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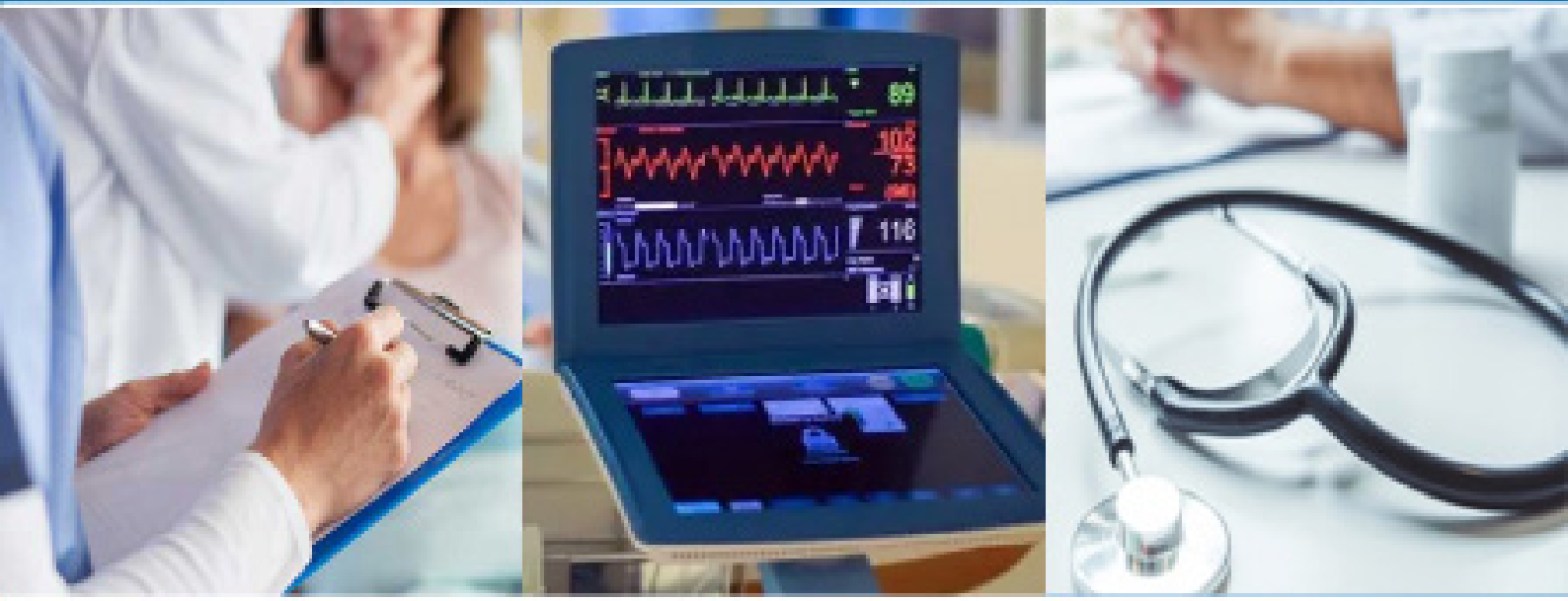

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CONTENTS

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ORIGINAL ARTICLES

CASE REPORT

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Original Article

TSH receptor autoantibody levels in patients with non-toxic diffuse and nodular goiter

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ABSTRACT

Aims: To investigate thyroid stimulating hormone (TSH) receptor antibody (TRAb) levels in patients with diffuse and nodular goiter and in patients which undergo thyroid operation.

Methods: 40 patients with non-toxic diffuse goiter (NTDG), 20 patients with non-toxic nodular goiter (NTNG), 20 patients undergo thyroid operation, and 34 healthy subjects were involved. Thyroid function tests, TRAb levels were measured. All the patients were done thyroid sonography. In the opereation group, preoperative, postoperative 10th and 30th day TRAbs were studied.

Results: TRAb was significantly elevated in 20% of patients with NTNG, 30% of patients with NTDG and 35% of patients in the operation group ($p>0.05$). No TRAb(+) patient was found in the control group. TRAb levels in the postoperative period in the operated group were higher than in the preoperative period.

Conclusion: TRAb was found in euthyroid patients with goiter, different from the control group. In the group operated for goiter, postoperative TRAb levels were higher than preoperative levels. These findings indicated that autoimmunity may be involved in the development of non-toxic goiter.

Keywords: TSH receptor antibody, non-toxic, diffuse goiter, nodular goiter

INTRODUCTION

Goiter is enlargement of the thyroid gland. The normal thyroid gland has a volume of 7-10 ml and weighs 10-20 g.[1] When the thyroid volume exceeds 18-19 ml in women and 25 ml in men, it is defined as goiter.[2] Goiter may be diffuse or nodular and may be accompanied by a thyroid hormone disorder. Epidemiologically, it is classified in 2 ways: goiter in more than 10% of the population or in 5% of children aged 6-12 years is called endemic goiter; if this rate is less than 5%, it is called sporadic goiter.[3] The primary cause of goiter is iodine deficiency. However, despite adequate iodine prophylaxis, goiter cannot be eradicated completely. Goiter is not observed in every individual living in the same endemic area. The incidence of goiter may also be different in regions with similar iodine intake. Based on all these, it is obvious that other factors are also involved in the development of goiter. In particular, autoimmune mechanisms have been shown to play a role in goiter development.[4]

Autoimmune diseases of the thyroid gland are the most common of all autoimmune endocrinopathies. Many factors have been shown to be indicative of autoimmunity in the thyroid. HLA-DR, a major histocompatibility complex (MHC) class II antigen, is associated with autoimmune diseases and has been shown to be present in autoimmune thyroid. Infiltration of the thyroid gland with activated T lymphocytes, decreased T suppressor/T helper lymphocyte ratio in the blood and various autoantibodies also point to this autoimmunity. These include anti-thyroid peroxidase (anti-TPO) antibody, anti-thyroglobulin (anti-TG) antibody, and thyroid stimulating hormone (TSH) receptor antibody (TRAb). While the first two cause thyroid cell damage, TRAB affects the function and growth of the gland.[5-7]

TRAbs are heterogeneous, some of them act as full agonists or full antagonists of TSH, while others act as partial agonists. Those that bind to the receptor and stimulate cell function play a role in Graves' disease, those that inhibit cell function play a role in idiopathic myxedema, those that stimulate cell growth play a role in non-toxic goiter and those that inhibit cell growth play a role in the etiology of atrophic thyroiditis.[8,9] In the literature, TRAbs have been shown to be present in the circulation of patients with non-toxic goiter at various rates. The presence of these antibodies in endemic or sporadic cases of goiter suggests that autoimmunity is involved in the pathogenesis of goiter. In these patients, it has been found that non-toxic goiter starts as a result of prolonged action of an antibody which is not as potent as in Graves' disease and the picture progresses to nodular goiter.[10-12]

The aim of this study was to determine the level of TRAB, a humoral marker of thyroid autoimmunity, in patients with non-toxic diffuse and non-toxic nodular goiter from various iodine-deficient regions in the Black Sea region of Turkiye and to determine preoperative and postoperative TRAB levels in a group of patients operated for nodular goiter.

METHODS

This thesis study was conducted between January 1994 and December 1994 at the Ondokuz Mayıs University Faculty of Medicine Hospital. There was no ethical approval requirement at the time of this study, therefore ethical approval was not obtained. Institutional approval was obtained. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients

The study consisted of 114 subjects in total. Non-toxic diffuse goiter (NTDG) was 40, non-toxic nodular goiter (NTNG) was 20, operation group was 20 and the control group consisted of 34 healthy subjects. All participants were euthyroid and were not taking any medication that would affect thyroid function. Patients with allergic, rheumatologic or other autoimmunity-related diseases and those with suspected thyroid malignancy were excluded.

The study group (NTDG+NTNG) patients came from various provinces of the Black Sea region. The patients and their numbers are given in the table below (Table 1).

Table 1. Provinces of the patients

Province	Number (%)
Samsun	31 (52)
Amasya	8 (13)
Giresun	6 (10)
Ordu	9 (15)
Çorum	2 (3.3)
Tokat	4 (6.7)
Total	60 (100)

In the first part of the study, NTDG, NTNG and healthy volunteers were compared and this part was designed cross-sectionally. In the 2nd part, preoperative and postoperative TRAb levels of 20 NTNG patients with an indication for surgery were analyzed.

Goiter was staged according to Pan American Health Office (PAHO) criteria:[13]

Grade 0a: No goiter

Grade 0b: Goiter present on palpation only. No visible hyperplasia when the neck is in extension

Grade I: Palpable goiter present. Hyperplasia visible on neck extension

Grade II: Hyperplasia visible when the neck is in neutral position

Grade III: Very large hyperplasia identifiable from a distance

Laboratory

TSH, total thyroxine (T4), free T4, total triiodothyreonine (T3) and free T3 were measured by chemiluminescence method. In the first part of the study, euthyroid individuals with goiter were identified and after the diagnosis was confirmed, blood samples were taken from the participants, centrifuged at 3500 rpm and serum was separated. Sera were stored at -20^{0}C until the time of the experiment. In the second part of the study, blood samples were taken from 20 NTNG patients with an indication for operation 1 day before the operation and on the 10th and 30th days after the operation. They were centrifuged at 3500 rpm and stored in the same way.

All serum samples of the experimental and control groups were removed from the deep freezer at the same time and TRAb levels were analyzed under the same conditions. TRAb levels were analyzed with Byk-Sangtec Diagnostica GmbH&Co.KG radioreceptor assay kit specific for TRAb. During the analysis, an ICN brand gamma counter with serial number 92122237 was used in the Central Laboratory of Ondokuz Mayıs University.

This assay method is based on the principle of competitive binding of radiolabeled TSH and TRAbs from patient serum to bind to soluble porcine TSH receptors in the experimental medium. The experimental procedure and steps are as follows:

1. 50 µl each of reference serum, positive control serum and patient serum were pipetted into test tubes. For detection of non-specific binding (NSB), the same amount of reference serum was added to the NSB tubes.
2. 100µl of porcine TSH receptor was added to each test tube and mixed with vortex. For NSB, 100 µl of distilled water was added instead of TSH receptor.
3. Allowed to stand at room temperature for 20±5 minutes.
4. 100µl of ^{125}I-labeled bovine TSH was added to all tubes and mixed with vortex.
5. Again incubated for 2 hours at room temperature.
6. 1 ml polyethylene glycol (PEG) was added to all tubes and mixed with vortex.
7. Centrifuged in a refrigerated centrifuge at 3000 rpm for 30 min.
8. After centrifugation, the supernatant was immediately aspirated with an aspirator and pasteur pipette and removed from the experimental medium.
9. The radioactivity of the pellet remaining at the bottom of the tubes was counted in a gamma counter in the ^{125}I channel.

Experimental results were evaluated with the following formula:

$$F\%= 100 X [1 - cpm_{sample} - cpm_{NSB} / cpm_{reference\ serum} - cpm_{NSB}]$$

F%: Level of immunoglobulin that inhibits the binding of labeled TSH

cpm_{sample}: cpm (count per minute) of patient serum

$cpm_{reference\ serum}$: cpm of reference serum

1: The number at which binding of specific ^{125}I-TSH is considered 100%.

Normal population studies have shown that TSH binding inhibition (F%) is not greater than 15% in normal subjects. TSH binding inhibition greater than 15% indicates the presence of TRAb activity.[14]

Values with F%<15% are considered negative for antibody. TRAbs measured by this method are called immnunglubulins that inhibit TSH binding.

Test characteristics were studied for quality control of the experiment;

a. According to the assay procedure, the binding of the reference serum had to be 20-30%.

It was evaluated by the formula BN= ($cpm_{reference\ serum}$/total activity) x 100 and found to be 28%.

b. Nonspecific binding had to be below 9%.

BNSB= ($cpm_{non\text{-}specific\ binding}$/total activity) x 100 and was found to be 7.4%.

c. Assay precision was assessed by repeated measurements of the positive control and intra-assay variation was found to be 8.3%.

Measurement of Thyroid Gland Volume

To examine the correlation of TRAbs with thyroid volume, thyroid ultrasonography (USG) was performed by the same radiologist. The volume of each thyroid lobe was calculated by the formula (height x width x thickness) x (π/6) and then the volume of each lobe was summed to determine the total thyroid volume. Total thyroid volume was divided by body weight to obtain the thyroid volume/body weight ratio.[15]

Statistical Analysis

Data were expressed as mean ± standard error. For statistical analysis, Student's t test was used to compare the mean age of the patient group with NTDG, the patient group with NTG (diffuse+nodular) and the control group. Mann-Whitney U test was used to compare the mean age of the patients with NTNG, patients operated for nodular goiter and the control group. Mann-Whitney U test was used to compare the mean age between genders. Chi-square test was used to compare the gender distribution between groups and chi-square test was used to compare the distribution of patients with TRAb (+). Chi-square test in dependent groups was used to compare the distribution of patients with TRAb (+) in the preoperative and postoperative (10^{th} and 30^{th} day) period in the operation group. Friedman test was used to compare the F% values of the operation group and Wilcoxon paired two-sample test was used for pairwise comparisons. Correlation analysis was used to evaluate the relationship between thyroid volume and F% values reflecting TRAb levels in patients with TRAB (+) in the whole patient group (NTDG+NTNG).

Table 2. Mean age and gender distribution in the groups

Groups		Patient number	Age (mean±SD)
1	Non-toxic diffuse goiter Male Female	40 5 35	31.38±1.52 35.2±4.43 30.83±1.62
2	Non-toxic nodular goiter Male Female	20 2 18	34.83±2.12 22±2 36.28±2.09
3 (1+2)	Non-toxic goiter (diffuse+nodular) Male Female	60 7 53	32.53±1.24 33.43±3.93 32.68±1.32
4	Control group Male Female	34 5 29	32.41±1.03 35±3.84 32.1±1.03
5	Operated for NTNG Male Female	20 3 17	38.3±1.9 36.33±3.18 38.65±1.73

SD: Standard deviation, NTNG: Non-toxic nodular goiter

Table 3. Comparison of groups according to TSH level

Groups		TSH (μIU/ml)	p
1	Non-toxic diffuse goiter	0.98±0.106	NA
2	Non-toxic nodular goiter	0.817±0.7	
3 (1+2)	Non-toxic goiter (diffuse+nodular)	0.927±0.08	
4	Operated for NTNG	0.681±0.108	
5	Control	0.964±0.08	

TSH: Thyroid stimulating hormone, NTNG: Non-toxic nodular goiter

Table 4. F% levels and TRAb(+) patient distribution of the groups

Groups		Patient number	F%	Number of TRAb (+) patients (%)
1	Non-toxic diffuse goiter	40	11.18±1.76	12 (30)
2	Non-toxic nodular goiter	20	6.27±1.67	4 (20)
3 (1+2)	Non-toxic goiter (diffuse+nodular)	60	9.54±1.49	16 (26.6)
4	Operated for NTNG Pre-operatif Post-operatif 10^{th} day Post-operatif 30^{th} day	20	 7.91±2.1 23.84±1.83 21.98±2.01	 7 (35) 17 (85) 15 (75)
5	Control group	34	4.21±0.79	0 (0)

TRAb: TSH receptor antibody, TSH: Thyroid stimulating hormone, NTNG: Non-toxic nodular goiter

RESULTS

A total of 114 people participated in the study. The NTDG group consisted of 40, the NTNG group of 20, and the control group of 34 healthy volunteers. Other 20 people underwent total thyroidectomy due to nodular goiter. There was no difference in gender distribution between the groups. The operated group had a higher mean age than the other groups (p<0.05) (Table 2).

There was no significant difference between the groups in terms of TSH level (Table 3).

Table 4 shows the TRAb distribution and F% values of the experimental and control groups. As can be seen, 30% of the NTDG group, 20% of the NTNG group, 26.6% of the diffuse+nodular NTG group and 35% of the operation group (in the preop period) had TRAb (+) patients. While there was no significant difference between the experimental groups in this respect, there was a significant difference between the experimental groups and the control group because of the absence of TRAb (+) patients (p<0.001). When the distribution of TRAb (+) patients in the group operated for NTNG in the preoperative and postoperative 10th and 30th days, the distribution of TRAb (+) patients was higher in the postop 10th day compared to the preop (p<0.001). There were more TRAb (+) patients on postop 30^{th} day compared to preop (p<0.05). There was no significant difference between postop days 10 and 30 (Table 4).

The distribution of TRAb (+) patients and F% values were compared by gender in the experimental and control groups. Women in the NTDG group had more TRAb (+) patients than women in the control group ($p<0.001$). There were also significantly more TRAb (+) women in the NTNG group ($p<0.05$). The distribution of TRAb (+) patients in men ($p<0.05$) and women ($p<0.001$) in the operation group was higher than in the control group (Table 5).

Table 5. F% levels and TRAb(+) patient distribution of the groups according to gender

Groups		Gender	Number	F%	Number of TRAb (+) patients (%)
1	Non-toxic diffuse goiter	Male	5	6.04±2.69	0 (0)
		Female	35	11.97±2.28	12 (34.2)
2	Non-toxic nodular goiter	Male	2	17.4±4.9	1 (50)
		Female	18	5.03±1.6	3 (16.6)
3 (1+2)	Non-toxic goiter (diffuse + nodular)	Male	7	9.28±2.82	1 (15)
		Female	53	9.57±1.65	15 (37.5)
4	Operated for NTNG	Male	3	13±6.6	2 (66.6)
		Female	17	7.01±2.22	5 (29.4)
5	Control group	Male	5	5.72±2.23	0 (0)
		Female	29	3.51±0.82	0 (0)

TRAb: TSH receptor antibody, NTNG: Non-toxic nodular goiter

Thyroid volume was measured by USG in patients with non-toxic goiter. The correlation between thyroid volume and F% levels in TRAb (+) patients was investigated. As shown in Table 6, no significant correlation was found (Table 6).

Table 6. Correlation between thyroid volume and F%

Patient group	Patient number (%)	F%	Tiroid volume (ml/kg)	r	p
TRAb (+) patients in the NTNG+NTDG group	16 (26.6)	26.02±2.25	0.47±0.45	0.26	>0.05

TRAb: TSH receptor antibody, NTNG: Non-toxic nodular goiter, NTDG: Non-toxic diffuse goiter

DISCUSSION

In the first part of this study, TRAb levels were studied to investigate the role of autoimmune mechanism in the development of goiter in patients with non-toxic diffuse goiter and nodular goiter admitted to our hospital from various provinces of the Black Sea region. In the second part of the study, the changes in TRAb levels before and after the operation in a group of patients with an indication for operation due to NTNG were analyzed.

Autoimmune diseases are caused by disturbances in immunoregulation. These disorders trigger autoimmune diseases by leading to the activation of T lymphocytes that cannot tolerate the body's autoantigens. In this process of abnormal immune reaction to the body's own antigens, environmental agents may play a role in the onset of the disease. In autoimmune diseases, target cell integrity and functions are altered in affected tissues and organs. Clinical symptoms occur as a result of tissue abnormalities due to humoral or cellular immunity or both. Autoimmune thyroid diseases occur with similar mechanisms, have a wide clinical spectrum and may lead to hypothyroidism or hyperthyroidism or the individual may become euthyroid despite the disease.[16]

The stimulation of thyroid growth by increased TSH due to iodine deficiency is accepted as the main factor in the development of goiter. However, various clinical situations have been observed which show that this mechanism alone is not sufficient to explain goiter formation. These are; thyroid growth despite TSH suppression with thyroxine, recurrence in operated patients despite thyroxine treatment, goiter in hyperthyroid patients with low TSH, similar thyroid function tests in patients with and without goiter living in the same region, failure to eradicate goiter despite adequate iodine prophylaxis. Today, many factors such as genetics, natural goitrogens, radiation, metabolic syndrome and obesity have been shown to cause goiter.[17-20] When Graves' disease is considered from this point of view, it has been found that antibodies similar to TRAbs observed in this disease are also present at various rates in patients with toxic and non-toxic goiter. The TSH receptor is encoded by a gene localized on chromosome 14q31 and functions through 4 different G proteins. These are Gs, phospholipase C, G13 and Gi. The TSH receptor is most highly expressed on the basolateral membrane of thyrocytes and regulates the functioning of the thyroid gland.[21] TRAbs' affinity for the TSH receptor is higher than TSH. Among these antibodies, those that stimulate adenylate cyclase lead to Graves' disease, those that inhibit adenylate cyclase lead to hypothyroidism, those that stimulate phosphotidyl inositol pathway lead to goiter formation and those that inhibit this pathway lead to atrophic thyroiditis, whichever type is predominant leads to clinical development.[22-24]

Non-toxic goiter is TSH-independent enlargement of the thyroid gland and patients can be euthyroid or hypothyroid. Patients are mostly euthyroid. It may be diffuse or nodular.[25,26] In our study, all participants were euthyroid. The distribution of patients was as follows: 40 non-toxic diffuse goiter, 20 non-toxic nodular goiter and 20 operated non-toxic nodular goiter (Tables 2, 3).

The incidence of goiter increases with age and the incidence of multinodular goiter is higher in the elderly.[4,20] In our study, it is not a coincidence that the operation group was statistically older.

In many studies conducted since 1986, TRAb has been detected in the serum of patients with non-toxic goiter.[27] In our study, TRAb was present in 26% of 60 patients with non-toxic goiter, while TRAb was negative in the control group. In addition, while 30% of patients with NTDG had TRAb (+), this rate was 20% in patients with NTNG, which is statistically similar (Table 4). These results are consistent with the above literature suggesting that autoimmune mechanisms may play a role in the development of goiter.

In studies, antibody positivity or increase in the amount of antibodies is observed after thyroid surgery and radioactive iodine treatment. The reason for this has been shown to be the development of antibody response against thyroid antigens released into the circulation or the passage of intrathyroidal accumulated antibodies from the thyroid to the circulation.[28,29] In our study, the number of TRAb(+) patients and TRAb levels on the 10th and 30th postoperative days were found to be higher compared to the preoperative period. This was again considered as a sign of the presence of autoimmunity.

Table 5 shows that the majority of the participants in our study were women. In addition, the number of TRAb(+) women is more dominant in the experimental groups than in the control group. Female gender is a risk factor for goiter. The female dominance in our study is consistent with the literature.[4]

In a study by Lee et al.[30] no correlation was found between TRAb level and thyroid volume in patients who underwent surgery for Graves' disease. In another study, thyroid volume was measured by thyroid tomography in hyperthyroid patients and no correlation was found with TRAb.[31] In our study, the relationship between TRAb level and thyroid volume was also examined in patients with TRAb(+) and no correlation was found as above (Table 6).

Limitations

This study has some limitations. The most important one is that this is an old study conducted 30 years ago. Recent studies are needed to support our findings.

CONCLUSION

In this study, TRAb was found in euthyroid patients with goiter, different from the control group. In the group operated for goiter, postoperative TRAb levels were higher than preoperative levels. These findings indicated that autoimmunity may be involved in the development of non-toxic goiter.

ETHICAL DECLARATIONS

Ethics Committee Approval

This specialty thesis was conducted in 1994, ethical approval was not obtained for the study as there was no requirement for ethical approval at that time, it was conducted after institutional approval was obtained.

Informed Consent

All patients signed and free and informed consent form.

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.

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Original Article

Evaluation with spiral computed tomography angiography after intravascular stent application in atherosclerotic renal artery stenosis

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ABSTRACT

Aims: With the development of spiral scanning, computed tomography angiography (CTA) is preferred over conventional angiography in many vascular applications. Reduced respiratory and motion artifacts and ability to catch arterial phase during one inspiration are the advantages of spiral CTA. Our aim in this study is to evaluate the value of spiral CTA in demonstrating stent integrity, stent patency, and renal artery/stent relationship after renal artery stenting.

Methods: 15 patients (12 male and 3 female) who had renal artery metallic stents were included in this study. Systolic and diastolic blood pressure and creatinine values of the patients were measured before and after the stent. Patients were examined by CTA after renal artery stenting. In renal artery segments with renal artery stenosis and stenting on CTA; stent diameter, stent length, integrity, luminal contrast enhancement and intraluminal calcification were evaluated with 1 mm axial reconstructed images and "post-process" techniques multiplanar reformat (MPR), maximum intensity projection (MIP), shaded surface display (SSD), and virtual intravascular endoscopy (VIE).

Result: Of the stenosis in which stents were placed, 1 was located in the proximal renal artery, 4 were in the mid-renal artery, and 10 were ostial. The whole stent was visualized in 8 cases. Among the MPR images, the axial plane was the best to depict the lumen in 13 cases. The stent lumen was best visualized on oblique MPR images in the axial plane. The visibility of the stent lumen decreased in MIP images with increased slice thickness. In cases where stenosis was considered due to intimal hyperplasia within the stent, no stenotic appearance was observed on MPR and MIP images. In all patients, stent and wall calcifications were observed separately from the contrast medium on MPR and MIP images. On SSD images, the stent could not be distinguished from contrast material and vascular wall calcifications in all patients. In VIE images, the renal artery ostium and the stent were viewed from the aortic lumen in all patients. The stent was observed as patent in 14 cases. In one case, occlusion was demonstrated proximal to the stent.

Conclusion: Spiral CTA is a noninvasive procedure in evaluating the integrity of the stent, stent patency and renal artery/stent relationship after renal artery stenting.

Keywords: Spiral CT Angiography, renal artery stenosis, renal artery stenting

INTRODUCTION

Atherosclerotic renal artery stenosis (RAS) is the most common cause of secondary hypertension and may lead to resistant hypertension, progressive deterioration of renal function, and cardiac destabilization syndromes, including pulmonary edema, acute coronary syndrome and heart failure, despite adherence to guideline-directed medical treatment.[1] Due to the variable prevalence of RAS, radiological methods are crucial for diagnosis. Conventional angiography (DSA) is considered the gold standard in diagnosis. Its greatest advantage is that it allows for widely accepted therapeutic interventions, such as percutaneous transluminal angioplasty and stent placement, to be performed immediately after the diagnostic examination.[2]

Color Doppler ultrasound of the renal artery plays a significant role in diagnosing RAS due to its non-invasive and repeatable nature. However, this method requires a long examination time to visualize the main renal artery. A previous study determined that Doppler ultrasound examination for predicting RAS offered 82.90% sensitivity, 70% specificity, an 85% positive predictive value, and a 66.7% negative predictive value.[3] The use of magnetic resonance angiography (MRA) as a non-invasive method has also been increasing in recent years. In patients with a high clinical suspicion of RAS, MRA is 87% sensitive in the detection of >50% stenosis. However, MRA is relatively nonspecific compared with CA and results

in significant overestimation of RAS in nearly one third of patients.[4,5]

With the development of spiral scanning, computed tomography angiography (CTA) has increasingly become the preferred method over DSA in many vascular applications.[6,7] The most important advantage of spiral CTA is its ability to minimize artifacts caused by respiration and patient movement, while capturing arterial phase data of intravenously administered contrast material within a single breath-hold. Significant advancements in spiral CTA have been achieved through post-processing techniques such as multiplanar reformat (MPR), maximum intensity projection (MIP), shaded surface display (SSD), and virtual intravascular endoscopy (VIE).[8] By selecting appropriate scanning parameters and post-processing techniques, spiral CTA has found widespread use in the evaluation of various pathologies, including aortic aneurysms and dissections, pulmonary embolism, and RAS.[9-11]

The aim of this study is to investigate the efficacy and adequacy of spiral CTA in demonstrating stent integrity, patency, and the relationship between the stent and renal artery following renal artery stenting.

METHODS

This cross-sectional study was conducted at the Radiology Department of Gazi University Faculty of Medicine from August 1996 and March 2001. The study was produced from a thesis before 2020 and institutional approval was received. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A total of 15 patients who underwent intravascular metallic stent placement in the renal artery due to RAS were included in the study. The patients' systolic and diastolic blood pressure values, as well as creatinine levels, were recorded before and after stent placement. Post-stent follow-up spiral CTA examinations were performed on the first day and at the 44th month after stent placement. Three patients underwent two spiral CTA examinations and one DSA. The spiral CTA was performed using a HiSpeed CT/i (GE Medical Systems, Milwaukee, USA) device. Initial images were used to determine the localization of the renal stents and the scanning area. The CTA was performed after administering 100-130 cc of non-ionic contrast material at a rate of 2.5-3 cc/sec via an automatic injector, through a 20G intravenous cannula in the antecubital vein, with a minimum of 100 cc (1.5 cc/kg). The scanning duration was approximately 19 seconds. The renal artery segments with RAS and stent placement were recorded.

Stent diameter and length were measured to assess the presence of stenosis. Maximum diameter measurements were taken from 1-mm axial reformatted images of the stent from the location where the stent was best visualized on standard axial images. Stent length was measured using oblique reformatted images, referencing the stent plane.

In all patients, MPR, MIP, SSD, and VIE images were generated using standard software. Stent integrity, lumen, presence of intraluminal calcification, and stenosis were evaluated and compared using MPR and MIP images. SSD images were used to assess the stent, intraluminal contrast enhancement, and wall calcifications, while VIE evaluated the visibility of the renal artery ostium, stent patency, and the lumens of renal artery segments distal and proximal to the stent.

The stents were expanded and released according to the manufacturer's recommendations by inflating the balloon at the nominal pressure, assuming they reached the desired diameter. Measurements were taken before and after stent deployment, and these two measurements were compared.

Density measurements were performed in all patients to evaluate renal artery and aortic contrast enhancement, as well as stent patency. For density measurements, a section where the lumen was best visualized on 1-mm reconstructed standard axial images was selected. Densities were measured in Hounsfield units (HU) from a 5 mm^2 area at the midsection of the abdominal aorta, the segment of the renal artery distal to the stent, and the contralateral renal artery.

In all cases, the kidney size, contrast enhancement, and cortical thickness were evaluated using the 1-mm reconstructed standard axial images.

Statistical Analysis

All data were analyzed with Microsoft Excell program v.10 (Microsoft Corporation, Redmond, WA, USA). Numerical data are given as mean and standard deviation (SD). Categorical variables are given as numbers and percentages.

RESULTS

The study included 15 patients, 12 men and 3 women, aged between 40 and 70 years (mean age 58.0±10.4 years). Fourteen of the patients were hypertensive, and one was normotensive. The mean pre-procedural systolic blood pressure of the hypertensive patients was 161.6±20.1 mmHg, and the mean diastolic blood pressure was 95.3±10.2 mmHg. In the follow-up after stent placement, the mean systolic blood pressure was measured as 140.0±22.9 mmHg, and the mean diastolic blood pressure as 86.0±20.2 mmHg. The mean serum creatinine level was 1.4±0.5 mg/dl before the procedure and 1.2±0.4 mg/dl after the procedure. Six patients had impaired renal function before the procedure (creatinine >1.4 mg/ml). In four of these patients, a decrease in creatinine levels was observed after the procedure, while in two patients, elevated creatinine levels persisted.

Of the stenoses treated with stent placement, one was located in the proximal renal artery, four in the mid-renal artery, and ten in the ostial. In eight patients, the stent was fully visualized, whereas in seven patients, it was not fully visualized. In 13 cases, the optimal plane for visualizing the lumen was determined to be axial on the MPR images. In one case, due to artifacts caused by the stent, the lumen was only partially visible in the axial plane. In another case, the best visualization of the stent integrity was obtained in the sagittal and coronal planes due to the angle formed between the stent and the aorta (Figures 1, 2).

In MIP images obtained with increased slice thickness, the best plane for visualizing the stent lumen in 10 cases was the axial plane with thicknesses between 1.5 and 2.1 mm. In 4 cases, the stent lumen was only partially visible in the axial plane with thicknesses between 1.2 and 2.1 mm. As a result, the stent lumen was best visualized in the oblique MPR images in the axial plane. In the MIP images with increased slice thickness, the visibility of the stent lumen decreased as the slice thickness increased.

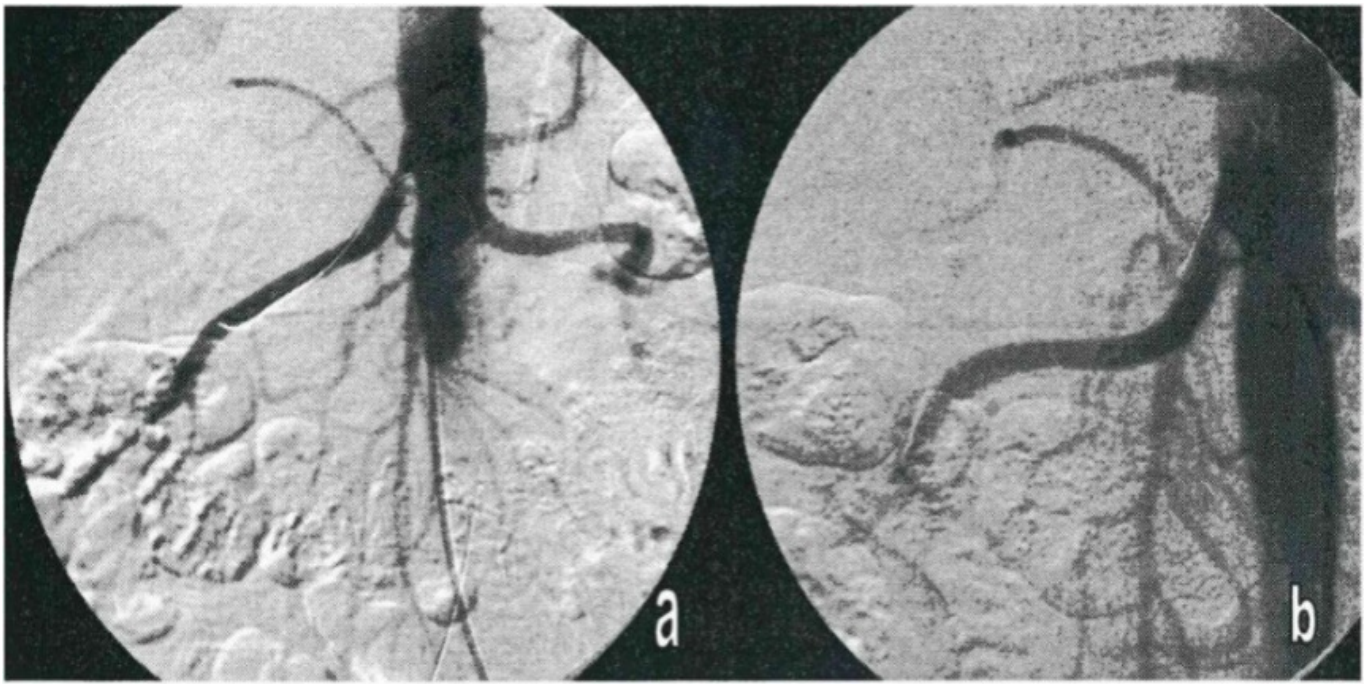

Figure 1. (a) A 75% ostial stenosis in the right renal artery is shown. (b) Following stent placement, this segment appears patent (open and unobstructed)

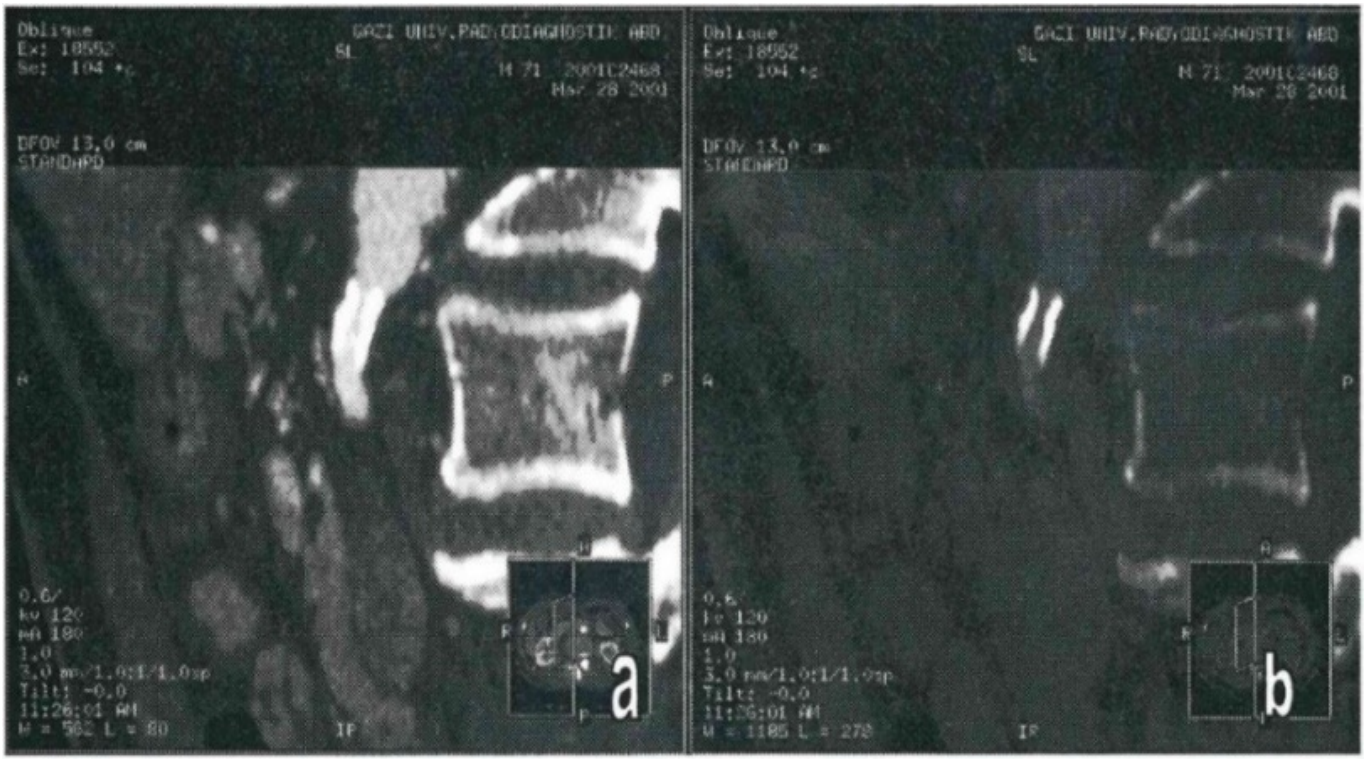

Figure 2. In the same case, a 0.6 mm thick oblique MPR image obtained from the sagittal plane, with the stent used as a reference (a: windowing for vascular structures, b: windowing for the stent), shows the stent as patent

In the evaluation of all the obtained images, the renal artery and stent level were observed to be patent in 14 cases. However, in one case, an occlusion was detected in the proximal segment of the renal artery on the stent side, and no contrast enhancement was observed in the stent lumen (Figures 3-7).

In one patient, oblique MPR images obtained in the axial plane revealed stenosis in the renal artery just proximal to the stent. In cases suspected of stenosis due to in-stent intimal hyperplasia, no stenotic appearance was observed in the MPR and MIP images.

In all patients, the stent was visualized separately from the contrast material in the MPR and MIP images. Vascular wall calcifications were separately visualized from the contrast material in the MPR and MIP images of 13 patients. In all patients, the vascular structures distal to the stent were displayed on MIP images in accordance with the degree of contrast enhancement. The continuity of the vascular structures was best observed in MIP images with thicknesses ranging from 7.3 to 10.7 mm.

With SSD, the stent could not be differentiated from the contrast material and vascular wall calcifications in any of the

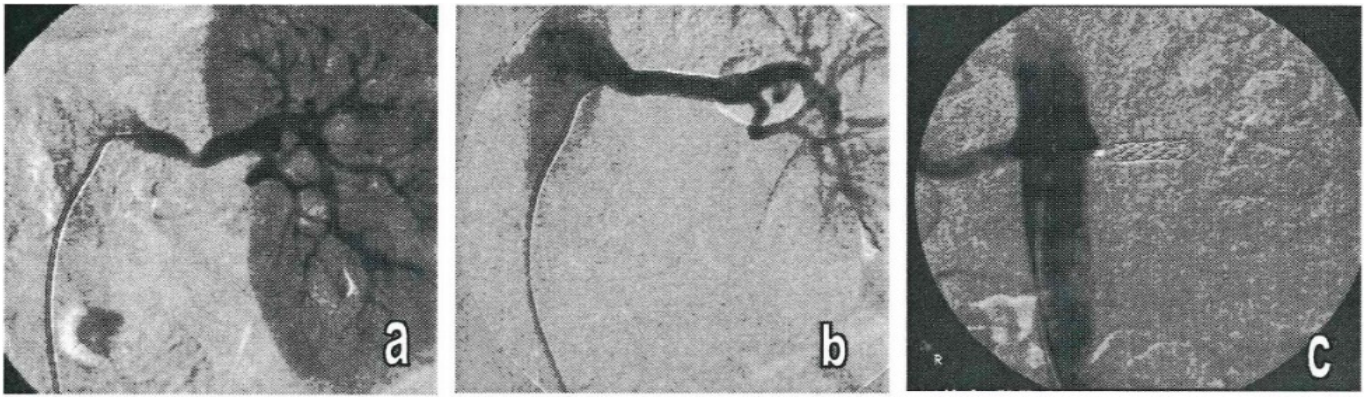

Figure 3. (a) A 70% stenosis in the midsection of the left renal artery, (b) stent placement following dissection that developed after balloon dilation, (c) 4.5 years later, angiographic follow-up showing occlusion in the left renal artery

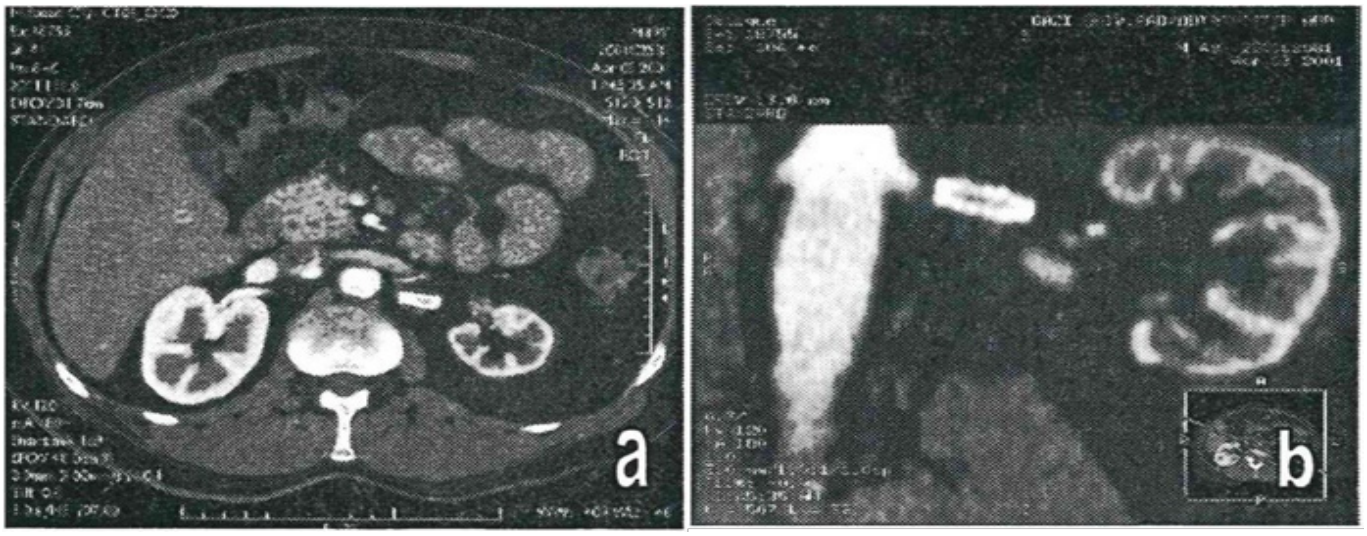

Figure 4. (a) In the same case, 4.5 years later, the spiral CTA follow-up shows a 1 mm reconstructed standard axial image obtained from volumetric data, and (b) a 0.7 mm thick MPR image in the coronal plane demonstrates a reduction in the size of the left kidney (long axis: 60 cm) and cortical thinning. Both kidneys are visible in the nephrogram phase

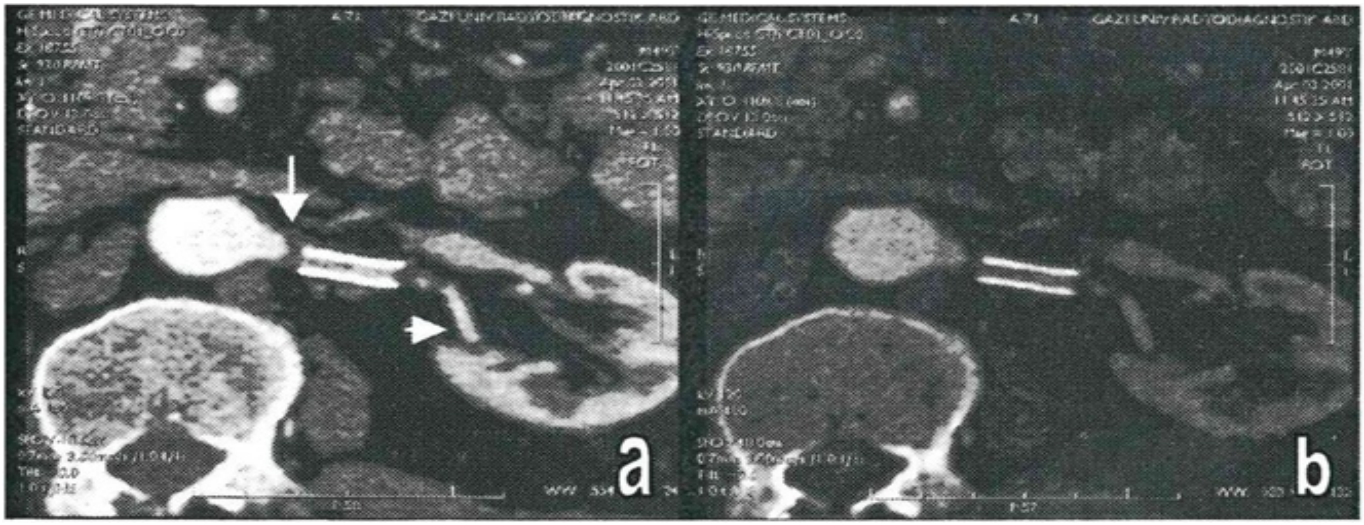

Figure 5. In the same case, oblique MPR images (0.7 mm thick) obtained from the axial plane using the stent as a reference (a: windowing for vascular structures, b: windowing for the stent) show: (a) an occlusion (arrow) in the proximal left renal artery with no opacification of the stent lumen, and (b) opacification in the segmental branches of the renal artery distal to the stent (arrowhead). Additionally, cortical thinning in the left kidney is noted

patients. However, the stent was observed to be wider than the renal artery at its localization site.

In VIE images, the threshold value was selected between 97 and 206. In all patients, the renal artery ostium and the stent were visualized from the aortic lumen. The stent lumen and the area distal to the stent were evaluated. The stent was patent in 14 cases, while occlusion was observed proximal to the stent in one case. In all patients, the stent lumen was observed with contour irregularities.

In one patient, bilateral accessory arteries were observed in both MIP and SSD images. Additionally, in 3 cases where stenosis was detected in the contralateral renal artery on

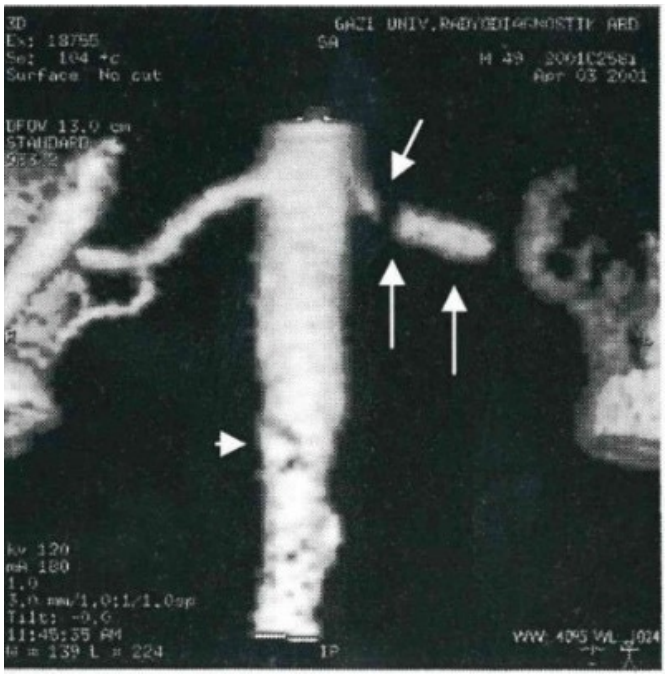

Figure 6. In anteriorly viewed SSD images of the same case, the right renal artery is seen to be patent, while an occlusion (arrow) is visible in the proximal left renal artery. Due to the density of the stent (double arrow), intraluminal contrast material, and aortic wall calcification exceeding the selected density threshold, they cannot be distinguished from each other. Aortic wall calcification is partially visible as contour irregularities (arrowhead)

angiography, the stenotic segment was shown in both MIP and SSD images (Figure 8). In the patient with stent occlusion, density measurements taken from the area adjacent to the distal end of the stent were found to be significantly lower. In all other cases, no significant differences in density values were detected.

DISCUSSION

With the advancement of spiral CTA, volumetric data can now be obtained without respiratory artifacts during the peak arterial vascular opacification following peripheral contrast material injection, allowing for the creation of two-dimensional (2D) and three-dimensional (3D) images.[12] When the reconstruction interval is selected to be smaller than the collimation and three images are reconstructed per rotation, sufficient images for 3D diagnosis can be generated. As the interval decreases, the partial volume effect is also reduced, facilitating the visualization of small vessels.[13] Additionally, reducing the reconstruction interval will increase the number of images that make up the scanning volume, as well as the time required for post-processing and evaluation, and the storage space needed for these images. In our study, a reconstruction interval of 1 mm was used for all cases.[14,15]

Narrow collimation increases both axial and longitudinal resolution. However, it also increases pixel noise while reducing the distance scanned within the procedure time. The

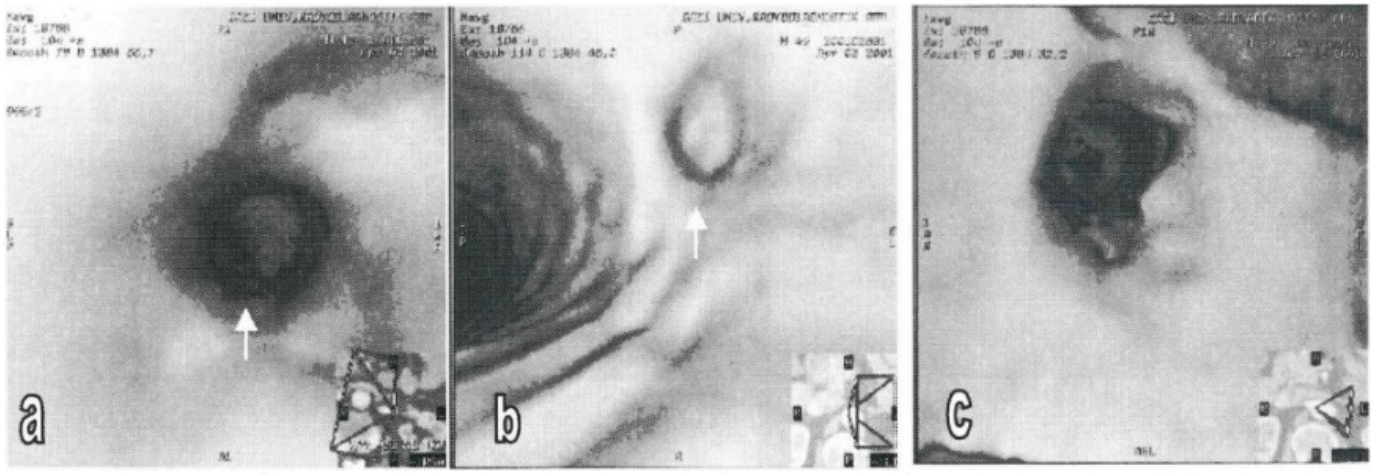

Figure 7. In the VIE images of the same case: (a) the occlusion (arrow) proximal to the stent is visualized from within the stent lumen, (b) the occlusion (arrow) in the proximal left renal artery is shown from the aortic lumen, and (c) the appearance of the blocked stent lumen distal to the occlusion is depicted from the aortic lumen

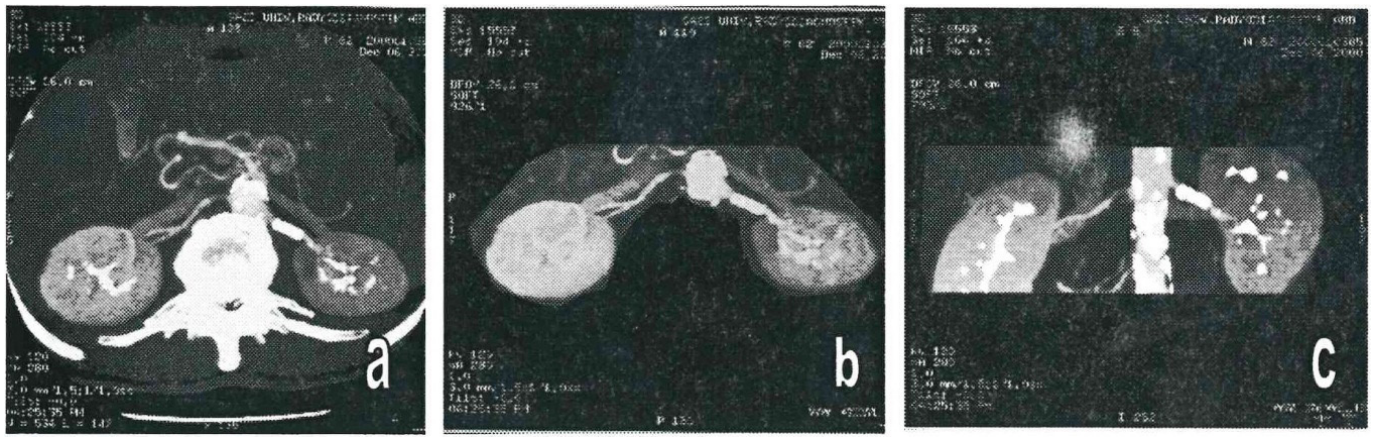

Figure 8. (a) The initial MIP image including the entire scanning volume is shown. After removing the bone structures, MIP images showing the entire scanning volume are presented from (b) an inferior and (c) anterior view. Windowing has been applied to visualize the vascular structures. In this case, there is up to 90% stenosis in the proximal right renal artery, and a stent is visible in the left renal artery

best results in vascular imaging are achieved when collimation finer than the diameter of the relevant vessel is used, combined with an increased pitch to enhance the scanning distance. Studies indicate that a collimation of 2 mm and a pitch of 1.5-2 are optimal for visualizing renal arteries and achieving the best image resolution.[16] In this study, for the purpose of demonstrating renal arteries and stents, 14 cases were scanned using 3 mm collimation, a table speed of 3 mm/s, and a pitch of 1:1, while 1 case utilized 3 mm collimation, a table speed of 4.5 mm/s, and a pitch of 1.5:1 (Figure 4). Therefore, the use of 3 mm collimation without increasing the pitch resulted in a slight decrease in longitudinal resolution.

During spiral CTA imaging, the patient moves in the z-axis direction (the direction of table movement), necessitating interpolation algorithms to obtain axial images from the volumetric data acquired. In reconstructions performed using the 180° linear interpolation technique, information from two angles with a 180° difference is utilized. This minimizes artifacts caused by the partial volume effect.[17] In this study, the interpolation algorithm used in the system was 180°.

In spiral CTA examinations, another important point is the use of contrast media. Sufficient arterial enhancement is necessary for a successful CTA while minimizing venous and parenchymal opacification.[18,19] This can be achieved when an appropriate scanning delay time is utilized. Delay time can be determined in three ways: First, predicting the delay time based on heart rate, blood pressure, and the patient's circulatory status; second, using small test injections; and third, employing techniques like Smart Prep (General Electric Medical Systems), which initiate scanning when an increase in attenuation is detected in the relevant vascular area. Kaatee and colleagues evaluated the delay times obtained through a fixed delay time with test injections in a group of 70 patients presenting clinical findings of renovascular hypertension and ischemic nephropathy, regarding their effectiveness in achieving maximal opacification in the renal arteries. In the first group, a fixed delay time was applied, while in the second group, they added 5, 10, 15, and 20 seconds to the time found after a test injection (15 ml of contrast medium at a rate of 3 ml/s). Statistical analysis revealed no significant difference between the two methods.[20] In our study, for visualizing the renal arteries and stents in all cases, 100-130 cc of contrast medium was administered at an injection speed of 2.5-3 ml/s, with a dosage of 1.5 cc/kg, ensuring it was not less than 100 cc. The delay times were determined as follows: 25 seconds for 7 cases, 20 seconds for 4 cases, and 10 seconds for 1 case.

In our study, all cases were processed using post-processing techniques to create MPR, MIP, SSD, and VIE images. MPR refers to coronal, sagittal, or oblique single voxel thickness planes formed by stacking axial slices. This technique is particularly effective in displaying anatomical connections that vary in any direction. In all cases, the stent was visualized separately from the intraluminal contrast. The stent appeared similar in density to the calcifications and bony structures. MPR images allow for the evaluation of the relationship, patency, and positioning of the metallic stent and vascular structures.[21]

MIP creates images by projecting imaginary rays through the reconstructed three-dimensional matrix of image data, marking the maximum attenuation value selected along each ray onto a grayscale image. The maximum attenuation value encountered by each ray is encoded into a two-dimensional projection image. The grayscale of MIP reflects relative X-ray attenuation. Additionally, the absence of a threshold value in MIP allows for the evaluation of structures with different attenuations.[21] MIP is highly sensitive in differentiating vascular calcifications from intraluminal contrast. Calcium appears five times more frequently in MIP than in SSD. Furthermore, MIP enables the differentiation of intravascular metallic stents from intraluminal contrast.[21,22] In our study, we visualized the distinction between the stent and intraluminal contrast in all cases using MIP. However, due to their high attenuation, the stent, vascular calcifications, and bony structures appeared similar in density across all cases.

In fourteen cases, the continuity of the renal artery distal to the stent was observed in thickened oblique images. In one case, MIP images showed an occlusion at the proximal stent, and due to collateral flow, the vascular structures distal to the stent were visualized. In all cases, when evaluating vascular structures using windowing in the thickened oblique MIP images obtained from the stent plane, the stent lumen could not be visualized due to its high attenuation. However, with wider windowing, the lumen was better visualized. The most significant limitation of MIP is its dependence on the degree of arterial contrast enhancement. In our study, in cases where optimal contrast enhancement could not be achieved in the renal arteries, the remaining vascular structures distal to the stent were visualized more weakly. MIP allows for the evaluation of the relationship between the metallic stent and vascular structures, as well as the position of the stent.

SSD images are created by selecting a threshold value by the user. In this process, voxels in the reconstructed three-dimensional matrix with attenuation values greater than the threshold are set to white, while those with attenuation values below the threshold are set to black, thus generating a digital image. Vascular calcification, intraluminal contrast, and the metallic stent all have attenuation above the selected threshold, resulting in these structures appearing white. Consequently, the stent lumen cannot be distinguished. Using SSD images, it is not possible to assess the stenosis or patency of the segment where the stent is placed.[23] In our study, in all cases, the stent was observed in the vascular lumen as contour overflow on SSD images, and the stent appeared similar to calcification and intraluminal contrast.

VIE is a three-dimensional perspective of digital fiber optic endoscopy.[8] It enables preoperative assessment for planning surgical or interventional treatments and serves as a non-invasive method for monitoring treatment outcomes. VIE can effectively demonstrate ostial or luminal narrowing in RAS. It allows for the differentiation of eccentrically located and calcified plaques in the ostial and distal lumen. Moreover, it provides detailed visualization of grafts or stents, assessing their position and relation to the aorta and its branches.[4,24,25] Additionally, VIE plays a significant role in demonstrating metallic prostheses within the aortic lumen, facilitating the evaluation of their patency and positioning.[26] In our study, VIE images were generated for all cases, and in 14 patients, the stent lumen was observed to be patent. In one case, occlusion at the proximal end of the stent was visualized both from the aortic lumen and the stent lumen.

Spiral CTA has the most significant advantage of being a non-invasive method, eliminating the need for arterial injection.

It is also a rapid technique, and the radiation dose used is lower.[27] However, its most notable disadvantage is the risk of contrast-induced nephrotoxicity, which increases in patients with pre-existing renal dysfunction.[28]

CONCLUSION

Spiral CTA can be effectively used as a non-invasive method for assessing stent integrity, patency, and the relationship between the stent and renal artery following intravascular stent placement in RAS, in conjunction with scanning parameters and post-processing techniques. This provides a significant advantage in clinical applications and improves the diagnosis and treatment processes for patients.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was produced from a thesis before 2020, and institutional approval was received.

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The author declare they have no conflicts of interest.

Financial Disclosure

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

Author Contributions

The author declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

A comparative analysis of predisposing factors for delirium in hospitalized patients during and after COVID-19 restriction periods

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ABSTRACT

Aims: The COVID-19 pandemic has had a significant impact on hospitalized patients, with delirium emerging as a common and severe complication, especially during periods of strict restrictions. The influence of environmental and psychosocial factors on delirium during different phases of the pandemic remains underexplored. This study aimed to assess the differences in predisposing factors for delirium between the restriction and relaxed periods of the COVID-19 pandemic.

Methods: In this retrospective study, 102 patients diagnosed with delirium between January 2020 and December 2023 were included. Patients were divided into two groups based on their admission periods relative to the COVID-19 pandemic restrictions. Group 1 (n = 64) consisted of patients admitted during the period of strict COVID-19 measures (11 March 2020 – 30 June 2021), while group 2 (n = 38) included those admitted after the restrictions were lifted (1 July 2021 – 30 June 2023). Demographic and clinical data were collected using the hospital's electronic information system and patient files.

Result: The mean age of the patients was 72.4±11.5 years (range: 50 to 92 years), and 51% of them were male. There were no significant differences in the distribution of age, gender, and comorbidities across the two groups. Group 1 had a significantly higher ratio of patients with COVID-19 infection compared to group 2 (60.9% vs. 36.8%, p=0.024). Sleep deprivation was more common in group 1 than in group 2 (87.5% vs. 68.4%, p=0.037). The duration of delirium was significantly longer in group than in group 2 (3 vs. 2 days p=0.045). Patients in group 1 had a significantly longer hospital stay compared to those in group 2 (9 vs. 6 days p<0.001). Although the mortality rate was observed to be higher in group 1 compared to group 2, this difference was not statistically significant (18.8% vs. 10.5%, p=0.400).

Conclusion: During the restriction period of the COVID-19 pandemic, patients with delirium exhibited higher rates of COVID-19 infection, increased sleep deprivation, and longer delirium episodes compared to those during the relaxed period. The prolonged delirium duration and extended hospital stays observed in the restriction period suggest that environmental and psychosocial factors may have contributed to more severe outcomes.

Keywords: COVID-19, delirium, hospitalized patients, infection, pandemic restrictions, predisposing factors, sleep deprivation

INTRODUCTION

The COVID-19 pandemic has had a significant impact on the physical, cognitive, and mental health of individuals, with some experiencing long-term effects even after their initial recovery from the virus. One concerning outcome is the development of delirium, a state of acute confusion and disorientation, which has been observed both during the active phases of COVID-19 infection as well as in the post-recovery period.[1-3]

Delirium is characterized by sudden changes in attention, awareness, and cognitive function, typically caused by an underlying medical condition and not related to any pre-existing neurocognitive disorder.[4] It is frequently observed in elderly hospitalized individuals and ICU patients, with an incidence reported to be between 15% and 50%.[5,6] Several studies have defined risk factors for delirium in COVID-19 patients, including advanced age, male sex, living conditions, prolonged treatment duration, a history of neurodegenerative diseases, and the presence of infections and renal-retention indicators.[7-9] These are often aggravated by pandemic-related stressors, such as social distancing, disrupted routines, and diminished social contact.[10] Furthermore, in COVID-19 survivors, particularly those with severe respiratory failure and prolonged ICU delirium, cognitive impairments, including deficits in memory, attention, and executive function, have been observed.[11]

There have been conflicting reports on the effect of COVID-19 restrictions on delirium. Some studies have indicated that COVID-19 restrictions do not have a significant impact

on delirium, whereas others have reported an increased risk of delirium due to these restrictions.[12-14] Given these conflicting reports, we hypothesized that predisposing factors contributing to the development of delirium may vary between periods of strict COVID-19 restrictions, characterized by social isolation, reduced social interaction, and limited access to healthcare, and periods when these restrictions were lifted. Therefore, this study aimed to assess the differences in predisposing factors for delirium between the restriction and relaxed periods of the COVID-19 pandemic.

METHODS

Following the principles set forth in the Declaration of Helsinki, this single center retrospective study was conducted at the İstanbul Atlas University Medicine Hospital Neurology Clinical from 1 January 2020 to 1 December 2023. The study received approval from the İstanbul Atlas University Clinical Researches Ethics Committee (Date: 18.12.2023, Decision No: 10/31). The İstanbul Atlas University Ethics Committee waived the requirement of informed consent due to the retrospective nature of the research. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A total of 140 patients diagnosed with delirium were retrospectively examined. The diagnosis of delirium was established based on the DSM-V Delirium Diagnostic Criteria.[15] Eligibility criteria required patients to be over 18 years old, hospitalized for longer than 24 hours, with a Glasgow Coma Scale (GCS) score above 10, non-intubated, and without any neurological or psychiatric diagnoses. Patients suffering from acute ischemic stroke, dementia, epilepsy, undergoing psychiatric treatment, or those admitted to the ICU were excluded. Following the exclusion process, 102 patients were included in the study.

Demographic and clinical data were collected using the hospital's electronic information system and patient files. The first case of COVID-19 in Turkey was identified on March 11, 2020, followed by the implementation of strict measures to combat the pandemic. These measures included mandatory mask-wearing, social isolation, halting of air travel, curfews, shifting to online learning, the temporary closure of cafes and restaurants, and the cancellation of public events. Pandemic measures began to be lifted on June 1, 2021, transitioning the country into a normalcy process after more than a year of restrictions and pandemic management efforts.[16,17] Accordingly, patients were divided into two groups based on their hospital admission dates. Group 1, during the COVID-19 pandemic when strict measures were enforced (11 March 2020–30 June 2021); and group 2, the period after the lifting of COVID-19 pandemic measures (1 July 2021–30 June 2023).

Statistical Analysis

All data were analyzed with IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA). Numerical data determined to be normally distributed based on the results of Kolmogorov-Smirnov tests are given as mean ± standard deviation (SD) values while non-normally distributed variables are given as median (25^{th}-75^{th} quartile) values. For comparisons between groups, Student t-test and Mann-Whitney U test were used in line with the normality of the considered distribution. Categorical variables are given as numbers and percentages, and inter-group comparisons were conducted with Chi-square and Fisher exact tests. Significance was accepted at $p<0.05$ (*) for all statistical analyses.

RESULT

The study included 102 patients, comprising 52 females and 50 males, with an age range of 50 to 92 years (mean age: 72.4±11.5 years). Among the patients, 62.7% were hospitalized during the time of strict COVID-19 restrictions (group 1), whereas 37.3% were admitted when the restrictions were relaxed (group 2). In both groups, the leading comorbid conditions were congestive heart failure, hypertension, and diabetes mellitus. There were no significant differences in the distribution of age, gender, and comorbidities across the two groups (Table 1).

Table 1. Demographic characteristics of patients

Variables	COVID-19 pandemic		p
	Restriction period (group 1) n=64	Relaxed period (group 2) n=38	
Age, years	73.3±11.5	70.8±11.4	0.289
Gender, n (%)			
Male	34 (53.1)	18 (47.4)	0.683
Female	30 (46.9)	20 (52.6)	
Marital status, n (%)			
Married	37 (57.8)	28 (73.7)	0.137
Single	27 (42.2)	10 (26.3)	
Comorbidities, n (%)			
Congestive heart failure	43 (67.2)	28 (73.7)	0.515
Hypertension	48 (75.0)	30 (78.9)	0.810
Diabetes mellitus	41 (64.1)	28 (73.7)	0.137
Cognitive disorders	26 (40.6)	17 (44.7)	0.836
Hearing disorders	24 (37.5)	14 (36.8)	0.999
Visual disorders	7 (10.9)	4 (10.5)	0.999
Trauma history, n (%)	9 (14.1)	5 (13.2)	0.999

Numerical variables were shown as mean ± standard deviation or median (IQR). Categorical variables were shown as numbers (%)

Comparison of various clinical and physiological variables between patients hospitalized during the restriction period and those admitted during the relaxed period of the COVID-19 pandemic revealed several notable differences. Group 1 had a significantly higher ratio of patients with COVID-19 infection compared to group 2 (60.9% vs. 36.8%, p=0.024). Sleep deprivation was more common in group 1 than in group 2 (87.5% vs. 68.4%, p=0.037). Although the incidence of hypoxemia was higher in group 2 (71.1%) compared to Group 1 (53.1%), this difference did not reach statistical significance (p=0.096). The duration of delirium was significantly longer in group than in group 2 (3 vs. 2 days p=0.045). Patients in group 1 had a significantly longer hospital stay compared to those in group 2 (9 vs. 6 days p<0.001). Although the mortality rate was observed to be higher in group 1 compared to Group 2, this difference was not statistically significant (18.8% vs. 10.5%, p=0.400). Other variables such as the presence of anemia, hyperglycemia, body temperature abnormalities, renal failure, dehydration, surgical intervention, and catheter use showed no statistically significant differences between the two groups (Table 2).

Table 2. Clinical characteristics of patients

Variables	COVID-19 pandemic		p
	Restriction period (group 1) n=64	Relaxed period (group 2) n=38	
COVID-19 infection, n (%)	39 (60.9)	14 (36.8)	0.024*
Sleep deprivation, n (%)	56 (87.5)	26 (68.4)	0.037*
Hypoxemia, n (%)	34 (53.1)	27 (71.1)	0.096
Organ failure, n (%)	2 (3.1)	3 (7.9)	0.358
Bladder catheter, n (%)	9 (14.1)	9 (23.7)	0.284
Central venous catheter, n (%)	4 (6.3)	2 (5.3)	0.136
Anemia	34 (53.1)	26 (68.4)	0.149
Hyperglycemia, n (%)	38 (59.4)	21 (55.3)	0.836
Body temperature, n (%)			
Normal	41 (64.1)	25 (65.8)	0.763
Hypothermia	2 (3.1)	2 (5.3)	
Hyperthermia	21 (32.8)	11 (28.9)	
Renal failure, n (%)	12 (18.8)	8 (21.1)	0.801
Dehydration, n (%)	6 (9.4)	4 (10.5)	0.999
Surgical intervention, n (%)	14 (21.9)	7 (18.4)	0.802
Delirium duration, days	3 (2-4)	2 (1-3)	0.045*
Hospital stay, days	9 (6-12)	6 (4-10)	<0.001*
Mortality, n (%)	12 (18.8)	4 (10.5)	0.400

Numerical variables were shown as mean ± standard deviation or median (IQR). Categorical variables were shown as numbers (%). * p<0.05 shows statistical significance

DISCUSSION

To the best of our knowledge, this is the first study to examine the factors predisposing to delirium during the COVID-19 restriction and relaxation periods. Despite similar demographic characteristics, the study found notable differences in several clinical and physiological parameters between the groups during the restriction period and the relaxed period of the COVID-19 pandemic. Patients hospitalized during the strict COVID-19 restrictions had a significantly higher rates of COVID-19 infection, more frequent sleep deprivation, and a longer delirium episodes compared to those admitted during the relaxed period.

Studies carried out before the COVID-19 pandemic recognized delirium as a well-established complication in hospitalized older adults, associated with long-term cognitive and functional decline.[18-20] Previous studies have emphasized various factors that predispose older adults to delirium, such as advanced age, preexisting cognitive or functional impairments, sensory deficits (vision or hearing), and multiple chronic conditions.[21-23] In our study, these predisposing factors were present in the majority of cases, consistent with previous studies. However, we found no significant difference in the distribution of these predisposing factors between the restriction and relaxed periods of the COVID-19 pandemic.

Delirium has been identified as a serious complication of COVID-19, associated with poorer outcomes such as higher in-hospital mortality, increased ICU admissions, longer hospital stays, and more in-hospital complications.[24-26] During the COVID-19 pandemic, the recognition and treatment of delirium were further complicated by staff shortages, the use of personal protective equipment, strict isolation measures with limited visitation, and the heightened use of sedative medications.[27] COVID-19 quarantine measures have been associated with adverse psychological effects in the general population.[28] Sun and colleagues conducted a qualitative study on the psychological experiences of COVID-19 patients during hospitalization, finding that in the early stages of the disease, emotions such as anger, anxiety, and worry were prevalent, while psychological states such as loneliness, anxiety, helplessness, and depression emerged during the quarantine period.[29] In Japan, a study examined the incidence of delirium in emergency department patients during the COVID-19 pandemic, comparing the periods before and after visitor restrictions were enforced. The study reported a 3.79-fold increase in delirium incidence after the restrictions.[30] In the present study, during the restriction period of the COVID-19 pandemic, the frequency of delirium cases, as well as the occurrence of COVID-19 infection in these cases, was higher. The combination of social isolation and quarantine, particularly in the absence of family members, is thought to increase the risk of delirium.[25] As normal visitation policies resume compared to the early pandemic, involving family members in delirium prevention strategies, such as the Family-Augmented-HELP program, may improve the effectiveness of delirium prevention in hospitals.[31] These may explain the higher frequency of delirium during the restriction period. Additionally, as restrictions were anticipated during the peak periods of COVID-19 infection, a higher rate of COVID-19 infection may have been observed in delirium cases during these times. Conversely, during the relaxation period, patients may have acquired community immunity through vaccination programs. However, this study lacked information on the vaccination status of the patients.

Another factor connected to delirium is the presence of sleep disorders.[32] The mechanism of delirium remains incompletely understood, but a leading hypothesis involves neurotransmitter imbalance, particularly in the regulation of dopamine, acetylcholine, and tryptophan.[33,34] This same imbalance is also commonly observed in cases of sleep deprivation, further linking disrupted sleep patterns to the development of delirium.[35] Moreover, disturbances in these neurotransmitter systems, particularly within the serotonergic system, are thought to influence both immune function and inflammatory responses, which may increase susceptibility to severe cases of COVID-19.[36] In fact, it has been reported that 85.4% of patients hospitalized with COVID-19 who developed delirium experienced alterations in their sleep-wake cycle, highlighting the close relationship between sleep disruption and cognitive decline.[37] In the present study, during the restriction period of the pandemic, we found a significantly higher frequency of sleep deprivation compared to the relaxed period, which likely contributed to the prolonged delirium episodes observed in our patient population. These findings are consistent with prior research indicating a rise in sleep problems during the pandemic period, compared to pre-pandemic period, in both the general population and hospitalized individuals.[38-41] A study of 1,062 participants in Italy found that sleep disturbances, depression, and anxiety worsened during the COVID-19 quarantine periods, but two years later, subjective sleep quality improved, and

both sleep disturbances and sleep onset latency decreased. It was also noted that the improvement in sleep disorders was accompanied by a decline in depressive and anxiety symptoms.[42] This findings underscores the importance of addressing sleep disturbances in delirium management, particularly during periods of heightened stress, such as the COVID-19 pandemic.

Another important finding of this study was that both delirium duration and hospital stay were significantly longer during the restriction period compared to the relaxed period. The extended hospital stay could be attributed to the higher rates of COVID-19 infection and sleep deprivation during the restriction period, potentially contributing to more prolonged and severe delirium episodes. Prolonged hospital stays are associated to worse patient outcomes, including a higher risk of developing complications such as delirium.[43] Additionally, while the mortality rate during the restriction period was higher, this difference did not reach statistical significance. This non-significant trend suggests that, even in non-ICU settings, factors such as prolonged delirium episodes and complications associated with COVID-19 could have contributed to the higher mortality rate.

Limitations

This study has several limitations that should be taken into account. First, the single-center, retrospective design limits the generalizability of our findings. Since the study was conducted at one hospital, the results may not reflect the experiences of different healthcare settings, patient populations, or regions that experienced different degrees of COVID-19 impact and restrictions. Additionally, the lack of consistent data on the use of standardized tools for delirium diagnosis, such as the Confusion Assessment Method (CAM), is a limitation. Second, patients in the ICU were excluded from the study. ICU patients tend to experience more severe forms of delirium due to factors such as mechanical ventilation, sedation, and organ dysfunction. Including ICU patients might have revealed different patterns and more severe risk factors for delirium, providing a broader perspective on the impact of COVID-19 and associated restrictions on patients with critical illness. Third, the lack of data regarding vaccination status may have influenced the differences in COVID-19 infection rates between the restriction and relaxed periods. Additionally, we did not collect detailed data on the medications used by the patients. Certain medications, such as sedatives or antipsychotics, may affect the development of delirium.[44-46] Finally, more systematic evaluation of psychosocial factors, such as through psychological surveys or assessments, could have provided a clearer understanding of how social isolation influenced delirium development. Future studies incorporating multicenter data, ICU populations, vaccination status, and more comprehensive assessments of psychosocial factors could offer more detailed insights into the wide range of delirium risk factors during pandemic periods. This, in turn, may contribute to the development of more effective prevention strategies.

CONCLUSION

During the restriction period of the COVID-19 pandemic, patients with delirium exhibited higher rates of COVID-19 infection, increased sleep deprivation, and longer delirium episodes compared to those during the relaxed period. Although other predisposing factors such as age and comorbidities were similar between the two periods, the prolonged delirium duration and extended hospital stays observed in the restriction period suggest that environmental and psychosocial factors may have contributed to more severe outcomes. This indicates that stressors like social isolation and the absence of family support during strict pandemic restrictions could have exacerbated the severity of delirium.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was performed in accordance with the Declaration of Helsinki, and was approved by the İstanbul Atlas University Medicine Hospital Clinical Researches Ethics Committee (Date: 18.12.2023, Decision No: 10/31).

Informed Consent

The need for informed consent was waived under the approval of the Local Ethics Committee due to the retrospective design.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The author declare they have no conflicts of interest.

Financial Disclosure

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

Author Contributions

The author declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

The impact of earthquake-related fear on sleep quality in hypertensive patients living in İstanbul

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ABSTRACT

Aims: The COVID-19 pandemic has had a significant impact on hospitalized patients, with delirium emerging as a common and severe complication, especially during periods of strict restrictions. The influence of environmental and psychosocial factors on delirium during different phases of the pandemic remains underexplored. This study aimed to assess the differences in predisposing factors for delirium between the restriction and relaxed periods of the COVID-19 pandemic.

Methods: In this retrospective study, 102 patients diagnosed with delirium between January 2020 and December 2023 were included. Patients were divided into two groups based on their admission periods relative to the COVID-19 pandemic restrictions. Group 1 (n = 64) consisted of patients admitted during the period of strict COVID-19 measures (11 March 2020 – 30 June 2021), while group 2 (n = 38) included those admitted after the restrictions were lifted (1 July 2021 – 30 June 2023). Demographic and clinical data were collected using the hospital's electronic information system and patient files.

Result: The mean age of the patients was 72.4±11.5 years (range: 50 to 92 years), and 51% of them were male. There were no significant differences in the distribution of age, gender, and comorbidities across the two groups. Group 1 had a significantly higher ratio of patients with COVID-19 infection compared to group 2 (60.9% vs. 36.8%, p=0.024). Sleep deprivation was more common in group 1 than in group 2 (87.5% vs. 68.4%, p=0.037). The duration of delirium was significantly longer in group than in group 2 (3 vs. 2 days p=0.045). Patients in group 1 had a significantly longer hospital stay compared to those in group 2 (9 vs. 6 days p<0.001). Although the mortality rate was observed to be higher in group 1 compared to group 2, this difference was not statistically significant (18.8% vs. 10.5%, p=0.400).

Conclusion: During the restriction period of the COVID-19 pandemic, patients with delirium exhibited higher rates of COVID-19 infection, increased sleep deprivation, and longer delirium episodes compared to those during the relaxed period. The prolonged delirium duration and extended hospital stays observed in the restriction period suggest that environmental and psychosocial factors may have contributed to more severe outcomes.

Keywords: COVID-19, delirium, hospitalized patients, infection, pandemic restrictions, predisposing factors, sleep deprivation

INTRODUCTION

The COVID-19 pandemic has had a significant impact on the physical, cognitive, and mental health of individuals, with some experiencing long-term effects even after their initial recovery from the virus. One concerning outcome is the development of delirium, a state of acute confusion and disorientation, which has been observed both during the active phases of COVID-19 infection as well as in the post-recovery period.[1-3]

Delirium is characterized by sudden changes in attention, awareness, and cognitive function, typically caused by an underlying medical condition and not related to any pre-existing neurocognitive disorder.[4] It is frequently observed in elderly hospitalized individuals and ICU patients, with an incidence reported to be between 15% and 50%.[5,6] Several studies have defined risk factors for delirium in COVID-19 patients, including advanced age, male sex, living conditions, prolonged treatment duration, a history of neurodegenerative diseases, and the presence of infections and renal-retention indicators.[7-9] These are often aggravated by pandemic-related stressors, such as social distancing, disrupted routines, and diminished social contact.[10] Furthermore, in COVID-19 survivors, particularly those with severe respiratory failure and prolonged ICU delirium, cognitive impairments, including deficits in memory, attention, and executive function, have been observed.[11]

There have been conflicting reports on the effect of COVID-19 restrictions on delirium. Some studies have indicated that COVID-19 restrictions do not have a significant impact on delirium, whereas others have reported an increased risk of delirium due to these restrictions.[12-14] Given these conflicting reports, we hypothesized that predisposing factors contributing to the development of delirium may vary between periods of strict COVID-19 restrictions, characterized by social isolation, reduced social interaction, and limited access to healthcare, and periods when these restrictions were lifted. Therefore, this study aimed to assess the differences in predisposing factors for delirium between the restriction and relaxed periods of the COVID-19 pandemic.

METHODS

Following the principles set forth in the Declaration of Helsinki, this single center retrospective study was conducted at the İstanbul Atlas University Medicine Hospital Neurology Clinics from 1 January 2020 to 1 December 2023. The study received approval from the İstanbul Atlas University Clinical Researches Ethics Committee (Date: 18.12.2023, Decision No: 10/31). The İstanbul Atlas University Ethics Committee waived the requirement of informed consent due to the retrospective nature of the research.

A total of 140 patients diagnosed with delirium were retrospectively examined. The diagnosis of delirium was established based on the DSM-V Delirium Diagnostic Criteria.[15] Eligibility criteria required patients to be over 18 years old, hospitalized for longer than 24 hours, with a Glasgow Coma Scale (GCS) score above 10, non-intubated, and without any neurological or psychiatric diagnoses. Patients suffering from acute ischemic stroke, dementia, epilepsy, undergoing psychiatric treatment, or those admitted to the ICU were excluded. Following the exclusion process, 102 patients were included in the study.

Demographic and clinical data were collected using the hospital's electronic information system and patient files. The first case of COVID-19 in Turkey was identified on March 11, 2020, followed by the implementation of strict measures to combat the pandemic. These measures included mandatory mask-wearing, social isolation, halting of air travel, curfews, shifting to online learning, the temporary closure of cafes and restaurants, and the cancellation of public events. Pandemic measures began to be lifted on June 1, 2021, transitioning the country into a normalcy process after more than a year of restrictions and pandemic management efforts.[16,17] Accordingly, patients were divided into two groups based on their hospital admission dates. Group 1, during the COVID-19 pandemic when strict measures were enforced (11 March 2020 – 30 June 2021); and group 2, the period after the lifting of COVID-19 pandemic measures (1 July 2021 – 30 June 2023).

Statistical Analysis

All data were analyzed with IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA). Numerical data determined to be normally distributed based on the results of Kolmogorov-Smirnov tests are given as mean ± standard deviation (SD) values while non-normally distributed variables are given as median (25^{th}-75^{th} quartile) values. For comparisons between groups, Student t-test and Mann-Whitney U test were used in line with the normality of the considered distribution. Categorical variables are given as numbers and percentages, and inter-group comparisons were conducted with Chi-square and Fisher exact tests. Significance was accepted at $p< 0.05$ (*) for all statistical analyses.

RESULT

The study included 102 patients, comprising 52 females and 50 males, with an age range of 50 to 92 years (mean age: 72.4±11.5 years). Among the patients, 62.7% were hospitalized during the time of strict COVID-19 restrictions (group 1), whereas 37.3% were admitted when the restrictions were relaxed (group 2). In both groups, the leading comorbid conditions were congestive heart failure, hypertension, and diabetes mellitus. There were no significant differences in the distribution of age, gender, and comorbidities across the two groups (Table 1).

Table 1. Demographic characteristics of patients

Variables	COVID-19 pandemic		p
	Restriction period (group 1) n=64	Relaxed period (group 2) n=38	
Age, years	73.3±11.5	70.8±11.4	0.289
Gender, n (%)			
Male	34 (53.1)	18 (47.4)	0.683
Female	30 (46.9)	20 (52.6)	
Marital status, n (%)			
Married	37 (57.8)	28 (73.7)	0.137
Single	27 (42.2)	10 (26.3)	
Comorbidities, n (%)			
Congestive heart failure	43 (67.2)	28 (73.7)	0.515
Hypertension	48 (75.0)	30 (78.9)	0.810
Diabetes mellitus	41 (64.1)	28 (73.7)	0.137
Cognitive disorders	26 (40.6)	17 (44.7)	0.836
Hearing disorders	24 (37.5)	14 (36.8)	0.999
Visual disorders	7 (10.9)	4 (10.5)	0.999
Trauma history, n (%)	9 (14.1)	5 (13.2)	0.999

Numerical variables were shown as mean ± standard deviation or median (IQR). Categorical variables were shown as numbers (%). SD: Standard deviation

Comparison of various clinical and physiological variables between patients hospitalized during the restriction period and those admitted during the relaxed period of the COVID-19 pandemic revealed several notable differences. Group 1 had a significantly higher ratio of patients with COVID-19 infection compared to group 2 (60.9% vs. 36.8%, p=0.024). Sleep deprivation was more common in group 1 than in group 2 (87.5% vs. 68.4%, p=0.037). Although the incidence of hypoxemia was higher in group 2 (71.1%) compared to Group 1 (53.1%), this difference did not reach statistical significance (p=0.096). The duration of delirium was significantly longer in group than in group 2 (3 vs. 2 days p=0.045). Patients in group 1 had a significantly longer hospital stay compared to those in group 2 (9 vs. 6 days p<0.001). Although the mortality rate was observed to be higher in group 1 compared to Group 2, this difference was not statistically significant (18.8% vs. 10.5%, p=0.400). Other variables such as the presence of anemia, hyperglycemia, body temperature abnormalities, renal failure, dehydration, surgical intervention, and catheter use showed no statistically significant differences between the two groups (Table 2).

Table 2. Clinical characteristics of patients

Variables	COVID-19 pandemic		p
	Restriction period (group 1) n=64	Relaxed period (group 2) n=38	
COVID-19 infection, n (%)	39 (60.9)	14 (36.8)	0.024*
Sleep deprivation, n (%)	56 (87.5)	26 (68.4)	0.037*
Hypoxemia, n (%)	34 (53.1)	27 (71.1)	0.096
Organ failure, n (%)	2 (3.1)	3 (7.9)	0.358
Bladder catheter, n (%)	9 (14.1)	9 (23.7)	0.284
Central venous catheter, n (%)	4 (6.3)	2 (5.3)	0.136
Anemia	34 (53.1)	26 (68.4)	0.149
Hyperglycemia, n (%)	38 (59.4)	21 (55.3)	0.836
Body temperature, n (%)			
Normal	41 (64.1)	25 (65.8)	0.763
Hypothermia	2 (3.1)	2 (5.3)	
Hyperthermia	21 (32.8)	11 (28.9)	
Renal failure, n (%)	12 (18.8)	8 (21.1)	0.801
Dehydration, n (%)	6 (9.4)	4 (10.5)	0.999
Surgical intervention, n (%)	14 (21.9)	7 (18.4)	0.802
Delirium duration, days	3 (2-4)	2 (1-3)	0.045*
Hospital stay, days	9 (6-12)	6 (4-10)	<0.001*
Mortality, n (%)	12 (18.8)	4 (10.5)	0.400

Numerical variables were shown as mean ± standard deviation or median (IQR). Categorical variables were shown as numbers (%). * p<0.05 shows statistical significance

DISCUSSION

To the best of our knowledge, this is the first study to examine the factors predisposing to delirium during the COVID-19 restriction and relaxation periods. Despite similar demographic characteristics, the study found notable differences in several clinical and physiological parameters between the groups during the restriction period and the relaxed period of the COVID-19 pandemic. Patients hospitalized during the strict COVID-19 restrictions had a significantly higher rates of COVID-19 infection, more frequent sleep deprivation, and a longer delirium episodes compared to those admitted during the relaxed period.

Studies carried out before the COVID-19 pandemic recognized delirium as a well-established complication in hospitalized older adults, associated with long-term cognitive and functional decline.[18-20] Previous studies have emphasized various factors that predispose older adults to delirium, such as advanced age, preexisting cognitive or functional impairments, sensory deficits (vision or hearing), and multiple chronic conditions.[21-23] In our study, these predisposing factors were present in the majority of cases, consistent with previous studies. However, we found no significant difference in the distribution of these predisposing factors between the restriction and relaxed periods of the COVID-19 pandemic.

Delirium has been identified as a serious complication of COVID-19, associated with poorer outcomes such as higher in-hospital mortality, increased ICU admissions, longer hospital stays, and more in-hospital complications.[24-26] During the COVID-19 pandemic, the recognition and treatment of delirium were further complicated by staff shortages, the use of personal protective equipment, strict isolation measures with limited visitation, and the heightened use of sedative medications.[27] COVID-19 quarantine measures have been associated with adverse psychological effects in the general population.[28] Sun and colleagues conducted a qualitative study on the psychological experiences of COVID-19 patients during hospitalization, finding that in the early stages of the disease, emotions such as anger, anxiety, and worry were prevalent, while psychological states such as loneliness, anxiety, helplessness, and depression emerged during the quarantine period.[29] In Japan, a study examined the incidence of delirium in emergency department patients during the COVID-19 pandemic, comparing the periods before and after visitor restrictions were enforced. The study reported a 3.79-fold increase in delirium incidence after the restrictions.[30] In the present study, during the restriction period of the COVID-19 pandemic, the frequency of delirium cases, as well as the occurrence of COVID-19 infection in these cases, was higher. The combination of social isolation and quarantine, particularly in the absence of family members, is thought to increase the risk of delirium.[25] As normal visitation policies resume compared to the early pandemic, involving family members in delirium prevention strategies, such as the Family-Augmented-HELP program, may improve the effectiveness of delirium prevention in hospitals.[31] These may explain the higher frequency of delirium during the restriction period. Additionally, as restrictions were anticipated during the peak periods of COVID-19 infection, a higher rate of COVID-19 infection may have been observed in delirium cases during these times. Conversely, during the relaxation period, patients may have acquired community immunity through vaccination programs. However, this study lacked information on the vaccination status of the patients.

Another factor connected to delirium is the presence of sleep disorders.[32] The mechanism of delirium remains incompletely understood, but a leading hypothesis involves neurotransmitter imbalance, particularly in the regulation of dopamine, acetylcholine, and tryptophan.[33,34] This same imbalance is also commonly observed in cases of sleep deprivation, further linking disrupted sleep patterns to the development of delirium.[35] Moreover, disturbances in these neurotransmitter systems, particularly within the serotonergic system, are thought to influence both immune function and inflammatory responses, which may increase susceptibility to severe cases of COVID-19.[36] In fact, it has been reported that 85.4% of patients hospitalized with COVID-19 who developed delirium experienced alterations in their sleep-wake cycle, highlighting the close relationship between sleep disruption and cognitive decline.[37] In the present study, during the restriction period of the pandemic, we found a significantly higher frequency of sleep deprivation compared to the relaxed period, which likely contributed to the prolonged delirium episodes observed in our patient population. These findings are consistent with prior research indicating a rise in sleep problems during the pandemic period, compared to pre-pandemic period, in both the general population and hospitalized individuals.[38-41] A study of 1,062 participants in Italy found that sleep disturbances, depression, and anxiety worsened during the COVID-19 quarantine periods, but two years later, subjective sleep quality improved, and

both sleep disturbances and sleep onset latency decreased. It was also noted that the improvement in sleep disorders was accompanied by a decline in depressive and anxiety symptoms.[42] This findings underscores the importance of addressing sleep disturbances in delirium management, particularly during periods of heightened stress, such as the COVID-19 pandemic.

Another important finding of this study was that both delirium duration and hospital stay were significantly longer during the restriction period compared to the relaxed period. The extended hospital stay could be attributed to the higher rates of COVID-19 infection and sleep deprivation during the restriction period, potentially contributing to more prolonged and severe delirium episodes. Prolonged hospital stays are associated to worse patient outcomes, including a higher risk of developing complications such as delirium.[43] Additionally, while the mortality rate during the restriction period was higher, this difference did not reach statistical significance. This non-significant trend suggests that, even in non-ICU settings, factors such as prolonged delirium episodes and complications associated with COVID-19 could have contributed to the higher mortality rate.

Limitations

This study has several limitations that should be taken into account. First, the single-center, retrospective design limits the generalizability of our findings. Since the study was conducted at one hospital, the results may not reflect the experiences of different healthcare settings, patient populations, or regions that experienced different degrees of COVID-19 impact and restrictions. Additionally, the lack of consistent data on the use of standardized tools for delirium diagnosis, such as the Confusion Assessment Method (CAM), is a limitation. Second, patients in the ICU were excluded from the study. ICU patients tend to experience more severe forms of delirium due to factors such as mechanical ventilation, sedation, and organ dysfunction. Including ICU patients might have revealed different patterns and more severe risk factors for delirium, providing a broader perspective on the impact of COVID-19 and associated restrictions on patients with critical illness. Third, the lack of data regarding vaccination status may have influenced the differences in COVID-19 infection rates between the restriction and relaxed periods. Additionally, we did not collect detailed data on the medications used by the patients. Certain medications, such as sedatives or antipsychotics, may affect the development of delirium.[44-46] Finally, more systematic evaluation of psychosocial factors, such as through psychological surveys or assessments, could have provided a clearer understanding of how social isolation influenced delirium development. Future studies incorporating multicenter data, ICU populations, vaccination status, and more comprehensive assessments of psychosocial factors could offer more detailed insights into the wide range of delirium risk factors during pandemic periods. This, in turn, may contribute to the development of more effective prevention strategies.

CONCLUSION

During the restriction period of the COVID-19 pandemic, patients with delirium exhibited higher rates of COVID-19 infection, increased sleep deprivation, and longer delirium episodes compared to those during the relaxed period. Although other predisposing factors such as age and comorbidities were similar between the two periods, the prolonged delirium duration and extended hospital stays observed in the restriction period suggest that environmental and psychosocial factors may have contributed to more severe outcomes. This indicates that stressors like social isolation and the absence of family support during strict pandemic restrictions could have exacerbated the severity of delirium.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was approved by the İstanbul Atlas University Medicine Hospital Clinical Researches Ethics Committee (Date: 18.12.2023, Decision No: 10/31).

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 author declare they have no conflicts of interest.

Financial Disclosure

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

Author Contributions

The author declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

Evaluation of the relationship between weight loss and oxidative stress in obese, type 2 diabetic patients by thiol/disulfide balance

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ABSTRACT

Aims: Diabetes mellitus (DM) and obesity continue to be an important problem in all world. It is known that there is a close relationship between DM and obesity and that both diseases have a course intertwined with inflammatory processes. In order to determine the clinical severity of these two diseases and to predict complications, clinical tools are needed to evaluate patients in terms of inflammation and oxidative stress. Anthropometric measurements and various known and novel inflammatory biomarkers are being tested for this purpose. Thiol/disulfide is a biomarker whose role in inflammatory processes and defense against oxidative stress is known and whose clinical value is still under investigation. In this study, we aimed to determine the relationship between body weight change and thiol/disulfide balance under clinical follow-up in obese patients with type 2 DM.

Methods: Our study was conducted in a single center with a prospective design between December 2023 and April 2024. The study was completed with a total of 46 patients. Age, comorbidities, height, body weight, waist and hip circumference measurements were performed; glycated hemoglobin, albumin, leukocyte, neutrophil and c-reactive protein values were recorded. After 3 months, the same data were obtained again. Blood samples obtained during these two examinations were analyzed for native thiol, total thiol, and disulfide.

Results: Of the 46 patients, 30 patients lost more than 5% weight during the study period (group 1) and the remaining 16 patients were defined as group 2. There was no difference between groups 1 and 2 in terms of age (p=0.211) and comorbidities (p=>0.005) at the beginning of the study. Inflammatory markers and thiol markers were similar between the groups at the beginning of the study (p=>0.05). Native thiol (263.20-316.51; p=0<0.001), total thiol (296.91-355.63; p=<0.001) and disulfide (9350.84-10845.39; p=0.024) were increased in group 1 cases during the study period. Disulfide/native thiol (6.41-6.19; p=0.199), disulfide/total thiol (5.67-5.50; p=0.207), native/total thiol (88.65-88.99; p=0.206) did not change. In group 2 cases, native thiol (272.81-289.59; p=0.135), total thiol (307.22-322.18; p=0.173), disulfide (3916.43-10609.44; p=0.059), disulfide/native thiol (6.51-6.23; p=0.178), disulfide/total thiol (5.75-5.54; p=0.2187), native/total thiol (88.49-89.92; p=0.188) did not change.

Conclusion: There were no differences between patients who lost and gained weight during the study period in terms of comorbidities, age and anthropometric measurements at the beginning of the study. There was a statistically significant change in thiol markers in patients who lost weight.

Keywords: Diabetes mellitus, obesity, inflammation, oxidative stress, thiol/disulfide balance

INTRODUCTION

The incidence of diabetes mellitus (DM) and obesity are increasing rapidly together, often leading to significant complications, morbidities and numerous deaths.[1] In obesity, the reasons for increased oxygen consumption are mechanical load and increased myocardial metabolism. Consequently, the formation of superoxide, hydroxyl radical and hydrogen peroxide resulting from mitochondrial respiration increases. The relationship between obesity and increased oxidative stress is known, although not fully elucidated.[2] As BMI increases, the percentage of adipose tissue increases and correlated with this, oxidative stress increases. It can be hypothesized that the prevalence of metabolic diseases increases due to this inflammatory dominant process. We hypothesize that oxidative stress decreases with sugar regulation and weight loss in diabetic patients. This change can be detected by looking at thiol/disulfide balance. Based on this situation, in this study, we aimed to show that oxidative stress decreases with weight loss in obese diabetic patients.

METHODS

The study, which had a single-arm design without a prospective control group, was conducted between December 15, 2023 and April 15, 2024 at Kırıkkale University Faculty of Medicine, Department of Internal Medicine. The study was approved by the Kırıkkale University Faculty of Medicine Non-interventional Clinical Researches Ethics Committee (Date: 14.12.2024, Decision No: 25/04). All patients signed and free and informed consent form. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients between the ages of 18 and 65 with type 2 DM, obese and insulin users were included in the study. Inclusion criterias were being between the ages of 18-65, having a diagnosis of type 2 DM, being followed with any subcutaneous insulin regimen and body-mass index (BMI) of 40 kg/m^2 and above. Exclusion criterias were patients with DM other than type 2, patients not using subcutaneous insulin, patients with a body-mass index less than 40 kg/m^2, pregnancy, patients who participated in the study but did not attend the control examination, refusing to participate in the study, withdrawing from the study.

Patients' age, additional chronic diseases and routine laboratory values (WBC, neutrophils, albumin, HbA1c) were obtained from the hospital information system. Anthropometric measurements were obtained as described and recorded in the case report form. The venous blood sera obtained from the participants during the outpatient clinic examination were separated and stored in clean and dry eppendorf tubes at -80° in a deep freezer until the time of the study. Participants were given a written case number on leaving the hospital and were asked to present this number at the 3rd month examination if they wished to continue working. The same process was repeated for the patients who applied to the 3rd month follow-up examination and volunteered to continue the study, and data and blood were collected. The data obtained were recorded on case report forms. The admission and control data of the patient group were tabulated by paying attention to patient anonymity and confidentiality.

Blood samples taken from the participants in a biochemistry tube with an 8-hour fasting condition were centrifuged at 1500 rpm for 10 minutes. The samples obtained were divided into ependorf tubes. These samples were stored at -80°C. All samples were run simultaneously once the target number of cases was reached. From these samples, native thiol, total thiol and disulfide measurements were performed by Erel and Neşelioğlu[3] using the methodology described by them.

By examining the weights of the patients at the time of initial admission and control examination, patients who lost more than 5% weight during the study period were classified as "group 1" and the other patients as "group 2". The categorical variables in the study were presented as frequency (n) and percentage (%) and analyzed with Pearson chi-square and Fisher's Exact test). In independent groups, independent sample t analysis was applied when both groups to be compared met the normality assumption. Mann-Whitney U was applied in cases where both groups did not meet the normality assumption. In the data that met the assumption of normal distribution, dependent groups t test was applied, otherwise Wilcoxon Signed Ranks test was applied. Data analysis was performed with IBM SPSS 27.0 package program (IBM Corp., Armonk, NY). p values less than 0.05 were considered statistically significant.

RESULTS

A total of 46 patients were analyzed in the study; all of the participants were obese, female patients with type 2 DM who were being followed with any subcutaneous insulin regimen. The age of the patients ranged from 34 to 66 years with a median value of 58.5 (SD: 8.65) (Table 1).

Table 1. Parameters of insulin-using diabetic morbidly obese patients at admission

	Mean	Min-Max	SD
Height (cm)	154.37	140.00-166.00	4.95
Weight (kg)	103.87	80.00-146.00	13.67
BMI (kg/m^2)	43.55	39.95-64.03	5.11
Waist circumference (cm)	124.54	105.00-152.00	11.42
Hip circumference (cm)	133.76	115.00-189.00	13.96
Age (years)	56.15	34.00-66.00	8.65

Min: Minimum, Max: Maximum, BMI: Body-mass index, SD: Standard deviation

Anthropometric measurements of the patients were analyzed at the time of initial presentation and during the follow-up examination. The 30 patients who were found to have lost more than 5% weight at the control examination were categorized as group 1. The remaining 16 patients were categorized as group 2.

The mean native thiol values in group 1 subjects were 263.20 (11.50-352.90) at the beginning of the study and 316.51 (228.00-466.60) at the end of the study. The final native thiol values were statistically significantly higher than the initial values in group 1 patients (z=-4.288, p=<0.001; Figure 1).

The mean total thiol values in group 1 subjects were 296.91 (124.30-370.75) at the beginning of the study and 355.63 (253.10-517.75) at the end of the study. The final total thiol values were significantly higher than the initial values in group 1 patients (z=-4.330, p=<0.001; Figure 2).

The mean disulfide values in group 1 subjects were 29350.84 (6.40-23225.00) at the beginning of the study and 10845.39 (12.55-27425.00) at the end of the study. The final disulfide values were statistically significantly higher than the initial values in group 1 patients (z=-5.027, p=<0.001; Figure 3).

The mean disulfide/native thiol values in group 1 patients were 6.41 (4.89-7.96) at the beginning of the study and 6.19 (5.07-7.40) at the end of the study. These values were not statistically significant (t=1.315, p=0.199).

The mean disulfide/total thiol values in group 1 patients were 5.67 (4.46-6.86) at the beginning of the study and 5.50 (4.60-6.45) at the end of the study. These values were not statistically significant (t=1.290, p=0.207).

In group 1 patients, the mean native thiol/total thiol values were 88.65 (86.27-91.09) at the beginning of the study and 88.99 (87.10-90.80) at the end of the study. These values were not statistically significant (t=-1.294, p=0.206, Table 2).

The mean disulfide/native thiol values in group 2 patients were 6.51 (45.21-7.68) at the beginning of the study and 6.23 (5.13-7.01) at the end of the study. These values were not statistically significant (t=1.415, p=0.178; Figure 4.10).

In group 2 patients, the mean disulfide/total thiol values were 5.75 (4.72-6.66) at the beginning of the study and 5.54 (4.65-6.15) at the end of the study. These values were not statistically significant (t=1.384, p=0.187).

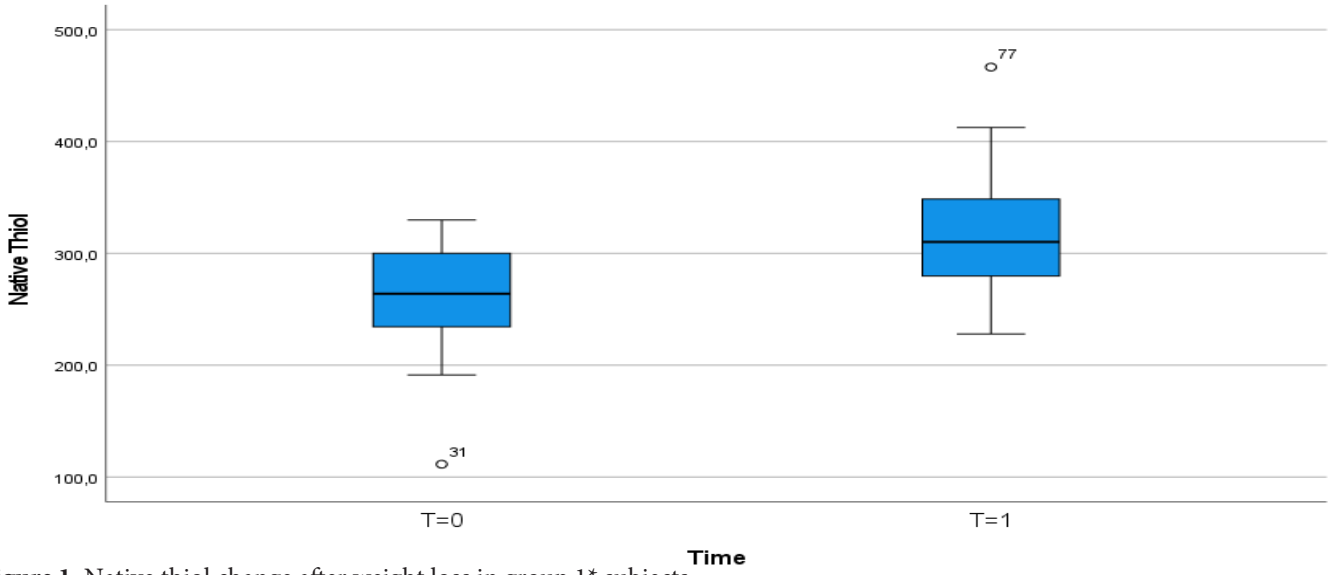

Figure 1. Native thiol change after weight loss in group 1* subjects

*Morbidly obese diabetic patients who lose more than 5% weight on follow-up

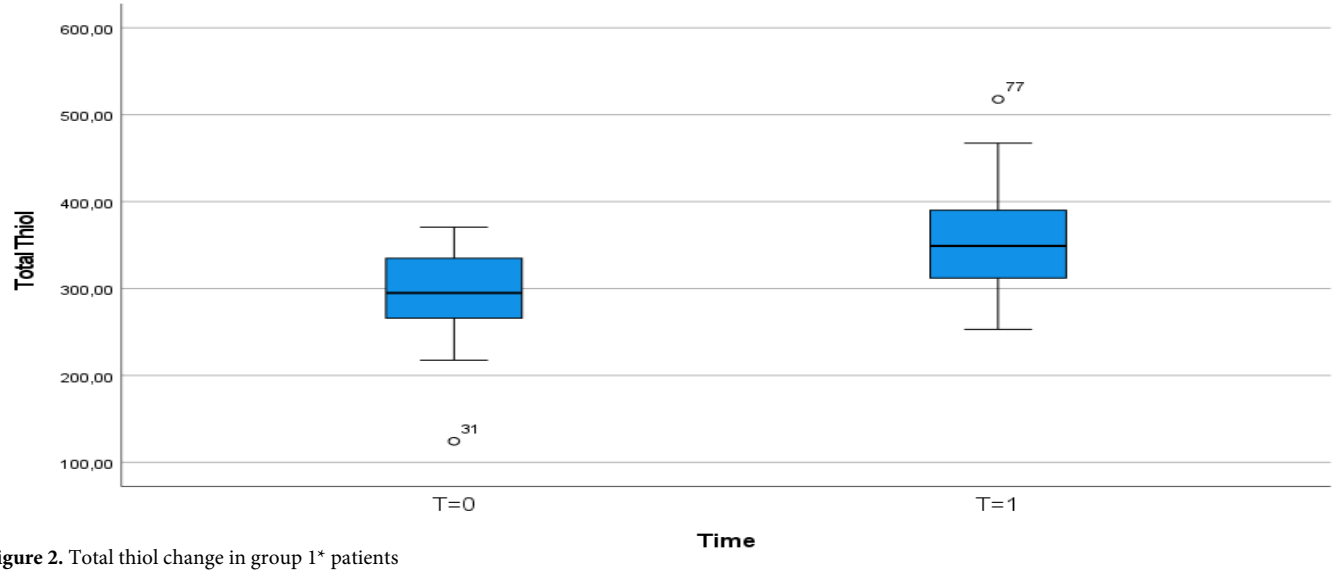

Figure 2. Total thiol change in group 1* patients

*Morbidly obese diabetic patients who lose more than 5% weight on follow-up

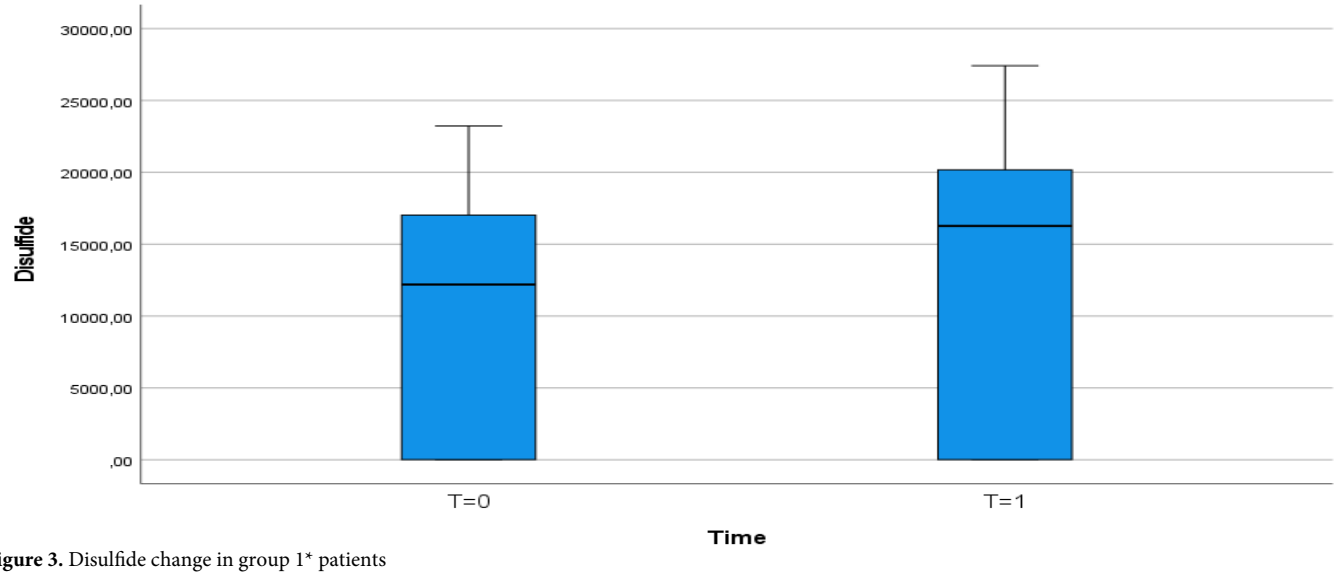

Figure 3. Disulfide change in group 1* patients

*Morbidly obese diabetic patients who lose more than 5% weight on follow-up

Table 2. Changes in thiol parameters in group 1 patients.

	T	Mean	min	max	SD	p (t/z)
Native thiol	**0**	263.20	111.50	329.90	47.80	<0.001
	1	316.51	228.00	466.60	50.70	(-4.288)
Total thiol	**0**	296.91	124.30	370.75	53.64	<0.001
	1	355.63	253.10	517.75	56.42	(-4.330)
Disülfide	**0**	9350.84	6.40	23225.0	9190.40	0.024
	1	10845.39	12.55	27425.0	10545.3	(-2.262)
Disülfide/ native thiol	**0**	6.41	4.89	7.96	0.79	0.199
ive thiol	**1**	6.19	5.07	7.40	0.52	(1.315)
Disülfide	**0**	5.67	4.46	6.86	0.62	0.207
Total thiol	**1**	5.50	4.60	6.45	0.41	(1.290)
Native thiol	**0**	88.65	86.27	91.09	1.24	0.206
Total thiol		88.99	87.10	90.80	0.82	(-1.294)

The mean disulfide values in group 2 patients were 3916.43 (12.40-16775.00) at the beginning of the study and 10609.44 (13.50-23275.00) at the end of the study. These values were not statistically significant (t=-2.039, p=0.059).

Table 3. Relationship between thiol parameters at the beginning of the study

	GR	Mean	min	max	SD	p (t/U)*
Native thiol	**1**	263.20	111.50	329.90	47.80	0.508
	2	272.81	200.80	352.90	43.82	(-0.668)
Total thiol	**1**	296.91	124.30	370.75	53.64	0.520
	2	307.22	225.60	391.60	46.68	(-0.648)
Disulfide	**1**	9350.84	6.40	23225.0	9190.40	0.189
	2	3916.43	12.40	16775.0	7002.61	(183.00)
Disülfide/ native thiol	**1**	6.41	4.89	7.96	0.79	0.682
ative thiol	**2**	6.51	5.21	7.68	0.71	(-0.413)
Disulfide/ total thiol	**1**	5.67	4.46	6.86	0.62	0.670
Tal thiol	**2**	5.75	4.72	6.66	0.56	(-0.429)
Native thiol/ total thio	**1**	88.65	86.27	91.09	1.24	0.676
Thiol/total thiol	**2**	88.49	86.68	90.57	1.11	(0.420)

*The test for disulfide measurements was performed with Mann-Whitney U and the U score is presented. For the remaining parameters, t scores are presented, min: Minimum, max: Maximum, SD: Standard deviation

In group 2 patients, the mean native thiol/total thiol values were 88.49 (86.68-90.57) at the beginning of the study and 88.92 (87.70-90.69) at the end of the study. These values were not statistically significant (t=-1.379, p=0.188).

Thiol/disulfide parameters at the beginning of the study and their differences between the groups were analyzed. The mean native thiol values at the beginning of the study were 263.20 (115.50-329.90) for group 1 and 272.81 (200.80-352.90) for group 2. There was no significant difference between the groups in native thiol values at the beginning of the study (p=0.508; t=-0.668).

The mean total thiol values at the beginning of the study were 296.91 (124.30-370.75) for group 1 and 307.22 (225.60-391.60) for group 2. There was no significant difference between the groups in total thiol values at the beginning of the study (p=0.520; t=-0.648).

The mean disulfide values at the beginning of the study were 9350.84 (6.40- 23225.00) for group 1 and 3916.43 (12.40-16775.00) for group 2. There was no significant difference between the groups in disulfide values at the beginning of the study (p=0.189; U=183.00).

The mean disulfide/native thiol values at the beginning of the study were 6.41 (4.89-7.96) for group 1 and 6.51 (5.21-7.68) for group 2. There was no significant difference between the groups in disulfide/native thiol values at the beginning of the study (p=0.682; t=-0.413).

Disulfide/total thiol values at the beginning of the study were 5.67 (4.46-6.86) for group 1 and 5.75 (4.72-6.66) for group 2. There was no significant difference between the groups in disulfide/total thiol values at the beginning of the study (p=0.670; t=-0.429).

The mean native thiol/total thiol values at the beginning of the study were 88.65 (86.27-91.09) for group 1 and 88.49 (86.68-90.57) for group 2. There was no significant difference between the groups in native thiol/total thiol values at the beginning of the study (p=0.676; t=0.420; Table 3).

Other Findings

The difference in the comorbidities of group 1 and group 2 patients was investigated. In group 1, 16 patients had hypertension, 3 had CAD, 4 had CKD and 9 had hyperlipidemia. In group 2 patients, 6 had hypertension, 3 had CAD, 3 had CKD and 2 had hyperlipidemia. Chi-square analysis revealed no significant difference between the groups in terms of having hypertension (p=0.475), CAD (p=0.342), CKD (p=0.681) and hyperlipidemia (p=0.282) and no significant difference in terms of age (p=0.211) at the beginning of the study.

We aimed to determine whether the patients were similar in terms of additional infectious and inflammatory pathologies at initial presentation. For this purpose, CRP, WBC, neutrophil and albumin levels were analyzed. No difference was found between the groups in terms of these four parameters (p=>0.05).

Anthropometric measurements taken at the beginning of the study and HbA1c values and their differences between the groups were analyzed. Body weight (p=0.212), BMI (p=0.062), waist circumference (p=0.404), hip circumference (p=0.229), HbA1c (p=0.525) values did not differ between the groups at the beginning of the study.

DISCUSSION

The most important result of our study is the correlation between weight loss and inflammatory markers with varying statistical power. These inflammatory markers are anthropometric measurements that have been well characterized by cohort studies and finally thiol mechanism related markers that have been recently studied in the literature. The parameters we defined in these two categories moved in the same direction and at different rates in obese diabetic patients who achieved weight loss.

Today, it is possible to talk about obesity as a chronic inflammatory disease and there is strong evidence of a relationship between pathologically increased adipose tissue and increased inflammation in obese patients.[4,5] This situation is similar in terms of diabetes. Studies indicate a higher

incidence of type 2 diabetes in healthy people with elevated inflammatory markers.[6] Aouacheri et al.[7] did not detect a correlation between the duration of diabetes and the severity of oxidative stress,but found a significant relationship between HbA1c and the severity of oxidative stress. It is also possible to mention a relationship between parameters associated with inflammation in diabetes and hyperglycemia. In a study of 70 people in Indonesia, a significant relationship was found between waist circumference and HbA1c in type 2 diabetes patients.[8] In our study, we found a significant difference in patients who achieved weight loss, similar to theother parameters we evaluated.

Clinical evidence suggests that the association of diabetes with central obesity is stronger than the association with total body adipose tissue.[9] Central obesity has been associated with decreased glucose tolerance, alterations in glucose-insulin homeostasis, reduced metabolic clearance of insulin and decreased insulin-stimulated glucose excretion.[10] In obese people, oxidative damage develops in the increased visceral adipose tissue itself before metabolicdisorders occur.[11]

Stevens et al.[12] found that waist circumference had better discriminatory power for diabetes than body mass index. Kulak et al.[13] reported that diabetes risk score increased significantly with increasing waist circumference. In a study conducted in Iran to determine the risk of developing diabetes, Fahrimeh et al.[14] observed that BMI and waist circumference were significant risk factors for diabetes in a 10-year follow-up.

We believe that our findings are similar to these outcomes. In our patient group in whom thiol/disulfide biomarkers showed significant changes, we found a decrease in BMI and waist circumference in the same way and in the same direction.

There are many studies on the role of thiol group-containing molecules in the defense against oxidative stress. Thiol/disulfide reduction buffering mechanism, reducing activity on radicals, chelator-like activity profile have been proposed as physiological mechanism of action.[15] The relationship between disruption of thiol/disulfide homeostasis and chronic inflammatory processes has been hypothesized in the literature based on this mechanism. Strong evidence has been obtained for the presence of impaired thiol/disulfide homeostasis in many diseases ranging from common chronic diseases to some malignancies.[16] In a study on thiol/disulfide in prediabetic patients, a significant positive correlation was found between disulfide and fasting blood glucose (p=0.017) and HbA1c (p=0.011), and a negative correlation between native thiol and fasting blood glucose (p=0.004).[17] In a study conducted in type 1 DM patients, a significant relationship was found between CRP, fasting blood glucose, HbA1c,disulfide/native thiol and disulfide/total thiol.[18] Eryılmaz et al.[19] examined breast cancer patients with thiol-disulfide inoutpatient clinic conditions and reported that disulfide values were significantly higher than the control group. Jankovic et al.[11] found that glutathione (GSH) levels, an intracellular thiol, were significantly decreased in visceral and subcutaneous adipose tissues in obese women. They explained this with the increase in NADPH oxidase enzyme production and ROS mechanism in adipose tissue.

The findings that thiol/disulfide homeostasis correlates with increased inflammatory process have been discussed above. Although there are many publications in the literature in terms of biomarkers, findings for clinical practice are relatively limited. In 2019, a prospective study conducted by Schillern et al.[20] managed to associate serum thiol levels with disease severity in type 2 DM patients, but found its ability to predict long-term complications insufficient.

In addition to the aforementioned findings, our study suggests that this correlation continues with the dampening of the inflammatory process. In their study with middle-aged and obese mice, Wong et al.[21] reported that mice treated with β-mercaptoethanol (BME), an antioxidant involved in thiol metabolism, gained less fat mass and more lean mass than those that were not. They found that BME users had reduced plasma lipid peroxidation, abdominal adipose tissue inflammation, muscle and liver fat infiltration, and liver and plasma CRP and insulin resistance. Similarly, in another study, Hildebrandt et al.[22] showed that the use of N-Acetyl Cysteine (NAC), a thiol metabolism-associated antioxidant effective on reactive oxygen species, decreased fat mass but increased insulin resistance in obese people without diabetes. In a double-blind placebo-controlled 20-week study of alpha lipoic acid, another thiol antioxidant, 360 obese individuals were randomized to oral alpha lipoic acid 1.200 or 1.800 mg/day or placebo. The treatment resulted in significantly greater weight loss compared to the placebo group.[23] In a randomized trial conducted in Iran, type 2 diabetics were given capsules containing 300 mg lipoic acid or placebo daily for 8 weeks. There was a significant reduction in postprandial glucose and insulin resistance with lipoic acid.[24]

Based on the existing correlations and the outcomes of thiol-related medical therapies, one could argue that there is hope for medical therapies targeting the thiol mechanism. However, it should be noted that weight loss may not affect all inflammatory cytokines together. A study published by Rosc et al.[25] confirmed that weight loss decreased CRP in morbidly obese patients, but failed to detect this decrease in terms of TNF-a and IL-6. Therefore, it would be erroneous to consider every weight loss or decrease in a marker associated with inflammation as an indication of widespread and absolute anti-inflammatory efficacy in the whole system.

Today, society as well as the medical world is aware of obesity and the dangers it poses to health. However, in our experience, people and even health professionals tend to view old age and co-morbidities as barriers to weight loss and lifestyle changes towards weight loss.[26,27]

During our study, we found that the age of the patients who lost weight and gained weight did not differ at the beginning of the study. Likewise, we found that the existing additional chronic diseases of the patients were similar in the weight loss and weight gain groups. The body weight and composition of the patients were similar at the beginning of the study. In a study conducted by Leyden et al.[28] found that in patients followed with an approach centered on lifestyle changes, patients over 65 years of age achieved 7.2% weight loss with this approach and patients under 65 years of age achieved 6.9% weight loss, and reported that age did not affect weight loss success. A prospective study by Finucane et al.[29] went beyond these findings and associated higher age with better weight loss success. According to our clinical experience, patients often complain of being too overweight to lose weight and ignore exercise recommendations. In our study, we found that the initial weight and BMI values of the patients were not significant. When the literature on this subject is examined, it

is seen that BMI is often not correlated with successful weight loss.[30] However, it is important to note that there are contrary findings that weight loss is more successful with high or low BMI.[31,32]

The most important strength of our study, in our opinion, is that it was blinded by design. It was unclear which patient would be in which group until the patients presented for a follow-up examination and their final weight was determined. In addition, because our design included anthropometric and routine laboratory measurements, we consider our study to be more than a laboratory experiment, but a research focused on daily clinical practice and concrete outcomes.

Limitations

The most important limitation of our study is the limited number of patients and the imbalance between the groups. Although we are pleased that our obese patients lost weight, we obviously did not anticipate that the number of patients would be so much in favor of those who lost weight. We interpreted this imbalance as patients who were under strict physician supervision may have paid more attention to life changes due to the feeling of being under observation and being re-evaluated. Obviously, this imbalance should be seen as an outcome of the study.

Another limitation that we inferred from the study results is the lack of time. The majority of the inflammatory markers we evaluated in our study were similar in both groups at the beginning of the study, a significant change was found in the weight loss group during the study period and no significant change was found in the weight gain group during the study period. Under these conditions, it was expected that there would be a difference in the outcome between the groups, but we did not reach this result. We attributed this to the insufficient duration of the study. In a design with an equivalent start and moving in different directions, a cross-sectional measurement made prematurely may not detect the divergence, while a second cross-sectional observation after a while may notice this divergence. Therefore, more consistent results can be obtained with longer-term measurements.

CONCLUSION

We think that thiol antioxidant therapies may increase the anti-inflammatory effect in tissues in obese and diabetic patients. Thus, in addition to encouraging weight loss in obese and diabetic patients, antioxidant therapies may pave the way for studies to protect against the negative effects of obesity and diabetes by reducing the damage of oxidative stress in the early period.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was approved by the Kırıkkale University Faculty of Medicine Non-interventional Clinical Researches Ethics Committee (Date: 14.12.2024, Decision No: 25/04).

Informed Consent

All patients signed and free and informed consent form.

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 the authors declare that they have all participated in the design, execution, and analysis of the study and that they have approved the final version

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Case Report

Management of pulmonary tuberculosis and hypersensitivity reaction to antituberculosis drugs in a patient presenting with recurrent psoas abscess

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ABSTRACT

Psoas abscess is a difficult disease to diagnose. *Mycobacterium tuberculosis* (MTB) can cause psoas abscess. First generation anti-tuberculosis (anti-TB) drugs are used in the treatment of TB, side effects may occur during treatment; one of these side effects is hypersensitivity reactions. In this case report, we aimed to present a patient who presented with recurrent psoas abscess occurs after pulmonary tuberculosis and developed hypersensitivity reaction to antituberculosis drugs and the treatment method we applied. A 44-year-old male patient presented with fever, cough and right flank pain. He had hypothyroidism and received antibiotherapy plus drainage treatment for recurrent psoas abscesses. His family history was unremarkable and respiratory auscultation were normal. Fever was 37.8°C. WBC: 6.640/mm^3, CRP: 70 mg/L, ESR: 33 mm/h were elevated. Liver dynamic computed tomography (CT) showed psoas abscess, drainage was provided. Chest X-Ray showed infiltrations. Pulmonary tuberculosis was thought to be the etiology of recurrent psoas abscess, thorax CT, culture and acide resistant staining (ARS) were planned from sputum and abscess. No growth was observed in abscess culture and MTB was not detected. Sputum ARS was positive. With the initiation of HRZE treatment, the patient developed sudden dyspnea, high fever, and skin rashes, and the treatment was terminated. Premedication was decided to be performed before the drug and progressive drug loading was performed to determine the responsible drug. The patient, who had no new allergic reaction during the progressive drug loading period, was discharged and methylprednisolone tablets were prescribed for 21 days, bilastine (in case of need) and desloratadine tablets were prescribed for 6 months together with TB drugs. Tuberculosis is among the important causes of morbidity and mortality in developing countries. At the beginning of treatment, patients should be told about the side effects that may occur with the drugs they use. In patients who develop hypersensitivity reactions, temporary or permanent discontinuation of drugs and often hospitalization of the patient is required. Antihistamines and steroids may need to be used for the control of severe reactions. In our case, we wanted to emphasize that patients may develop tuberculosis even if they do not present with pulmonary symptoms and that drug side effects should always be kept in mind and the necessity and importance of premedication and gradual drug loading therapy in patients with hypersensitivity reactions.

Keywords: Recurrent psoas abscess, pulmonary tuberculosis, hypersensitivity reaction, antituberculosis therapy

INTRODUCTION

Tuberculosis (TB) is the 10th most common cause of death worldwide and the most common cause of death among infectious causes since 2007.[1] *Mycobacterium tuberculosis* (MTB) and *M. africanum* (seen in West and East Africa) bacilli are the most common human TB agents, causing approximately 98% of TB infections worldwide.[2] Primary tuberculosis infection is silent in 95% of cases and results as the latent period. In 5% of cases, it causes primary TB disease.[3] In this stage, mycobacteria may settle in the surrounding tissues and extrapulmonary organs via hematogenous and lymphogenous routes. Extrapulmonary TB occurs if reactivation occurs in foci outside the lung.[2] Extrapulmonary TB is seen in approximately 35% of all patients in Turkey and is more common in women in the adult group.[4] Psoas abscess is a rare disease which is usually difficult to diagnose and diagnosed late. Psoas abscess is more common in children and young people than in the elderly.[5] The classical findings of psoas abscess include abdominal or low back pain, limping and fever.[6] MTB may cause psoas abscess or pyogenic psoas abscess may develop in the course of pulmonary TB. First-generation anti-tuberculosis (anti-TB) drugs, which are short-term, standard drug regimen, are used in treatment. Some

serious side effects may be observed during treatment; one of these side effects is hypersensitivity reactions. The most common clinical manifestations of hypersensitivity are skin rash and fever. If a patient with hypersensitivity is given a higher dose of the same drug, anaphylactic shock may rarely develop. Drugs are discontinued and the responsible drug is determined by skin tests or drug trials under hospital conditions. The responsible drug is tried to be found by using individual drugs.[4] In this case report, we aimed to describe a patient who presented with recurrent psoas abscess resulting in the diagnosis of pulmonary TB and developed hypersensitivity reaction to anti-TB drugs and the treatment method we applied.

CASE

A 44-year-old male patient presented with fever, dry cough and right flank pain for 1 week. He had no known history of pulmonary disease. He was being treated for hypothyroidism as an comorbid disease. He had receiving antibiotherapy plus drainage treatment for recurrent psoas abscesses. He did not complain of weight loss, night sweats or hemoptysis. He was a non-smoker. There was no known history of allergy. His family history was unremarkable. Physical examination revealed normal respiratory auscultation and no abdominal tenderness. Temperature was 37.8°C, pulse rate was 90/min, and blood pressure was 110/70 mmHg. He was not desaturated on room air. Laboratory tests revealed WBC: 6.640/mm^3, C-reactive protein 70 mg/L, erythrocyte sedimentation rate 33 mm/h. No pathology was found in renal and liver function tests and elisa test for HIV or HCV/HBV. Dynamic computed tomography (CT) of the liver was reported as "There is a collection extending from the localization of the liver capsule and abdominal muscle plans posteriorly on the right to the psoas muscle and paraspinal region subcutaneously, measuring 12x5.5 cm in coronal sections in the thickest part, with mild peripheral contrast after IV contrast" (Figure 1). Interventional radiology opinion was obtained for psoas abscess and drainage of the abscess was provided and serous drainage was observed. Chest X-Ray showed infiltrations (Figure 2). Considering that the source of recurrent psoas abscess could be pulmonary TB, a thorax CT was ordered. Thorax CT revealed "There are mild patchy ground-glass density increases in the right lung upper lobe and middle lobe. There is reticulonodular infiltration at the right lung lower lobe hilar level and laterally." (Figure 3) In the differential diagnosis, psoas abscess due to tuberculosis was considered and culture and ARS were sent from the patient's sputum and abscess sample. It was decided to start HRZE regimen (isoniazid, rifampicin, pyrazinamide, ethambutol) for the patient with positive sputum ARS results. The treatment was terminated after the first dose upon the development of sudden dyspnea, high fever, skin rashes and hypotension with the initiation of treatment. It was decided to premedicate the patient who was treated for anaphylaxis before tuberculosis drugs and gradual drug loading was performed to determine the responsible drug. Day 1 isoniazid 50mg, day 2 isoniazid

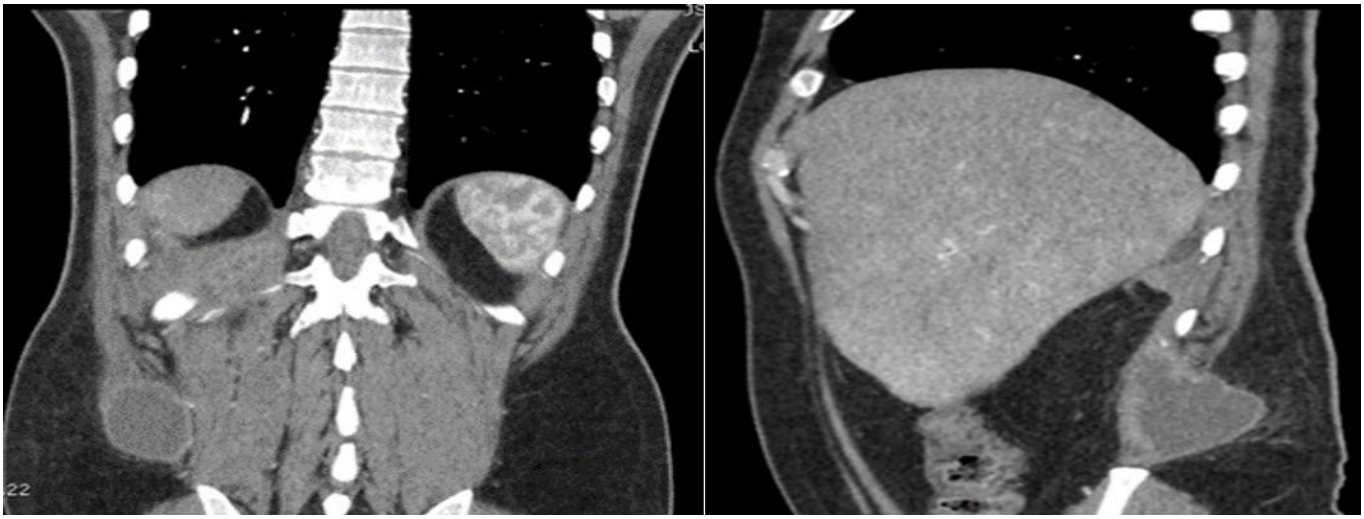

Figure 1. The dinamic liver computed tomography revealed that there was a psoas abcess

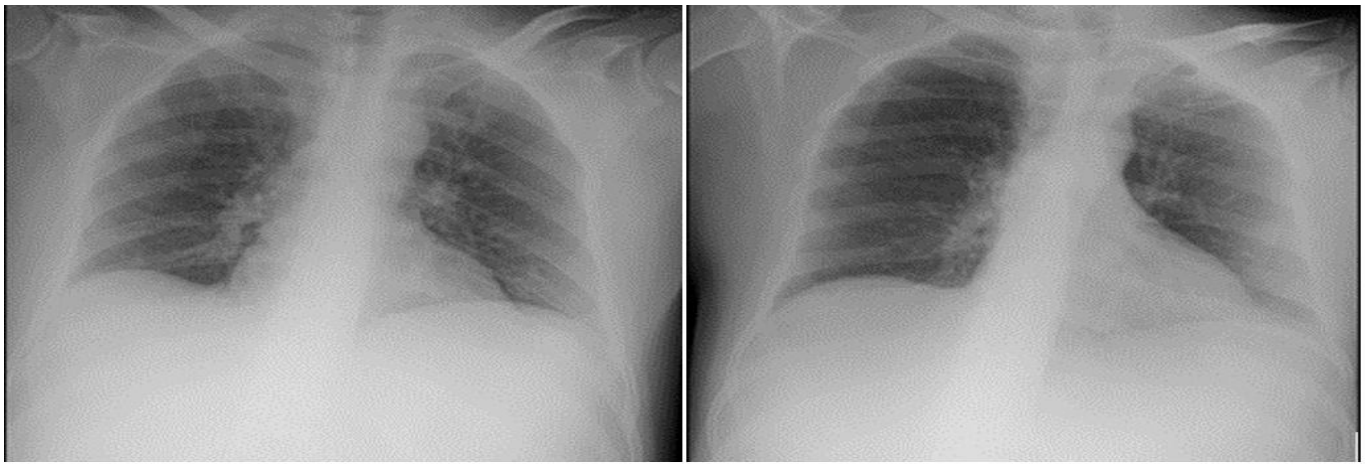

Figure 2. Chest X-Ray showed an infiltration (pre and post hospitalization X-Rays)

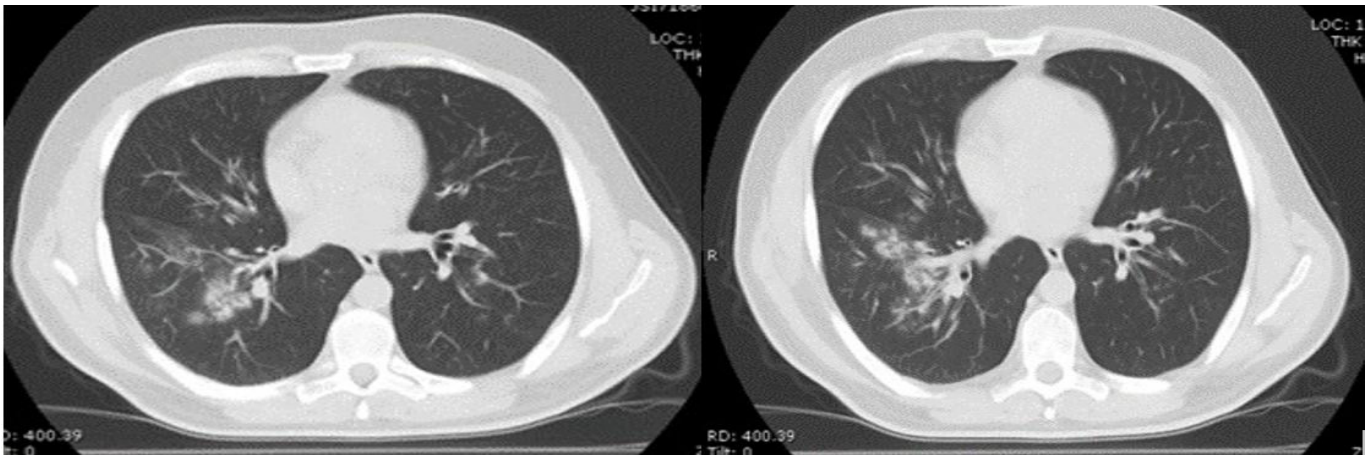

Figure 3. Chest computed tomography showed mild patchy ground-glass density increases in the right lung upper lobe and middle lobe. And reticulonodular infiltration at the right lung lower lobe hilar level and laterally

300 mg, day 3 isoniazid 300 mg + rifampicin 150 mg, day 4 isoniazid 300 mg + rifampicin 300 mg, day 5 isoniazid 300 mg + rifampicin 600 mg, day 6 isoniazid 300 mg + rifampicin 600 mg + pyrazinamide 250 mg, day 7 isoniazid 300 mg + rifampicin 600 mg + pyrazinamide 500 mg, day 8 day isoniazid 300 mg + rifampicin 600 mg + pyrazinamide 2000 mg, day 9 isoniazid 300 mg + rifampicin 600 mg + pyrazinamide 2000 mg + ethambutol 250 mg, day 10 isoniazid 300 mg + rifampicin 600 mg + pyrazinamide 2000 mg + ethambutol 500 mg, day 11 isoniazid 300 mg + rifampicin 600 mg + pyrazinamide 2000 mg + ethambutol 1500 mg and day 12 full dose HRZE treatment. After the treatment, a control chest X-ray was taken (Figure 2). The patient who had no new allergic reaction during the treatment period was discharged and methylprednisolone tablets for 21 days, bilastine and desloratadine tablets for 6 months were prescribed together with tuberculosis drugs. The patient, who had no history of new allergy on follow-up examination, is still being followed up by us.

DISCUSSION

Tuberculosis TB is an important cause of morbidity and mortality in developing countries. It is transmitted from a TB patient to a healthy person through the airway. The infectiousness of patients practically ends in 2-3 weeks with effective treatment. The disease is suspected with the patient's anamnesis, physical findings and chest X-Ray. The definitive diagnosis of pulmonary tuberculosis is bacteriologic. In our country, every tuberculosis patient should be treated with DGT (directly supervised treatment). Treatment regimens have two phases: the initial phase and the maintenance phase. The initial period is the period in which rapidly multiplying bacilli are cleared. Four drugs (HRZE) are used in this period. It usually lasts 2 months in new cases. In the maintenance period, intermittently multiplying bacilli that show activation from time to time are cleared. It usually lasts 4 months in new cases. HR is used.[7,8]

At the beginning of treatment, patients should be told about the most common side effects that may occur with the drugs they use. Patients should be seen by the physician at least once a month and their symptoms should be discussed privately, their history should be taken in terms of side effects and physical examinations should be performed. The most common side effects are gastrointestinal and cutaneous side effects in the form of nausea and vomiting. Side effects are usually observed in the first three months of treatment[9] In patients who develop hypersensitivity reactions, temporary or permanent discontinuation of drugs and hospitalization of the patient is frequently required. The most common clinical findings of hypersensitivity are skin rash and fever. What to do in case of a hypersensitivity reaction: Stop all medication given to the patient. The patient is referred to hospital. In the hospital, the responsible drug/drugs are identified by skin tests or drug trials. The responsible drug is tried to be found by using individual drugs. Once the responsible drug is identified, the patient is started on a new non-allergic treatment. Antihistamines and steroids may be required for the control of severe reactions.[10] In our case, the patient had complaints of right flank pain, fever and cough. The patient had a history of recurrent psoas abscess and when recurrent psoas abscess was detected on computed tomography, TB was considered as one of the etiologies and both abscess and sputum ARS and culture were sent. The patient's abscess material ARB was negative, sputum ARS was positive and HRZE regimen was started, but our patient developed hypersensitivity reaction to the drugs. Treatment success was achieved with gradual drug loading and premedication.

CONCLUSION

In this case, we wanted to emphasize that it should be kept in mind that tuberculosis may develop in patients with extrapulmonary complaints even if they do not present with pulmonary symptoms, side effects should always be kept in mind in patients with pulmonary tuberculosis, and the necessity and importance of premedication and progressive drug loading treatment in patients with hypersensitivity reaction.

ETHICAL DECLARATIONS

Informed Consent

The patient signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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.

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