic drug monitoring and its clinical outcome as well as response of IMIDs patients to anti-ChE agents are worth of further in depth exploration and pursuing. They are essential for better diagnosis, treatment, and management of IMIDs.

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