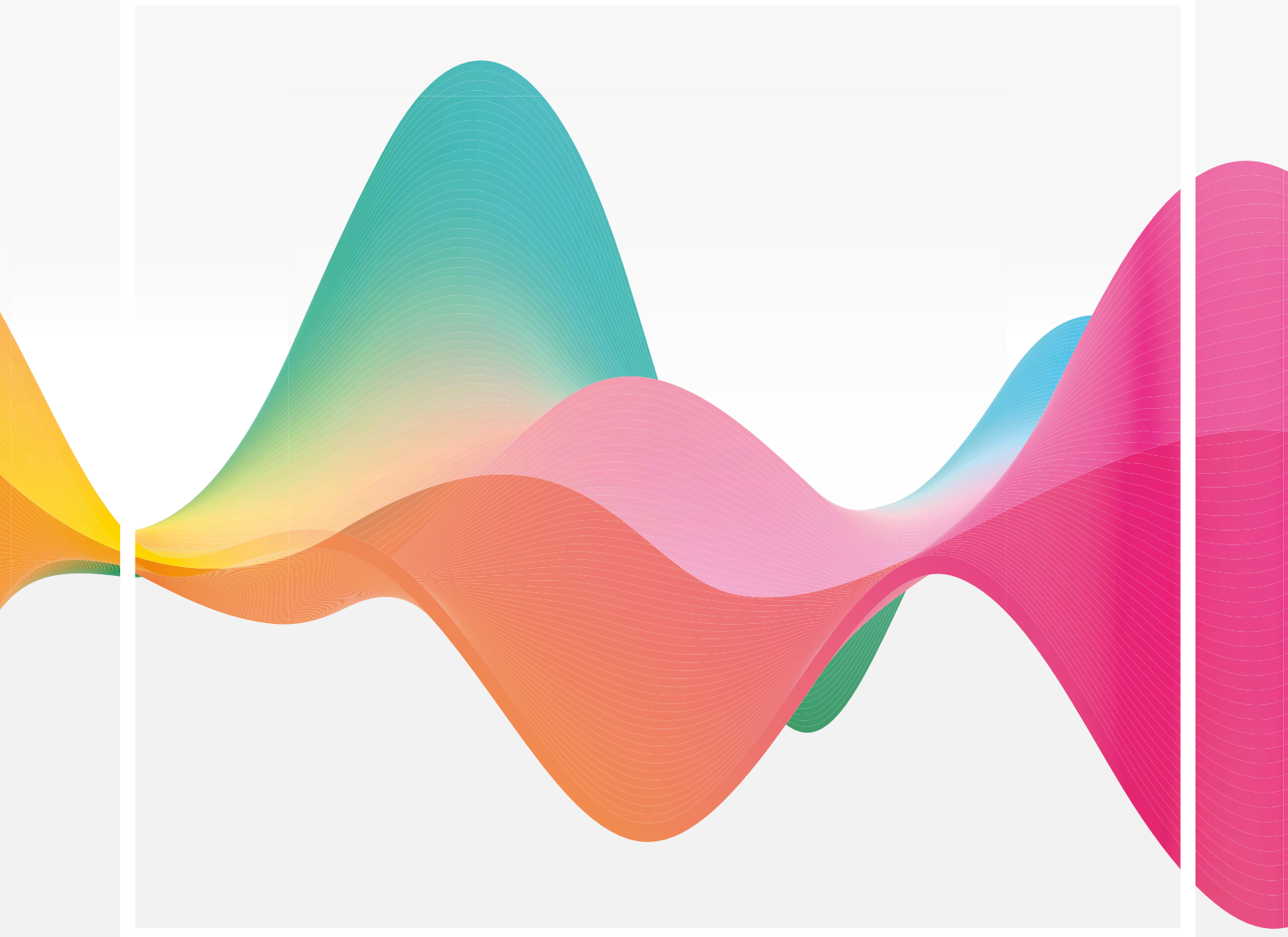
RATING ACADEMY PUBLISHING
E-ISSN: 2791-6022
DOI: 10.26900/jsp

HEALTH SCIENCES QUARTERLY

International Peer-Reviewed and Open Access Electronic Journal

Formerly Name: JOURNAL OF SCIENTIFIC PERSPECTIVES
E-ISSN: 2587-3008



Volume: 1
Issue: 1
2021

HEALTH SCIENCES QUARTERLY

E-ISSN: 2791-6022
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Formerly Name: Journal of Scientific Perspectives
E-ISSN: 2587-3008

International Peer-Reviewed and Open Access Electronic Journal

Volume 1
Issue: 1
April 2021

https://journals.gen.tr/jsp
hsq@ratingacademy.com.tr
Address: Sarıcaeli Köyü ÇOMÜ Sarıcaeli Yerleşkesi, Teknopark, No: 119
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ABSTRACTING & INDEXING

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ABOUT THE JOURNAL

About the Health Sci. Q.

Health Sciences Quarterly (Health Sci. Q.) journal as known by the name of "Journal of Scientific Perspectives" until April 2021 which has been published since 2017 is an international peer-reviewed journal of RATING ACADEMY. It is published quarterly in January, April, July, and October. All manuscripts submitted for publication are evaluated by the editor-in-chief, section editor, editorial board, and referees. In addition, the journal provides a medium for highlighting selected articles reporting highly significant original findings, as Editor's Choice Manuscripts.

Aims and Scope

Health Sciences Quarterly (Health Sci. Q.) is an open-access journal that publishes original research papers, case reports, and reviews, clinical studies covering a wide range of subjects in life sciences and medicine as well as clinical and experimental investigations only in English.

Researchers in health sciences will find much of great use and interest in the Health Sci. Q..

HSQ aims to supply scientists of health with resources in order to provide the scientific knowledge through the publication of peer-reviewed, high quality, scientific papers and other material on all topics related to Medicine, Pharmacy and pharmaceutical sciences, Dentistry, Nursing, Bioethics, History of medicine, Health economics, Pharmacoeconomics, Medical education, Public health, and Epidemiology.

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EDITORIAL

Dear colleagues,

We are here with the first issue of Health Sciences Quarterly (HSQ). We continue our way as HSQ with its new name by guiding ourselves with the knowledge, values, and academic background of the Journal of Scientific Perspectives (JSP), which has been published since 2017.

We have a great ambition to carry the flag we received from JSP to better places. We will study hard to become an esteemed scientific journal with our new editorial board including valuable scientists from the international academic community.

In this way, we would like to thank former editor-in-chief Prof.Dr. Özlem Yayıntaş, editorial board, referees, authors, and everyone who contributed to the journal.

Health Sciences Quarterly (HSQ) is an open-access journal that publishes original research papers, case reports, and reviews, clinical studies covering a wide range of subjects in life sciences and medicine as well as clinical and experimental investigations.

This issue includes a letter to the editor, six original articles, and a review article. Hope to meet in the upcoming issues with new studies.

Kind regards.

Hasan Erbay. MD, PhD, MBGPH
Editor-in-chief

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Volume : 1
Issue : 1
2021

E-ISSN: 2791-6022
https://journals.gen.tr/jsp

Received: 2021-03-09

Acccepted: 2021-03-11

LETTER TO THE EDITOR

Ethical view of telemedicine practices

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To the Editor

Telemedicine—the utilization of clinical data and innovation to progress distanced clinical care can change the patient-centered approach. Telemedicine can coordinate distance monitoring and diagnostic instruments with computerized cooperation and suggestions to better interact with patients when they are not in a hospital. Despite these preferences, there is still some doubt as to how telemedicine applications may affect care. Guaranteeing that telemedicine is ethically admissible requires projection and consideration of four potential issues: the disruption of the patient-physician relationship, jeopardizing patient privacy, impelling one-size-fits-all applications, and the impulse to expect that innovation should be efficient [1].

Citation: Pekesen M, Kocak E, Kacar M, Vatanoglu-Lutz E. Ethical view of telemedicine practices, Health Sci. Q. 2021; 1(1) : 1-2. https://doi.org/10.26900/hsq.1.1.01

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The Patient-Physician Relationship

One of the sound premises of the physician-patient relationship is the remedial value1 of an in-person clinic experience. This is contemplated in doctors' attention on an in-depth history and physical just as in the contemporary account models. We are educated as doctors about the significance of the patient-physician relationship as the foundation of encouraging shared trust and empathy. This notion is likewise reflected by guidelines. Moreover, as society turns out to be more accustomed to electronic communication, our clinical practices can advance, as well. It is essential to address and resolve issues about the loss of the patient-physician relationship so they don't impede modalities that can improve access to or the quality of care [2].

Threats to Patient Privacy

The privacy concern is rightful. Patients may not know who will interact and share their clinical data precisely. That data is accessible on various devices and PCs, expanding the potential for security gaps, which may sabotage patients' acknowledgment of telemedicine. The asynchronous communication also brings along an ambiguity about who specifically will interact, which may raise further protection concerns. Fundamentally, a powerful protection and security plan is utilized with any new telemedicine program and be informed to patients to earn the patient's trust [3].

One Size may not Fit All

Another significant issue for telemedicine is ensuring we don't impel similar "remedies" on patients with different clinical conditions, requirements, and tendencies. Patients vary significantly in their selection of new devices and programs. Text messages may function remarkably for one patient yet not another. A few patients may incline towards a patient portal to a visit, while others may not have a PC to access them [2]. These distinctions in access to innovation may increase the existing medical services access and equality issues associated with demographic and socioeconomic status. Patient-centered innovation isn't one-size-fits-all [4].

New is not Automatically Better

The fourth issue is how telemedicine may affect the quality of care and whether its utilization will have unintended outcomes [3]. As with any new medication or device, telemedicine should be assessed for how successfully it functions, and whether it creates any negative experiences, however, the assessment does not have to be a large randomized controlled trial. It is substantial for the clinical profession to apply its evidence-based ethos to telemedicine as opposed to accepting that innovation is better—to adjust the excitement about telemedicine's potential with consideration of the requirement for an unbiased assessment [2].

Conclusion

We should consider similar ethical issues with telemedicine as we have consistently done in caring for our patients. If the preserve a sound patient-physician relationship, patient privacy, promote equality in access and treatment and seek the optimal results, telemedicine can improve clinical practice and patient care in manners that are comfortable with our teaching and ethical values.

Funding
This study has not received a specific grant from funding organizations in the public, commercial, or nonprofit sectors.

Conflict of interest
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this editorial letter.

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HEALTH SCIENCES QUARTERLY

Volume : 1
Issue : 1
2021

E-ISSN: 2791-6022
https://journals.gen.tr/jsp

Received: 2021-01-28

Accepted: 2021-02-25

ORIGINAL ARTICLE

Long-term effect of intravenous iron carboxymaltose treatment on oxidative stress in women with iron deficiency anemia

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Abstract

This study aims to clarify the effects of intravenous iron supplementation on biomarkers for oxidative stress in women with iron deficiency anemia. This is a cross-sectional review of 40 healthy women and 40 women who underwent intravenous iron treatment due to anemia. Biochemical markers for oxidative stress were determined for both healthy controls and anemic patients. These markers were also evaluated at hour 1 and day 30 of intravenous iron treatment. The patients with anemia had significantly higher catalase activity and total oxidant status (TOS) but significantly lower nitrate and total anti-oxidant status (TAS) than the healthy controls ($p=0.0245$, $p<0.0001$, $p=0.0437$ and $p<0.0001$ respectively). At hour 1 of intravenous iron treatment, nitrate, nitrite, nitric oxide, total thiol and TAS values were significantly lower and TOS values were significantly higher than those before the administration of treatment ($p=0.0322$, $p=0.0003$, $p=0.0005$, $p<0.0001$, $p<0.0001$ and $p=0.004$). At day 30 of intravenous iron treatment, catalase activity, nitrate, total thiol and TOS values were significantly lower than those before the administration of treatment ($p=0.0332$, $p=0.0015$, $p=0.0391$ and $p<0.0001$ respectively) and at hour 1 of treatment ($p=0.0498$, $p<0.0001$, $p=0.0004$ and $p<0.0001$ respectively). At day 30 of intravenous iron treatment, nitric oxide and TAS values were significantly higher than those before the administration of treatment ($p=0.0480$ and $p=0.001$ respectively) and at hour 1 of treatment ($p<0.0001$ for both). Intravenous iron replacement prompts oxidative stress at hour 1 of infusion in adults with anemia but this increase resolves partially in the following 30 days.

Keywords: *Anemia, iron, oxidative stress*

Citation: Pektas G, Kirli I. Long-term effect of intravenous iron carboxymaltose treatment on oxidative stress in women with iron deficiency anemia, Health Sci. Q. 2021; 1(1) : 3-9. https://doi.org/10.26900/hsq.1.1.02

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Introduction

The World Health Organization defines anemia as blood hemoglobin values of less than 12 g/dl in women and 13 g/dl in men. Generally, complete blood count, peripheral smear, reticulocyte count and serum iron indices are included in the evaluation of the cause of anemia. The lower blood hemoglobin, iron (<70.1 µg/l), ferritin (<30 ng/l), transferrin saturation (<15%), and iron-binding capacity (>13.1 µmol/l) are the basic findings for the diagnosis of iron deficiency anemia. [1–3]. Iron deficiency and related anemia are commonly encountered in patients with chronic renal disease, chronic heart failure, inflammatory bowel diseases, malignancies and abnormal uterine bleeding [1,4]. Iron deficiency anemia can also affect patients who have undergone childbirth or surgery [4,5]. Intravenous iron treatment has been developed to correct the iron deficiency and related anemia [6]. The rationale behind this treatment is that the reticuloendothelial system (RES) immediately causes absorption of iron and it would allow quick provide to the bone marrow [7]. Commercially available intravenous iron products are essentially low molecular weight iron dextran/sucrose or isomaltoside; sodium ferric gluconate or carboxymaltose formulations [8]. These drugs using for replacement therapy are colloidal solutions that contained iron-oxyhydroxide nanoparticles with a carbohydrate ligand [7,8]. Iron-carbohydrate complexes with lower stability are largely dissolved in plasma and thus, iron molecules can leak into plasma before their uptake by the RES [9,10]. It has been hypothesized that this leak of "labile" iron can directly bind to plasma proteins so that oxidative stress is induced. Animal studies have shown that non-specific uptake of circulating iron by different organs might lead to inflammation and even tissue injury [11–14].

This study aims to clarify the short term and long term effects of intravenous iron replacement on biomarkers for oxidative stress in women with iron deficiency anemia.

Materials and Methods

The present study was approved by the Ethical Committee of Mugla Sitki Kocman University Medical School Hospital where it was undertaken between January 2020 and March 2020. This study was conducted in accordance with the guidelines of Helsinki Declaration so that all participants were informed about the study design and their written consents were obtained.

Study Design

This is a cross-sectional analysis of 40 patients diagnosed with iron deficiency anemia and 40 healthy controls. All of the patients with iron deficiency anemia and healthy controls were adult females. The women with iron deficiency anemia underwent intravenous iron treatment (ferric carboxymaltose, 500 mg/10 ml) as soon as the diagnosis of anemia was made. Complete blood count, biochemical analyses and biochemical evaluation for oxidative stress were simultaneously performed for the patients with iron deficiency anemia and healthy controls. The biochemical evaluation for oxidative stress markers were reproduced at hour 1 and day 30 of intravenous iron treatment.

The patients with acute and chronic systemic diseases, the patients who have been already under treatment for iron deficiency anemia, the patients who were diagnosed with infections in the preceding four weeks, the patients who were using any drugs (including vitamin and mineral supplements), the patients with a habit of smoking and/or alcohol consumption, the patients with any dietary restriction, pregnant and breastfeeding women were excluded.

Laboratory Studies

Venous blood samples were retrieved in early morning after 8 hours of fasting. In order to avoid further oxidation, they were immediately centrifuged at 3600 g for 10 minutes after retrieval and then stored at -80 C for biochemical measurements. Complete blood count was made by means of an XN-1000 Sysmex hematology auto-analyzer and biochemical determinations were made by using Beckman Coulter Olympus AU 2700 system.

Plasma catalase activity was colorimetrically determined using an assay kit containing a stopping solution based on Jeong method [15]. The measurement of serum ferroxidase activity was based on the oxidation of o-dianizidine. Since serum ferroxidase activity was highest at pH: 5.1, serum was mixed with acetate buffer at this pH and then added to the dianizidine. As O-dianizide is oxidized by ferroxidase, alterations in color occur and the enzyme activity was measured kinetically at 460 nm [16].

Plasma nitrite/nitrate levels were measured by a modification of the procedure described by Braman and Hendrix [17] using the purge system of a Sievers Instruments Model 270B Nitric Oxide Analyzer (NOA 228; Sievers Instruments Inc., Boulder, CO, USA). Plasma

samples were diluted and deproteinized using chilled 100% ethanol (plasma/ethanol = 1:2 vol/vol), and a saturated solution of VC13 in 1 M HCI was prepared and filtered prior to use.

Total thiol level was measured by using an automatic measurement method defined by Erel and Neselioglu (Roche Hitachi Cobas c501 automatic analyzer, Roche Diagnostics, USA). In this method, dynamic disulfide bonds (-S-S-) are reduced to thiol groups (-SH) by NaBH4 and then Elman's reagent was used to determine the amount of total thiol [18].

Total Antioxidant Status (TAC) [19] and Total Oxidant Status (TOS) [20].Assay Kit (Rel Assay Diagnostics, TR) were used for measurements. Measurements were made by the manual method. The TAS results were offered as mmol Trolox Eq/L, however, TOS results were presented µmol H2O2 Eq/L for serum.

Statistical Analysis

Collected data were analyzed by Statistical Package for Social Sciences version 19.0 (SPSS Inc., SPSS IBM, Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation whereas categorical variables were denoted as numbers of percentages. Shapiro Wilk test was used to analyze the distribution of data. Student t-test and Mann Whitney U test were used for the comparisons. Two-tailed p values less than 0.05 were accepted to be statistically significant.

Results

Table 1 compares the clinical and biochemical characteristics of the controls and anemic patients. The women with iron deficiency anemia had significantly lower hemoglobin, lower ferritin, higher platelet count, lower mean corpuscular volume, lower iron, higher erythrocyte sedimentation rate and higher C-reactive protein than the healthy controls ($p<0.05$ for each).

Figure 1 shows that the patients with anemia had significantly higher plasma catalase activity than the healthy controls (p=0.0245). Plasma catalase activity at day 30 of intravenous iron treatment was significantly lower than the plasma catalase activity before the administration of treatment (p=0.0332) and at hour 1 of treatment (p=0.0498). When compared to the hour 1 of intravenous iron treatment, serum ferroxidase activity was significantly lowered at day 30 of the treatment (p=0.0049) (Figure 2).

Figure 3 demonstrates that the patients with anemia had significantly lower concentrations of plasma nitrate than the healthy controls (p=0.0437). Plasma nitrate concentrations at hour 1 of intravenous iron treatment were significantly lower than those before the administration of iron treatment (p=0.0322). Plasma nitrate concentrations at day 30 of intravenous iron treatment were significantly higher than those before the administration of iron treatment (p=0.0015) and at hour 1 of treatment ($p<0.0001$).

Table 1. Clinical characteristics of the controls and anemic patients

	Control (n=40)	Anemia (n=40)
Age (years)	28.6±1.1	36.4±1.3
Hemoglobin (g/dL)	13.5±0.2	11.2±0.3*
Leukocyte count (x1000/µL)	7.3±0.3	6.3±0.3
Platelet count (x1000/µL)	248.3±7.8	309.9±11.7*
Mean corpuscular volume (fl)	86.8±4.6	74.7±3.9*
Glucose (mg/dL)	91.1±1.2	90.2±1.4
Urea (mg/dL)	21.6±0.8	21.8±1.3
Creatinine(mg/dL)	0.60±0.01	0.58±0.02
Albumin (g/dL)	4.6±0.10	4.57±0.04
Alanine transaminase (U/L)	15.3±1.4	14.2±1.4
Aspartate transaminase (U/L)	15.4±0.6	15.9±0.8
Lactate dehydrogenase (U/L)	168.6±3.6	163.7±5.7
Iron (µg/dL)	85.3±5.6	61.4±5.6*
Total iron binding capacity (µg/dL)	342.3±6.5	355.3±11.7
Transferrin saturation (%)	25.5±1.7	19.3±2.1
Ferritin (ng/ml)	33.9±3.1	7.43±0.8*
Vitamin B12 (pg/ml)	346.7±22.8	345.12±22.6
Erythrocyte sedimentation rate (mm)	8.6±0.9	13.6±1.6*
C-reactive protein (mg/L)	2.0±0.4	2.81±0.7*

*p<0.05 was accepted to be statistically significant.

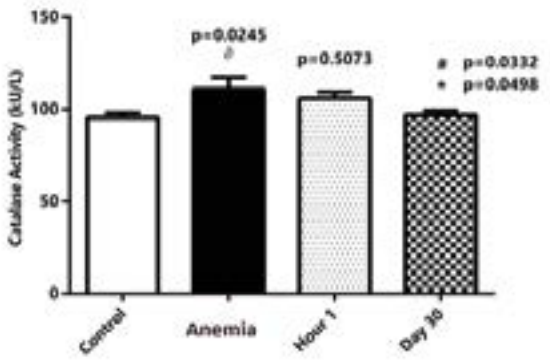

Figure 1. Catalase activity of the participants

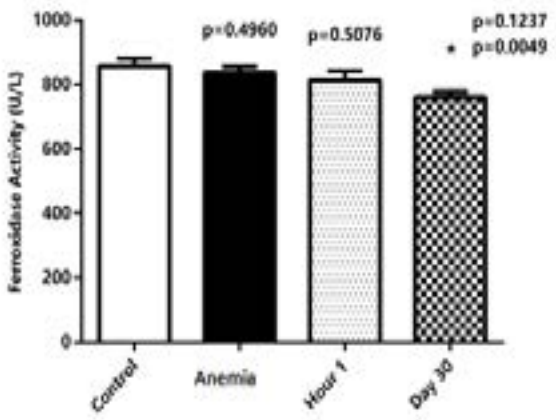

Figure 2. Ferroxidase activity of the participants

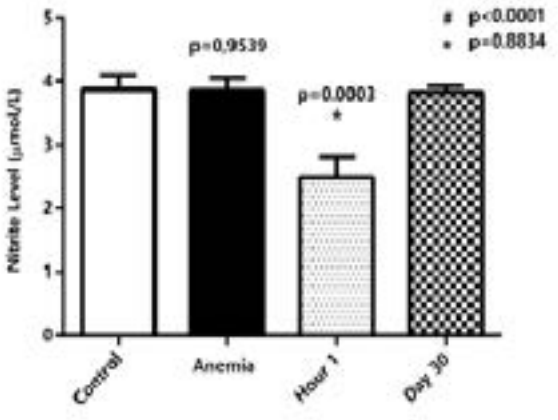

Figure 4. Nitrite levels of the participants

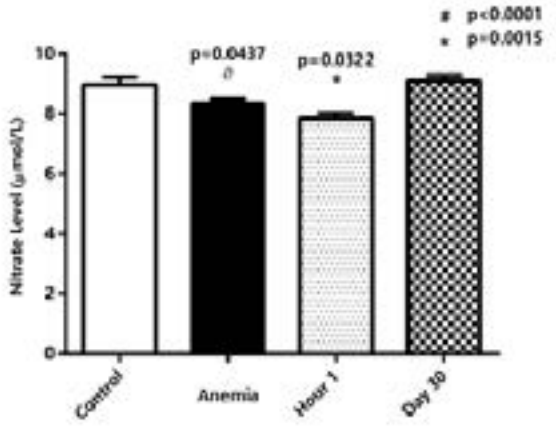

Figure 3. Nitrate levels of the participants

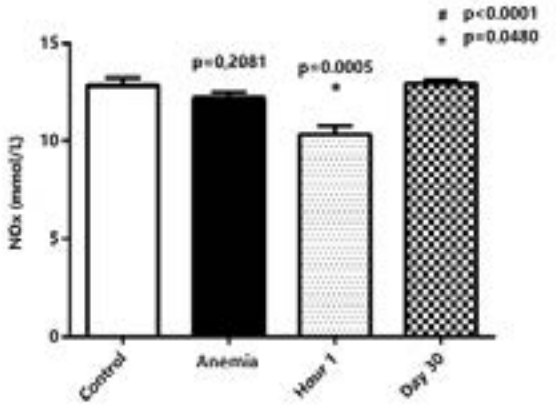

Figure 3. Nitrate levels of the participants

Figure 4 displays that plasma nitrite concentrations at hour 1 of intravenous iron treatment were significantly lower than those before the administration of iron treatment (p=0.0003). Plasma nitrite concentrations at day 30 of intravenous iron treatment were significantly higher than those at hour 1 of treatment (p=0.0001).

Plasma nitric oxide levels at hour 1 of intravenous iron treatment were significantly lower than those before the administration of treatment (p=0.0005). Plasma nitric oxide levels at day 30 of intravenous iron treatment were significantly higher than those before the administration of treatment (p=0.0480) and at hour 1 of treatment (p<0.0001) (Figure 5).

Serum total thiol levels at hour 1 of intravenous iron treatment were significantly lower than those before the administration of treatment (p<0.0001). Serum total thiol levels at day 30 of intravenous iron treatment were significantly lower than those before the administration of treatment (p=0.0391) and significantly higher than those at hour 1 of treatment (p=0.0004) (Figure 6).

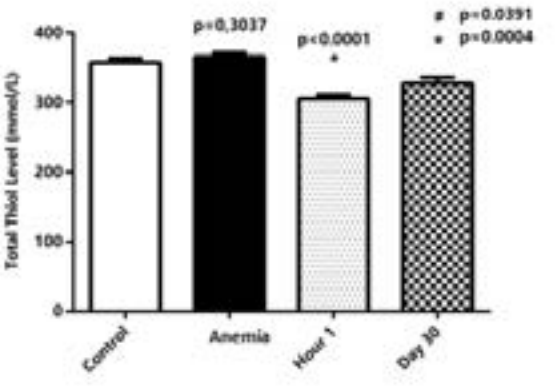

Figure 6. Total thiol levels of the participantsts

Figure 7 points out that the patients with anemia had significantly lower TAS than the healthy controls (p<0.0001). The TAS values at hour 1 of intravenous iron treatment were significantly lower than those before the administration of treatment (p<0.0001). The TAS values at day 30 of intravenous iron treatment

were significantly higher than those before the administration of treatment (p=0.001) and at hour 1 of treatment (p<0.0001).

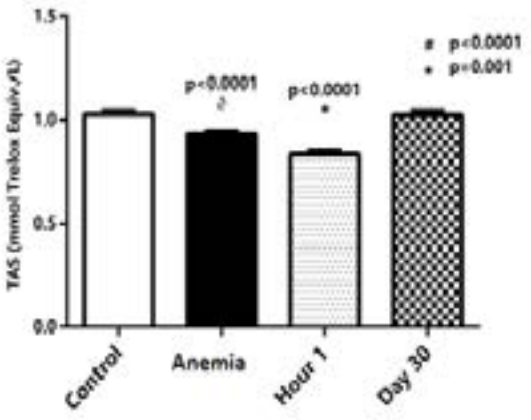

Figure 7. Total anti-oxidant status of the participants

Figure 8 indicates that the patients with anemia had significantly higher TOS than the healthy controls (p<0.0001). The TOS values at hour 1 of intravenous iron treatment were significantly higher than those before the administration of treatment (p=0.004). The TOS values at day 30 of intravenous iron treatment were significantly lower than those before the administration of treatment and at hour 1 of treatment (p<0.0001 for both).

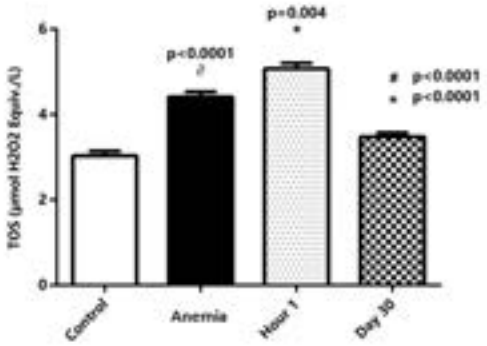

Figure 8. Total oxidant status of the participants

Discussion

Oxidative status refers to the equilibrium between oxidants and anti-oxidants in normally functioning cells [21]. If a pathological condition occurs, the equilibrium shifts towards the oxidants and oxidative stress emerges [22]. Oxidative stress causes oxidation in normally functioning cells which eventually results in cell death and tissue injury [21,22].

Being the major pro-oxidants, reactive oxygen species are produced by mitochondria during energy generation [23]. The main anti-oxidant mechanisms consist of water or lipid-soluble molecules that counteract and eliminate reactive oxygen species [24]. Thiols are the principal anti-oxidant molecules of which reduced thiol glutathione is the most significant. Moreover, dynamic thiol/disulfide homeostasis has been addressed as an indicator for oxidative stress [25]. Catalase is an enzyme which neutralizes hydrogen peroxide and fatty acid radicals. Similarly, ferroxidase activity of ceruloplasmin is an anti-oxidant mechanism that hinders the formation of free radicals from iron by accelerating the oxidation of Fe+2 to Fe+3 [24].

Bioactive nitric oxide originating from the nitrate-nitrite-nitric oxide pathway might reduce the mitochondrial synthesis of reactive oxygen species so that cytotoxicity and apoptosis could be prevented [26]. Such a mechanism of cytoprotection related with the enhancement of nitrate-nitrite-nitric oxide pathway has been specified in ischemia-reperfusion injury [27]. Nitrite and nitrate are endogenously synthesized by quick oxidation of nitric oxide which is derived by nitric oxide synthase [24,26]. Plasma levels of nitrate or the sum of plasma nitrate and nitrite concentrations reflect the activity of nitric oxide synthase [26,27].

It has been well established that hypoxia induces the production of reactive oxygen species. Similar to chronic obstructive pulmonary disease, iron deficiency anemia leads to tissue hypoxia which triggers the production of reactive oxygen species [28]. The deficiency of iron also interrupts the maintenance of sufficient ATP stores during oxidative phosphorylation in the mitochondria [29]. In order to adapt to hypoxia, transcriptional activator hypoxia-inducible factor-1 (HIF-1) is synthesized in patients with chronic anemia. This factor decreases mitochondrial mass and decelerates mitochondrial metabolism, reducing the production of reactive oxygen species [30].

The activity of the anti-oxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase is significantly lowered in adults with iron deficiency anemia than the healthy controls [31,32]. Additionally, iron deficiency anemia causes the upregulation of nitric oxide synthase and elevation of nitric oxide in otherwise healthy adults [32].

Complying with literature, the patients with anemia were found to have significantly higher TOS and

lower TAS than the healthy controls in this study. On the contrary, the patients with anemia had significantly higher plasma catalase activity and lower plasma nitrate level. This contradictory finding might be due to the relatively small cohort size, differences in measurement techniques and variations in the duration of iron deficiency anemia.

In vitro studies have demonstrated that parenteral iron therapy has a potential of releasing labile and redox-active iron and precipitate the formation of oxidants [33,34]. However, several animal studies have reported that intravenous iron treatment causes oxidative stress at varying severity [11–14]. Most of these animal studies have been performed with the iron doses that are higher than those used in clinical practice. It might be argued that these significantly higher doses are required to compensate for the shorter half-life of iron complexes in rodents [11,12].

A number of clinical studies have been conducted to evaluate how intravenous injection of various iron preparations would affect the biomarkers for oxidative stress [8–10]. Although these studies tend to report about the augmentative effects of intravenous iron complexes on oxidative stress, their findings should be interpreted carefully. The first reason is that hemodialysis patients make up the cohorts in the majority of the studies focusing on oxidative stress related with parenteral iron therapy. Since hemodialysis alone is a well-known underlying etiology for inflammation, oxidative stress and endothelial dysfunction, data about the oxidative stress markers in hemodialysis patients might have been biased. The second reason is the heterogeneity of the intravenously administered iron preparations. The majority of related studies have been performed with iron sucrose whereas only a few studies have been held with ferric gluconate, low molecular weight iron dextran, ferric carboxymaltose and iron sucrose similar complexes. The third reason is the heterogeneity in the selection of biomarkers for the assessment of oxidative stress. The fourth reason is the distinct distribution of various iron preparations in different tissues which end up with varying degrees of oxidative stress. For instance, iron sucrose similar complexes are concerned with significantly higher levels of oxidative stress in heart, liver and kidneys than iron sucrose.

As for the present study, the levels of TAS, nitrate, nitrite, nitric oxide, and total thiol were significantly reduced however; TOS levels were elevated in patients with anemia at hour 1 of intravenous iron treatment. At day 30 day of parenteral iron therapy, catalase activity, nitrate, total thiol and TOS values were significantly lowered and nitric oxide and TAS values were significantly elevated when compared to hour 1 and time of diagnosis.

Conclusion

These findings suggest that parenteral iron therapy prompts oxidative stress in adults with iron deficiency anemia. Oxidative stress increases markedly in hour 1 of intravenous iron infusion but this increase appears as a transient alteration which undergoes a partial recovery spontaneously in the following 30 days. Therefore, it would be prudent to assume that the elevation in oxidative stress might be a temporary change in otherwise healthy patients receiving intravenous iron treatment due to anemia. The power of the present study is limited by relatively small cohort size, inability to study all biomarkers for the evaluation of oxidative stress and lack of long term data. Further research is warranted to clarify the effects of intravenous iron administration on biomarkers for oxidative stress in anemic adults.

Funding
The author has no conflicts of interest to declare.

Conflict of interest
The author declared that this study has received no financial support.

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HEALTH SCIENCES QUARTERLY

Volume : 1
Issue : 1
2021

E-ISSN: 2791-6022
https://journals.gen.tr/jsp

Received: 2021-04-04

Acccepted: 2021-04-14

ORIGINAL ARTICLE

The prevalence of asthma-COPD overlap syndrome in women patients with biomass fuel utilizing

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Abstract

Asthma-chronic obstructive pulmonary disease overlap (ACO) indicates that its characteristics with pulmonary exaggerated reactivity and airflow limitation chronically. We aimed to investigate the differences among women non smoker participants who have asthma, chronic obstructive pulmonary disease (COPD) and ACO with biomass smoke exposure. Patients were examined at the outpatient clinic from September 2017 to March 2020. Non-smoker women patients aged ≥40 years, diagnosed with obstructive pulmonary disease were included in the study. pulmonary function tests (PFT), early reversibility testing (bronchodilator test), and sputum eosinophil analysis were performed to all patients. A total of 102 patients were included. The mean age was 46.95±9.50 years. In the differential diagnosis, 65 patients (63.7%) had asthma and 37 patients (36.3%) had COPD. Among COPD patients, 10 (27.0%) were diagnosed with ACO. The actual prevalence rates of COPD and ACO were 26.5% and 9.8%, respectively. Poisson regression analysis showed that COPD compared to asthma, while holding the others variable constant in the model, are expected to have 2.976 times greater rate for exacerbations. (IRR, 95% CI, 2.976 (0.687 to 1.494), 5.296 (1.203 to 2.130), P<0.001, Coef. 1.091, 1.667 respectively). Logistic Regression analysis demonstrated that, the count of sputum, blood eosinophil and total IgE results were correlated with the exacerbation times. Biomass smoke exposure in the women population is revealed as a significant factor for the diagnosis of ACO.

Keywords: *Chronic obstructive pulmonary disease, asthma, asthma-COPD overlap, biomass smoke*

Citation: Yormaz B. The prevalence of asthma-COPD overlap syndrome in women patients with biomass fuel utilizing. Health Sci. Q. 2021; 1(1), 11-17. https://doi.org/10.26900/hsq.1.1.03

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Introduction

Asthma and COPD are the most common lung diseases all over the World [1,2]. Chronic obstructive pulmonary disease (COPD) is characterized by permanent airflow obstruction the pulmonary parenchyma. Tobacco smoking is main cause of COPD, but increasing evidence suggests that 30% of COPD patients have never smoked. Exposure to high levels of indoor biomass smoke, and workplace exposure to dust and fumes are also known as independent risk factors for COPD. On the other hand, asthma may be a risk factor for the development of COPD [3-4].

Biomass is more frequently used for cooking and heating in rural areas of developing countries. Biomass-burning stoves emit significant quantities inhalable health-damaging pollutants. Exposure to biomass smoke has been shown to increase the risk for development of chronic bronchitis, COPD, and asthma [5-8].

Differential diagnosis of asthma and COPD is usually easy with age, symptoms, and spirometric examinations. However, it is not always possible to make a differential diagnosis of COPD with asthma, especially in the population above 40 years of age who is smoker or exposed to biomass smoke. On the other hand, there is a growing consensus that typical asthma and COPD manifestations can both exist simultaneously in a single patient. Therefore, the ACO is used at when the patient with asthma has COPD features or vice versa. [9,10] .

In this study, we aimed to determine the frequency of ACO and to make differential diagnosis of asthma and COPD in non-smoker women patients with long-term biomass smoke exposure

Materials and Methods

Participants

This study was planned prospectively. The study protocol was accepted by the Local Ethics Committee of University, and an informed consent was taken from all participants. Furthermore this study was performed according to the principles of the Declaration of Helsinki.

The patients were selected at the outpatient clinic of University Hospital from September 2017 to March 2020. Inclusion criteria were as follows: women patients aged 40 years diagnosed with asthma or COPD based on the medical records, non-smoker, biomass smoke exposure at least 20 years, and the use of inhaled drugs (bronchodilator and/or corticosteroid) for at least 12 months. Exclusion criteria were as follows: the presence of comorbid severe chronic respiratory disease (cystic bronchiectasis, pulmonary fibrosis, kyphoscoliosis, active neoplasm) and the inability to perform diagnostic spirometry.

Spirometric Tests

All spirometric examinations were carried out using a single pulmonary function testing system (Viasys Mastercope, Germany). A standard spirometric examination and early reversibility testing (bronchodilator test) were performed in all patients. Spirometry was performed 12 h after the use of long-acting bronchodilator and 24 h after. The patients inhaled 400 µg β2-agonist (salbutamol) aerosol (metered-dose inhaler) with a spacer and the test was repeated 20 min later to evaluate early reversibility.

Sputum collection and analysis

Sputum samples induced by the inhalation of 3% sterile saline solution with a nebulizer were collected as described previously. The nebulization with tidal breathing was continued for at least 10 min. The patient was asked to cough and expectorate at 5 min intervals during nebulization. The sputum samples were collected in sputum collection bottles and sent to the pathology laboratory. In the initial step of preparation, 5 cc alcohol-based solution was added to the sample for fixation and elimination of erythrocytes. After separation from supernatant by centrifugation, the sample was put into the BD PrepStain™ automatic staining machine and Papanicolaou's (PAP) stain was performed. The glasses were covered with a cover slip and subsequently examined under a light microscope. The eosinophil count was expressed in the ratio of eosinophils to total cell count. Therefore, at least 10 high-power fields were evaluated on each PAP-stained slide [11].

Diagnosis of asthma and COPD

The criteria used to diagnose asthma were as follows: (1) history of wheeze; (2) a positive early reversibility test; and (3) forced expiratory volüme in 1 second/ forced vital capacity (FEV1/FVC) >0.70 after 400 µg salbutamol inhalation. (12) The diagnosis of COPD was made in the patients with symptoms compatible with COPD and was not fully reversible airflow limitation (post-bronchodilator FEV1/FVC ratio 0.70).

Diagnosis of ACO

Major diagnostic criteria were as follows: (1) biomass smoke exposure for at least 20 years; (2) history of asthma before the age of 40; (3) an increase in the post-bronchodilator FEV1 400 mL and 15% of the baseline; (4) a sputum eosinophil ratio of 3%. Minor diagnostic criteria were as follows: (1) history of atopy or allergic rhinitis; (2) an increase in the post-bronchodilator FEV1 200 mL and 12% of the baseline; (3) peripheral eosinophilia (300 cells/μL); (4) increased total immunoglobulin E. The diagnosis of ACO was based on at least three major criteria and a minor criteria in patients with permanent airflow limitation (FEV1/ FVC 0.70).

Statistical Analysis

All statistical analysis enrolled with R Version 3.6.0 (www.r-project.org). Anderson Darling test and Levene test were used to check assumptions of normality and homogeneity of variances, respectively. Continuous variables were described as median (interquartile range), and analyzed with Kruskal Wallis test. After Kruskal Wallis test, post hoc analysis with Conover-Iman test was performed with a Bonferroni test with significance level set at $p<0.016$. Spearman's rho correlation analyses were applied to evaluate relationship between parameters. $p<0.05$ was considered statistically significant for general analyses. Box-plot with test and significance values was presented for the number of exacerbations within the last year according to patients groups. Scatter plot was presented to show for relationship between sputum eosinophil count and blood eosinophil count. The risk factor for the number of exacerbations within the last year was calculated in a model using Poisson regression, and it was expressed as an incidence rate ratio (IRR) with 95% confidence interval (CI). The independent variables in this model were patients groups, sputum and blood eosinophil counts, and Total IgE. Poisson regression is used to count variables. Due to the number of exacerbations within the last year had Poisson distribution, we used Poisson regression model to determine the risk factor of its.

Results

A total of 102 non-smoker women patients aged 40 years with a history of biomass smoke exposure for at least 20 years were included. Patients who were diagnosed as asthma in 63.7% (65/102) and COPD in 36.3% (37/102), Also ACO were diagnosed in 10 (27.0%) patients who were detected in COPD group (Figure 1).

The actual prevalence rates of COPD and ACO were 26.5% and 9.8%, respectively. Table 1 shows demographic, clinical and functional characteristics of patients.

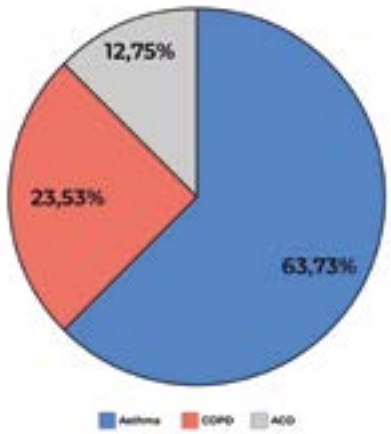

Figure 1. Distribution of patients according to diagnosis

Table 1. Demographic and clinical characteristics of patients

Characteristics	Asthma (n=65)	COPD (n=27)	ACO (n=10)	p-value
Age (year)	32 (24 – 39)a	51.5 (43 – 57.25)b	58 (45 – 64)	0.001
BMI	33 (28 – 37)	31 (28 – 35.25)	31 (28 – 36)	ns
Mean Exacerbations times (n, 12 months)	0 (0 – 1)a	2 (1 – 3)b	4 (3 – 5)c	<0.001
Survival of Exacerbations	1.7(1.1-2).3	2.5(1.5-3.1)	2.9/(2.3-3.7)	<0.001
FEV1 (%)	101.5 (84 – 11.25)a	56.5 (43.5 – 70.25)b	61 (46 – 75)b	<0.001
FVC (%)	100 (85.25 – 110.5)a	74 (60.5 – 85)b	84 (69 – 97)	<0.001
FEV1/FVC	82.5 (78 – 87.25)a	63.5 (56 – 68.85)b	60 (55 – 62)b	<0.001
Sputum eosinophil (%)	1 (0.20 – 2.50)a	0.50 (0.20 – 1.50)a	4.30 (3 – 5.20)b	<0.001
Blood eosinophil (cell/μL)	0.13 (0.07 – 0.30)a	0.04 (0.01 – 0.11)b	0.35 (0.19 – 0.40)c	<0.001
Total IgE (IU/mL)	18 (9 – 87)a	27.5 (8.75 – 72)a	134 (41 – 246)b	<0.001

p-value: Kruskal Wallis test, $p<0.001$was considered statistically significant, ns: not significant,Values were presented as median (interquartile range), Conover-Iman test with a Bonferroni correction was used to multiple comparisons, Different letters in rows indicated that statistically significant difference ,BMI: Body mass index, FEV1: Forced expiratory volûme in 1 second, FVC: Forced vital capacity.

The mean age of the study population was 36.95±2.50 (range, 24 to 64) years. There was a significant difference in the FEV1/FVC and FVC between asthma and COPD, between asthma and ACO patients, while no significant difference was found between COPD and ACO patients (Table 1). Also, there was a significant difference in the FEV1 between asthma and

COPD patients and between asthma and ACO patients (p=0.0001 and p=0.001, respectively), while there was no significant difference between COPD and ACO patients. Furthermore, we have found that there were significant differences in the reversibility of airflow limitation among patients groups. The reversibility of airflow limitation was the greatest in patients with ACO. The increase in post-bronchodilator FEV1 was significantly greater in the ACO group than COPD group and the asthma group (p<0.001). The increase in FEV1 was also significantly greater in the asthma group than in the COPD group (p<0.001). The number of the patients with a FEV1 of 200 mL and 12% in bronchodilator response was 18 (27.69%) in the asthma group, 4 (12.5%) in the COPD group and 8 (61.5%) in the ACO group. Kruskal Wallis test showed that there was a statistically significant difference in numbers of exacerbations within the last year according to patients groups. Post hoc analysis with Conover-Iman test was conducted with a Bonferroni correction applied, resulting in as significance level. The median (IQR) number of exacerbations for the asthma, COPD and ACO patients were 0 (IQR 0 – 1), 2 (IQR 1 – 3) and 4 (IQR 3 – 5), respectively. Also, the mean number of exacerbations within the last year for the asthma, COPD and ACO patients were 0.72 ± 0.91, 2.17 ± 1.55 and 3.77 ± 1.54, respectively (Figure 2). The number of exacerbations within the last year was statistically significant in the ACO group than in the asthma and COPD group. Also, the number of exacerbation within the last year was statistically significantly higher in the COPD group than in the asthma. Mean total IgE values were highest in ACO patients (p<0.001). Sputum hypereosinophilia was seen in 38.4%, 12.5%, 61.53% patients with asthma, COPD and ACO, respectively. There was a significant correlation between the blood and sputum eosinophil counts (Figure 3). However, no significant correlation between the post-bronchodilator FEV1 and blood and sputum eosinophil counts. There was also no significant correlation between the frequency of exacerbations and blood and sputum eosinophil counts. COPD compared to asthma, while holding the others variable constant in the model, are expected to have a rate 2.976 times greater for the number of exacerbations within the last one year. Furthermore ACO compared to asthma, while holding the others variable constant in the model, are expected to have a rate 5.296 times greater for the number of exacerbations within the last one year (Table 2). The assessment of sputum, blood eosinophil and total IgE count within the last year showed in Table 3. The effect of number of exacerbations within the last year was statistically significant in groups besides that, the count of sputum, blood eosinophil and total IgE results were correlated with the exacerbation times significantly per year. The survival of ACO patients was significantly better than of COPD patients (Figure 4). Predicted lung function was poor and worse in patient with COPD and Asthma groups but the prognosis was better in ACO patients with the improvement in FEV1 outcomes.

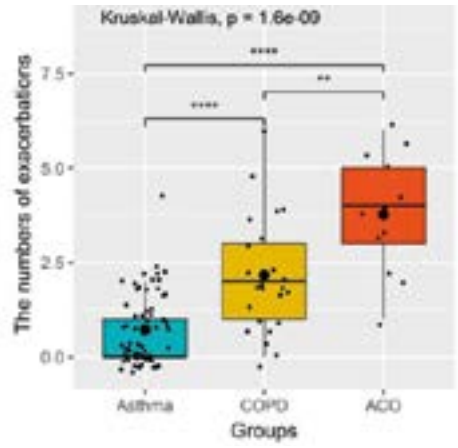

Figure 2. Exacerbations within the last year according to patients group

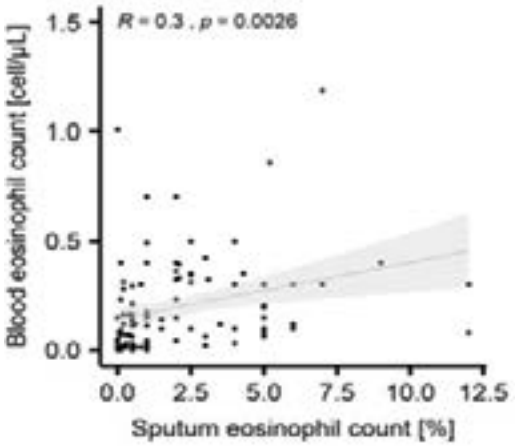

Figure 3. Correlation between blood and sputum eosinophil [%] count

Table 2. Poisson Regression for The Number of Exacerbations within the last one year

Parameters	Coef.	Std. Err.	IRR	95% Conf. Interval	p-value
Patients Groups					
Asthma	**Reference group**				
COPD	1.091	0.206	2.976	0.687 to 1.494	<0.001
ACO	1.667	0.237	5.296	1.203 to 2.130	<0.001

Coef.: Estimated Poisson regression coefficients, Std. Err.: Standard errors of the regression coefficients, z: Test statistics, 95% Conf. Interval: Confidence interval of poisson regression coefficients, IRR: Incidence rate ratio. p<0.001 was considered statistically significant, ACO: Asthma-chronic obstructive pulmonary disease overlap, COPD: chronic obstructive pulmonary disease

Table 3. Logistic Regression analysis of laboratory markers efficacy for evaluating the exacerbation time

Parameters	Coef.	Std. Err.	IRR	95% Conf. Interval	p-value
Sputum eosinophil count (%)	-0.018	0.043	0.981	-0.102 to 0.066	<0.001
Blood eosinophil count (cell/µL)	0.043	0.436	1.043	-0.812 to 0.897	<0.001
Total IgE (%)	0.001	0.001	1.001	-0.001 to 0.029	<0.001

Coef.: Estimated Poisson regression coefficients, Std. Err.: Standard errors of the regression coefficients, z: Test statistics, 95% Conf. Interval: Confidence interval of poisson regression coefficients, IRR: Incidence rate ratio. p<0.001 was considered statistically significant

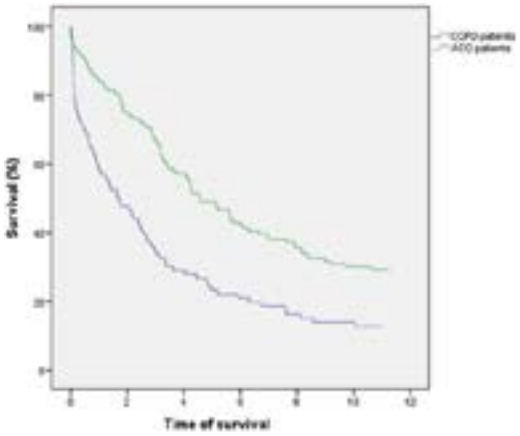

Figure 4. The survival of ACO patients was significantly better with median survival time, compared to COPD patients

Discussion

In developed countries, tobacco smoke is the common risk factor for COPD. On the other hand biomass smoke exposure is the most important factor in undeveloped countries, primarily. Biomass smoke exposure is estimated to effect 2 million women negatively every year [12-14].This study investigated the non-smoker women patients with asthma, COPD or ACO with biomass smoke exposure.

Data describing the pathophysiology of biomass smoke-related COPD emerges mainly from in vitro researchs. Acute exposure to biomass smoke lead to elevation in neutrophilic inflammatory reaction of pulmonary structure. Besides that eosinophilic and lymphocytic inflammation detected in Subchronic exposure. And also Chronic exposure is detected in experimental research characterized by increase in fibroblasts volume and collagen accumulation at bronchioles, and elevation in matrix metalloproteinases in the epithelial cells of lung. A research study demonstrated that smoke particules may lead to inflammatory response at lung structure. In an invitro study, it is revealed that plant smoke significantly evokes the expression of aryl hydrocarbon receptor (AHR) which lead to decline in anti-inflammatory way, also resulted to increasing in inflammation. Hence, pressive of AHR is a remedial destination for smoke-related exacerbation [15-18].

Patients who were over 40 years old, show with symptoms of chronic airways disease findings of asthma and COPD called as the asthma-COPD overlap syndrome (ACO); identified in the GOLD consensus as 'described by permanent limitation of air flow oftenly related with asthma and COPD features. Patients who were afflicted by ACO more prone to hyper-reactivity in pulmonary system than with COPD. Furthermore, patients with ACO tend to have more pulmonary exacerbations than s with COPD alone and asthma alone [19]. Solleiro-Villavicencio et al. found that Th2 inflammatory response which may cause to airway hyperresponsiveness, progressed mucus production evoked by the exposing of biomass smoke who have diagnosed of COPD. Various studies demonstrate a dose-response relationship between the biomass smoke exposure and the severity of airflow obstruction [20-24]. In evaluation of longutudinal meta-analysis showed that biomass-exposing has contributed to establishment of COPD than non-exposing situations. Furthermore, In an epidemiological research demonstrated that the rate of biomass smoke exposure was more than half among women population living in rural areas. Also this research suggested that the risk percentage of COPD was detected twice as much higher than cigarette smoking [25,26].

In this study, we have revealed that patients with ACO have better prognosis compared to COPD and asthmatic patients. Furthermore the overall survival of ACO patients hospitalised for exacerbation was poor than COPD and Asthma [27]. In a midterm research study, ACO was related with the decreasing in lung function than COPD or asthma alone [28]. The lung function of patients with ACO was worse than patients with COPD, however of obstruction of respiratory way and inflammation have better than patients with asthma. ACO patients with FEV1 under 50% of their predicted value had superior survival when compared to COPD patients with similar lung function. The variables (such as FEV1, FVC) used for evaluating the severity of illness and identify the risk of mortality, which can predict the prognosis of patients with

airflow limitation diseases like as COPD, ACO and Asthma [29] .

Kitaguchi et al. founded that only FEV1, FVC was significantly higher in the asthma group than in the ACO group. We have found that there were significant differences in spirometry parameters. There was also a significant difference detected in FEV1, FVC outcomes among the groups, while there was no significant difference detected between patients with COPD and ACO [30]. It is still unclear that whether sputum or blood eosinophil count is reliable and valid. Some studies have used sputum eosinophil in the diagnostic criteria of ACO. On the other hand, blood eosinophil count was considered as the main diagnostic marker of ACO. Both paremeters were used for diagnosis of ACO in present study. Furthermore It was suggested that peripheral blood eosinophil counts could be helpful for identifying the sputum eosinophilia in stable COPD patients [31-34]. Similar to these studies, present study demonstrated a signficant correlation between sputum and blood eosinophil results.

The studies demonstrated that the prevalence of ACO increased with increasing age. Present study determined that ACO patients was younger than COPD patients however this difference was not statistically significant. The frequency of exacerbations in ACO patients was significantly higher than asthma and COPD in our study correlated with the literature reviews [35,36]. Biomass smoke exposure, is oftenly overlooked in women who live at rural areas such as villages and also most important etiological factor for the diagnosis of COPD, However, the lack of the consensus on the diagnostic criteria for ACO makes the diagnosis difficult. Especially women who were exposed to biosmoke should be evaluated in terms of airway disease, not only asthma or COPD, but also ACO should be considered and treatment protocol should be arranged accordingly [37].

There were some limitations in this study. Firstly, this was a not a large population study however the ACO was a novel concept diagnosis and larger populations are required to obtain clues in the differential diagnosis of asthma, COPD and ACO. Secondly, we have not evaluate exhaled nitric oxide, DLco and DLco/alveolar volume in the differential diagnosis.

Conclusion

Biomass smoke exposure in women population is revealed as a significant factor for the diagnosis of ACO due to common used in rural areas for cooking or heating. Laboratory markers may be effective for, estimating the exacerbation time, separating the differences in airway diseases and resulted to the real diagnosis.

Funding
The author declared that this study has received no financial support.

Conflict of interest
The author has no conflicts of interest to declare.

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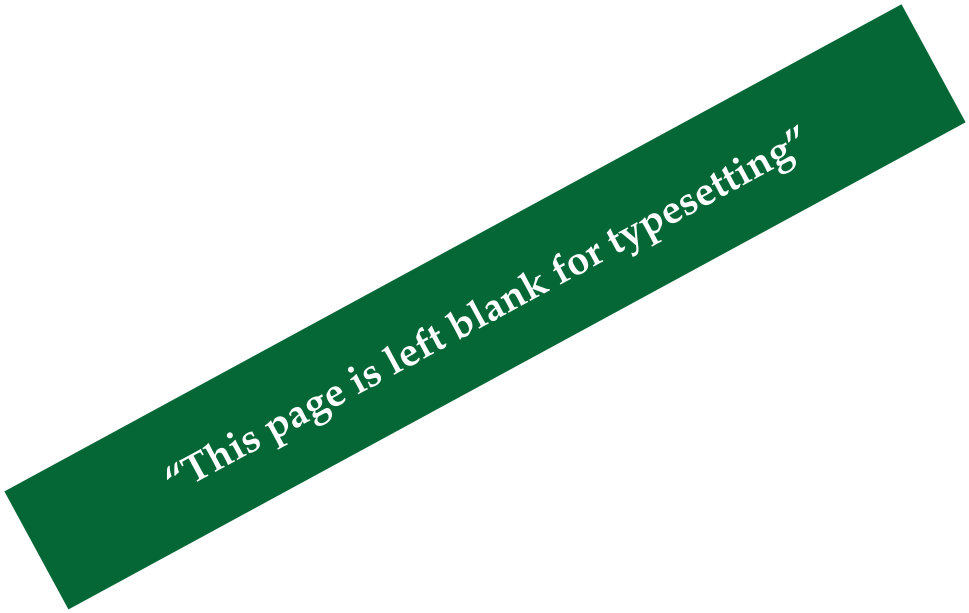
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HEALTH SCIENCES QUARTERLY

Volume : 1
Issue : 1
2021

E-ISSN: 2791-6022
https://journals.gen.tr/jsp

Received: 2021-03-07

Accepted: 2021-04-19

ORIGINAL ARTICLE

The association between low serum vitamin-B12 levels and hyperpigmentation in patients who use isotretinonin

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Abstract

Oral isotretinoin is the most effective agent in the treatment of acne vulgaris. The risk of pigmentation due to the systemic isotretinoin may be associated with decrease in serum levels of vitamin B12. The study aims to contribute to the literature by defining the association between the increase in pigmentation caused by oral isotretinoin (O-ISO) use and low vitamin B12 level (vit-B12). In our study we evaluated 144 patients who have facial acnes at medium degree according to FDA Acne Score and take O-ISO treatment with the dose 0.5 mg/ kg/ day for six months. The mean vit-B12 levels of the patients at the admission and 6th month and the existence of pigmentation at 6th month, the skin type and the skin layer at which the pigmentation occurs were evaluated. Association of vit-B12 level on admission and six months post drug use with the presence of pigmentation at six months, the type of skin and the skin layer in which pigmentation occurs were evaluated. In the patient group with pigmentation, the mean vit-B12 level after six months of drug use was statistically lower than the mean vit-B12 level on admission ($p<0.001$). In patients without pigmentation, difference between the mean levels of vit-B12 levels was not statistically significant ($p = 0,255$). As a result, it was determined that the mean vit-B12 level decreased due to O-ISO use and the association of hyperpigmentation and low vit-B12 level was statistically significant. Vit-B12 monitoring and supplementation, if necessary, can help us to prevent hyperpigmentation that may occur during the treatment.

Keywords: *Isotretinonin, hyperpigmentation, vitamin-B12, side effect*

Citation: Baysak S, Karagun E, Ayvaz HH. The association between low serum vitamin-B12 levels and hyperpigmentation in patients who use isotretino.Health Sci. Q. 2021; 1(1) : 19-24. https://doi.org/10.26900/hsq.1.1.04

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Introduction

Acne vulgaris is one of the most common skin disorders in the world, especially in the adolescence period, affecting 85-100% of individuals during any period of life. Prevalence of acne vulgaris is around 9.4%. The major pathogenic factors in the pathogenesis of acne vulgaris are increased sebum secretion, androgen stimulation, abnormal keratinization, and inflammation due to microbial colonization [1,2].

Many topical and systemic drugs can be used in the treatment of acne vulgaris. As topical treatments, antibiotics, azelaic acid, salicylic acid, benzoyl peroxide, retinoic acids, and combinations are commonly used. Antibiotics, hormonal agents and vitamin A derivatives (retinoids) are used as systemic treatment of acne vulgaris. Oral isotretinoin (O-ISO), a vitamin A derivative, is the most effective agent in the treatment of acne vulgaris [3]. O-ISO has been considered as the gold standard in the treatment of moderate to severe acne vulgaris [4,5].

Beside the local and cutaneous side effects such as hyper/hypopigmentation, excess sebum production, thinning of stratum corneum, inflammation of the skin and nasal hemorrhage, xerophthalmia, blepharoconjunctivitis, itching, photosensitivity, skin infections with Staphylococcus aureus; there have been rare but important systemic side effects of O-ISO such as hematological, musculoskeletal, endocrinologic, gastrointestinal, urinary and central nervous systems side effects [6,7]. Although the mechanism has not been fully understood, it has been documented that O-ISO may lead to decrease in vit-B12 and folic acid levels [8]. In this study, we aimed to contribute to the literature by defining a possible association between the increase of pigmentation and the low serum levels of vit-B12 caused by O-ISO.

Materials and Methods

This study was carried out as a prospective observational study between February 2016 and February 2017 in the Dermatology Clinic of Ağrı State Hospital after approval of the ethics committee of Van Regional Education & Research Hospital. This study was conducted according to the Declaration of Helsinki and all subjects provided informed consent.

The study included 144 patients who have topical and oral antibiotic-resistant moderate or severe facial acne vulgaris lesions and have been taking O-ISO (min 0,1- max 0,5 mg/kg/day) regularly for 6 months. Patients were selected from the group of patients who did not have any pigmentation disorder at the time of admission. The Fitzpatrick scale was used to evaluate the skin type before the treatment. The skin layer where the pigmentation occurred (dermis, epidermis, or both) was evaluated at the end of six months. Wood's lamp was used to determine the presence of pigmentation and the skin layer of pigmentation. The difference in serum vit-B12 levels at the time of referral and at six months after drug use, the presence and the depth of pigmentation and skin type were assessed.

Patients with any history of liver and/or renal failure, hyperlipidemia, malignity, dermatological or systemic diseases which cause pigmentation such as diabetes mellitus, atopic dermatitis etc. were excluded from the study. Furthermore, pregnant or planning to be pregnant, younger than 18 were not included either. Descriptive values of the quantitative measurements obtained in the study are given as mean, standard deviation, median, minimum and maximum levels and categorical measurements as frequency and percentage. Shapiro Wilk test was used as the preferred test of normality. Differences in the median of the quantitative variables between the groups were examined by the Mann Whitney-U test. The paired t test was used to compare the mean of the 6th month vit-B12 levels and B12 levels on admission and the Wilcoxon Signed Rank Test was used to compare the medians. Alpha level is accepted as 0.05 and $p < 0.05$ was considered as statistically significant. SPSS (ver. 21) program was used for statistical analysis.

Results

One hundred forty-four patients with acne vulgaris were included in this study. 60.4% (n=87) of the patients were female and 39.6% (n=35) of the patients were male. The mean age of the patients was 25.95±4.8. Other features of the patients such as skin type, the presence of pigmentation after the treatment and distribution of this pigmentation (epidermal, dermal or both) are presented in Table 1. The mean vit-B12 level at time of admission was similar in individuals with and without pigmentation ($p > 0.05$). Six months after the start of treatment, the mean vit-B12 level in the group without pigmentation was significantly higher than the group with pigmentation ($p = 0.013$)

(Table 2). In the group with pigmentation, the mean vit-B12 levels at six months after drug use was found to be significantly lower than the mean of vit-B12 measured at time of admission (p <0.001). In the group without pigmentation, there was no significant difference between the two mean vit-B12 levels (p> 0.05) (Table 3). Moreover, among the pigmented group patients, the mean vit-B12 values was not statistically significant according to the pigmentation layer (epidermal, dermal, both) (p=0,454).

Table 1. Sociodemographic characteristics and clinical and laboratory findings

		n	%
Sex	Female	87	60.4
	Male	57	39.6
Skin Type	II	9	6.3
	III	80	55.6
	IV	55	38.2
Pigmentation after the treatment	Yes	20	13.9
	No	124	86.1
Epidermal	Yes	16	11.1
	No	128	88.9
Epidermal-Dermal	Yes	13	9
	No	131	91
Dermal	Yes	17	12.5
	No	127	(87.5)

Table 2. Vitamin-B12 levels before and after treatment of pigmented and non-pigmented group

	Pigmentation	n	Mean	Median	Standard Deviation	Minimum	Maximum	p
Vit-B12 at time of admission	Yes	20	294.70	295.00	67.624	185	412	0.534
	No	124	307.38	300.00	73.865	170	456	
Vit-B12 after 6 months of O-ISO use	Yes	20	253.45	250.00	64.191	170	406	0.013
	No	124	299.75	300.00	79.043	130	470	

Table 3. Comparison of pre- and post-treatment vitamin-B12 levels between pigmented and non-pigmented group

Pigmentation		n	Mean	Median	Standard Deviation	Minimum	Maximum	p
Yes	Vit-B12 at time of admission	20	294.70	295.00	67.624	185	412	<0.001
	Vit-B12 after 6 months of O-ISO use	20	253.45	250.00	64.191	170	406	
No	Vit-B12 at time of admission	124	307.38	300.00	73.865	170	456	0.255
	Vit-B12 after 6 months of O-ISO use	124	299.75	300.00	79.043	130	470	

Discussion

In the study, the increase of pigmentation due to O-ISO treatment was found to be associated with a decrease in vit-B12 levels. This pigmentation increase could occur in all layers of the skin and the association was more evident in Type-IV skin type.

The amount of pigmentation in the skin may differ due to hereditary and/or acquired causes. Increase in hormones and enzymes leading to deterioration in melanocyte distribution and increase in melanin synthesis can lead to hyperpigmentation [9]. Drug-induced hyperpigmentation accounts for 10-20% of acquired hyperpigmentation. This hyperpigmentation may develop due to melanin storage, nonspecific cutaneous inflammation, post-inflammatory reaction, accumulation of specific pigment fragments of the drug or deposition of the triggering agent [6].

The frequency of mucocutaneous side effects during the O-ISO treatment can be seen as high as 95-100% depending on the dose [10-12]. It is established that the frequency of pigmentation due to O-ISO is 2-3.2% [13,14]. The mechanism of O-ISO causing hyper/hypopigmentation is not fully understood [15]. It is believed that initiation of low-dose and regular 3 months O-ISO treatment facilitates improvement of skin color due to the increase in collagen synthesis and dermal vascularization, cell differentiation and extracellular matrix stabilization [16,17]. Though, it is reported that high doses of O-ISO with a longer duration of therapy or an added treatment leads to hyperpigmentation [6,14-17]. O-ISO and glycolic acid combination results in an increased risk of hyperpigmentation, which is also associated with postinflammatory pigmentation [14,15]. Cytokines along with mediators such as leukotrienes, prostaglandins and thromboxanes are responsible for post-inflammatory hyperpigmentation [18,19]. Exposure to sunlight, results in proopiomelanocortin-derived peptides to cause hyperpigmentation by stimulating pigmentation in exposed areas [20]. In the study, 13.9% of participants developed hyperpigmentation after six months of O-ISO use. The reason for a higher percent of hyperpigmentation than what is reported in the literature may be the cumulative effect resulting from the 6-month of O-ISO use, impaired enzyme metabolism and increase in post-inflammatory reactions. The high altitude at the site where the study was conducted and the arrival angle of sunlight may have contributed to the high frequency of hyperpigmentation. In addition, the rate of pigmentation being higher in Type IV skin type, may have contributed to the increase in pigmentation due to postinflammatory processes [21].

Karadağ et al. [13] reported that vit-B12 levels dropped after six months of O-ISO therapy and that liver function was impaired. Gökalp et al. [8] reported similar findings after four months of therapy. Kamal et al. reported that the vit-B12 level after 45 days of O-ISO treatment did not change significantly. They also claimed that the decrease in vit-B12 levels determined in their and other studies in the literature could be a result of the cumulative effect of O-ISO use for a longer period [22]. In our study, we also came to the conclusion that the significant drop in vit-B12 level after treatment is the result of the cumulative effect of O-ISO therapy for six months. This cumulative effect may be due to the degradation of absorption, transport, storage of vit-B12, as well as alteration of dietary habits due to psychological or other organ effects developed in the individual, resulting in an inadequate intake of vit-B12. Melanin is synthesized from tyrosine via tyrosinase enzyme. DNA and RNA molecules responsible for the expression of this enzyme, can be disrupted in vit-B12 deficiencies leading to abnormal pigment responses [20]. The hyperpigmentation in the presence of Vit-B12 deficiency is due to decreased glutathione levels and the over-activation of tyrosinase and/or related proteins caused by defective DNA synthesis. It has also been expressed that hyper-homocysteinemia leads to cysteine accumulation which increases the amount of melanin and leads to erroneous melanin production in keratinocytes from melanocytes [23-25]. In our study, a decrease in vit-B12 levels in the 6-month O-ISO use may lead to abnormal pigment metabolism. And, there was a significant decrease in vit-B12 levels, in the 6th month of O-ISO treatment in the group with pigmentation while no significant difference in vit-B12 level was seen in the group without pigmentation. This suggests that the low vit-B12 level that is observed in patients using O-ISO may lead to an increase in pigmentation along with the Fitzpatrick skin type and the geographical features of the area where patients are present.

To the best of our knowledge, there has been no

study that shows any association of O-ISO-related pigmentation and vit-B12 deficiency with skin type in the literature. It has been shown that post-inflammatory hyperpigmentation was more frequent in dark-skinned individuals during the treatment of acne [18]. Boen et al. reported that hyperpigmentation was more frequent in Fitzpatrick Type 3-4 patients in acne treatment, though this side-effect was temporary [26]. For this reason, some authors suggest that in Fitzpatrick type 3 and 4 patients who undergo acne treatment, more attention should be paid for drug selection and dosing to avoid dyschromia [27-28]. In our study more pigmentation in type IV patients may be related to bigger melanocytes and more pigment secretion despite the same acne severity. The abnormal response to vit B12 changes of these cells may be stronger. To the best of our knowledge, there has been no study that shows the association of pigmentation due to O-ISO and changes due to vit-B12 deficiency with the depth of pigmentation. The melanin accumulation in the dermal macrophages is more common in the basal layer of the epidermis. This has been attributed to melanocyte stimulation, nonspecific cutaneous inflammation, photosensitivity reaction, and faulty melanin excretion from macrophages caused by O-ISO use [6-29]. The rate of dermal hyperpigmentation being higher in our study was in accordance with findings from the literature. The decrease in vit-B12 level was significant in the hyperpigmentation at all depths of the skin. These results can be attributed to the fact that macrophages are more frequently present in the dermis.

Our study has some limitations. It is a cross-sectional study with a relatively small sample size. There should be equal numbers of patients in each types of skin type (especially I and II), but in the present study we included type III and IV skin types more. Therefore, our results should be verified by prospective longitudinal future studies with larger sample sizes.

Conclusion

The study suggests that decreased vit-B12 levels due to O-ISO use for 6-months may be associated with hyperpigmentation development. Therefore, we believe that monitoring and supplementation of vit B12, if necessary, and regular use of sunscreens in the patients under O-ISO treatment will reduce the risk of hyperpigmentation that may occur during treatment.

Funding

The authors declared that this study has received no financial support.

Conflict of interest

The authors have no conflicts of interest declared.

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HEALTH SCIENCES QUARTERLY

Volume : 1
Issue : 1
2021,
E-ISSN: 2791-6022
https://journals.gen.tr/jsp

Received: 2021-03-09
Accepted: 2021-04-19

ORIGINAL ARTICLE

Evaluation of the relationship between IL-10, IL-17, IL-23 levels and disease activity of systemic lupus erythematosus and vitamin D status

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Abstract

Systemic lupus erythematosus (SLE) is a multisystemic, autoimmune connective tissue disease with a variable course and prognosis. We intended to determine IL-10, IL-17 and IL-23 cytokines and vitamin D levels in SLE patients, which we think play role in the pathogenesis of the disease. Forty SLE patients and 20 healthy controls were included in our study. Levels of IL-10, IL-17 and IL-23 were measured by sandwich ELISA method. Quantitative data are expressed as mean ± Standard deviation and median range (maximum-minimum) values. The data were analyzed at 95% confidence interval, and cases where the p value was less than 0.05 were considered statistically significant. IL-10 and IL-17 levels of the control and patient groups were compared and no significant difference was found (p=0.333, p=0.99). IL-23 levels of the patient group were found to be higher than the control group and were found to be statistically significant (p<0.001). No significant relationship was found between disease duration or SLEDAI score and IL-23 levels(p=0.476). 25 (OH) vitamin D levels of the patient group were found to be lower than the control group and were statistically significant (p=0.003). No significant relationship was found between IL-10 and IL-17 levels and vitamin D. Significant relationship was found between IL-23 and vitamin D levels (p=0.019). In our study, there was no significant difference between the groups in terms of IL-10 or IL-17, while IL-23 levels were found to be significantly higher in SLE patients. Vitamin D levels were found to be lower in the patient group with SLE compared to the control group, and a negative correlation was found between the disease duration and IL-23. Specific blocking of the IL-23 immune pathway can be an effective and safe treatment option in the treatment of SLE.

Keywords: *Systemic lupus erythematosus, IL-10, IL-17, IL-23, Vitamin D.*

Citation: Genc Cetin B, Senturk T, Aydin N. Evaluation of the relationship between IL-10, IL-17, IL-23 levels and disease activity of systemic lupus erythematosus and vitamin D status. Health Sci. Q. 2021;1(1):25-30. https://doi.org/10.26900/hsq.1.1.05

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Introduction

Systemic lupus erythematosus (SLE) is a multisystemic, autoimmune, inflammatory disease with different laboratory and clinical features, characterized by a variable course and prognosis. Although the etiopathogenesis of the disease is not known exactly, genetic factors are the strongest determinants of the disease. Chemical substances, hormonal and environmental factors are other reasons that trigger the disease. As a result of abnormal regulation of T cells, events such as impaired immune tolerance, abnormal response to autoantigens, abnormal signal transmission between T cell receptors also contribute to SLE autoimmunity [1]. Interleukin-17 (IL-17) is an inflammatory cytokine, derived from Th 17 cells that has many functions in the regulation of tissue inflammation, B lymphocyte proliferation and antibody secretion in SLE patients [2]. Interleukin-23 (IL-23) molecule is needed in the stabilization and development of Th17 cells. IL-23 is predominantly secreted by antigen presenting dendritic cells and macrophages [3]. Interleukin-10 (IL-10) has positive effects on B cell differentiation, proliferation and autoantibody formation, and dysregulation in this cytokine is thought to be associated with many infectious and autoimmune diseases, including SLE [4]. Vitamin D is a hormone in steroid structure. In addition to calcium and bone metabolism, it also has effects on immune system cells related to cell growth, proliferation, apoptosis and SLE pathophysiology. Vitamin D suppresses B and T cell proliferation, differentiation and immunoglobulin secretion. Thus, vitamin D inhibits the secretion of inflammatory cytokines such as IL-17 while increasing the anti-inflammatory cytokine levels such as IL-10 [5,6]. In our study, in the light of the above information, we intended to measure IL-10, IL-17 and IL-23 cytokines and vitamin D levels in SLE patients, which we think may be effective in the pathogenesis of the disease, and to investigate their possible relationship with clinical and laboratory data.

Materials and Methods

Patient Selection

Our study was validated by the Adnan Menderes University Medical Faculty, Ethics Committee on 12.09.2013 with the number 56989545/050.04-201. Forty patients diagnosed with SLE who were followed in Adnan Menderes University Medical Faculty Internal Medicine Rheumatology Clinic and 20 healthy controls similar in sex and age to the SLE cases. Those included in the control group had no medical history and were not using any medication. SLE patients were selected according to the American Rheumatology Association criteria [7]. SLE disease activation scores (SLEDAI) were calculated by determining the clinical findings and organ involvement of the patients in terms of SLE [8]. All SLE patients participating in our study had received or continued treatments such as hydroxychloroquine, steroid and/or cyclophosphamide. Those who used antiepileptic drugs or anticoagulants and those who received vitamin D replacement within 6 months in the control and patient groups were not included in the study.

Laboratory Analysis

In order to evaluate the kidney involvement due to SLE, complete urine analysis and 24-hour urine analysis of the patients were taken into consideration. After excluding stones, infections, and other causes, patients with 5 or more erythrocytes at high magnification were considered hematuric. Patients with proteinuria more than 500 mg a day and patients whose protein excretion increased by >500 mg according to their previous examinations were considered proteinuric. After the infection was excluded, seeing 5 or more white blood cells at high magnification under the microscope was considered as pyuria. Serum complement (C3, C4) levels of the patients were measured by nephelometric method (reference range C3: 85-200 mg / dL, C4: 20-50 mg / dL), anti-double stranded DNA (anti-ds DNA) levels were measured by ELISA technique. In the whole blood test performed in terms of hematological findings, platelets were evaluated as <100.000/mm3 thrombocytopenia, and <4000/mm3 white blood cell leukopenia after drug-related causes were excluded. Direct and indirect Coombs tests were performed for immune hemolytic anemia in patients with anemia. After 5 cc of blood taken from the cases was centrifuged at 3000 rpm for 10 minutes, their serum samples were separated to measure IL-10, IL-17 and IL-23. Diasource ELISA Human IL-10 (Belgium) kit was used for IL-10 measurement. The kit was studied with the sandwich ELISA method, which gave quantitative results. 100 µl of serum samples and standart were put in to the wells and it was incubated for two hours at 21 degrees Celcius. Then, 100 µl serum sample and 50 µl anti-IL-10-HRP Conjugate were added to the wells. It was incubated at room temperature with gentle stirring for two hours and the solutions were washed. Finally,

50 µl of the reaction stopping solution was added to the wells, readings were made at 450 and 490 nm in the spectrophotometer. The results read here were multiplied by 2, taking into account the dilution factor. The Ebioscience ELISA Human IL-17 (United States) kit was used for IL-17 measurement. The kit was studied with the sandwich ELISA method, which gave quantitative results. A mixture of 100 µl serum and standart were incubated for 2.5 hours at 21 degrees Celcius. Then 100 µl biotinylated antibodies were put into each well. It was incubated at room temperature with gentle stirring and shaking for one hour. After incubation, the solutions were washed and 100 µl streptavidin solution was added and incubated at 21 degrees Celcius for 45 minutes. After the solutions were washed properly, 100 µl of the composition named TMB substrate solution was put into wells and incubated for 30 minutes. Finally, 50 µl of reaction stopping solution was put into the wells and read at 450 nm in the spectrophotometer. The results read here were multiplied by 2, taking into account the dilution factor. The Ebioscience ELISA Human IL-23 (United States) kit was used for IL-23 measurement. The kit was studied with the sandwich ELISA method, which gave quantitative results. Similarly, after removing all serum samples and standards and washing appropriately, 100 µl Biotin Conjugate, 100 µl Avidin HRP and 100 µl TMB Substrate solutions were added respectively. After 15 minutes of incubation at room temperature, the color change of each plate was evaluated and 100 µl of the reaction stopping solution was added and the absorbances were read at 450 nm in the spectrophotometer. The results read here were multiplied by 2, taking into account the dilution factor. 25 (OH) vitamin D was serologically studied by HPLC (high-performance liquid chromatography) method. Evaluation for 25 (OH) vitamin D level; <10 ng / ml severe deficiency, <20 ng / ml deficiency, 20-30 ng / ml insufficiency, 32-100 ng / ml is considered sufficient.

Statistical Analysis

Medcalc 9 (Acacialaan 22, B-8400 Ostend, Belgium) and Statistical Package for the Social Sciences (SPSS) 22 programs were used to analyze. The compliance of the data for normal distribution was examined with Kolmogorov-Smirnov test. To compare two independent groups, Independent-Samples T test was used. Mann-Whitney U test was used with Monte Carlo simulation technique. Quantitative data are expressed as mean ± SD and median Range (max-min) values in the tables. Categorical data are expressed as n (number) and percentages (%). The data were analyzed at 95% confidence interval, and cases where the p value was less than 0.05 were considered as statistically significant.

Results

In our study, 40 patients diagnosed with SLE whose treatments are ongoing and 20 healthy controls were evaluated retrospectively. Thirty eight (95%) of the SLE patients were female and 2 (5%) were male. The control group was 6 (30%) males and 14 (70%) females. The mean age of the patient group was 35.5±13.4 years; mean duration of disease was found to be 6.1 ±5.9 years. The mean age of the control group was 36.1 ±14.7 years. The clinical manifestations of SLE patients are summarized in Table 1. Using these data, the mean SLEDAI score of all patients was calculated as 6.95. The SLEDAI score of 13 (32.5%) patients was found to be between 0-3, 17 (42.5%) patients between 4-10, and 10 (25%) patients as ≥ 11. Serum IL-10 levels in the control and patient groups were compared, no statistically significant difference was found (p=0.333). Similarly, IL-17 levels of the control and patient groups were compared. It was not statistically significant different (p=0.99)

Table 1. Demographic, laboratory and clinical characteristics of the patients and the control group

	SLE patients n:40 (%)	**Control n:20 (%)**
Mean Age	35.5 ±13.4	36.1 ±14.7
Gender (Female)	38 (95%)	14 (70%)
Mean Duration of Disease (years)	6.1 ±5.9	
Skin Lesion	25 (62.5%)	
Kidney Involvement	26 (65%)	
Joint Involvement	4 (10%)	
Hematological Involvement	6 (15%)	
Low C3	17 (42.5%)	
Low C4	25 (62.5%)	
SLEDAI Score (mean)	6.95	

Table 2. IL-10 and IL-17 levels of SLE and control group

	Control		SLE		P value
	Median (Max-Min)	Mean	Median (Max-min)	Mean	
IL-10 (pg/ml)	8.33 (181.19-8.33)	65.94	55.44 (547.63-8.07)	99.72	0.333
IL-17 (pg/ml)	11 (22-5)	12.14	12.15 (177.26-2.74)	17.23	0.990

Table 3. IL-23 levels of SLE and control group

	n	IL-23 Mean (pg/ml) ±SD	P value
Control	20	345.53 ±191.86	p<0.001
Patients	40	921.79 ±607.23	

Table 4. 25 (OH) vitamin D levels in SLE patients and control group

	n	25 (OH) vitamin D Mean (ng/ml) ±SD	P value
Control	20	22.63 ±8.1	p=0.003
Patient	40	15.87 ±6.47	

(Table 2). When we compare serum IL-23 levels of the control and patients, IL-23 levels of the SLE patients were higher than the control group and statistically significant (p<0.001) (Table 3). The relationship between IL-23 levels and SLEDAI scores and disease duration of the patient group was evaluated. There was not relationship between disease duration or SLEDAI score and IL-23 (p=0.476). While the mean IL-23 levels of 26 patients with active kidney pathology were 966.82 pg/ml, the mean IL-23 levels of 14 patients without active kidney pathology were 896.6 pg/ml. Although the mean IL-23 levels of patients with active kidney pathology were found to be higher than those without, there was not statistically significant difference between them (p=0.734). When the 25 (OH) vitamin D levels of the SLE and control groups were compared, the vitamin D levels of the patient group (mean 15.87 ng/ml) were lower than the control group (mean 22.63 ng/ml) and were statistically significant (p=0.003). Vitamin D was sufficient 4 (20%) of the control group and 9 (45%) of the control group had vitamin D insufficiency, 6 (30%) had vitamin D deficiency, and 1 (5%) had severe vitamin D deficiency. Vitamin D was sufficient in 1 (2.5%) of the patient group and 7 (17.5%) had vitamin D insufficiency, 25 (62.5%) had vitamin D deficiency and 7 (17.5%) had severe vitamin D deficiency (Table 4). The relationship between vitamin D levels and SLEDAI score, disease duration, renal involvement, steroid and hydroxychloroquine use was evaluated in the patient group. It was observed that the longer the disease duration, the lower the vitamin D levels and the results were statistically significant (p=0.020) (Figure 1). There was not significant relationship between the SLEDAI score, renal involvement, hydroxychloroquine or steroid use and vitamin D levels (p=0.247, p=0.634, p=0.927 and p=0.562 respectively). Serum IL-10, IL-17 and IL-23 and vitamin D level were compared. While no

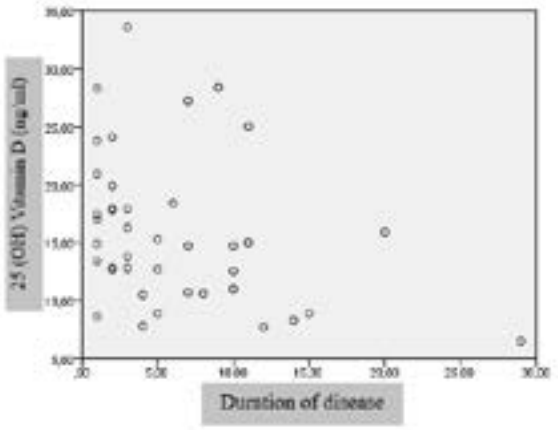

Figure 1. Negative correlation between vitamin D levels and disease duration.

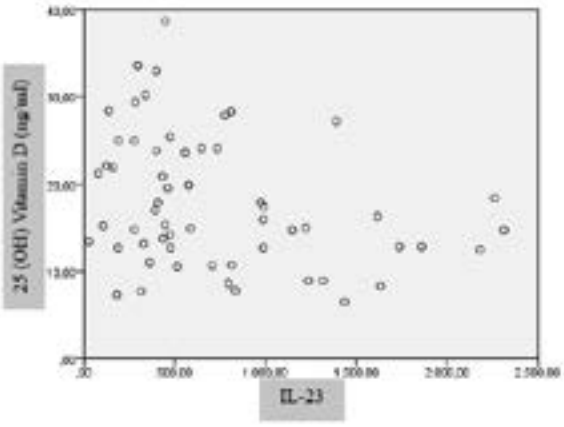

Figure 2. Negative correlation between IL-23 and vitamin D levels.

significant relationship was found between IL-10 and IL-17 levels and vitamin D, a statistically significant relationship was found between vitamin D and IL-23 (p=0.019) (Figure 2).

Discussion

In our study, vitamin D levels and serum IL-10, IL-17, IL-23 levels were measured in control and patient groups similar in age and gender. There was not significant difference between the patient and control groups in terms of IL-10 and IL-17 levels, so the relationship between serum IL-10 and IL-17 levels couldn't be evaluated with clinical and laboratory data of the patients. Our results have been found different from some previous studies on this subject. IL-10 levels were investigated in the study of Waszczykowska et al. (1999), which consisted of 63 SLE patients and 16 healthy control groups. IL-10 levels increased three times in SLE patients compared to the healthy controls and it was correlated with SLEDAI score ($p<0.001$) [9]. In our study, 39 patients (97.5%) received any immunosuppressive treatment, whereas 35 patients (55.5%) received treatment in this study. In addition, while 25% of the patients were active in our study, 50.8 % of them were active in this study. The different outcomes between two studies might be related to differences such as treatment rates and disease activity among the patients included in the study. Wong et al. (2008) compared IL-17 and IL-23 in 80 SLE patients and 40 control groups. IL-17 and IL-23 levels were higher in SLE patients compared to controls ($p<0.05$) [10]. However, in our study, no significant difference was observed between the groups in terms of IL-17, while IL-23 levels were found significantly higher in SLE patients. In the study of Wong et al. (2008), while IL-17 level correlated with disease activity in the SLE group without renal involvement, no significant difference was observed between the groups in terms of disease activity in IL-23. In our study, there was not significant relationship between IL-23 and disease activity, duration or renal involvement. This data we have obtained is similar to the work of Wong et al. Considering the differences between the two clinical studies, the mean SLEDAI score of the patients was 8, while it was 6.95 in our study. In this study, 50% of the patients had kidney involvement, while in our study, kidney involvement was 35%. While the mean disease duration was 6.1 years in our study, it was 12.4 years in this study. Many factors such as patients' mean SLEDAI scores, renal involvement, duration of disease may be the reason for the difference in results in terms of IL-17. SLE is a complex disease that causes autoimmune inflammation and can cause many events in the immune system. Therefore, when the immune, genetic and environmental mechanisms are fully understood, specific inflammatory pathways that mediate the disease can be targeted. Recent studies in the literature suggest that IL-23 may play a role in the pathogenesis of SLE, correlate with disease activity and be a predictor for response to immunosuppressive therapy. In the study of Mok et al. (2010) serum IL-23 was found to be elevated in active SLE patients who presented with cutaneous manifestations and serositis, further supporting a role of IL-23/Th17 in the pathogenesis of SLE [11]. It is important to note that not all manifestations of SLE are associated with increased IL-23 levels, suggesting the variability in the mechanisms of manifestations in SLE [12]. In another study by Dedong et al. (2019), it was mentioned that IL-23 can be used as a predictor in response to immunosuppressive therapy in patients with active lupus nephritis [13]. Specific blocking of the IL-23 immune pathway can be an effective and safe treatment option in the treatment of many autoimmune diseases, including SLE. In a multi-center study investigating the efficacy and safety of IL-12 and IL-23 inhibitor ustekinumab in SLE patients, the primary end point was SRI4 (SLEDAI-2K responder index) response. In the study, ustekinumab provided significant improvement compared to placebo [14]. In the study of Shahin et al. (2017), 25 (OH) vitamin D, IL-17 and IL-23 levels were compared in 57 SLE patients and 42 control groups [15]. Vitamin D levels were significantly lower in SLE patients ($p=0.001$). A negative correlation was found between the vitamin D level and IL-17 and IL-23 ($p<0.05$). These data are similar to the results of our study. Vitamin D is involved in bone metabolism and has immune regulatory functions as well as a nutrient source for many tissues and organs. When the vitamin D levels were examined, vitamin D levels were lower in SLE patients, and a negative correlation was found between the disease duration and IL-23. In our study, although 85% of patients in the SLE group used corticosteroids, no relationship was found between vitamin D and corticosteroid use. However, the regularity of corticosteroid use and the inability to measure cumulative doses should be considered. Hydroxychloroquine can lead to vitamin D deficiency by inhibiting 1α hydroxylation of 25(OH) D. However, in our study, no significant relationship was found between vitamin D levels and hydroxychloroquine use. Due to the high prevalence of vitamin D deficiency in healthy individuals, it may be recommended to measure vitamin D at the time of SLE diagnosis. Serum cytokine concentrations are affected by many factors

such as production, tissue or cell storage, degradation and elimination [16].

Conclusion

In conclusion, we evaluated vitamin D and cytokine levels in SLE patients receiving treatment. However, if the patient groups in whom treatment was not initiated were examined, we would have obtained different results. Since SLE is a disease with low prevalence, the number of cases included in our study is one of the limitations of our study. Future studies will be needed whether IL-23 levels might be a biomarker of lupus as well as predictor of response to biologics targeting the IL-23 pathway.

Acknowledgements
The data of the study were obtained from the thesis of Beyza Genc Cetin.

Funding
This research was funded by the Adnan Menderes University Research Foundation, Aydin, Turkey.

Conflict of interest
The authors have no conflicts of interest declared.

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HEALTH SCIENCES QUARTERLY
Volume : 1
Issue : 1
2021
E-ISSN: 2791-6022
https://journals.gen.tr/jsp

Received: 2021-03-12
Accepted: 2021-04-12

ORIGINAL ARTICLE

Perceptions of cadaver in physiotheraphy students and approaches to use of cadavers for anatomy education

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Abstract

We aimed to determine how physiotheraphy students' percieve cadavers and what kind of approach they have adopted for use cadavers and how cadaver education has changed their feelings and emotions in anatomy education. Data form that consist twelve expressions were used for determing of students' perception about cadavers. Fifty students (100 forms) were participated in research. In the data form prepared, 12 questions were included in order to determine the approach of the students, while an expression question was included to determine the emotional question at the first encounter with the cadaver. Most of participants have adopted expression before the cadaver education was "Dead human bodies shown in public areas without educational purposes affect cadaver donation adversely." (4.52±0.79). While they have adopted after the cadavers education was "Human is valuable asset. Therefore, while person was both alive or after death, value and respect must be given to the human body." (4.60±0.93). When the quastionaire data (before and after) were compared, statistically significant differences were found in expression of "Dead human bodies shown in public areas without educational purposes affect cadaver donation adversely" (p=0.037) and "3D modeling or working on the human models is more useful than studying on cadavers in anatomy education" (p=0.005). It was observed that the number of participations was decreased for the first expression and in contrast with increased for the second expression. Physiotheraphy students regard to cadavers for in terms of human aspect and value and attribute to him/her aspecial value in terms of contribute to education. Students who were studying on cadavers in anatomy education tend to see cadaver as an education a material. We thought that these results could be help to shape and improve the anatomy education.

Keywords: *Anatomy education, cadaver, perception of students, physiotheraphy students,*

Citation: Bilir A, Ertekin T, Turamanlar O, Guzel H, Atay E. Perceptions of cadaver in physiotheraphy students and approaches to use of cadavers for anatomy education. Health Sci. Q. 2021; 1(1) : 31-36. https://doi.org/10.26900/hsq.1.1.06

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Introduction

With the medical education given before graduation, it is aimed that students gain basic knowledge and skills, comprehend social ethics and gain general medical skills [1]. Human anatomy, the oldest known medical science, is defined as the most important component of medical education, and it is given to students in the form of theoretical and practical courses in the first years of medical faculties in our country [2]. In addition to basic anatomical knowledge, students are also taught to solve clinical problems that they will encounter later [3].

Advances in technology have provided many new opportunities for anatomy education. It is stated that especially anatomy practical courses are a very valuable occasion for the students of medical faculty and health sciences faculties in terms of both making a significant contribution to education and allowing them to gain a professional competence [4]. Despite the possibilities of advanced modeling and three-dimensional modeling presented by technological developments, cadaver dissection continues the most important component of anatomy courses [5-7]. Although different educational methods are used in anatomy education, cadaver dissection is still at the center of anatomy courses [8, 9]

The use of human cadavers in anatomy education is considered important in terms of enabling students to learn the human body one-to-one, touch the human body and apply some skill-oriented operations. One of the memories that students will never forget is the first encounter with the cadaver in the anatomy practical courses [4,6]. In this period of time, people experience conflicts about their prejudices and the concepts required by their profession. For this reason, a questionnaire study was applied on physiotherapy students to determine how they perceive cadaver, what kind of approach they adopted for cadaver use in anatomy education, and how cadaver education changed their feelings and thoughts.

Materials and Methods

Data collection forms previously used by Ögenler et al. [10] and Erbay et al. [11] were revised to determine the change in physiotherapy students' perception of cadavers and their approach to cadaver use in anatomy education. In the data form prepared, 12 questions were included in order to determine the approach of the students, while an expression question was included to determine the emotional question at the first encounter with the cadaver. The questionnaire was applied to the first-year students (50 participants) of the Department of Physiotherapy and Rehabilitation of Afyon Kocatepe University twice, before cadaver training and five weeks after cadaver training in 2017. The scale, which is prepared to determine the approaches of the participants, is 5-point Likert type. In the scale, there were five statement, including "Strongly Disagree, Disagree, Undecided, Agree, Strongly Agree", and the participants were asked to choose the one that best suits them. While the data were transferred to the computer environment, these options were recorded in the same order between 1-5 points. Result data was shown as mean, standard deviation, frequency and percentages. The distribution of the data was analyzed using the Kolmogorov Smirnov test, and the Paired Samples T test was used for subgroup comparisons. The question determining the emotional expression at the moment of encountering the cadaver was shown in percentages according to the expression chosen by the students. Local clinical ethics committee approval was obtained for our study (Afyon Kocatepe University, 2017-194).

Results

Fifty students participated in the study (31 female, 19 male) and the data were evaluated on 100 forms (Figure 1). While "Dead human bodies shown in public areas without educational purposes affect cadaver donation adversely" is the opinion most adopted by the participants before cadaver training (4.52±0.79), the least adopted opinion is "Whatever the purposes are, a dead person's body should not be used for training" (1.96±0.7). While "Human is valuable asset.

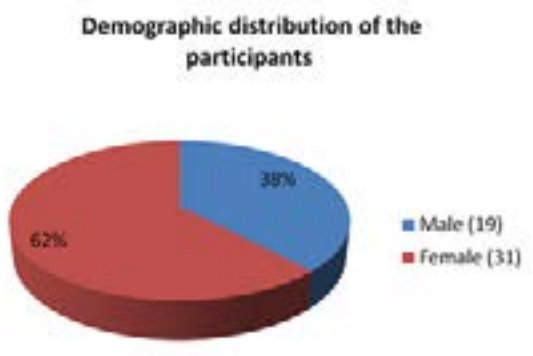

Figure 1. Demographic distribution of the participants

Table 1. The expressions in the Data Form and the frequency, percentage, mean and standard deviations of the answers given by the students

STATEMENTS		Frequency (%)					Mean±SD	P value
		1	2	3	4	5		
Human is valuable asset. Therefore; while person was both alive or after death, value and respect must be given to the human body.	B	2 (4)	-	3(6)	12 (24)	33 (66)	4.48±0.93	0.468
	A	2 (4)	-	3 (6)	12 (24)	39 (78)	4.60±0.93	
Whatever the purposes are, a dead person's body should not be used for training.	B	13 (26)	26 (52)	11 (22)	-	-	1.96±0.70	0.305
	A	12 (24)	35 (70)	2 (4)	-	1 (2)	1.86±0.67	
Experience of working with cadavers contributes to the medical students to get rid of prejudices about the dead human body and the death itself.	B	2 (4)	3 (6)	-	19 (38)	15 (30)	3.84±1.06	0.224
	A	-	2 (4)	7 (14)	26 (52)	15 (30)	4.08±0.78	
Within the framework of the right of privacy, to cover the face of cadaver during the dissection is a humanitarian curtousy and respect that should not to be neglected.	B	-	6 (12)	9 (18)	16 (32)	19 (38)	3.96±1.03	0.153
	A	4 (8)	7 (14)	6 (12)	18 (36)	15 (30)	3.66±1.27	
During the dissection-demonstration, cadaver is only an object. Cadaver is supposed to be adopted and seen only as an object.	B	7 (14)	8 (16)	14 (28)	15 (30)	6 (12)	3.10±1.23	0.583
	A	3 (6)	12 (24)	13 (26)	13 (26)	9 (18)	3.26±1.19	
Taking a souvenir photo with cadaver by students should not be objected.	B	22 (44)	7 (14)	7 (14)	6 (12)	8 (16)	2.42±1.54	0.167
	A	17 (34)	8 (16)	4 (8)	8 (16)	13 (26)	2.84±1.66	
Before facing with cadavers first, a lecture should be given to the students to make them prepared emotionally and intellectually for it.	B	2 (4)	10 (20)	6 (12)	25 (50)	7 (14)	3.50±1.09	0.157
	A	3 (6)	8 (16)	20 (40)	17 (34)	2 (4)	3.14±0.95	
The studies on cadavers do not provide a significant contribution to the physiotherapy students in terms of improving their medical-surgical skills.	B	16 (32)	22 (44)	6 (12)	5 (10)	1 (2)	2.06±1.02	0.063
	A	10 (20)	20 (40)	6 (12)	14 (28)	-	2.48±1.11	
Working with cadavers is also important not only in terms of studying the human body, but also acquiring a professional physiotherapist identity for physiotherapy students.	B	3 (6)	3 (6)	1 (2)	25 (50)	18 (36)	4.04±1.09	0.185
	A	1 (2)	4 (8)	4 (8)	35 (70)	6 (12)	3.82±0.82	
It is a student right to refuse to work on cadavers because of religious and conscientious reasons and it must be respected.	B	2 (4)	4 (8)	9 (18)	21 (42)	14 (28)	3.82±1.06	0.260
	A	1 (2)	-	5 (10)	35 (70)	9 (18)	4.02±0.68	
Dead human bodies shown in public areas without educational purposes affect cadaver donation adversely.	B	1 (2)	1 (2)	-	17 (34)	31 (62)	4.52±0.79	**0.037***
	A	2 (4)	1 (2)	4 (8)	23 (46)	20 (40)	4.16±0.95	
Three-dimensional modeling or working on the human models is more useful than studying on cadavers in anatomy education.	B	10 (20)	18 (36)	12 (24)	7 (14)	3 (6)	2.50±1.15	**0.005***
	A	1 (2)	16 (32)	14 (28)	13 (26)	6 (12)	3.14±1.07	

*; A statistically significant difference is observed in the opinion in the statement, A; after cadaver experience, B; after cadaver experience, %; Percentage SD; Standart deviation, 1; Strongly disagree, 2; disagree, 3; Undecided, 4; Agree, 5; Strongly agree

Therefore; while person was both alive or after death, value and respect must be given to the human body" is the opinion most adopted by the participants after cadaver training (4.6±0.93), the least adopted opinion is "Whatever the purposes are, a dead person's body should not be used for training" (1.86±0.67), (Table 1).

A statistically significant difference was observed in the "Dead human bodies shown in public areas without educational purposes affect cadaver donation adversely" opinion when the survey data before and after cadaver training were compared (p=0.037) and there has been a decrease in the number of people who agree with this opinion. In addition, a statistically significant difference was observed in the "Three-dimensional modeling or working on the human

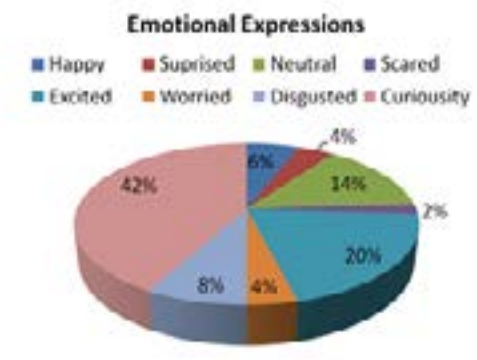

Figure 2. The emotional reactions of physiotherapy students in their first cadaver experience.

models is more useful than studying on cadavers in anatomy education" opinion (p=0.005) and it was found that the agreement to this opinion increased. "Curiosity" was the most salient emotion with a rate of 42% in the responses to the emotional expression at the time of encountering with the cadaver. The inclusion of the expressions "Excited" (20%) and "Neutral" (14%) following this expression show us that positive opinions majority (Figure 2).

Discussion

The opinion about worthiness and dignity of human and human body is admitted by the participants. Expression with the highest mean value in terms of the degree of adoption support this opinion. The main controversy under this issue is that the dead human body is seen as educational material. Is a "thing" as educational material merely an object related with no moral relevance? It was determined in a study in England, 26% of the students stated that the cadaver was just an object, an undecided attitude about this issue was taken 26% of them [12]. The perceptions of students and lecturer are also different from each other on this issue [11]. While anatomists tend to be indecisive and accepting in the approach of considering the cadaver as only an object in the educational process [10], the approach of students considering cadaver only as an object is more majority in this study. Even the experiences with cadavers, students could not affect their opinions on this issue. It is possible to say that the reason for these differences with the literature are the differences in perception and professionalism between the lecturers and those who have recently faced cadaver experience.

Performing some manipulative operations on cadaver and/or interacting with cadaver for educational purposes is sometimes not a situation that people can easily overcome. The refusal to work on cadavers is a students' right that should be respected if students do not want, and the opinions of these students on this issue are clearly seen in our study. At this point, when viewed from the student's perspective, it should not be overlooked that psychological attitudes or religious belief of students may sometimes take priority over education. In addition, another result of our study is that the integration of a course aimed at emotionally and intellectually preparing for the cadaver experience into anatomy education should be one of the primary educational parameters.

Being a tool (model) for an important practice such as anatomy education and wanting to contribute to this process can be regarded as virtuous behavior. It is also worth emphasizing that people who have a strict approach to the worhty of human beings and the human body defend the thesis that their bodies are too valuable to be used as cadavers, but these people do not respect their own bodies as required. There are some studies emphasizing their contribution to education and the values of the human bodies used in dissection laboratories [4, 10, 13]. In our study, the value attributed to cadavers was clearly demonstrated, and the opinion that cadavers should not be displayed in public places for non-educational purposes and that this approach would negatively affect cadaver donation was majority. This result is due to the importance of cadaver education which is an indispensable part of the anatomy education and the empathy the students establish with the person who donated herself/himself as a cadaver.

Lewis et al. [14], state that detailed anatomical knowledge yields a high level of tissue and organ manipulation by improving the efficiency and safety of a surgeon in order to heal and save a patient. They argue that while anatomy can also be learned from textbooks, atlases, computer models and projections, dissection is the most efficient method. Based on these arguments, they concluded that dissectible cadavers prepared fresh or prepared with alternative methods will increase knowledge and skill in surgical education and specific surgeries. In addition to all these mentioned elements, it is reported that learning a new procedure with daily practices on living beings is quite dangerous for education and that practices on cadavers increase the education experiences.

In our study, before cadaver experience, students opposed the opinion that three-dimensional modeling or working on the human models is more useful than studying on cadavers in anatomy education, while it was observed that this approach was completely reversed after cadaver experience. It is noteworthy that the participants tend to prefer alternative methods, although they have received a cadaver course. It can be said that this tendency puts forward the necessity of studying and discussing on different education models that include cadaver. Similar results were associated in a study in which such a different model was put on the agenda and evaluated [15]. As a result of the survey study conducted by Yavuz et al. [16] on medical faculty students, they reported that

cadaver dissection is a better education method for students than models, facilitates the understanding of course subjects, and is an important tool in associating basic sciences with clinical sciences In addition, they also concluded that the students saw the cadavers in a more respectable position than the other dead and that a lesson that prepares students to encounter cadavers emotionally and intellectually should reduce the fear and stress that will be experienced in students. They also reported that cadaver dissection is a positive factor in the formation of doctor identity. Three possible reasons underlying students' negative attitudes towards cadaver in anatomy education can be listed as follows: In anatomy practical courses experience of watching and seeing the cadaver under the control of a lecturer rather than contact with the cadaver, psychological and physiological difficulties of working with cadavers, the cadaver was not respected as much as they expected. Considering the fact that the aforementioned reasons can be increased, we would like to bring to the attention of anatomy lecturers that physiotherapy students want to work with alternative learning models besides cadavers.

There is a common positive opinion that working with cadavers will contribute to the process of gaining the identity of a physiotherapist as well as learning human anatomy. However, it should not be overlooked that lecturers and students have different approaches in this regard. In our study, students supported this opinion, but remain in the middle in terms of importance. However, according to the approach of the lecturers, this issue is much more important [10, 13, 17-21]. In fact, there was nothing strange with this situation. Although the students also think in parallel with the lecturers on this issue, they do not only express strong enough opinion on the importance of the subject [20]. People who have not yet completed the education process cannot be expected to have a perspective with a broad perspective about the outcomes of this course as much as the lecturers. The fact that the students agree with the lecturers about their contribution to the physiotherapist identity before and after cadaver course is an indication of the adoption of a professional identity and value, which is one of the main goals of education, for both parties.

Conclusion

Physiotherapy students care about the cadaver in terms of its humanitarian aspect and worth, and attribute a special worth to it in terms of contributing to anatomy education. Students who study on cadavers tend to adopt cadavers as an educational material. Students respect the cadaver as the body of a dead person. Before the cadaver experience, physiotherapy students have a similar opinion to anatomists and medical faculty students with regard to on the acceptance of the cadaver as an educational material and the superiority of cadaver over 3-dimensional modeling and plastic models. However, after the cadaver experience significant differences were found in these thoughts. The emotional reactions of physiotherapy students to the cadaver did not reveal a traumatic picture, on the contrary, they showed a curiosity and a desire to learn about the dead human body.

Ethical debates about the use of cadavers in anatomy education for years continue with the intervention of different approaches. This study, which focuses on the students' perspective on cadavers, which is an object of the health-related education process for lecturers, is expected to serve as a mirror to the anatomy education of our country from a different perspective. It is thought that conducting more studies on cadaver use, anatomy education and their ethical dimension and evaluating the subject from different perspectives can bring different approaches to anatomy education.

Acknowledgments
This study was presented as a poster as a summary text at the 18th National Anatomy Congress, 25–27, September 2017; Bolu, Turkey.

Funding
The authors declared that this study has no financial support.

Conflict of interest
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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HEALTH SCIENCES QUARTERLY
Volume : 1
Issue : 1
2021
E-ISSN: 2791-6022
https://journals.gen.tr/jsp

Received: 2021-03-29
Accepted: 2021-04-08

ORIGINAL ARTICLE

The relationship between midwifery students' acceptance of violence between couples and level of aggression: A multicentered study

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Citation: Gokyildiz Surucu, S, Bilgic D, Daglar, G, Aydin Ozkan S, Turan Z, Guler H. et. al. The relationship between midwifery students' acceptance of violence between couples and level of aggression: A multicentered study. Health Sci. Q. 2021; 1(1) : 37-43. https://doi.org/10.26900/hsq.1.1.07

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Abstract

The study was aimed to identify the relationship between acceptance of violence between couples and level of aggression among first and fourth year midwifery students in various universities in Turkey. This is a cross-sectional descriptive study. Personal Information Form, Acceptance of Couple Violence Scale and Aggression Scale were used to collect the data. In the study, the number of the first year students was 1843, and the number of the fourth year students was 1337. There was a weak positive relationship between Aggression Scale and Acceptance of Couple Violence Scale. Acceptance of violence between couples was found to increase with the increase in aggression level. Adolescents' views on aggression between boys and girls are of great importance to provide an opportunity for early intervention and to maintain healthy relationships. It may be suggested that midwifery departments providing health education include these subjects in their curriculum.

Keywords: Dating, violence, aggression, flirt, youth

Introduction

Violence is a phenomenon that has been encountered in every society and in every period of the human history. According to the definition of the World Health Organization (WHO), violence; a danger of injury or injury is death, psychological damage, developmental disorder or deprivation, intentional physical exertion, force or threat to a person, group, or community. Every year, 1.6 million people in the world lose their lives due to violence. Violence is one of the leading causes of death among people aged between 15 and 44 worldwide. It is the cause of death in 14% of men and 7% of women. More than death from violence, people's lives are affected by violence-related problems including injury and physical, sexual, reproductive and mental health problems. Violence could be committed by individuals as harming themselves or it could occur among people and societies, as well. Some examples of interpersonal violence include domestic violence, partner violence, flirt violence, and violence committed in care centers [1].

Dating or flirting is defined as two people's maintaining a relationship by fully and evidently participating in social relationships or activities together until marriage or until one or both of the couples wish to end the relationship. Flirt violence is the intentional sexual, physical and psychological attack committed by one of the people dating [2-5]. Puberty is a period which starts from the age of 10 and continues until 20s and which includes biological, psychological, social development and maturing. Some of the main developmental issues in this period include identity, independency, intimacy, sexuality, and success. Adolescents face new relationship patterns in these ages. They want to be approved by their friends by building new and wiser relationships with both genders. Some adolescents who have problems in this period can develop various antisocial behaviors including violence. Individuals react in different ways when there is something wrong about their relationship. For instance, children growing up in violent families cannot learn how to control their anger and demonstrate violent behaviors that can reach to much more dangerous extents in adulthood [4]. It is reported that violence is gradually increasing in the relationships of adolescent and young people with the opposite sex; the relationships are observed to commonly include physical, verbal and sexual violence, jealousy, and controlling behaviors [2,3,5].

This study aims to identify the relationship between acceptance of violence between couples and level of aggression among first and fourth year midwifery department students in Turkey.

Materials and Methods

Research Design

The study is cross-sectional descriptive in nature.

Target Population and the Sample

This study was carried out in midwifery programs in Turkey between January and June 2015. Target population of this study was the 1st year and 4th year students enrolled in the midwifery departments that provided 4-year education through undergraduate programs in faculties and colleagues in Turkey. Except for the private universities, there are 32 midwifery departments in Turkey. Four universities were excluded from the study because they did not have 1st and 4th year students. The sample of the study was 3180 students. Of the students' 1843 were first year students and 1337 were fourth year students. The forms were given to the students in an envelope, and they were asked to fill these forms themselves. The forms were administered to 1st year students in the fall semester, and 4th year students in the spring semester, a closer time to graduation.

Data Collection Tools

The data were collected through "Personal Information Form", "Acceptance of Couple Violence Scale" (ACVS) and "Aggression Scale" (AS).

Personal Information Form

This scale includes 19 questions that aimed to identify students' socio-demographic features and their perceptions and attitudes towards violence.

Table 1. Socio-demographic characteristics of the participants

Characteristics	n (3180)	%
Class		
1.Class	1843	58
4. Class	1337	42
Marital Status		
Single	3094	97.3
Married	86	2.7
Place of Birth		
Village	227	55
Town	1203	37 8
City	1750	55
Place of Longest Location		
Village	515	162
Town	1036	32.6
City	1629	51.2
Family Type		
Nuclear Family	2549	80.2
Extended Family	544	17.1
Divided Family	87	2.7
Education Level of Mother		
Illiterate	366	11.5
Literate	97	3.1
Primary School	1873	58.9
Secondary School	397	12.5
High School	365	11.5
University	82	2.6
Working Status of Mother		
Yes	312	9.8
No	2868	90.2
Education Level of Father		
Illiterate	63	2
Literate	36	1.1
Primary School	1370	43.1
Secondary School	575	18.1
High School	786	24.7
University	350	11
Working Status of Father		
Yes	3108	97.7
No	72	2.3

Acceptance of Couple Violence Scale

The scale which was developed by Foshee et al. (1992), and was adapted to Turkish by Sezer (2008). Of the 11 items, 1st, 3rd, and 4th items are related with acceptance of male violence committed to women, 5th, 6th, and 8th items are related with acceptance of female violence committed to men, and 2nd, 7th, 9th, 10th, and 11th items are related with acceptance of violence between couples generally. The items in the scale are responded on four options as 1= strongly disagree, 2=disagree, 3=agree, and 4=strongly agree. While higher scores to be obtained from the scale indicate high level of acceptance of violence between couples, lower scores indicate lower acceptance levels [4].

Table 2. Findings about relationship between socio-demographic characteristics of the participants and ACVS/AS

Characteristics	ACVS	Physical Aggression	Verbal Aggression	Anger	Hostility	Indirect Aggression
	$\overline{X}$ ± SD	$\overline{X}$ ± SD	$\overline{X}$ ± SD	$\overline{X}$ ± SD	$\overline{X}$ ± SD	$\overline{X}$ ± SD
Class*						
1. Class	17.45±6.46	15.93±6.54	12.85±3.43	20.56±5.07	18.42±5.20	13.28±4.14
4. Class	15.81±6.19	15.28±6.67	12.55±3.70	19.92±5.35	17.44±5.35	12.82±4.27
	p<0.05	p<0.05	p<0.05	p<0.05	p<0.05	p<0.05
Age*						
20 and	17.43±6.41	16.07±6.59	12.90±3.44	20.66±5.10	18.52±5.22	13.33±4.17
21 and	16.00±6.30	15.19±6.58	12.53±3.66	19.87±5.29	17.43±5.26	12.78±4.22
	p<0.05	p<0.05	p<0.05	p<0.05	p<0.05	p<0.05
Marital Status*						
Single	16.78±6.38	15.67±6.57	12.73±3.55	20.31±5.19	18.04±5.25	13.08±4.18
Married	15.84±6.91	15.23±7.43	12.58±3.64	19.55±5.75	17.17±5.75	12.92±5.00
	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05
Place of Birth**						
Village	18.32±6.95	15.64±6.05	12.78±3.45	20.25±4.99	17.82±4.79	12.96±3.77
Town	16.69±6.08	15.58±6.41	12.69±3.50	20.45±5.08	18.13±5.09	13.05±4.25
City	16.60±6.51	15.72±6.79	12.75±3.59	20.19±5.31	17.96±5.44	13.11±4.22
	p<0.05	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05
Place of Longest Location**						
Village	17.30±6.17	15.49±6.28	12.59±3.51	20.62±5.35	18.24±5.18	13.23±4.09
Town	16.74±6.25	15.71±6.44	12.75±3.51	20.40±5.05	18.15±5.06	13.07±4.27
City	16.60±6.55	15.68±6.79	12.75±3.58	20.12±5.25	17.86±5.42	13.03±4.19
	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05
Family Type**						
Nuclear Family	16.59±6.38	15.75±6.63	12.73±3.59	20.29±5.26	17.98±5.35	13.11±4.25
Extended Family	17.54±6.5	15.34±6.25	12.68±3.39	20.37±4.97	18.17±4.82	12.93±3.98
Divided Family	16.89±6.05	15.14±7.65	12.85±3.42	19.85±5.07	17.92±5.59	12.94±4.18
	p<0.05	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05
*t test, ** ANOVA test						

Aggression Scale

The scale was developed by Buss and Perry (1992), and was adapted to Turkish by Can (2002). The scale has 34-items and has five sub-dimensions named "physical aggression", "verbal aggression", "anger", "hostility", and "indirect aggression". The scale is a 5-point likert type and the responses include 1=extremely uncharacteristic, 2=somewhat uncharacteristic, 3=neither uncharacteristic nor characteristic, 4=somewhat characteristic, and 5=extremely characteristic [6].

Ethical Considerations

The ethical approval was obtained from the Non-Interventional Research Ethics Board of Cukurova University. The aim of the study was explained to the

participants, and their written consent was obtained prior to the attendance of the research. The participants were assured that the information they provided would remain confidential and that they could leave the study at any time.

Table 3. Findings about relationship between several characteristics and ACVS/AS

Characteristics	ACVS	Physical Aggression	Verbal Aggression	Anger	Hostility	Indirect Aggression
	$\overline{X}$ ± SD	$\overline{X}$ ± SD	$\overline{X}$ ± SD	$\overline{X}$ ± SD	$\overline{X}$ ± SD	$\overline{X}$ ± SD
Education Level of Mother**						
Illiterate	17.34±6.36	15.10±6.19	12.64±3.52	20.05±5.23	17.66±4.83	13.01±4.02
Literate	17.56±5.74	15.52±6.21	12.87±3.45	20.62±5.32	17.77±5.13	12.74±3.83
Primary School	16.54±6.31	15.61±6.55	12.67±3.58	20.27±5.23	18.00±5.34	13.02±4.28
Secondary School	16.68±6.26	16.02±6.81	12.67±3.38	20.25±4.95	18.21±5.40	13.15±4.12
High School	16.55±6.42	16.06±7.14	13.17±3.63	20.52±5.25	18.13±5.24	13.38±4.25
University	19.43±8.80	15.89±6.34	12.54±3.49	20.56±5.41	18.62±5.31	13.20±3.92
	p<0.05	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05
Working Status of Mother*						
Yes	16.51±6.76	15.52±6.78	12.82±3.42	20.29±5.28	18.03±5.28	13.02±4.09
No	16.79±6.36	15.68±6.58	12.72±3.56	20.29±5.19	18.01±5.27	13.08±4.21
	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05
Education Level of Father**						
Illiterate	18.40 ± 6.89	14.52 ± 6.08	13.46 ± 3.83	19.67 ± 4.88	17.75 ± 5.39	12.52±3.60
Literate	16.92 ± 5.75	14.00 ± 6.19	12.31 ± 2.60	18.50 ± 4.38	16.39 ± 4.63	12.25±3.89
Primary School	16.78 ± 6.31	15.50 ± 6.48	12.65 ± 3.58	20.32 ± 5.22	17.89 ± 5.19	13.00±4.21
Secondary School	16.80±6.33	15.60±6.49	12.84±3.39	20.22±5.16	18.16±5.30	12.96±4.12
High School	16.19±6.03	16.04 ± 6.65	12.85 ± 3.66	20.35 ± 5.25	18.20±5.30	13.24±4.28
University	17.58±7.45	15.90±7.20	12.46±3.44	20.46±5.25	18.07±5.47	13.33±4.26
	p<0.05	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05
Working Status of Father*						
Yes	16.77±6.42	15.68±6.61	12.73±3.55	20.30±5.91	18.02±5.28	13.07±4.19
No	16.29±5.56	14.89±6.21	12.54±3.46	19.89±5.76	17.71±4.79	13.08±4.54
	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05
Witnessing Violence*						
Yes	16.78±6.33	15.76±6.72	12.77±3.54	20.46±5.16	18.22±5.29	13.19±4.25
No	16.73±6.47	15.53±6.46	12.69±3.57	20.05±5.27	17.72±5.23	12.91±4.13
	p>0.05	p>0.05	p>0.05	p<0.05	p<0.05	p>0.05
Violence by parent*						
Yes	17.02±6.38	17.40±7.24	13.35±3.66	21.51±5.29	19.21±5.39	14.12±4.31
No	16.69±6.40	15.21±6.35	12.57±3.50	19.98±5.13	17.70±5.19	12.80±4.13
	p>0.05	p<0.05	p<0.05	p<0.05	p<0.05	p<0.05
Violence topic was covered in the lessons*						
Yes	16.22±6.13	15.56±6.55	12.75±3.58	20.24±5.19	17.96±5.30	13.00±4.23
No	17.54±6.69	15.80±6.66	12.70±3.51	20.37±5.23	18.08±5.22	13.18±4.16
	p<0.05	p<0.05	p<0.05	p<0.05	p<0.05	p<0.05
*t test, ** ANOVA test						

Analysis of the Data

The data of the study were analyzed using SPSS 20.0 for Windows package programming. In addition to the descriptive statistical criteria (means, standard deviations, minimum and maximum values and percentages), t-test (independent samples t-test) and ANOVA were used in comparing the scale scores. The relationship between the scales was analysed using correlation analysis [7]. 1843 were first year students and 1337 were fourth year students. 57.8% of the participants stated that they witnessed violence and 20.5% were exposed to violence by their mother or father, they also stated that they were exposed mostly to psychological violence (47%). 59.4% of the participants stated that violence topic was covered in the courses and 51% of these students stated that they covered this topic during their university education.

An evaluation of the participants' ACVS and AS scores according to their socio-demographic features showed that there were no significant differences in terms of their marital status, and the place they lived longest ($p>0.05$). An evaluation of the participants' ACVS and AS sub-scales according to the participants' grade level showed that there was a significant difference between the first and fourth year students. First year students' acceptances of violence and aggression levels were higher. An evaluation of ACVS and AS sub-scales according to the participants' age shows that there was a significant difference between violence, and aggression level and age ($p<0.05$). Students in lower age group were found to have higher violence and aggression levels. A significant difference was detected in ACVS according to the place of birth ($p<0.05$). It was found that those who were born in a village had higher ACVS mean scores than those who were born in a town or city. There was a significant difference in ACVS according to the type of family ($p<0.05$). ACVS mean scores of the participants living in an extended family were found to be higher (Table 2). According to the evaluation of ACVS and AS according witnessing violence, there was no difference in terms of ACVS, but there was a significant difference in terms of anger and hostility sub-scales of AS. The participants who witnessed violence were found to have higher anger and hostility mean scores. All AS sub-scale scores of the participants who were subjected to violence by their parents were found to be higher. There was a significant difference between being subjected to violence and AS scores ($p<0.05$) (Table 3). An analysis of the relationship between ACVS and AS sub-scales showed that there was a positive and weak relationship between acceptance of violence and aggression levels.

Discussion

A variety of harmful effects on each of the individual partners in the dating relationship of adolescents and young adults is reported to be associated with aggression and violence. These effects include lower self-esteem, reduced self-worth, increased self-blame, anger, hurt, and anxiety [8]. Studies indicate that partner violence is an important social problem [9-17].

In their study involving 1st year and 4th year nursing students, Aslan et al. (2008) reported that 4th year students were subjected to more violence and committed more violence [9]. The present study found that there was a decrease in acceptance of violence rates with the increase in age and grade levels of the students. Unlike the study conducted by Aslan et al., this study did not include committing or being subjected to violence cases. Instruction of this issue in the participants' courses might have had positive contributions. Foshee et al. (2005) found that partner violence was higher in those having low socio- economic level and mothers with low education level. A study investigating the effect of place of living on the dating violence in America reported that young people living in South America had higher dating violence rates in comparison to the young people living in other areas. According to the researchers, this case might result from the fact that the south part has a dominant violence culture and more traditional gender roles [18]. Studies that compare people living in rural areas and cities demonstrate that dating violence rates were higher in people living in rural areas; and the authors explained this case as well with gender roles [19]. The present study shows similarity with previous studies because those who were born in rural areas were found to have higher acceptance of violence scores.

Studies show that witnessing violence or being subjected to violence at home affects individuals' violence and aggression behaviours. Pradubmook-Sherer (2011) conducted a study with 1296 young people aged between 14 and 19 and found that those punished by their parents were more subjected to partner violence; and those with higher financial levels and families with higher education levels were less subjected to partner violence [20]. Black et al. (2015) found that young people who were subjected to violence at home, at school, and in society tended to accept partner violence more [21]. Gover, Kaukinen & Fox (2008) reported that those subjected to violence and domestic violence in childhood experienced more partner violence [12]. In their study including high school students, Earnest and Brandy (2016) found that those who were subjected to violence at home, who witnessed violence, and who did

not feel safe at school were subjected to more partner violence [22]. This study found that those exposed to violence in their families had higher aggression levels.

Conclusion

The participants' acceptance of violence levels was low and there was a positive, slight relationship with their aggression levels. The students' acceptance level decreased with the increase in their age and grade levels. Views of young adults forming a major part of young population and how much they accept or approve violence in their dating relationships are of importance so that solutions to this issue could be found.

Acknowledgements

We would like to thank to all of the participants. This study was presented as an oral presentation at the The 8th World Conference on Educational Sciences in Madrid on February 2016.

Funding

This study was not funded by any organisation.

Conflict of interest

There are no conflicts of interest with respect to the authorship and/or publication of this article.

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HEALTH SCIENCES QUARTERLY

Volume : 1
Issue : 1
2021

E-ISSN: 2791-6022
https://journals.gen.tr/jsp

Received: 2021-03-22

Accepted: 2021-04-08

REVIEW ARTICLE

Optical coherence tomography-angiography: A new diagnostic and follow-up tool for glaucoma

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Abstract

Glaucoma is an optic neuropathy and is one of the leading causes of irreversible vision loss worldwide. There are studies on the role of vascular dysfunction in the pathogenesis of glaucoma. Evaluation of intraocular blood flow will be useful in elucidating the pathogenesis. Various techniques are available for the diagnosis and follow-up of patients with glaucoma. Optical coherence tomography angiography (OCTA) has emerged as a new technology to detect the vascular effects of the glaucoma. Optical coherence tomography angiography (OCTA) is a new technology and many publications have been made in the field of glaucoma. In this article, we aimed to review the studies conducted on the role of OCTA technology in glaucoma and to draw attention to how OCTA can be helpful for diagnosis of glaucoma and follow-up of patients with glaucoma. Whole literature through by PubMed for the keywords of optical coherence tomography angiography and glaucoma were scanned. This review included articles up to February 2021. Only English languages articles were included. Optical coherence tomography angiography provides a rapid and noninvasive quantitative assessment of the microcirculation of the retina, optic nerve, and choroid. Optical coherence tomography angiography uses the action of red blood cells as an intrinsic contrast agent. It has high reproducibility. Optical coherence tomography angiography studies have shown that microcirculation in the superficial optic nerve, peripapillary retina and the macula are reduced in glaucoma patients. Optical coherence tomography angiography parameters in the peripapillary region are thought to be better biomarkers in advanced glaucoma than OCT parameters. Recent literature shows that OCTA has the potential to provide useful information in the diagnosis and follow-up of patients with glaucoma.

Keywords: *Glaucoma, optical coherence tomography angiography, optic nerve.*

Citation: Inan S, Inan UU. Optical coherence tomography-angiography: A new diagnostic and follow-up tool for glaucoma.Health Sci. Q. 2021;1(1):45-51. https://doi.org/10.26900/hsq.1.1.08

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Introduction

Glaucoma is an important cause of irreversible vision loss worldwide. Increased intraocular pressure (IOP) and impaired ocular blood flow are two important factors contributing to the development and progression of glaucoma [1]. These changes in ocular perfusion pressure caused by the difference in mean arterial pressure and intraocular pressure were thought to cause glaucomatous optic neuropathy due to ischemic damage by causing ischemia in the optic nerve [2]. In the Early Manifest Glaucoma study, it was stated that low ocular perfusion pressure is a risk factor in the progression of glaucoma [3]. Barbados Eye study and Los Angeles Latino eye study also showed a relationship between low ocular perfusion pressure and the prevalence of glaucoma [4,5]. Fluorescein angiography (FA) and ICG angiography studies have shown changes in blood flow in glaucoma. However, these investigations allow the flow to be evaluated more qualitatively than quantitatively. Color doppler USG is problematic in terms of resolution. Laser flowmetry has been evaluated as a limited application due to reproducibility and difficulty in clinical application. Doppler OCT studies also lacked sensitivity in measuring blood flow. Early diagnosis is important in glaucoma. Thus, functional and structural tests are crucial in the diagnosis and follow-up of glaucoma [6-8].

In this brief review article, we aimed to review information about the role of Optical Coherence Tomography-Angiography (OCTA) in the glaucoma management. We collected English written literature conducting OCTA studies on glaucoma and summarized the place of OCTA in eyes with glaucoma.

Optical Coherence Tomography-Angiography

Optical coherence tomography angiography has emerged as a non-invasive, quantitative, fast and new technology for evaluating ocular vascularity. It is based on optical coherence tomography (OCT) [6,7]. Non-invasive imaging and evaluation of the microcirculation in the optic nerve head and peripapillary retina is possible by using OCTA [8,9]. Parameters used in OCTA analysis include foveal avascular region, choriocapillaris, foveal and optic nerve head vessel density (VD) and flow index. Optical coherence tomography angiography is noninvasive as no contrast material is required. Its advantages are its high resolution and high repeatability compared to other modalities. Projection artefact and motion artefact are its disadvantages. It cannot directly measure blood flow rate either, its images are static [6,10]. Especially two parameters used frequently in the literature are vessel density (VD) and flow index (FI). These measurements are used to represent perfusion

OCTA in Glaucoma

OCTA of papillary and peripapillary area in Glaucoma

Studies have shown that optic nerve head and peripapillary retina show a decrease in VD and flow indexes in eyes with primary open-angle glaucoma (POAG) [8,11,12]. It is known that the peripapillary retinal nerve fibre layer (pRNFL) is mainly affected in the lower and upper quadrants in perimetric and early glaucoma. OCTA can help show the relationship between vascular and neuronal changes in glaucomatous eyes [13].

It was Jia et al. who published the first report on the optic nerve head (ONH) in OCTA [14]. Liu et al. showed that the density of peripapillary vessels in eyes with glaucoma was decreased in eyes with glaucoma compared to normal eyes [12]. Subsequently, several studies presented differences in ONH and microcirculation of the peripapillary region between glaucoma, glaucoma suspects and normal patients. Eyes with glaucoma with higher pre-treatment IOP values showed the largest difference in the optic disc compared with normal eyes, but no difference was found in the macular or peripapillary areas. This has been explained by the decrease in vascular density in the optic disc due to vascular compression in glaucoma associated with pre-treatment IOP values [15,16]. One potential reason for the lower discriminatory power of the optic disc from OCTA parameters can be explained as the significant heterogeneity in optic disc morphology. Vascular crowding of the large vessels in the optic disc also makes it difficult to specifically examine microvascularity. The pathophysiology of glaucomatous damage in the optic disc and the peripapillary areas is different, and it can explain the difference in the impairment of parameters of OCTA between two areas [17].

OCTA and RNFL Relationship in Glaucoma

There are studies with different evaluations about the correlation of structural changes in OCTA and glaucoma. Chen et al. reported that although there was no difference in RNFL thickness, glaucoma patients had significantly lower peripapillary vessel density

compared to normal subjects [18]. Some studies have shown a strong correlation between RNFL and OCTA parameters [19,20]. Pradhan et al. reported that the decrease in vascular density and RNFL thinning differed in different peripapillary sectors in eyes with POAG compared to normal eyes [21]. Macular and peripapillary VD have been shown to decrease in eyes with glaucoma [22]. Peripapillary VD differences may be helpful in diagnosis. Other studies have shown that there is no correlation between OCTA parameters and structural changes.

A strong correlation have been reported between peripapillary vessel density of the inferotemporal and superotemporal sectors and visual field loss [23,24].

OCTA of Macular Area in Glaucoma

In a study evaluating the diagnostic accuracy of macular scans in control and mild glaucoma eyes, it was shown that the vascular density in the outer field has a higher diagnostic performance compared to the inner field vascular density [25]. The superotemporal and inferotemporal macula have been found to the most susceptible macular areas to glaucoma. These areas are mostly located within the 6x6 mm area but outside the central 3x3 mm area [26,27]. 6 × 6 mm macular scans may, therefore, give rise to higher diagnostic accuracy. In one study, the internal macular vessel density gradually decreased, while the internal macular thickness did not change during a follow-up period of 13.1 months [28]. In another study, a correlation was found between RNFL thickness in the peripapillary area and VD; however, the correlation was not found in all groups [13]. The inner macular thickness is suggested to be better indicator than the inner macular vessel density in the detection of glaucoma disease [29]. The differences between studies may be due to differences in the area chosen for measurements of inner vessel density and inner retinal thickness [30]. Decreases in OCTA VD may occur before the structural and functional deterioration in glaucoma suspects. This situation suggested that OCTA may be helpful in early diagnosis and follow-up of glaucoma [31]. The percentage reduction in macular vessel density in early glaucoma eyes was lower than the percentage reduction in macular ganglion cells thickness, whereas this ratio was similar in preperimetric eyes [32]. Rapid reduction in macular vessel density has been associated with severe glaucoma [33].

It has been suggested that glaucoma is associated with decreased vascular density in the macular region; however, the precise role of this parameter in the diagnosis and progression of glaucoma is unclear [34].

OCTA in Different Types and Stages of Glaucoma

Hou et al. reported significantly higher intraocular vascular density asymmetry in those with glaucoma suspicion compared to normal eyes [35]. Yarmohammadi et al. showed that the mean parafoveally vessel density in the eyes of patients with preperimetric POAG was significantly different from that of normal eyes [36]. Lee et al. found that low perfusion peripapillary retinal areas in OCTA coincided with the RNFL defect. Optical coherence tomography angiography can provide us with information about ocular perfusion at different stages of eyes with glaucoma [37]. A significantly higher peripapillary vessel density has been found in eyes with normotensive glaucoma (NTG) compared to eyes with POAG, but no significant difference has been found in structural and functional parameters [38]. The patients with POAG have been found to have lower peripapillary vascular density compared to normal eyes [39]. No significant difference in peripapillary OCTA parameters in terms of blood flow index and vessel density has been found between NTG and POAG [40]. A significant decrease in peripapillary VD has been found in eyes with primary angle-closure glaucoma (PACG) [41]. The vascular density in both parafoveal and peripapillary regions has been shown to be significantly lower in PACG eyes than in normal eyes. They showed that poorly controlled PACG eyes had lower vascular density in the peripapillary area than well-controlled PACG eyes. Optic nerve head and peripapillary vascular changes correlated well with disease and severity of glaucoma, and this may be an important indicator of disease progression [42]. Rao et al, found a reduction in VD in PACG but did not find this change in angle-closure without glaucoma [43]. The circumpapillary VD in the eyes with angle-closure was significantly lower after acute angle-closure [44]. A significantly reduced peripapillary VD has also been reported in eyes with pseudoexfoliative glaucoma [45].

When the studies were evaluated, it was thought that OCTA parameters in the peripapillary region were better biomarkers compared to OCT parameters in advanced glaucoma. The peripapillary small vessel density was also found to be associated with the severity of glaucomatous visual field damage in eyes with advanced POAG [46].

Association of OCTA with Visual Field in Glaucoma

Optical coherence tomography angiography parameters (VD, FI) have been shown to have a moderate and high correlation with visual field parameters [11,14,47,48]. When peripapillary vascular density of POAG patients with visual field defect in one eye and normal visual field in the other eye are compared with each other and with normal eyes, the mean peripapillary vascular density was found to be higher in unaffected eyes of patients with POAG than in other affected eyes. However, no significant difference was found from normal eyes [36]. The correlation between the visual field mean deviation (MD) and OCTA parameters has been found to be stronger than the correlation between visual field MD and OCT parameters. Therefore, vascular loss as a OCTA finding has been suggested as a better biomarker than structural changes for worse visual function in eyes with glaucoma [9].

OCTA in Follow-Up of Glaucoma

In one study, it was stated that deep VD values measured by OCTA may indicate the risk of impaired visual function in patients with glaucoma [49]. There are also studies showing the improvement in VD measurements with the decrease in IOP after the treatment [50]. Although OCTA provides us with various evidence on the vascular pathogenesis of glaucoma, the clinical application of this information is still under investigation. The contradictions between studies present uncertainties in establishing the causal link.

OCTA in Myopic Patients with Glaucoma Suspicion

In a OCTA study evaluating myopic and normal eyes with and without POAG, the relationships between peripapillary vessel density and mean visual field sensitivity in POAG with and without high myopia was investigated [51]. It has been suggested that peripapillary vascular density may be useful in monitoring disease progression in high myopic eyes with glaucoma [52]. In another study, it was shown that the macular VD in the deep capillary plexus decreased significantly faster in highly myopic glaucomatous eyes than those without high myopia. It has been stated that these findings may be important in risk assessment of myopic POAG patients [53]. In the evaluation of glaucoma in highly myopic eyes, a multimodal approach with papillary anatomic and circumpapillary microperimetric assessments has been proposed for to be important [54]. As studies on myopic glaucoma increase, OCTA may be an important tool in the follow-up of myopic glaucoma.

OCTA of Choriocapillaris in Glaucoma

Kwon et al. observed parafoveal visual field defects in 96% of eyes with choroidal microvascular dropout (CMvD) and only 39% of eyes without CMvD, suggesting that this may provide a clinical overview of the spatial location of damage in glaucomatous eyes. Recent studies support that blood flow disruption can also occur in the deep layers of the retina and choroid, in addition to the superficial layers [55]. A higher frequency of choroidal microvascular dropout (CMvD) in eyes with glaucoma with parapapillary gamma zone has been reported to be associated with glaucoma progression or central visual field defects [56]. Eyes with choroidal microvascular dropout (CMvD) have been shown to be closely associated with the nocturnal diastolic blood pressure drop. Accordingly, the modulation of nighttime DBP decreases can be achieved by 24-hour ambulatory blood pressure monitoring of CMvD patients. Thus, it has been suggested that glaucoma progression can be prevented or slowed down [57].

OCTA and Diurnal Variation

Mansouri et al. found that diurnal IOP variations had no significant effect on peripapillary and macular vessel density in eyes with glaucoma [58]. In another study, daily changes in IOP, mean ocular perfusion pressure (MOPP) and retinal vessel density (RVD) were significantly higher in POAG eyes compared to healthy eyes. Compared to the study of Mansouri et al., in this study RVD measurement, blood pressure and MOPP evaluation were performed in the evening. According to these findings, they suggested that daily RVD changes may indicate the hemodynamic variation of POAG [59].

Conclusion

Current OCTA studies show that microcirculation is reduced in various stages of glaucoma. Optical coherence tomography angiography has come into our practice as a new objective approach to diagnosis and follow-up in glaucoma. It may be advantageous in certain types of glaucoma such as myopic glaucoma, or detection of progression of the advanced glaucoma. It seems that OCTA will take place in the management of glaucoma as an adjunctive tool in the future. However, there is no evidence that it is superior to standard structural and functional investigations in ability to

detect the glaucomatous disease. Whether impaired microcirculation in glaucomatous eyes induces neuronal damage or already glaucomatous damaged tissue with reduced consumption induces impaired microcirculation remains to be clarified. In conclusion, although there is insufficient evidence to use this technology in the very early diagnosis of glaucoma, further OCTA studies will help explain the relationship between perusion and glaucoma pathogenesis. It will be beneficial to use various functional and structural tests together in the diagnosis and follow-up of glaucoma.

Funding
The authors declared that this study has received no financial support.

Conflict of interest
The authors have no conflicts of interest declared.

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HEALTH SCIENCES QUARTERLY

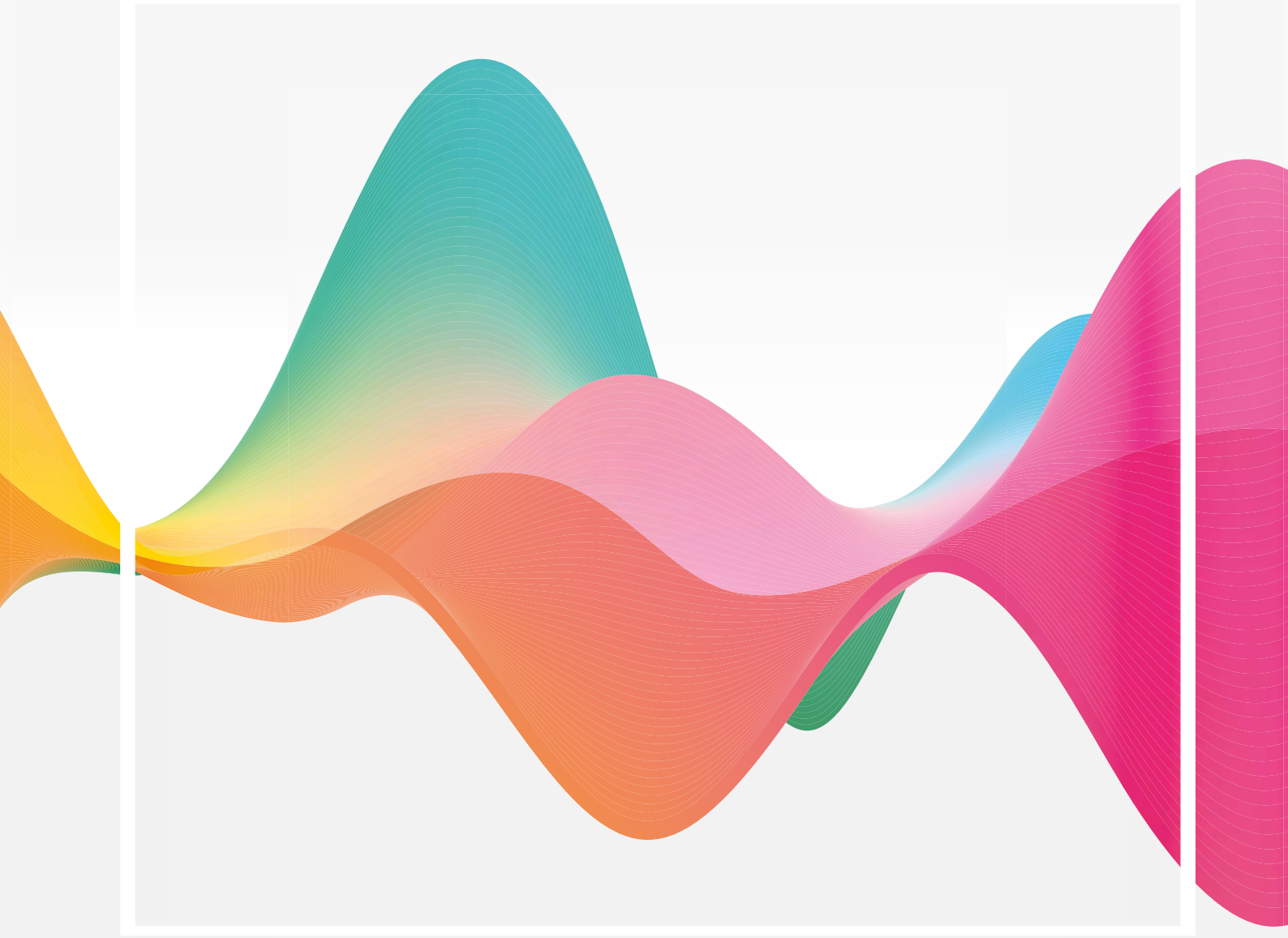
E-ISSN: 2791-6022

DOI: 10.26900/jsp

Volume 1

Issue: 1

2021



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