KASTAMONU MEDICAL JOURNAL

Original Article / Özgün Makale

DOI: 10.51271/KMJ-0023

Kastamonu Med J 2021; 1(4): 105-109

An investigation of the association between lipoxin A4 levels and metabolic syndrome parameters in patients with metabolic syndrome

Metabolik sendromlu hastalarda lipoksin A4 düzeyleri ile metabolik sendrom parametreleri arasındaki ilişkinin araştırılması

Sedat Gülten[1], Fatih Akçay[2]

[1]Kastamonu University, Faculty of Medicine, Department of Medical Biochemistry, Kastamonu, Turkey
[2]Atatürk University, Faculty of Medicine, Department of Medical Biochemistry, Erzurum, Turkey

ABSTRACT

Aim: Metabolic syndrome (MS) is a significant public health problem and has the potential to increase the risk of developing cardiovascular diseases (CVD), the risk of type 2 Diabetes Mellitus (T2DM), the risk of stroke and the risk of a heart attack. MS has recently been considered an inflammatory disease. Lipoxins (LXs) are, on the other hand, bioactive lipid molecules synthesized from arachidonic acid (AA) and show potent anti-inflammatory and pro-resolving activities in vivo and in vitro conditions. In this study, we aimed to evaluate serum levels of LXA4 in MS patients and explore the relationship of serum LXA4 levels with MS components [waist circumference, blood pressure, serum high-density lipoprotein (HDL), and triglyceride (TG) levels].

Material and Method: In this study, the sample was composed of 39 patients diagnosed with MS and 32 healthy age- and sex-matched individuals. We measured serum LXA4 levels adopting the enzyme-linked immunosorbent assay (ELISA) method with "Human Lipoxin A4 ELISA Kit". While collecting the blood samples from the subjects, we noted their ages, sex, physical examination findings, and anthropometric measurements [height, weight, waist circumference, and body mass index (BMI)]. Additionally, we obtained their serum TG, low-density lipoprotein (LDL), HDL, glucose, and cholesterol levels.

Results: While we could not find any significant differences between the groups by age and sex ($p>0.05$), the groups significantly differed by weight, waist circumference, BMI, systolic blood pressure, diastolic blood pressure, TG, HDL, and FBG ($p<0.05$ for TG; $p<0.001$ for others). Moreover, serum levels of LXA4 significantly differed between the groups ($p<0.05$). Within-group comparisons showed that while serum levels of LXA4 significantly differed between male subjects ($p=0.01$), it was not the case for females ($p>0.05$). In both groups, there were negative correlations between serum LXA4 levels and waist circumference ($r=-0.368$ $p=0.02$). Yet, we found such an association only among male patients ($r=-0.516$ $p=0.02$).

Conclusion: Overall, we found serum LXA4 levels to be significantly low in MS patients ($p<0.05$). Yet, it still needs to be elucidated whether this impairment is a cause or a result of MS. Finally, we discovered this impairment and its significant correlations with some MS parameters to be only in male patients, suggesting that serum LXA4 levels may vary by sex in MS patients.

Keywords: Lipoxin A4, metabolic syndrome, metabolic syndrome parameters

ÖZ

Amaç: Metabolik sendrom (MS) önemli bir halk sağlığı sorunudur ve kardiyovasküler hastalık (KVH) geliştirme riskini, tip 2 Diabetes Mellitus (T2DM) riskini, felç riskini ve kalp krizi riskini artırma potansiyeline sahiptir. MS son zamanlarda inflamatuar bir hastalık olarak kabul edilmiştir. Lipoksinler (LX'ler) ise, araşidonik asitten (AA) sentezlenen biyoaktif lipid molekülleridir ve in vivo ve in vitro koşullarda güçlü anti-inflamatuar ve pro-çözücü aktiviteler gösterirler. Bu çalışmada, MS hastalarında serum LXA4 düzeylerini değerlendirmeyi ve serum LXA4 düzeylerinin MS bileşenleri [bel çevresi, kan basıncı, serum yüksek yoğunluklu lipoprotein (HDL) ve trigliserit (TG) düzeyleri] ile ilişkisini araştırmayı amaçladık.

Gereç ve Yöntem: Çalışmaya, MS tanısı almış otuz dokuz hasta ile kontrol grubu olarak yaş ve cinsiyet yönünden benzer özelliklere sahip otuz iki sağlıklı birey dahil edilmiştir. Serum LXA4 düzeylerinin ölçümü ELISA yöntemi ile "Human Lipoxin A4 ELISA Kit " kullanılarak gerçekleştirildi. Hasta ve kontrol grubundaki bireylerin kan alma sırasında yaşı, cinsiyeti, fizik muayene bulguları, antropometrik ölçümleri [boy, kilo, bel çevresi, vücut kitle indeksi (VKİ)] kaydedilmiştir. Ek olarak, serum TG, düşük dansiteli lipoprotein (LDL), HDL, glukoz ve kolesterol ölçümleri yapılmıştır.

Bulgular: Hasta ve kontrol grubu arasında yaş ve cinsiyet parametrelerinde istatiksel olarak anlamlı bir bir farklılık gözlemlenmedi ($p>0,05$) ancak ağırlık ($p<0,001$), bel çevresi ($p<0,001$), vücut kitle indeksi ($p<0,001$), sistolik kan basıncı ($p<0,001$), diyastolik kan basıncı ($p<0,001$), TG ($p<0,05$), HDL ($p<0,001$) ve glukoz parametrelerinde anlamlı farklılık gözlemlendi. Gruplar arasında serum LXA4 düzeyleri de farklıydı ($p<0,05$). Sadece kadınlar değerlendirildiğinde serum LXA4 düzeyleri farklı değildi ($p>0,05$). Sadece erkekler değerlendirildiğinde ise serum LXA4 düzeyleri arasındaki fark anlamlıydı ($p=0,01$). Tüm katılımcılarda serum LXA4 düzeyleri ile bel çevresi arasında negatif korelasyon ($r:-0,368$ $p=0,02$) bulunmaktayken bu korelasyonu cinsiyet açısından incelediğimizde sadece erkeklerde olduğu gözlemlenmiştir ($r:-0,516$, $p:0,002$).

Sonuç: Serum LXA4 düzeyleri MS'li hastalarda düşüktür ($p<0,05$). Ancak bu düşüklüğün MS'ye mi neden olduğu ya da MS'nin sonucu mu olduğu bilinmemektedir. Bu düşüklüğün ve korelasyonların sadece erkeklerde bulunması ise LXA4 düzeylerinin MS hastalarında cinsiyetler arası farklı olabileceğini göstermektedir.

Anahtar Kelimeler: Lipoksin A4, metabolik sendrom, metabolik sendrom parametreleri

Corresponding Author / Sorumlu Yazar:
Sedat Gülten, sgulten@kastamonu.edu.tr

Received / Geliş: 19.10.2021 **Accepted / Kabul**: 30.11.2021

Cite this article as / Bu makaleye atıf için: Gülten S & Akçay F. An investigation of the association between lipoxin A4 levels and metabolic syndrome parameters in patients with metabolic syndrome. Kastamonu Med J 2021; 1(4): 105-109

INTRODUCTION

Metabolic syndrome (MS) is one where various pathologies (e.g., insulin resistance, increased visceral adipose tissue, atherogenic dyslipidemia, and endothelial dysfunction) coexist (1). MS is a noteworthy public health issue that is increasingly posing a clinical threat worldwide, together with increased energy intake, obesity, and sedentary lifestyle. It has the potential to increase the risk of developing CVD within 5-10 years by two times, the risk of type T2DM by five times (2), the risk of stroke 2-4 times, and the risk of a heart attack 3-4 times (3). MS is also considered to be a first-degree risk factor for atherothrombotic complications (4).

MS is accompanied by a distinctive, chronic, low-grade inflammation. Yet, the inflammation, where massive tissue damage does not occur, is not accompanied by infection or autoimmunity. Some scholars propose to use the term "metaflammation" for this inflammatory state, meaning metabolically triggered inflammation (5), while some others suggest using the term "parainflammation" to express such an intermediate state between the inflammatory state and the basal level (6). Whichever term is used, the inflammatory process in MS bears unique characteristics, and its mechanism has not been fully elucidated yet (7).

Lipoxins (LXs) are mediators synthesized from arachidonic acid (AA) with effective anti-inflammatory and immunoregulatory properties; the LXA4 and LXB4 are the main components of this series. LXs, demonstrating robust anti-inflammatory effects, are produced in response to infection, trauma, and inflammation (8-10). They emerge during cell-cell interactions as a result of reactions catalyzed by 5-lipoxygenase (LO) followed by 12-LO or 15-LO enzymes (8).

Lipids, such as leukotrienes (LT) and platelet-activating factor (PAF), and cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), are endogenous proinflammatory mediators. LXs, particularly LXA4, reduce the synthesis of these proinflammatory mediators in vivo and in vitro, leading to inhibition of leukocyte-related inflammation (10).

It is now clearly known that the resolution of inflammation is a dynamically regulated process by mediators in lipid structures such as LXs, resolvins, and protectins (11). These mediators increase monocyte production, decrease vascular permeability, and inhibit polymorphonuclear cell proliferation (11). It was also suggested that LXs, triggering the resolution of inflammation, stimulate lymphatic drainage of leukocytes (12). Moreover, insufficient resolution of inflammation may cause many prevalent chronic diseases such as arthritis, diabetes, and atherosclerosis (13,14).

In this study, we aimed to measure serum levels of LXA4, which is a solid endogenous anti-inflammatory factor and has a triggering impact on the resolution of inflammation in MS, and to explore the relationship between LXA4 and some MS parameters (waist circumference, systolic and diastolic blood pressure, fasting blood glucose (FBG), serum triglyceride (TG), and high-density lipoprotein (HDL)) and other anthropometric measurements (weight and body mass index (BMI)).

MATERIALS AND METHOD

Research Design

We carried out the present case-control study in Atatürk University, School of Medicine, Department of Biochemistry in July 2014, with the approval of the Clinical Research Ethics Committee of the School of Medicine (no. B.30.2.ATA.0.01.00/105). In the study, we recruited 39 patients (15 males and 24 females) aged 27-71 years, who applied to Internal Medicine, Endocrinology, and Cardiology outpatient clinics in Ondokuz Mayıs University and were diagnosed with MS according to the National Cholesterol Education Program Adult Treatment Panel 3 (NCEP ATP III)-2001 criteria. The control group was composed of 32 healthy individuals (19 males and 13 females) with similar ethnic origin, age, and socio-cultural characteristics with the patient group, who applied for general health check-ups and did not meet the MS criteria or had at most one. We used serum samples obtained from the control group for research purposes and aliquoted and kept at -80°C.

We noted demographic information (age and sex), physical examination findings (blood pressure, pulse, fever, and respiratory rate), and anthropometric measurements (height, weight, waist circumference, and BMI) of the subjects while collecting their blood samples.

Yet, we had to exclude those with systemic diseases (e.g., malignancy and connective tissue disease), trauma and infection history up to 2 weeks ago, and anti-inflammatory medication.

Anthropometric Measurements

We measured height with a stadiometer (cm) in an upright position without shoes while keeping the occipital protuberance, back, heel, and gluteus maximus in contact with the measurement plane. Then, we took the subjects, wearing only a patient gown, to the weight measurement. Next, we measured waist circumference using a tape measure (cm) on the middle of the line passing through the lower edge of the 12th rib and the line passing through the anterosuperior crista iliaca over the underwear after a slight expiration in an upright position. Following height, weight, and waist circumference measurements, we calculated BMI using the relevant formula (kg/m^2).

Physical Examination

We calculated blood pressure considering the mean value of two measurements performed in 5-minute intervals with a standard, calibrated mercury sphygmomanometer with cuff, in an upright position, on an empty stomach, and at rest. Hence, we generated systolic and diastolic arterial blood pressure data.

Collection and Storage of Blood Samples

We took and centrifuged venous blood samples into biochemistry tubes without anticoagulants after 12 hours of fasting and separated the serum. Then, we placed the samples in a deep freezer at -80°C on the same day.

Laboratory Kits and Working Methods

We worked on FBG, total cholesterol, TG, and HDL in a biochemistry laboratory using Roche Diagnostics kits on a Roche Hitachi Cobas 8000 autoanalyzer. We calculated LDL levels using the Friedewald formula [Friedewald formula: LDL=Total Cholesterol – (HDL + TG / 5)].

We then measured serum LXA4 levels through the ELISA method using the "Human LXA4 ELISA Kit" (Cusabio, Cat No: CSB-E09689h) following the manufacturer's instructions. The measuring range of the kit was between 0.625-40 pg/mL.

Statistical Analysis

We analyzed the data using the "SPSS 19.0 for Windows" (SPSS Inc., IL, USA) program. We presented the categorical variables as number (n) and percentage (%) while demonstrating quantitive variables as median (minimum, maximum) and mean±standard deviation. Since the data pertaining to LXA4, weight, waist circumference, age, TG, BMI, and HDL showed normal distributions, we used a student's t-test to compare the groups by these variables. Yet, we used a Mann-Whitney U test to compare the groups by systolic blood pressure, diastolic blood pressure, and FBG because these variables showed non-normal distributions. Finally, we utilized Pearson's or Spearman's correlation analysis to explore the associations between quantitative variables. We considered a p-value of <0.05 statistically significant.

RESULTS

Table 3 presents the weight, waist circumference, BMI, systolic blood pressure, diastolic blood pressure, TG, HDL, and FBG values of the groups.

While the mean serum LXA4 level of the female patients was 790±297 pg/mL. it was 915±210 pg/mL for the female controls. Accordingly. the female patients had a lower mean serum LXA4 level compared to those in the control group. but the difference was not statistically significant. On the other hand. while the male patients had a mean LXA4 level of 652±213 pg/mL. it was 826±160 pg/mL for the male controls. and the difference was statistically significant (p= 0.01).

We used Pearson's correlation analysis to explore the relationship between LXA4 and MS parameters. Accordingly. we found significant negative correlations between LXA4 and waist circumference (r=-0.368 p=0.002) and weight (r=-0.285 p=0.016) in the patient group. We also determined significant negative correlations between LXA4 and waist circumference (r=-0.516 p=0.002) and BMI (r=-0.433 p=0.011) in male patients.

DISCUSSION

MS is a significant public health issue that is increasingly posing a clinical threat across the world. together with increased energy intake. obesity. and sedentary lifestyle. Overall. the International Diabetes Federation estimates that a quarter of the world's adult population has MS (15).

The present research aimed to investigate whether LXA4. which shows both anti-inflammatory and pro-resolving properties. is reduced in MS. which is now accepted as an inflammatory disease. Particularly. we explored the relationship between LXA4 and MS components (waist circumference. triglyceride. blood pressure. FBG. and HDL. according to NCEP ATP III-2001and MS Diagnostic criteria (16).

The susceptibility to chronic inflammatory diseases is probably due to a defect in signaling pathways or synthesis of lipid-structured pro-resolving mediators such as LXs. In fact. these mediators were previously shown to have potential therapeutic impacts on inflammatory states (168.169).

Table 1. Distribution of the Groups by Sex

Group	Female	Male	Total	p
Control	13 (%40.6)	19 (%59.4)	32	0.079
Patient	24 (%61.5)	15 (%38.5)	39	

We could not find a significant difference between the patient and control groups by sex ($\chi 2 = 3.08$; $p>0.05$).

Table 2. Distribution of the Groups by Age

Group	M±SD	p
Control (years)	51±5.1	0.917
Patient (years)	51±12.7	

There were also no significant differences between the groups by age (p>0.05).

Table 3. Physical Examination Findings of the Groups

	Group	M±SD	Median	Min-Max	p
Weight (kg)	Control	74.8±15.4	76.00	48-115	<0.001
	Patient	89.9±15.6	90.00	61-124	
Waist circumference (cm)	Control	89.0±14.2	90.00	60-120	<0.001
	Patient	112±14.6	112.00	85-145	
BMI (kg/m²)	Control	26.8±5.47	26.00	17.1-46	<0.001
	Patient	33.8±5.82	34.20	23-48	
Systolic blood pressure (mmHg)	Control	108±8.59	110.00	90-120	<0.001
	Patient	127±15.4	130.00	100-180	
Diastolic blood pressure (mmHg)	Control	69.4±7.16	70.00	60-80	<0.001
	Patient	77.7±8.72	80.00	60-100	
TG (mg/dL)	Control	180±118	138.00	44-668	<0.05
	Patient	241±121	199.00	94-594	
HDL (mg/dL)	Control	47.2±13.2	45.850	18.6-84	<0.001
	Patient	30.6±11.2	29.200	7.1-72.9	
FBG (mg/dL)	Control	89.9±15.4	87.00	62-133	<0.001
	Patient	195±83.9	173.00	60-387	

We concluded that the patient and control groups significantly differed by weight. waist circumference. BMI. systolic blood pressure. diastolic blood pressure. HDL. FBG. and TG (p<0.05 for TG. p<0.001 for others).

Table 4. Comparison of LXA4 Between the Groups

	Lipoxin A4 (M±SD)	p
Control (32)	875±217	0.02
Patient (39)	737±273	

We determined that the LXA4 levels of the patient group were significantly lower than those of the control group (p<0.05).

Table 5. Distribution of LXA4 Levels by Sex between the Groups

	Groups	M±SD	p
Male	Control	826±160	0.01
	Patient	652±213	
Female	Control	915±210	0.19
	Patient	790±297	

Serum and placental LXA4 levels of pregnant women with preeclampsia (PE) were found to be significantly lower than those of ordinary pregnant women. LXA4 is known to terminate inflammation. perhaps the primary cause of PE. and increase its resolution. Also. the mRNA and protein expressions of 5-lipoxygenase (LO). 12-LO. and 15-LO - enzymes involved in LXA4 production - were discovered to be significantly decreased in women with PE. Moreover. in experimental mouse models with PE. blockade of LXA4 signaling induced PE and. then. symptoms were relieved with the administration of LXA4. Therefore. it was claimed that LXA4 deficiency might be responsible for PE (17).

The previous research suggested that AA and LXA4 levels are low in mice and humans with alloxan-induced type 1 diabetes mellitus (T1DM) and T2DM. It was also observed that T1DM

induced by chemical molecules did not develop in the case of pre-administration of AA. eicosapentaenoic acid (EPA). and docosahexaenoic acid (DHA). which are the precursors of LXs. resolving. and protectins. respectively. or in transgenic mice producing large amounts of EPA and DHA. LXs. resolvins. and protectins inhibit the production of TNF-α. IL-6. and reactive oxygen products. which suggests that they function as endogenous antidiabetic molecules and may be helpful in the prevention of T1DM and prevention and treatment of T2DM (18).

In a study on mice with MS. the researchers measured plasma LXA4 and LTB4 levels following aseptic trauma induced in the tibias of mice. The results revealed that LXA4 levels decreased 0.5 times while LTB4 levels increased 2.8 times after trauma in mice with MS. On the other hand. plasma LXA4 levels increased 2.2 times. whereas LTB4 levels decreased 0.6 times in the control group. These findings may indicate that the humoral inflammation termination pathways are impaired in patients with MS (19).

Yu et al. (28) showed that low serum LXA4 levels are associated with an increased incidence of MS. Another study found similar findings to previous studies showing a negative correlation between MS and LXA4. (29) In a study. the prevalence of MS was found to be 32.3%. 36.2%. and 45.9% in men with mild. moderate. and severe periodontitis. respectively. The severity of periodontitis was shown to be positively associated with extensive MS only in men. but this relationship could not be determined in women. In men. severe periodontitis showed a higher risk of MS than those without or with mild periodontitis (relative risk 1.43. 95% CI 1.17–1.73) (30).

We found serum LXA4 levels in MS patients to be significantly lower than in the control group. Our research is among the pioneering studies investigating LXA4 levels in patients with MS. In addition. although the mean LXA4 level was lower in the female patients compared to the female controls. such a decrease was not statistically significant. Yet. the male patients had significantly lower LXA4 levels than the male controls.

The difference in LXA4 levels between male and female patients may be due to the small sample size or associated with the compartments where adipose tissue is stored; subcutaneous adipose tissue can store less amount of fat in males than in females (20). As a result. while females gain weight in the hips and thighs (pear-shaped body) due to the increase in fat in the subcutaneous fat tissue. while men meet an apple-shaped body appearance as gaining weight. Visceral adipose tissue inflammation is more prevalent in apple-shaped bodies (21).

Visceral adipose tissue inflammation is key in the relationship between obesity and MS. In addition. decreased production of pro-resolving mediators in the visceral adipose fat compartment in obese individuals bears the most significant role in the development of low-grade chronic inflammation. Consequently. it is not surprising to encounter increased visceral adipose tissue and low LXA4 levels among males (21). overlapping the relationship between LXA4 and waist circumference in our study. We found a negative association between LXA4 and waist circumference in all subjects. Considering only males. we reached the same result; however. it was not the case among females. To our best knowledge. the relevant literature does not host findings related to the link between sex and LXA4.

Exercise has an anti-inflammatory effect. reduces IL-6 and TNF-α levels. and prevents T2DM development (18). Therefore. it is not prudent to air that exercise reduces the infiltration of M1 phenotype macrophages into adipose tissue and can convert the macrophage phenotype in adipose tissue from M1 to M2 (22).

Intraperitoneal injection of relatively low doses of resolvin E1. a pro-resolving mediator like LXA4. increases insulin sensitivity significantly by inducing the expression of adiponectin and glucose transporter 4 (GLUT4) in adipose tissue and has a significant protective effect against hepatic steatosis. In addition. protectin D1. also a pro-resolving mediator. increases adiponectin expression in adipose tissue (23).

It is often suggested that obesity results from a deficiency in the production of pro-resolving mediators in addition to increased activity of inflammatory eicosanoid-producing pathways. In particular. decreased synthesis of omega-3-derived pro-resolving mediators in inflammatory subcutaneous and visceral adipose tissues is a prevalent condition in obese patients (24). It has recently been shown that the visceral and subcutaneous adipose tissues of the obese have a deficiency in producing PD1 and RvD1. A deficiency in pro-resolving mediators was also reported in non-obese patients having a peripheral vascular disease with inflammation in subcutaneous adipose tissue (25). This finding may suggest that pro-resolving mediator production mechanisms are disrupted in inflammatory processes.

The literature seems to have shown not much interest in the relationship of LXA4 with MS components. Some studies previously showed LXA4 does not affect or lower blood pressure (26.18). In a lipopolysaccharide-induced mouse preeclampsia model. BML-111. an LXA4 analog. was demonstrated to reduce systemic blood pressure in vivo (26). Feuerstein and Siren (18) showed that mice experienced no change to arterial blood pressure or heart rate following administration of LXA4 and LXB4 through the mesenteric artery. In our study. we could not find significant differences between LXA4 levels in the subjects with blood pressure lower and higher than 130/85 mmHg.

Although no study in the literature directly investigated the relationship between LXA4 and blood glucose. it was previously shown that LXA4 reduces insulin resistance and activates peroxisome proliferator-activated receptor-gamma (PPARγ) like antidiabetic drugs glitazones and thiazolidinediones (27). Therefore. these effects of LXA4 may be helpful to reduce blood glucose. In our study. we compared those with glucose levels lower and higher than 110 mg/dL but found no significant difference between the groups by LXA4 level. In addition. there was no correlation between LXA4 and FBG.

Our literature review did. unfortunately. not result in a study examining the LXA4-HDL relationship. In our study. we could not detect significant differences between the LXA4 levels of those with HDL values <40 mg/dL (males) and <50 mg/dL (females) and those with ≥40 mg/dL (males) and ≥50 mg/dL (females). respectively.

The traditional approach to treating inflammatory diseases is to inhibit the effects of proinflammatory chemical mediators. such as eicosanoids. cytokines. and ROS. on inflammation. Thus. PGs and LTs have been popular therapeutic targets in the development of anti-inflammatory and anticancer drugs. In fact. their discovery and elucidation of their relationship

with biochemical pathways have led to a better understanding of the pathogenesis of many inflammatory diseases. including rheumatoid arthritis and asthma. Consequently. many drugs that are receptor antagonists of proinflammatory PGs and LTs or inhibit their biosynthesis have been developed and are currently used in therapy. Among these. celecoxib and rofecoxib. which are selective COX-2 inhibitors used in treating arthritis. are prominent. There are also many anti-LT drugs available. like zilueton (5-LO inhibitor) and montelukast and zafirlukast (LT-D receptor antagonists) used to treat asthma and allergies.

To be able to tell whether serum lipoxin a4 levels can be an early biomarker in metabolic syndrome. with more patients. prospective studies and are required to reach more definite conclusions about the functionality of these parameters in diagnosing the disease..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission Clinical Research Ethics Committee of the School of Medicine (no. B.30.2.ATA.0.01.00/105).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Acknowledgments: This paper was produced from the thesis in medical specialty training.

REFERENCES

1. Kaur J. A comprehensive review on metabolic syndrome. Cardiol Res Pract 2014; 2014: 943162.
2. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009; 120: 1640-5.
3. Alberti KG, Zimmet P, Shaw J. IDF Epidemiology Task Force Consensus Group. The metabolic syndrome--a new worldwide definition. Lancet 2005; 366: 1059-62.
4. Grundy SM. Metabolic syndrome: connecting and reconciling cardiovascular and diabetes worlds. J Am Coll Cardiol 2006; 47: 1093-100.
5. Hotamisligil GS. Inflammation and metabolic disorders. Nature 2006; 444: 860-7.
6. Medzhitov R. Origin and physiological roles of inflammation. Nature 2008; 454: 428-35.
7. R. Monteiro. "Chronic inflammation in the metabolic syndrome: emphasis on adipose tissue." in Oxidative Stress. Inflammation and Angiogenesis in the Metabolic Syndrome. R. Soares and C. Costa. Eds. 2009. pp. 65–83. Springer Science. Nerw York. NY. USA.
8. Romano M, Recchia I, Recchiuti A. Lipoxin Receptors Eicosanoid Receptors and Inflammation. Sci World J 2007; 7: 1393–412.
9. Fiore S, Serhan CN. Formation of lipoxins and leukotrienes during receptor-mediated interactions of human platelets and recombinant human granulocyte/macrophage colony-stimulating factor-primed neutrophils. J Exp Med 1990; 172: 1451-7.
10. Serhan CN. Lipoxins and novel aspirin-triggered 15-epi-lipoxins (ATL): a jungle of cell-cell interactions or a therapeutic opportunity?. Prostaglandins. 1997; 53: 107-37.
11. Serhan CN. Systems approach to inflammation resolution: identification of novel anti-inflammatory and pro-resolving mediators. J Thromb Haemost 2009; 7: 44-8.
12. Arita M, Yoshida M, Hong S, et al. Resolvin E1, an endogenous lipid mediator derived from omega-3 eicosapentaenoic acid, protects against 2,4,6-trinitrobenzene sulfonic acid-induced colitis. Proc Natl Acad Sci U S A 2005; 102: 7671-6.
13. Serhan CN, Yacoubian S, Yang R. Anti-inflammatory and proresolving lipid mediators. Annu Rev Pathol 2008; 3: 279-312.
14. Maderna P, Godson C. Lipoxins: resolutionary road. Br J Pharmacol 2009; 158: 947-59.
15. International Diabetes Federation: The IDF consensus worldwide definition of the metabolic syndrome. http: //www.idf.org/metabolic-syndrome.
16. Levy BD, Kohli P, Gotlinger K, et al. Protectin D1 is generated in asthma and dampens airway inflammation and hyperresponsiveness. J Immunol 2007; 178: 496-502.
17. Karp CL, Flick LM, Park KW, et al. Defective lipoxin-mediated anti-inflammatory activity in the cystic fibrosis airway. Nat Immunol 2004; 5: 388-92.
18. Xu Z, Zhao F, Lin F, et al. Preeclampsia is associated with a deficiency of lipoxin A4, an endogenous anti-inflammatory mediator. Fertil Steril 2014; 102: 282-90.
19. Feuerstein G, Siren AL. Mesenteric vascular responses to i.v. administration of lipoxin A4 and lipoxin B4 in the conscious rat. FEBS Lett. 1988; 232: 51-5.
20. Su X, Feng X, Terrando N, et al. Dysfunction of inflammation-resolving pathways is associated with exaggerated postoperative cognitive decline in a rat model of the metabolic syndrome. Mol Med 2013; 18: 1481-90.
21. Titos E, Clària J. Omega-3-derived mediators counteract obesity-induced adipose tissue inflammation. Prostaglandins Other Lipid Mediat 2013; 107: 77-84.
22. Titos E. Rius B. González-Périz A. et al. Resolvin D1 and its precursordocosahexaenoic acid promote resolution of adipose tissue inflammation byeliciting macrophage polarization toward an M2-like phenotype. J Immunol 2011; 15: 5408–18.
23. González-Périz A. Horrillo R. Ferré N. et al. Obesity-induced insulin resistanceand hepatic steatosis are alleviated by omega-3 fatty acids: a role for resolvinsand protectins. FASEB J 2009; 23: 1946–57.
24. Neuhofer A, Zeyda M, Mascher D, et al. Impaired local production of proresolving lipid mediators in obesity and 17-HDHA as a potential treatment for obesity-associated inflammation. Diabetes 2013; 62: 1945-56.
25. Mauro CR, Ilonzo G, Nguyen BT, et al. Attenuated adiposopathy in perivascular adipose tissue compared with subcutaneous human adipose tissue. Am J Surg 2013; 206: 241-4.
26. Lin F, Zeng P, Xu Z. Treatment of Lipoxin A4 and its analogue on low-dose endotoxin induced preeclampsia in rat and possible mechanisms. ReprodToxicol 2012: 34; 677–85.
27. Sobrado M, Pereira MP, Ballesteros I. Synthesis of Lipoxin A4 by 5-Lipoxygenase Mediates PPARγ- Dependent. Neuroprotective Effects of Rosiglitazone in Experimental Stroke. J Neurosci 2009; 29: 3875-84.
28. Yu D, Xu Z, Yin X, et al. Inverse Relationship between Serum Lipoxin A4 Level and the Risk of Metabolic Syndrome in a Middle-Aged Chinese Population. PLoS One 2015; 10: e0142848.
29. Kim OS, Shin MH, Kweon SS, et al. The severity of periodontitis and metabolic syndrome in Korean population: the Dong-gu study. J Periodontal Res 2018; 53: 362-8.
30. Doğan ESK, Doğan B, Fentoğlu Ö, Kırzıoğlu FY. The role of serum lipoxin A4 levels in the association between periodontal disease and metabolic syndrome. J Periodontal Implant Sci 2019; 49: 105-13.