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Table of Contents

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Does The Frequency of Diabetes Increase in Covid-19 Patients? Cross-Sectional Study

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ABSTRACT

Objectives: The aim of this study was to investigate frequency of diabetes mellitus (DM) in patients diagnosed with Covid-19 and whether Covid-19 had effect on high HbA1c.

Methods: Data of DM patients with Covid-19 were analyzed cross-sectionally. In Covid-19, the effect of DM patient frequency and mortality was investigated.

Results: 2057 patients diagnosed with Covid-19 were included in the study. Among these patients, total 192 patients (9.25%) were treated with the diagnosis of DM. 73 (41 males-32 females) were newly diagnosed with DM (38.02%). 119 patients (48 males and 71 females) were previously diagnosed with DM. Eight of DM patients died. Among all Covid-19 in patients followed up, 90 patients died. Mortality of DM patients was not statistically significant compared to mortality of all patients (p = 1.000 x = 0). Of the patients who were followed up with diagnosis of DM, whose HbA1c were observed in the last 3 months, 16 of 20 patients had increase in HbA1c, and 4 patients had decrease in HbA1c. The mean increase was 1.05.

Conclusion: The frequency of new diagnosis DM in patients with Covid-19 was found to be quite high. There was increase in HbA1c in Covid-19 patients, and Covid-19 was thought to affect the pancreas.

Keywords: Covid-19, Diabetes Mellitus, HbA1c, ARDS, PCR

"Coronavirus Disease 2019 (Covid-19)", which has a wide clinical spectrum from asymptomatic cases to cases that result in acute respiratory distress syndrome (ARDS) requiring intensive care, was declared as a pandemic by the World Health Organization (WHO) on March 11, 2020, and continues to spread rapidly across the globe. 1 According to the literature and clinical observations, age, being male and chronic diseases, especially hypertension and Diabetes Mellitus (DM), are seen as risk factors. [2]

The prevalence of DM seen to affect the course and mortality of Covid-19 was 5% in a study in China, 17% in a study in Italy and 25.2% in a study in New York. [3-5]

In a study conducted in England, it was shown that Covid-19 progressed more severely in people with diabetes and DM was an important risk factor for hospitalization in patients with Covid-19. [6]

It is stated that cytokines released in Covid-19 patients may affect the exocrine and endocrine pancreas, destroy immune-mediated β-cells, and cause type 1 DM and worsening of insulin resistance in patients with type 2 DM previously. [7, 8]

In our study, we aimed to investigate the frequency and prognosis of DM and whether Covid-19 had an effect on high HbA1c in patients hospitalized with the diagnosis of Covid-19 in our hospital.

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METHODS

The data of all Covid-19 patients who received inpatient treatment between March 16, 2020, in which Covid-19 started to appear in our country and the first case was detected in our province, and July 14, 2020 were analyzed retrospectively through the Hospital Information Management System. 2,057 patients were included in the study. Covid-19 was diagnosed if the PCR test was positive and/or in accordance with the Ministry of Health Covid-19 guidelines through clinical, laboratory and imaging findings. From these inpatients, 192 of those who received DM treatment were identified, and their HbA1c values during the time they were treated in hospital, whether they had HbA1c in the last 3 months (90 days) and their prognosis were recorded. Exclusion criteria were determined as being non-Covid-19 patients, patients with HbA1c < 6.5 and patients under 18 years of age.

Ethical Approval

Since our study was retrospective, informed consent was not obtained from the patients. Ethics committee approval was obtained from our hospital for this study.

Statistical Analysis

Numerical data obtained in the study were expressed as arithmetic mean±standard deviation (SD), while categorical data were expressed as frequency (percentage). Statistical analyses were performed using the SPSS 22.0 software package. Pearson Correlation Analysis was used for the relationship between two numerical variables. $p < 0.05$ was considered statistically significant.

RESULTS

Of 2,057 patients included in the study, a total of 192 patients (9.25%), 89 males (mean age: 55.3) and 103 females (mean age: 57.4), were treated with the diagnosis of DM. The mean age of the patients diagnosed with DM was 56.5 years (min:26-max:83). The mean HbA1c level of patients with DM diagnosis was 9.5 (min:6.5-max:18) 73 (41 males and 32 females) of these patients were not previously diagnosed with DM, and they were accepted as newly diagnosed patients (38.02%). The mean HbA1c value of newly diagnosed patients was 8.62% (min:6.5-max:16.5). There were 119 patients (48 males, 71 females; mean HbA1c: 10.04 (min: 6.5-max: 18)) previously diagnosed with DM. 8 (8.88%) of DM patients died (mean HbA1c: 9.2 (min:6.9-max:10.9)) (Table1). Among all Covid-19 inpatients followed up, 90 (4.3%) patients died. The mortality of DM patients was not statistically significant compared to the mortality of all patients ($p = 1.000$ x = 0). Table-1

When the HbA1c values of DM patients followed up were examined in the last 3 months (90 days), 20 patients had their HbA1c checked in the last three months, and while 16 patients had an increase in HbA1c, 4 patients had a decrease in HbA1c. The mean increase was 1.05.

Table 1. DM data and statistical comparison of Covid-19 patients.

	DM patients			Total Covid-19 (%)	*P* X_2
	Newly diagnosed (%)	Previously diagnosed (%)	Total DM (%)		
Number of patients	73 (38)	119 (62)	192 (100)	2057 (100)	
Gender					
Male	41 (56.1)	48 (40.3)	89 (46.3)	1031 (50.1)	
Female	32 (43.9)	71 (59.7)	103 (53.7)	1026 (49.9)	
Age (mean)	53.7 Min:31 Max:83	58.1 Min:26 Max:82	56.5 Min:26 Max:83	48.7 Min:18 Max:98	
HbA1c	8.62 Min:6.5 Max:16.5	10.04 Min:6.5 Max:18	9.5 Min:6.5 Max:18		
Died		8 (8.88)		90 (4.3)	1.000 0

Min.: minimum | Max.: maximum, $p < 0.05$

DISCUSSION

Our study examined 2,057 patients and found that 9.25% of Covid-19 patients were treated with a DM diagnosis. Singh AK *et al*. detected DM in 5% of patients in a study in which 20,982 patients were investigated by the Centers for Disease Control and Prevention (CDC) in China, where the prevalence of DM was 10.9%. [3] In a study conducted by Grasselli G *et al*. in Italy, the number of DM patients in 1,591 patients with severe Covid-19 was recorded as 180 (17%). [4] In a retrospective case series with 393 patients in New York, Goyal P *et al*. found that Covid-19 was accompanied by DM in 25.2% of patients. [5] In our study, this ratio was also in line with the literature.

The mortality rate among Covid-19 inpatients followed up was 4.3%, and the rate of DM patients who died was 8.88%. Although the mortality of DM patients increased compared to the mortality of all patients, it was not statistically significant. A study by Docherty AB *et al*. in the UK, showed that 19% of 16,749 patients hospitalized with Covid-19 between February and April 2020 had underlying diabetes, and that this was an important risk factor for hospitalization in Covid-19 patients. [6] In our study, although DM did not have a statistically significant effect on mortality in patients with Covid-19, the fact that DM rates were high among inpatient and deceased patients showed that DM was an important comorbid condition that should be considered during both hospitalization and clinical follow-up. We think that the early decisions taken in pandemic management in our country have been effective in the fact that the prevalence of diabetes and the number of deceased people with diabetes are less than expected in our study. We believe that informing the community and restrictions on people with chronic diseases when the first case appeared in our country have caused people with DM to protect and therefore prevent themselves from becoming infected. Regardless of the risk factors, we are of the opinion that measures such as wearing masks, social distance and hand washing during the pandemic are valuable in fighting the pandemic.

In our study, we found that the HbA1c value increased by an average of 1.05% in 38.02% of newly diagnosed DM patients and 16 of the previously diagnosed DM patients. It has been reported that cytokines released in Covid-19 patients may affect the exocrine and endocrine pancreas, destroy immune-mediated β-cells, and therefore lead to newly diagnosed Type 1 DM or deplete insulin reserve and cause worsening of insulin resistance in patients with previously diagnosed type 2 DM. [7, 8] As a result of our study, we believe that Covid-19 affects DM regulation and raises HbA1c level.

Our study had some limitations. The most important of these was that most patients had no HbA1c levels recorded in the last 3 months. More definitive results can be obtained as a result of studies conducted with more case series where HbA1c levels of the last 3 months are available.

In conclusion, Covid-19 may develop newly diagnosed DM, particularly by affecting the pancreas, and may raise HbA1c levels in patients with existing DM. Therefore, we think that it would be appropriate to examine Covid-19 patients in terms of DM and to closely monitor patients with DM.

CONCLUSION

Authors' Contribution

Study Conception: İS, SA,; Study Design: İS, SA,; Supervision: İS, SA,; Materials: İS, SA,; Data Collection and/or Processing: İS, SA,; Statistical Analysis and/or Data Interpretation: İS, SA,; Literature Review: İS, SA,; Manuscript Preparation: İS, SA, and Critical Review: İS, SA.

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The effect of certolizumab treatment on insulin resistance, lipid parameters and cardiovascular risk in patients with ankylosing spondylitis

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ABSTRACT

Objectives: To evaluate the effects of certolizumab treatment on insulin resistance (IR), lipid parameters, and cardiovascular (CV) risk in patients with ankylosing spondylitis (AS).

Methods: This prospective study included 80 consecutive patients with AS (52 males, 28 females) and 74 control subjects (48 males, 26 feemales). The AS patients and control group were compared in respect of basal values. All AS patients with active disease were treated with certolizumab. Biochemical profiles were obtained before and after 24 weeks of certolizumab treatment. Homeostatic model assessment-insulin resistance (HOMA-IR) was used to measure IR and the quantitative insulin sensitivity control index (QUICKI) was used to measure insulin sensitivity. The Framingham equation was used to evaluate CV risk factors.

Results: A statistically significant increase was determined in total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) values after 24 weeks of certolizumab treatment. No statistically significant change was determined in the plasma atherogenic index (PAI) and low-density lipoprotein cholesterol (LDL-C) values. A statistically significant decrease was determined in HOMA-IR and an increase in QUICKI. When the Framingham risk scoring was compared with the baseline values, a statistically significant decrease in risk was found at week 24.

Conclusions: Certolizumab therapy was associated with a significant increase in HDL-C, TC, and TG levels without any significant change in PAI and LDL-C, and was determined to increase insulin sensitivity and lower insulin resistance. There was also a significant reduction in SBP and 10-year Framingham risk scores at 24 weeks after the start of certolizumab therapy.

Keywords: Ankylosing spondylitis, Certolizumab, İnsulin resistance, Framingham risk scoring, Lipid parameters.

Ankylosing spondylitis (AS) is a chronic inflammatory disease of the axial skeleton characterized by low back pain, progressive spinal stiffness, enthesopathy, peripheral arthritis, and extra-articular symptoms. [1], which is more common in young adult males (male: female ratio 3-4: 1). [2] This disease is treated with non-steroidal anti-inflammatory drugs (NSAIDs) and tumor necrosis factor-alpha (TNF-α) inhibitors. The use of TNF-α inhibitory therapy is becoming increasingly common and has been shown to reduce pain and inflammatory markers by improving quality of life. [3]

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In patients with AS, endothelial dysfunction is observed in early disease, which can be combined with traditional cardiovascular disease (CVD) risk factors. [4] However, the relationship between inflammation, atherosclerosis, vascular dysfunction, and AS is multifactorial and still not fully understood. Disorders in lipid levels, especially low levels of serum high-density lipoprotein cholesterol (HDL-C), increased triglyceride levels (TG), and low-density lipoprotein cholesterol (LDL-C) concentrations have been proven to accelerate atherosclerosis. In some studies, the reduction in HDL-C has been reported more frequently in AS patients than in healthy control subjects. [5] This may be at least partly responsible for the increased CVD risk in patients with AS.

Increased insulin resistance (IR) is an important risk factor for CVD. [6] Patients with autoimmune connective tissue diseases have increased IR.7 TNF-α inhibitory therapy has effects on metabolism, including improvement in IR. [8] TNF-α inhibitory therapy facilitates the reduction in plasma glucose by blocking TNF-α and increasing insulin sensitivity. [9] A recent systematic review showed that there was a moderate relationship between homeostatic model assessment–insulin resistance (HOMA-IR), the quantitative insulin-sensitivity check index (QUICKI), and the hyperinsulinemic-euglycemic clamp technique, which is considered the 'gold standard' for peripheral insulin sensitivity. [10] The Framingham risk scoring system is a reliable method used to calculate the 10-year CVD risk .[11] In a study examining the effects of infliximab treatment with the Framingham equation before and after treatment in patients with AS, a significant decrease in Framingham equation was found after treatment. [12]

The aim of this study is to determine the effects of certolizumab treatment at baseline and at the 24th week of treatment on the risk of IR, lipid parameters, and CVD in patients with AS.

METHODS

This prospective study included all active AS patients who referred to the rheumatology outpatient clinic of Kahramanmaras Sütcü Imam University (KSU) for follow-up between February 2018 and February 2019. These patients were previously diagnosed with AS according to the 1984 New York classification criteria. [13] This study included 80 patients with AS (52 males and 28 females) and 74 controls (48 males and 26 females) with similar age and sex. The control group consisted of individuals who referred to the rheumatology outpatient clinic of KSU with complaints of arthralgia and myalgia and who did not have any rheumatologic disease based on physical examinations and laboratory findings, who were not diagnosed with any chronic disease previously, who were not receiving any medical therapy.

Disease activity of the AS patients was measured using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) method, and TNF-α inhibitor treatment (certolizumab) was started for patients who received NSAID therapy with BASDAI values ≥ 4 and not in remission. The study exclusion criteria for the AS patients was as follows: history of malignant disease, lupus or myelinating disease, severe kidney or liver disease, a history of hepatitis B or C, plasma fasting blood glucose (FBG) levels > 100 mg/dL, drug use affecting glucose and lipid metabolism, pregnancy and breast feeding, active infection and systemic corticosteroid treatment in the four weeks before the study. Chest X-ray, a tuberculin skin test, and interferon-gamma release test were performed on all AS patients. Certolizumab treatment was started one month after TB prophylaxis was initiated in patients with evidence of latent TB. Certolizumab treatment was administered subcutaneously, with an initial dose of 400 mg given at 0, 2, and 4 weeks, and a maintenance dose of 200 mg administered every two weeks starting at 6 weeks.

In the evaluation of the AS patients before any treatment and the control group, a record was made of age, gender, and body mass index (BMI) (kg/m^2). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were manually measured in the brachial artery by the same physician. After 12 hours of fasting overnight, venous blood samples were taken for the examination of total cholesterol (TC), LDL-C, HDL-C, and TG. The plasma atherogenic index (PAI) was calculated according to the log10 TG/HDL formula. [14] In addition to the above-mentioned values, the following data were collected from AS patients prospectively at baseline and at week 24; serum fasting insulin concentration (μIU/mL), FBG (mg/dL), pain severity using a 10-cm visual analogue scale (VASp), morning stiffness duration (minutes), modified Schober test (cm), chest expansion (cm), C-reactive protein levels (CRP) (mg/L) and erythrocyte sedimentation rate (ESR) (mm/h). HOMA-IR index model evaluations were used to measure IR. [15] The HOMA-IR index was

calculated as fasting insulin concentration (μIU/mL) × FBG (mg/dL)/405, assuming < 2.5 as the score of normal adults. The QUICKI was calculated using the formula of 1/log insulin (μU/mL) + log glucose (mg/dL). 16 The Framingham equation was used to assess the risk of CVD. 11 The Framingham equation takes into account the following variables: age, sex, SBP, and DBP, serum LDL-C and HDL-C levels, smoking status, and presence/absence of DM. Functional capacity was assessed using the Bath Ankylosing Spondylitis Disease Function Index (BASFI).

No patient took drugs known to affect glucose, lipid metabolism, or BP. Patients were warned not to make lifestyle changes or use a new drug without permission during the study period. This study was approved by the Ethics Committee of Kahramanmaras Sutcu Imam University Faculty of Medicine (Approval Date: November 25, 2017; Approval Number: 2017/17-05) and was conducted in accordance with the Helsinki Declaration of 1975. Informed consent was obtained from all the participants included in the study.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences software (SPSS for Windows, version 17.0). Conformity of the variables to normal distribution was investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk test). The Wilcoxon rank-sum test, or the Independent-samples Student's t-test were applied to continuous variables, as appropriate, to determine whether there was a significant difference between the groups in respect of the characteristics of patients. Results were expressed as median and mean ± standard deviation (SD) values. Changes observed before and after certolizumab treatment were evaluated using paired samples t-tests for normally distributed data and Wilcoxon analyses for data with non-parametric distributions. After treatment, Spearmen correlation analysis was used to establish the relationship between the variables. All p values were 2-tailed and a value of $p < 0.05$ was considered statistically significant.

RESULTS

The basal demographic and clinical characteristics of the AS patients and the control group are shown in Table 1. The PAI ($p = 0.004$) and TG ($p = 0.000$) values of the AS patients were determined to be statistically significantly higher than those of the control group, and the HDL-C (0.016) value was lower. No statistically significant difference was determined between the groups in respect of age, gender, BMI, TC, LDL-C, SBP and DBP (Table 1).

Compared to the baseline values, the values obtained after 24 weeks of certolizumab treatment

Table1. Baseline demographic and characteristics of AS patients and control group

	AS (n = 80)	Control (n = 74)	*P* - Value
Age (years)	35.05 ± 7.92	36.49 ± 12.05	0.455
Gender, Men, n (%)	52 (65.00)	48 (64.80)	0.936
Time Of Diagnosis (months)	46.41 ± 70.22	-	-
Atherogenic index of plasma	0.151 ± 0.217	0.074 ± 184	0.004
Body mass index, kg/m^2	27.83 ± 4.12	27.56 ± 4.08	0.954
Total cholesterol, mg/dL	175.1 ± 31.1	174 ± 30.2	0.645
Triglyceride, mg/dL	148.7 ± 52.7	131.6 ± 38.5	0.000
HDL cholesterol, mg/dL	43.1 ± 7.9	47.6 ± 9.7	0.016
LDL cholesterol, mg/dL	116.2 ± 28.1	115.5 ± 27.4	0.915
Systolic blood pressure, mmHg	124.2 ± 12.8	122.4 ± 11.9	0.837
Diastolic blood pressure, mmHg	78.8 ± 11.6	76.7 ± 10.8	0.158
Uveitis, n (%)	12 (15.0)	-	-
Peripheral joint involvement, n (%)	17 (21.2)	-	--
Inflammatory bowel disease, n (%)	6 (7.5)	-	-

Note: Variables are expressed as the mean ± standard deviation, AS, Ankylosing Spondylitis; HDL-cholesterol, high-density lipoprotein cholesterol; LDL- cholesterol, low-density lipoprotein cholesterol.

demonstrated a statistically significant decrease in ESR, CRP, BASDAI, BASFI, VASp, ASQoL and Morning Stiffness (minutes) as effects on the disease characteristics of AS patients (p = 0.000), and a statistically significant increase in the modified Schober, and chest expansion values (p = 0.000) (Table 2). Following 24 weeks of certolizumab treatment in AS patients, a statistically significant decrease was determined in FBG (p = 0.028), HOMA-IR (p = 0.014) and serum insulin level (p = 0.000) and a statistically significant increase in QUCKI (p = 0.004) compared to the pre-treatment values. (Table 3).

After 24 weeks of certolizumab treatment, a statistically significant increase was determined in TC, HDL-C, and TG values compared to baseline (p = 0.000, p = 0.004, p = 0.024, respectively), and no significant change was determined in LDL-C (p = 0.065) and PAI (log10 TG/HDL) (p = 0.624) values., a statistically significant increase was determined in the weight (p = 0.000) and BMI (p = 0.003) values, a decrease in SBP pp = 0.012) and no significant change in DBP (p = 0.254). The Framingham risk score, used to evaluate the 10-year CVD risk, there was determined to be a statistically significant decrease in risk at week 24 (p = 0.018) (Table 4).

DISCUSSION

There were four main findings that emerged from this study. First, the PAI and TG values of the AS patients were determined to be higher than those of the healthy control group and the HDL-C value was lower. Second, the ESR, CRP, BASDAI, BASFI, VASp, ASQoL and morning stiffness values were determined to have decreased and the modified Schober and chest expansion values to have increased after [24] weeks of certolizumab treatment. Third was

Tablo 2. Effect on disease characteristics of ankylosing spondylitis patients 24 weeks after certolizumab treatment

	Before certolizumab treatment	After 24 weeks of treatment	P-value
BASDAI	5.79 ± 1.12	3.28 ± 0.59	0.000
BASFI	5.41 ± 1.25	3.00 ± 0.60	0.000
AsQoL	13.12 ± 1.53	4.52 ± 1.75	0.000
VASp (cm)	7.8 ± 0.7	3.3 ± 1.2	0.000
Morning Stiffness (minutes)	95 ± 24	18 ± 11.3	0.000
Modified Schober (cm)	3.7 ± 1.1	5.5 ± 0.6	0.000
Chest Expansion (cm)	2.9 ± 0.8	5.3 ± 0.9	0.000
ESR, mm/h	24.4 ± 9.5	9.4 ± 4	0.000
CRP, mg/L	13.3 ± 11.1	5.2 ± 3.4	0.000

Note: Variables are expressed as the mean ± standard deviation, BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Disease Function Index; ASQoL, Ankylosing Spondylitis Quality of Life Questionnaire; VASp, Visual analogue scale for pain; ESR, erythrocyte sedimentation rate; CRP, C-Reactive Protein.

Tablo 3. Effects of 24-week certolizumab treatment on glucose, HOMA, QUICKI and insulin in patients with ankylosing spondylitis.

	Before certolizumab treatment	After 24 weeks of treatment	*P* - value
Fasting Blood Glucose, mg/dL	89.8 ± 9.3	87.9 ± 9.2	0.028
HOMA-IR	2.82 ± 1.5	2.28 ± 1	0.014
QUICKI	0.338 ± 0.029	0.346 ± 0.024	0.004
Insuline, mU/L	12.84 ± 1.29	10.65 ± 0.92	0.000

Note: Variables are expressed as the mean ± standard deviation, HOMA-IR, homeostatic model assessment–insulin resistance; QUICKI, quantitative insulin-sensitivity check.

Tablo 4. Effect of 24-week Certolizumab treatment on lipid profile and cardiovascular risk factors in patients with ankylosing spondylitis.

	Before certolizumab treatment	After 24 weeks of treatment	P-value
Total Cholesterol, mg/dL	175.1 ± 31.1	180 ± 30.5	0.000
Triglyceride, mg/dL	148.7 ± 52.7	150.7 ± 50.1	0.024
HDL cholesterol, mg/dL	43.1 ± 7.9	45.4 ± 6.9	0.004
LDL cholesterol, mg/dL	116.2 ± 28.1	117.5 ± 28.3	0.065
Atherogenic index of plasma	0.151 ± 0.217	0.156 ± 0.167	0.624
Systolic blood pressure, mmHg	124.2 ± 12.8	121.6 ± 9.9	0.012
Diastolic blood pressure, mmHg	78.8 ± 11.6	77.6 ± 9.8	0.254
Weight, kg	81.7 ± 12.6	83.5 ± 12.1	0.000
Body mass index, kg/m2	27.8 ± 4.1	28.6 ± 3.8	0.003
Framingham (10-Year CVD Risk)	4.67 ± 3.92	3.95 ± 3.05	0.018

Note: Variables are expressed as the mean ± standard deviation, HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CVD, cardiovascular disease.

that following 6 months of certolizumab treatment, there was a decrease in the FBG, HOMA-IR and insulin levels and an increase in the QUCKI value. Finally, the fourth significant finding was that after the certolizumab treatment, there was an in increase in weight, BMI, TC HDL-C and TG values, a decrease in SBP, and no change in DBP, LDL-C and PAI values. The Framingham risk score, which evaluates the 10-year CVD risk, showed a statistically significant decrease in risk at week 24.

There is strong evidence that TNF-α inhibitor therapy reduces the incidence of CVD events in patients with rheumatoid arthritis (RA), but there are conflicting results in limited data from patients with AS. [17, 18] In the results reported from the analysis in the Australian Rheumatology Association Database, where patients with RA, psoriatic arthritis (PsA), and AS, which were recently updated, patients who used biological drugs with a TNF-α inhibitor or another mechanism of action also had a decrease in CVD event rates compared with patients with biologically naive inflammatory arthritis, and it was shown that the decrease in CVD events disappeared in patients who stopped using biological drugs. In that report [19], it was also emphasized that there was no difference between RA, PsA, and AS in terms of CVD event risk, and that control of systemic inflammation in patients with inflammatory arthritis may reduce the CVD risk. In a study of patients with AS, Bozkirli *et al*., [12] determined a significant decrease in the Framingham risk score after 12 weeks of infliximab and associated the cause with a decrease in SBP. In the current study, patients were evaluated in respect of the 10-year CVD risk using the Framingham risk score, and when the 24th week of certolizumab treatment was compared with baseline, there was seen to be a significant reduction in the Framingham risk score in the 24th week. Consequently, it was thought that the decrease in SBP used in the Framingham risk calculations, as well as the increase in HDL-C levels, were effective.

In the BeSt study, which was planned to evaluate the effects of disease activity and anti-rheumatic treatment on BP in patients with RA, patients initially treated with infliximab were shown to have a lower mean BP than patients treated with DMARDs. [20] In another study, it was claimed that the improvements in microvascular endothelium-dependent functions provided by TNF-α inhibitor therapy might also contribute to a decrease in BP. [21] In this study, the decrease in SBP after the certolizumab treatment was associated with improved disease activation, NSAID use was reduced with effective treatment, and there was seen to be increased patient mobility, and improved endothelial function.

Effective anti-inflammatory therapy with TNF-α inhibitory therapy has been shown to reduce the risk of CVD despite increases in lipid levels. [17] Heslinga *et al*. [22] found that TNF-α inhibitory therapy was associated with moderate but broadly parallel increases in TC, LDL-C, and HDL-C, whereas PAI remained unchanged and significant lipid changes after TNF-α inhibitor therapy were only seen in patients with CRP

levels < 10 mg/L. Similarly, in a study by Mathieu *et al*. [23], 14 weeks of TNF-α inhibitor treatment increased TC and HDL-C levels, but there was no significant change in PAI levels. Similarly, in the current study with certolizumab, an increase was determined in TC, HDL-C, and TG levels after 24 weeks of treatment, but no statistically significant change was seen in PAI and LDL-C levels.

A previous study confirmed the significant negative effects of TNF-α on insulin-mediated glucose uptake and the development of IR. [24] Recently, a rapid and dramatic decrease in serum insulin levels and a rapid improvement in insulin sensitivity have been demonstrated in non-diabetic patients with AS treated with infliximab, which specifically binds to TNF-α with high affinity and neutralizes this cytokine. [24] In a study of patients with AS and RA by Kiortsis *et al*. [25] a significant decrease in HOMAR-IR and an increase in QUICKI were reported after infliximab infusion. With infliximab therapy, a rapid and dramatic decrease in serum insulin levels and a rapid improvement in insulin sensitivity have been shown in patients with AS without DM. [26] The current study results demonstrated a decrease in HOMAR-IR and insulin level, and an increase in QUCKI after 24 weeks of certolizumab treatment, consistent with studies in the literature. It was thought that the primary effects of the certolizumab treatment were the reduction of possible plasma TNF-α levels and the improvement of endothelial dysfunction by suppressing inflammation.

In this study results also showed a statistically significant decrease in FBG levels. There are conflicting results in the literature in this regard. In a study of patients with AS, PsA, and juvenile idiopathic arthritis, no significant FBG change was observed with three different TNF-α inhibitor drugs at 6 months. [27] In a study by Gonzalez-Gay *et al*., [28] although a significant increase in FBG was observed at 120 minutes after infliximab treatment, an improvement in IR was reported. In another study with infliximab in non-DM patients, Miranda-Filloy *et al*. [26] observed FBG to be 92.9 ± 9.2 mg/dL before infusion and 89.3 ± 7.4 mg/dL after infusion, and a statistically significant decrease in FBG was detected. In the current study, a significant decrease was determined in FBG levels, in parallel with the decrease in IR after 24 weeks of treatment with certolizumab. The possible causes were thought to be a decrease in HOMA-IR and insulin level, an increase in QUCKI levels, improvement of endothelial dysfunction, and a decrease in serum TNF-α levels.

TNF-α expression in adipose tissue is positively correlated with 24-hour energy expenditure and this cytokine has anorexic effects, increases lipolysis, and inhibits adipogenesis. [29, 30] Therefore, TNF-α is more likely to cause cachexia than obesity. In a study of patients with RA and spondyloarthritis (SpA), Luft *et al*. [31] showed that some patients (13.3%) who received TNF-α inhibitor treatment developed weight gain of average 5.5 kg (mean change in BMI 4.7 kg). In a recent study of patients with SpA using TNF-α inhibitory therapy, 0.9 kg of body weight gain over 2 years was demonstrated to be accompanied by a marked increase in visceral adipose tissue after six months, one, and two years. [32] The data obtained in the current study overlapped with results published in the literature. It can be predicted that the effects of TNF-α inhibitor treatment on weight and body composition could be explained by improvements in the patient's health, an increase in appetite due to control of disease activity, and a decrease in serum TNF-α, which has a cachectic effect.

Even though most of the previously published studies on the same subject have been conducted with a similar number of patients, the limitations of this study could be said to be the relatively small number of patients and limited follow-up time. Further studies of larger series with long-term follow-up are needed to confirm these preliminary results of TNF-α inhibitor (certolizumab) therapy on the risk of IR, lipid parameters and CVD in patients with AS.

CONCLUSION

TNF-α inhibitor therapy (certolizumab) was associated with a significant increase in HDL-C, TC, and TG levels without any significant change in PAI and LDL-C. Certolizumab therapy increases insulin sensitivity and lowers insulin resistance. There was also a significant reduction in SBP and the 10-year Framingham risk scores at 24 weeks after the start of certolizumab therapy. This risk reduction in CVD is an important finding because the most important cause of death for patients with AS is CVD.

Acknowledgement

None

Conflict of Interest

The authors declare that they have no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available because of privacy or ethical restrictions.

Authors' Contribution

Study Conception: HG, GYÇ,; Study Design: HG, GYÇ,; Supervision: HG, GYÇ,; Materials: HG, GYÇ,; Data Collection and/or Processing: HG, GYÇ,; Statistical Analysis and/or Data Interpretation: HG, GYÇ,; Literature Review: HG, GYÇ,; Manuscript Preparation: HG, GYÇ and Critical Review: HG, GYÇ.

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Evaluation of Anemia Frequency and Types in Patients with Subclinical and Clinical Hypothyroidism in the Endemic Goiter Region

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ABSTRACT

Objectives: Hypothyroidism is a disease that occurs as a result of thyroid hormone deficiency or rarely, due to ineffectiveness at the tissue level. While the prevalence of clinical hypothyroidism is reported to be 2-5% worldwide, of subclinical hypothyroidism it is 4-8.5%, with the prevalence of subclinical hypothyroidism in women over 60 years of age being 14-20%. Hypothyroidism affects many organs and systems in the body, one of which is the hematopoietic system. Thyroid hormone deficiency plays a role in the development of microcytic, normocytic and macrocytic anemia. The frequency of anemia in patients with hypothyroidism varies between 20-60%. In this study, our aim was to determine the regional prevalence of subclinical and clinical hypothyroidism in adult patients in our region and to evaluate the frequency and types of anemia in patients with hypothyroidism.

Method and Material: This study was conducted prospectively between 01.12.2012 and 01.05.2013 in the Faculty of Medicine, Endocrinology outpatient clinic. Included in the study were 96 patients who had subclinical hypothyroidism, 30 patients who had clinical hypothyroidism, and 100 healthy controls. Normal fT4 and fT3, high TSH values were used for the diagnosis of subclinical hypothyroidism, and low fT4 and/or fT3, high TSH values were used for the diagnosis of clinical hypothyroidism. The diagnosis of anemia was based on subclinical hypothyroidism, clinical hypothyroidism, and control group Hb value < 13g/dl in men and < 12g/dl in women.

Results: In our study, we found the prevalence of subclinical hypothyroidism to be 3.6%, and of clinical hypothyroidism to be 1.1%. We found the rate of anemia to be 30.2% in the subclinical hypothyroid patient group, 40% in the clinical hypothyroid patient group, and 25% in the control group. A statistically significant difference was shown between the clinical hypothyroidism group and the control group based on the frequency of anemia ($p = 0.033$). There was no statistical difference in the frequency of anemia between the subclinical hypothyroidism group and the control group ($p = 0.0586$). A statistically significant difference was found between the patient group (subclinical + clinical hypothyroidism) and the control group in terms of the frequency of anemia ($p = 0.049$). In the subgroup analysis of 66 anemic patients in the patient and control groups, in both groups the most common type of anemia was anemia of chronic disease, but there was no statistical difference between the groups in terms of anemia of chronic disease ($p = 0.223$).

Conclusion: We found that there was an increase in the frequency of anemia in patients with hypothyroidism and that the most common anemia subtype in hypothyroidism was anemia of chronic disease (normocytic).

Keywords: Anemia, Subclinical hypothyroidism, Clinical hypothyroidism

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Hypothyroidism is a disease that occurs because of thyroid hormone deficiency or, albeit rarely, ineffectiveness at the tissue level. Its prevalence varies from between communities, depending on demographic characteristics such as age, gender, race, and geographic region. While the prevalence of clinical hypothyroidism is reported to be 2-5% globally, the prevalence of subclinical hypothyroidism is reported to be 4-8.5%, and in women over 60 years of age 14-20%. [1] In hypothyroidism, there is a slowdown of the body's metabolism and all organs and systems are thus affected. Anemia occurs as a result of primary involvement of the hematopoietic system by multiple mechanisms. [2] Studies have reported the incidence of anemia in hypothyroidism to be 20-60%. [3] Anemia seen in hypothyroidism can be of hypochromic microcytic, normochromic normocytic or macrocytic type. The most common type of anemia is normochromic normocytic anemia. In hypothyroidism, depending on the metabolic slowdown, the need for oxygen in the body decreases, resulting in physiological hypoerythropoetinemia occurring in order to normalize the hematocrit level and normochromic normocytic anemia occurs. Macrocytic anemia in hypothyroidism can also develop due to malabsorption of vitamin B12 and/or folic acid. 4

Hypochromic microcytic anemia occurs as a result of menorrhagia caused by hormonal imbalances and iron malabsorption due to thyroid hormone deficiency. Macrocytic anemia develops due to impaired absorption of vitamin B 12 as a result of IF (Intrinsic Factor) deficiency and antibody development against gastric parietal cells in pernicious anemia, which can be seen together with autoimmune diseases of the thyroid. [2, 5]

In this study, our aim was to determine the prevalence of subclinical and clinical hypothyroidism in adult patients in our region and to evaluate the frequency and types of anemia in patients with hypothyroidism.

METHODS

This study was conducted prospectively between 01.12.2012 and 01.05.2013 in the Faculty of Medicine, Endocrinology outpatient clinic. The patients included in the study were selected from among the patients who applied to the endocrinology outpatient clinic between 01.12.2012 and 01.05.2013 for varying reasons. Thyroid function tests were performed and clinical and subclinical hypothyroidism diagnoses were made. 100 randomly selected healthy individuals with normal thyroid function were determined as the control group. Hemogram, iron, total iron binding capacity, ferritin, vitamin b12 and folate measurements were performed to determine the frequency and subtypes of anemia in 100 healthy control subjects with clinical and subclinical hypothyroidism. The Architect i 2000 (Abbott, USA) device was used to measure biochemical parameters, Architect c 1600 (Abbott, USA) device to measure iron and total iron binding capacity, and the Cell-Dyn Ruby (Abbott, USA) device for complete blood count.

Those who use thyroid hormone medication or have pre-existing thyroid disease, coronary artery disease, diabetes mellitus, uncontrolled hypertension, chronic kidney failure, recent acute bleeding (gastrointestinal-genitourinary-respiratory etc.), receiving anemia treatment, steroid treatment, hemolytic anemia, or hematological malignancies were excluded. Twelve of 108 patients with subclinical hypothyroidism and 5 out of 35 patients with clinical hypothyroidism were excluded from the study because they met one or more of the exclusion criteria.

Normal fT4 and fT3, as well as high TSH values, were used for the diagnosis of subclinical hypothyroidism, and low fT4 and/or fT3, high TSH values were used for the diagnosis of clinical hypothyroidism. Anemia was defined as Hb value < 13 g/dl in males and < 12 g/dl in females in the patient and control groups. In the determination of subgroups of patients with anemia, serum iron was defined as low in iron deficiency anemia, high serum total iron binding capacity and low ferritin value. In anemia of chronic disease, serum iron was low, serum total iron binding capacity was low, ferritin value was normal or high, and vitamin B 12 and folate values were defined as normal. It was defined as low serum vitamin B 12 level, high MCV value (> 100 fL) (macrocytosis) in anemia due to vitamin B 12 deficiency, and low serum folate level and high MCV value (> 100 fL) (macrocytosis) in folic acid deficiency.

Data were analyzed with the IBM SPSS Statistics 21.0 (SPSS, Inc, Chicago, IL, USA) package software. Continuous variables are given as mean ± standard deviation and categorical variables as numbers and percentages. T test was used to compare two groups, and One Way Anova method was used to compare more than two groups. The differences between the categorical variables were analyzed by Chi-square analysis. A $p < 0.05$ was considered statistically significant.

RESULTS

Clinical hypothyroidism was found in 30 (1.1%) of 2653 patients who applied to the outpatient clinic, and subclinical hypothyroidism was found in 96 (3.6%) patients. Demographic characteristics and mean laboratory values of the patient and control groups are given in Table 1.

When evaluated in terms of anemia frequency, in the subclinical hypothyroid patient group anemia was detected in 29 (30.2%) of 96 patients, in 12 (40%) of 30 patients in the clinical hypothyroid patient group, and in 25 (25%) of 100 patients in the control group. A statistically significant difference was found between the clinical hypothyroidism group and the control group in terms of the frequency of anemia ($p = 0.033$). There was no statistically significant difference in the frequency of anemia between the subclinical hypothyroidism group and the control group ($p = 0.058$). A statistically significant difference was however found between the patient group (subclinical+clinical hypothyroidism) and the control group in terms of the frequency of anemia ($p = 0.049$).

According to the gender subgroup, anemia was detected in 27 (32.9%) of 82 female patients and 2 (14.3%) of 14 male patients in the subclinical hypothyroidism group. In the clinical hypothyroidism group, anemia was present in 10 (40%) of 25 female patients and 2 (40%) of 5 male patients. In the control group, 19 (27.1%) of 70 female patients and 6 (20%) of 30 male patients had anemia. Anemia was detected in 37 (34.5%) of 107 female patients and 4 (21%) of 19 male patients with hypothyroidism. When all groups were taken into account, 56 (84.9%) of 66 anemic patients were female and 10 (15.1%) were male.

Causes of anemia in the patient and control groups

When the patients with anemia were examined in terms of anemia subtype, 6 out of 12 anemic patients in the clinical hypothyroidism group had anemia of chronic disease (50%), while iron deficiency anemia was found in 5% (41.7%) and B12 deficiency anemia was found in 1 (8.3%). 14 of 29 anemia patients in the subclinical hypothyroidism group were found to have anemia of chronic disease (48.3%), 12 of them had iron deficiency anemia (41.4%), 2 of them had B12 deficiency anemia (6.9%) and one had folate deficiency anemia (3.4%). Of 25 anemia patients in the control group, 13 (52%) had anemia of chronic disease, 11 (44%) had iron deficiency anemia, and 1 had B 12 deficiency anemia (4%) (Fig. 1).

When the three groups were compared with these data in terms of the causes of anemia, no statistical difference was found ($p = 0.178$ for chronic disease anemia, $p = 0.215$ for iron deficiency anemia, $p = 0.500$ for B12 deficiency and p value could not be cal-

Table 1. Demographic characteristics and laboratory values of the patient and control groups

	Clinical Hypothyroidism	Subclinical Hypothyroidism	Control Group	*P* value
Number	30	96	100	-
Gender (male/female)	5/25	14/82	30/70	0.025
Age	44.60 ± 14.48	34.97 ± 13.34	44.28 ± 17.60	< 0.001
TSH	36.16 ± 31.80	6.97 ± 2.41	1.43 ± 0.82	< 0.001
FT3	2.44 ± 0.47	3.16 ± 0.44	---	< 0.001
FT4	0.53 ± 0.16	1.01 ± 0.14	---	< 0.001
MCV	83.18 ± 6.08	79.67 ± 8.99	82.96±3.64	0.153
Anti TG positivity	76.6	75	---	0.412
Anti-TPO positivity	73.3	67.7	---	0.216
Hemoglobin	12.53 ± 1.13	12.59 ± 1.62	12.98 ± 1.33	0.114
Hematocrit	36.94 ± 3.35	37.49 ± 3.99	37.64 ± 3.66	0.672
Vitamin B12	337.07	271.93	315.53	0.058
Folic acid	7.57 ± 3.15	7.70 ± 3.31	7.63 ± 3.00	0.976
Iron	76.93 ± 32.68	79.78 ± 36.98	82.62 ± 38.04	0.726
Ferritin	53.50 ± 92.32	48.46 ± 52.41	64.03 ± 62.59	0.224

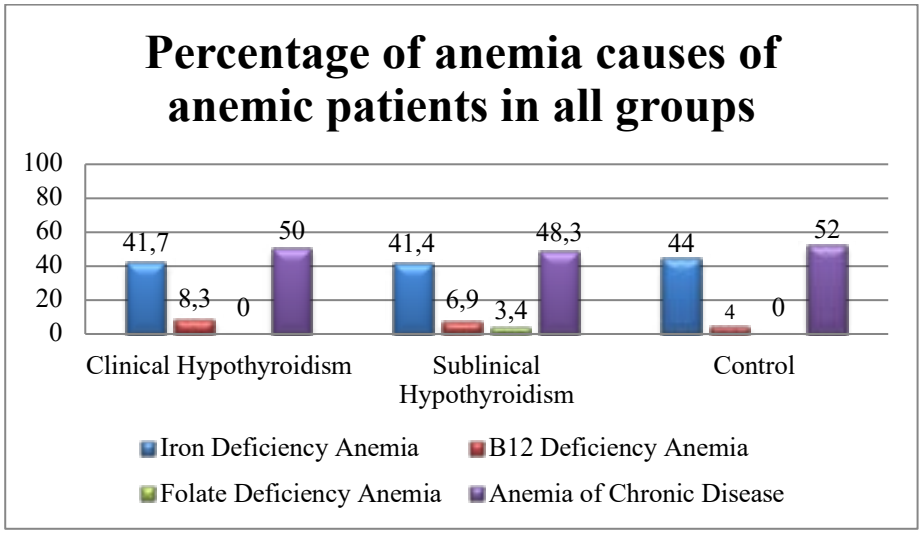

Fig. 1. Percentage of causes of anemia in anemic patients in all groups (%)

culated for folate deficiency).

In the distribution of the causes of anemia, of the 41 anemic patients in the patient group (subclinical + clinical hypothyroidism), chronic disease anemia was seen in 20 patients (48.8%), iron deficiency anemia in 17 patients (41.5%), B12 deficiency anemia in 3 patients (7.3%), and folate deficiency anemia in 1 patient. (2.4%). When the patient (subclinical+clinical hypothyroidism) and control groups were compared in terms of anemia causes, no statistical difference was found between them (p = 0.223 for chronic disease anemia, p = 0.257 for iron deficiency anemia, p= 0.317 for B12 deficiency anemia and p value could not be calculated for folate deficiency).

The most common type of anemia in clinical hypothyroidism, subclinical hypothyroidism and control groups was anemia of chronic disease (50%, 48.3%, 52%, respectively) and the second most common type of anemia was iron deficiency anemia (41.7%, 41.4%, 44%, respectively). The mean laboratory values of anemic patients in all three groups are given in Table 2.

Anemia type distribution according to the erythrocyte size of 66 anemic patients in the clinical hypothyroidism, subclinical hypothyroidism, and control groups was analyzed. It was found that among 12 anemic patients in the clinical hypothyroidism group, 2 patients (16.7%) had microcytic anemia and 10 patients (83.3%) had normocytic anemia, among 29 anemic patients in the subclinical hypothyroidism group, 10 patients (34.5%) had microcytic anemia and 19 patients (65.5%) had normocytic anemia, and among 25 anemic patients in the control group, 5 patients (20%) had microcytic anemia and 20 patients (80%) had normocytic anemia. In the patient group (subclinical + clinical hypothyroidism) of 41 anemic patients, 12 (29.3%) with microcytic anemia and 29 (70.7%) with normocytic anemia were detected. The most common type of anemia according to erythrocyte size in the patient and control groups was normocytic anemia. There was no statistically significant difference between the patient group (subclinical+clinical

Table 2. Laboratory values of anemia patients in all groups

	Clinical hypothyroidism (n:12)	Subclinical hypothyroidism (n:29)	Control Group (n:25)	*P* value
MCV	83.18 ± 6.08	79.67 ± 8.99	82.96 ± 3.64	0.509
Hematocrit	34.27 ± 1.30	33.37 ± 3.21	34.07 ± 2.08	0.736
Hb	11.61 ± 0.58	10.75 ± 1.26	11.65 ± 0.64	0.017
Ferritin	38.04 ± 51.30	23.23 ± 28.66	42.24 ± 61.64	0.436
Vitamin B12	272.50 ± 141.05	260.93 ± 93.90	328.36 ± 158.54	0.272
Folate	7.80 ± 2.45	7.80 ± 2.41	7.74 ± 3.78	0.839
Iron	54.42 ± 29.47	63.31 ± 42.26	69.80 ± 34.36	0.430

hypothyroidism) and the control group in terms of the frequency of microcytic anemia and the frequency of normocytic anemia ($p = 0.257$ and $p = 0.068$, respectively).

Anti TG and Anti TPO rates in the patient group

The mean Anti TG values of the patients in the subclinical hypothyroidism group were 109.26 IU/ml and the Anti TPO values were 325.74 IU/ml. The mean Anti TG values of the patients in the clinical hypothyroid group were 196.31 IU/ml and the Anti TPO values were 471.96 IU/ml. Of the 96 patients in the subclinical hypothyroidism group, the number with Anti TG positivity was 72 (75%) and of patients with Anti TPO positivity it was 65 (67.7%). Of the 30 patients in the clinical hypothyroidism group, the number with Anti-TG positivity was 23 (76.6%), and of patients with Anti-TPO positivity it was 22 (73.3%). Additionally, out of a total of 126 patients in the patient group (subclinical + clinical), the number of patients with Anti TG positivity was 95 (75.3%) and the number of patients with Anti TPO positivity was 87 (69%).

DISCUSSION

The frequency of clinical hypothyroidism in many large-scale studies has been reported as 1-2% in women and 0.1% in men, and it is less common than subclinical hypothyroidism. [6-8] In our study, the prevalence of subclinical hypothyroidism was 3.6% and the prevalence of clinical hypothyroidism was 1%. These results are similar to previous studies.

According to the data of the World Health Organization (WHO), the prevalence of anemia is reported as 24.8% globally, with a higher rate occurring in underdeveloped countries. [9] While in European countries the prevalence of anemia is around 14%, it reaches up to 25% in developing countries such as Turkey. 10 Similar to the literature, in our study the frequency of anemia in the control group was found to be 25%. In a study by Christ-Crain M *et al.*, it was reported that the frequency of anemia in hypothyroid patients varied between 20-60%. [3] In our study, we found the incidence of anemia in the patient group (subclinical hypothyroidism+clinical hypothyroidism) as 32.5%, compatible with the literature.

In a study by Mehmet E *et al*., it was observed that 86.5% of hypothyroid patients were female and 13.5% were male. 10 In our study, 84.9% of patients with hypothyroidism were female and 15.1% were male, and anemia was found in 34.5% of women with hypothyroidism and 21% of men with hypothyroidism. Considering all these results, it can be said that hypothyroidism is more common in women, and a risk factor for anemia is the presence of hypothyroidism.

Hashimoto's thyroiditis (Chronic Autoimmune Thyroiditis) is the most common cause of hypothyroidism in iodine-sufficient regions globally, and its frequency increases with age. [11] Anti TG is positive in 80-90% and Anti-TPO is positive in 90-100% in patients with chronic autoimmune thyroiditis. [12] In our study, Anti TG 75.3% and Anti TPO 69% were found positive in hypothyroid patients, which was consistent with the literature.

In a study by Chanchal Das *et al*. in India, they found that 31 (51.6%) of 60 hypothyroid patients had normochromic normocytic anemia. [13] In another study by Mehmet E *et al*., the rate of anemia of chronic disease was found to be 31% in patients with clinical hypothyroidism, and 24% in patients with subclinical hypothyroidism. [10] In our study, the most common type of anemia in hypothyroid patients was anemia of chronic disease (48.8%), and this rate was 48.3% in the subclinical hypothyroidism group and 50% in the clinical hypothyroidism group, which was consistent with the literature.

Iron deficiency anemia in hypothyroid patients occurs due to iron malabsorption or, in women, as a result of menorrhagia due to hormonal imbalance. In a study by Kosenli A *et al*., anemia was found in 85.7% of women with hypothyroidism and 14.3% of men with hypothyroidism, and it was demonstrated that a large percentage of anemia in women with hypothyroidism may be associated with menorrhagia. [14] In a study conducted by Mitra Kazemi J *et al*. investigating the effectiveness of hypothyroidism treatment on the frequency of anemia, it was found that 64 of 70 hypothyroid patients had improvement in hematological parameters after levothyroxine (st4) treatment. 15 In another randomized controlled double-blind study by Cinemre H *et al*., it was shown that female patients with subclinical hypothyroidism and iron deficiency anemia initially did not respond to oral iron replacement therapy, and then the addition of levothyroxine (st4) to the treatment increased serum iron levels, thus increasing the effectiveness of oral iron therapy and iron absorption in patients. [2] These results demonstrate that the presence of hypothyroidism should be evaluated in patients with anemia. In our study, the

rate of iron deficiency anemia in the subclinical hypothyroid patient group was 41.4%, the clinical hypothyroid patient group it was 41.7%, and the female sex ratio in the hypothyroid (subclinical + clinical) patient group was 84.9%. The rate of iron deficiency anemia in both patient groups was lower than in the control group. In our study, iron deficiency anemia was the second most common type of anemia after anemia of chronic disease.

The prevalence of vitamin B 12 deficiency increases with age. The most common cause of vitamin B 12 deficiency is malabsorption and insufficient intake. In a study by Mc Lean E *et al*., it was demonstrated that the prevalence of vitamin B 12 deficiency in Europe is between 1.6% and 10%. 16 In the Framingham study, the prevalence of vitamin B 12 deficiency in the elderly population was reported as 12%. 17 In our study, we found the prevalence of vitamin B 12 deficiency to be 4% in patients in the control group with a mean age of 44 years. In a study investigating the causes of anemia in patients with primary hypothyroidism, it was found that 6 (10%) of 60 patients with primary hypothyroidism had macrocytic anemia due to vitamin B 12 deficiency, and 3 of them had positive antiparietal cell antibodies that was related to pernicious anemia. [13] In another study, vitamin B12 deficiency was examined in patients with primary hypothyroidism, and it was observed that vitamin B12 levels were low in 46 (39.6%) of 116 hypothyroid patients (95 females, 21 males), while it was reported that the prevalence of anemia was not high in patients with vitamin B12 deficiency. [18] In our study, we found B12 vitamin deficiency in the hypothyroid patient group as 7.3%, and there was no significant difference compared to the control group.

Folic acid deficiency is very rare and occurs most often because of insufficient intake. Intestinal malabsorption can additionally also cause folate deficiency. 19 In thyroid hormone deficiency, along with folate malabsorption, folic acid deficiency occurs due to a decrease in the level of dihydrofolate reductase, which converts dihydrofolate to tetrahydrofolate (biologically active folic acid) at the liver level. [10] In our study, we found folic acid deficiency to be 2.4% in the patient group (subclinical+clinical hypothyroidism).

Anemia seen in patients with hypothyroidism can occur by various mechanisms. In this study, we found that there is an increase in the frequency of anemia in hypothyroidism and that the most common type of anemia is anemia of chronic disease (normocytic), which is consistent with the literature.

CONCLUSION

We found that there was an increase in the frequency of anemia in patients with hypothyroidism and that the most common anemia subtype in hypothyroidism was anemia of chronic disease (normocytic).

Authors' Contribution

Study Conception: KI, TA, EA,; Study Design: KI, TA, EA,; Supervision: KI, TA, EA,; Materials: KI, TA, EA,; Data Collection and/or Processing: KI, TA, EA,; Statistical Analysis and/or Data Interpretation: KI, TA, EA,; Literature Review: KI, TA, EA,; Manuscript Preparation: KI, TA, EA and Critical Review: KI, TA, EA.

Conflict of interest

No potential conflicts of interest relevant to this article were reported.

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Retrospective Evaluation of In-Hospital and Thirty-Month Mortality Parameters in Cases of Acute Coronary Syndrome

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ABSTRACT

Objectives: The aim of this study is to retrospectively assess, from the hospital records of patients, the clinical data of patients and the treatment strategies practiced on patients who were diagnosed as Acute Coronary Syndrome (ACS) and hospitalized and treated in the Hospital of Faculty of Medicine to research the effect of these data on occurrence of cardiovascular events and 30 months mortality.

Methods: It is a retrospective screening study in which patients hospitalized with the diagnosis of ACS between June 2007 and December 2008 in the Hospital of Faculty of Medicine Cardiology Clinic are evaluated by using patient file information and electronic data recording system information, and by calling patients. In-hospital and long-term follow-up deaths were the endpoints of the study. Statistical analysis was performed using SPSS (Version 15.0).

Results: 985 patients were included in the study who were diagnosed as ACS, hospitalized and treated in the hospital. The categorization of the patients subjected to the analysis (n:901) according to their diagnosis is as follows: 339 (38%) cases diagnosed as UAP, 206 (23%) cases diagnosed as NSTEMI, and 356 (39%) cases diagnosed as STEMI. 78,4 % of cases were male while 21,6 % were female. It was found that cases with hypertension, hyperlipidemia, obesity risk factor, and with a history of cardiovascular disease fall into the NSTEMI and UAP groups with a larger proportion. Among the groups, the UAP diagnosed cases have the largest and the STEMI diagnosed cases have the smallest ratio of using medicine groups such as beta blocker, calcium-canal blocker, ACE inhibitor, ARB, diuretic, statin, fibrate and nitrate before being hospitalized. In-hospital mortality was frequently encountered with a percentage of 7.6 % in STEMI cases, 2.4 % in NSTEMI cases, and 0.6 % in UAP cases. 30-months of follow-up data were obtained in all diagnosis groups for long-term mortality assessment. 70 (7.8 %) deaths were observed within the follow-up. According to diagnosis groups, death was observed in 22 (6.5 %) of UAP cases, 22 (10.7 %) of NSTEMI cases, and 26 (7.3 %) of STEMI cases. Correlation between long-term survival (30 months) and in-hospital statin usage and statin usage in discharge was not significant (p value respectively 0.1 and 0.16). Correlation between an approximate 30-months-survival and in-hospital ACE inhibitor/ARB inhibitor usage and ACE inhibitor/ARB inhibitor usage during discharge was significant ($p = 0.007$ and $p = 0.004$). It is also found that there was a significant correlation between survival in the same period of time and in-hospital beta blocker usage ($p = 0.01$). There was not a significant correlation between beta blocker usage during discharge and long-term survival ($p = 0.779$).

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Conclusion: Results of the unicentral retrospective scanning study which involves 901 ACS diagnosed patients prove to be similar to the ones obtained from GRACE and Euro Heart Survey prospective studies which were carried out in multi-central environment and among outnumbered patients.
Key words: Acute Coronary Syndrome, Beta Blocker, Mortality, RAS Blocker, Statin

Coronary artery disease, which is the most serious and most common clinical consequence of the atherosclerotic process, is one of the leading causes of death in today's developed countries. The clinical picture that occurs with sudden myocardial ischemia is called acute coronary syndrome (ACS). ACS patients constitute a heterogeneous group clinically in terms of severity of ischemia, anatomical features of coronary arteries, and prognostic features.

The term ACS is a broad concept which includes myocardial infarction with ST-segment elevation (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina pectoris (UAP). Serious reductions in both morbidity and mortality rates in acute coronary syndromes have been reported thanks to advanced treatment applications, increase in medical treatment options and clinical experience gained in the light of large-scale studies. As a matter of fact, intervention and treatment methods that reduce acute, short and long-term mortality and morbidity in acute coronary syndromes are recommended in detail in current treatment guidelines prepared in the light of clinical studies. [1, 2] However, the data on the drugs and applications recommended in these guidelines are obtained from clinical studies in which treatment regimens are applied under optimal conditions. In actual clinical practice, however, there is not enough research on the treatment approach in acute coronary syndromes and their effects on cardiovascular (CV) events. In other words, it is not known to what extent the positive results of the treatments shown in the guidelines in acute coronary syndromes are reflected in actual clinical practice.

This study aims at retrospectively evaluating the treatment strategies applied (Beta blocker, ACEinh/ARB and statin usage in particular) and clinical data based on hospital records of patients hospitalized with ACS diagnosis in University Hospital between June 2007 and December 2008, and investigating the effect of these clinical data to the CV mortality development within an approximately 30-months period. It is planned to use a retrospective method in order to ensure that the study reflects actual clinical practice.

METHODS

Before starting the research, ethics committee approval (No. 10-10/3) was obtained from the EUMF Research Ethics Committee on October 15, 2010. It is a retrospective screening study in which patients hospitalized with the diagnosis of ACS between June 2007 and December 2008 in the Hospital of Faculty of Medicine Cardiology Clinic are evaluated by using patient file information and electronic data recording system information, and by calling patients, who do not have sufficient follow-up data, by phone. In the light of the data obtained from the patient files of the patients hospitalized with the diagnosis of ACS, it was aimed to determine the effects of symptoms, physical examination, laboratory and imaging findings on mortality both in the in-hospital and in the follow-up periods. Symptoms at admission, CAD risk factors and accompanying diseases, physical examination findings, drug use histories, admission ECG findings, laboratory examinations (kidney function tests, hemogram, cardiac enzymes, thyroid function tests if performed, CRP, and HbA1C values), the procedures and timings (echocardiography, coronary angiography and percutaneous coronary intervention, thrombolytic therapy, stress test, CABG, etc.) obtained from the file records of the cases in the hospital archive were recorded in the case report forms. Complications developed during the in-hospital period (heart failure, shock, arrhythmia, infection, death, bleeding, cerebrovascular accident), drug groups used by the patients before hospitalization, drug therapy started at hospitalization, and treatment given during discharge were recorded in the case report forms. In order to obtain long-term survival data after discharge, the date of the last registration to the hospital and the information about the last application were recorded in the hospital registry system. Cases for whom sufficient data could not be reached from this registry system or those who did not apply to hospital again were called by phone and their current status was questioned and the information obtained was added to the case report forms.

In-hospital and long-term follow-up deaths were the endpoints of the study. In-hospital deaths were divided into two groups as cardiovascular and non-cardiac causes. While cardiogenic shock, pulmonary edema, cardiac arrest, ventricular fibrillation, cerebrovascular accident and pulmonary embolism are the causes of in-hospital cardiovascular death, non-cardiac causes of death involve bleeding, infection and other causes. Long-term cardiovascular deaths include sudden cardiac death, early period pump failure after coronary artery bypass surgery (CABG), myocardial infarction (MI), congestive heart failure (CHF), mesenteric ischemia and cerebrovascular accident, non-cardiac causes of death, kidney failure, infections, chronic obstructive pulmonary disease disease (COPD), malignancies, and other causes.

Statistical analysis was performed using SPSS (Version 15.0). Data are shown as mean ± standard deviation for continuous variables and as percentages for discontinuous variables. Variance analysis was used to compare group means, and chi-square test was used to compare percentages. Spearman (rho) test was used in correlation analyzes to determine in-hospital CV event development, mortality and mortality determinants in follow-up. In-hospital mortality was evaluated by logistic regression analysis, and mortality at follow-up was evaluated by Cox-regression analysis. Kaplan-Meier curves were drawn to evaluate the survival effect of beta-blocker, statin, and ACE inhibitor/ARB use. The probability value of $p \leq 0.05$ was accepted as statistically significant.

RESULTS

985 cases from archive information were sampled sequentially. When their diagnoses were examined, it was detected that 369 (37%) cases were followed with UAP, 236 (24%) cases with NSTEMI and 380 (39%) cases with STEMI. Eighty-four cases (30 UAP, 30 NSTEMI, and 24 STEMI diagnosed) whose follow-up data could not be reached through the hospital

Table 1. Characteristics of the cases in terms of cardiovascular disease and risk factors

Feature	*STEMI (356) n, (%)*	*NSTEMI (206) n, (%)*	*UAP (339) n, (%)*
Diabetes Mellitus	96 (27)	73 (35.4)	90 (26.5)
Hypertension	152 (42.7)	132 (64.1)	229 (67.6)
Hyperlipidemia	151 (42.4)	109 (52.9)	199 (58.7)
Obesity	137 (38.5)	92 (44.7)	151 (44.5)
Smoking	259 (72.7)	126, (61.2)	190 (56)
Family history	127 (35.7)	77 (37.4)	144 (42.5)
Alcohol	49 (13.8)	29 (14.1)	46 (13.6)
CVD history (total)	89 (25)	98 (47.6)	177 (52.2)
MI history	44 (12.4)	47 (22.8)	80 (23.6)
CHF history	3 (0.8)	2 (1)	5 (1.5)
Coronary angiography history	51 (14.3)	74 (35.9)	151 (44.5)
CABG history	16 (4.5)	40 (19.4)	61 (18)
PCI history	32 (9)	25 (12.1)	73 (21.5)
Valvuler intervention history	0	1 (0.5)	2 (0.6)
Peripheral artery disease history	6, (1.7)	4 (1.9)	8 (2.4)
History of atrial fibrillation	1, (0.3)	5 (2.4)	1 (0.3)
History of cerebrovascular accident	14, (3.9)	13 (6.3)	17 (5)
CIED history	1, (0.3)	1 (0.5)	3 (0.9)

STEMI: ST-elevation myocardial infarction; NSTEMI: non-ST-elevation myocardial infarction; UAP: unstable angina pectoris; CVD: cardiovascular disease, MI: myocardial infarction, CHF: congestive heart failure, CABG: coronary artery bypass graft, PCI: percutaneous coronary intervention, CIED: Cardiac Implantable Electronical Device

electronic data recording system and phone calls were not included in the analysis due to insufficient data. Statistical analysis was performed on a total of 901 (91.5%) remaining patients whose mortality data were available. The mean age of the study population was 60 ± 12.15 years, with 195 (21.6%) females and 706 (78.4%) males. The distribution of the patients included in the statistical evaluation according to their diagnoses is composed of 339 UAP (38%), 206 NSTEMI (23%) and 356 STEMI (39%) of cases.

The characteristics of the cases in terms of CV disease and risk factors are summarized in Table 1. The cases with diabetes in the NSTEMI group and the cases with hypertension, hyperlipidemia, obesity risk factors and a previous history of CV disease in the NSTEMI and UAP groups were found to be higher in percentage. It was observed that the history of smoking was higher in the STEMI group.

The drug groups used by the cases before hospitalization are summarized in Table 2. While the history of aspirin use was seen at higher rates in NSTEMI and UAP cases, the history of clopidogrel use was found at a higher rate in the UAP group. Among the diagnostic groups, the rate of use of beta-blockers, calcium channel blockers, ACE inhibitors, ARBs, diuretics, statins, fibrates and nitrates before hospitalization was the highest in patients with UAP, while the lowest rates were recorded in patients with STEMI (Table 2).

The drug groups administered in the hospital are summarized in Table 3 according to the diagnosis groups. Beta blocker, ACE inhibitor/ARB and statin treatments were found to be used at high rates in all groups. It was observed that these drug groups were used most frequently in NSTEMI cases among the diagnostic groups, followed by STEMI and UAP cases in order of frequency.

In-hospital complications and mortality

The complications developed within the hospital are summarized in Table 3. These complications include heart failure, sudden onset pulmonary edema, cardiogenic shock, cardiac arrest, severe ventricular arrhythmias (VT/VF), mechanical complications, development of AV block, bleeding, infection, deep vein thrombosis, pulmonary thromboembolism,

Table 2. Drug groups used before hospitalization according to diagnosis groups

Features	*STEMI (356)* *n, (%)*	*NSTEMI (206)* *n, (%)*	*UAP (339)* *n, (%)*
Acetylsalicylic acid	79 (22.2	83 (40.3)	181(53.4)
Clopidogrel	17 (4.8)	9 (4.4)	38 (11.2)
Other antiaggregants	1 (0.3)	5 (2.4)	5 (1.5)
Warfarin	0	5 (2.4)	6 (1.8)
Beta blockers	57 (16)	45 (21.8)	155 (45.7)
CCB	29 (8.1)	28 (13.6)	54 (15.9)
ACE inh.	42 (11.8)	53 (25.7)	100 (29.5)
ARB	21 (5.9)	28 (13.6)	79 (23.3)
Diuretics	33 (9.3)	46 (22.3)	117 (34.5)
Digitalis	2 (0.6)	4 (1.9)	8 (2.4)
Statins	37 (10.4)	34 (16.5)	93 (27.4)
Fibrates	2 (0.6)	1 (0.5)	11 (3.2)
Niacin	0	0	0
Ezetimibe	0	1 (0.5)	1 (0.3)
Antiarrhythmics	4 (1.1)	1 (0.5	3 (0.9)
Nitrates	34 (9.6)	37 (18)	113 (33.3)
Oral antidiabetics	42 (11.8)	39 (18.9)	65 (19.2)
Insulin	16 (4.5)	19 (9.2)	16 (4.7)

STEMI: ST-elevation myocardial infarction; NSTEMI: non-ST-elevation myocardial infarction; UAP: unstable angina pectoris; ACE: Angiotensin converting enzyme, ARB: Angiotensin I receptor blocker, PPI: proton pump inhibitor, CCB: calcium channel blockerbloker

Table 3. Beta blockers, RAS blockers and statins given to the diagnosis groups at the hospital

DRUG GROUP	*UAP* *n, (%)*	*NSTEMI* *n, (%)*	*STEMI* *n, (%)*
Beta blockers	291 (85.8)	184 (89.3)	291 (81.7)
ACE inh. / ARB	284 (83.8)	188 (91.3)	310 (87.1)
Statin	282 (83.2)	195 (94.7)	329 (92.4)

STEMI: ST-elevation myocardial infarction; NSTEMI: non-ST-elevation myocardial infarction; UAP: unstable angina pectoris, ACE inhibitor: Angiotensin converting enzyme inhibitor, ARB: Angiotensin I receptor blocker

cerebrovascular accident, and infection. All types of complications were seen at a higher rate in STEMI cases.

Cardiogenic shock (20 patients, 2.2%) was the leading cause of in-hospital mortality. The other 14 causes of death are as follows: 7 (0.8%) VF, 2 (0.2%) cardiac arrest, 2 (0.2%) pulmonary edema, 1 (0.1%) cerebrovascular accident, 1 (0.1%) gastrointestinal system bleeding, and 1 (0.1%) pulmonary embolism.

In-hospital mortality was detected with a frequency of 7.6% in STEMI, 2.4% in NSTEMI and 0.6% in UAP cases. In-hospital CV death was observed with the rates of 7% in STEMI, 2.4% in NSTEMI, and 0.6% in UAP cases (Table 4).

Beta blockers, RAS blockers and statins given at discharge

The distribution of drug groups given to the discharged cases is summarized in Table 5. Beta blocker use was found to be above 80% in all three groups. While ACE inhibitor use was higher in NSTEMI and STEMI cases, it was seen that the ARB group was more frequently applied in UAP cases. It was observed that the statin group was used most

Table 4. In-hospital complications observed in the diagnostic groups

In-hospital complication	*UAP* *n (%)*	*NSTEMI* *n (%)*	*STEMI* *n (%)*
Congestive Heart Failure	0	5 (2.4)	16 (4.5)
Acute Pulmonary Edema	0	4 (1.9)	13 (3.7)
Cardiogenic Shock	0	3 (1.5)	23 (6.5)
Cardiac Arrest	1 (0.3)	6 (2.9)	27 (7.6)
Ventricular fibrillation	1 (0.3)	2 (1.0)	27 (7.6)
Atrial fibrillation	1 (0.,3)	5 (2.4)	10 (2.8)
Sustained Ventricular Tachycardia	1 (0.3)	2 (1.0)	6 (1.7)
Mechanical complication	0	0	4 (1.1)
AV Block	2 (0.6)	2 (1.0)	12 (3.4)
Acute renal failure	3 (0.9)	11 (5.3)	17 (4.8)
Deep Vein Thrombosis	0	0	0
Pulmonary Thromboembolism	1 (0.3)	0	0
Cerebrovascular Accident	2 (0.6)	3 (1.5)	5 (1.4)
Bleeding	12 (3.5)	10 (4.9)	25 (7.0)
Bleeding with ERT tx	7 (2.1)	2 (1.0)	13 (3.7)
Infection	7 (2.1)	15 (7.3)	26 (7.3)
Mortality	2 (0.6)	5 (2.4)	27 (7.6)
Cardiovascular mortality (*)	2 (0.6)	5 (2.4)	25 (7.0)

STEMI: ST-elevation myocardial infarction; NSTEMI: non-ST-elevation myocardial infarction; UAP: unstable angina pectoris, AV: atrioventricular, ERT Tx: erythrocyte transfusion

(*) Pulmonary edema or cardiac arrest or VF or pulmonary embolism or cardiogenic shock

Table 5. Beta blocker, RAS blocker and statin rates given at discharge

Drug groups	*UAP n, (%)*	*NSTEMI n, (%)*	*STEMI n, (%)*
Beta blockers	273 (80.5)	183 (88.8)	305 (85.7)
ACE inh.	199 (58.7)	161 (78.2)	282 (79.2)
ARB	76 (22.4)	13 (6.3)	12 (3.4)
Statins	290 (85.5)	189 (91.7)	315 (88.5)

STEMI: ST-elevation myocardial infarction; NSTEMI: non-ST-elevation myocardial infarction; UAP: unstable angina pectoris, ACE inhibitor: Angiotensin converting enzyme inhibitor, ARB: Angiotensin I receptor blocker.

Table 6. Long-term mortality rates by diagnosis groups

Long-term mortality type	*UAP*	*NSTEMI*	*STEMI*
All-cause mortality	22 (%6.5)	22 (%10.7)	26 (%7.3)
Cardiovascular death (*)	13 (%3.8)	19 (%9.2)	18 (%5.1)
Death from non-cardiac causes	9 (%2.7)	3 (%1.5)	8 (%2.2)

*(Sudden cardiac death, pump failure after CABG, MI, CHF, mesenteric ischemia, cerebrovascular accident)

frequently in NSTEMI cases (91.7%) which was followed by STEMI cases (88.5%). (Table 5).

Long term mortality rates after discharge

In order to determine the long-term mortality rates of the patients after discharge, long term mortality rates were calculated by using the hospital electronic data recording system or by calling the patients who did not have a follow-up record in the data recording system. The mean follow-up period of the cases was calculated as 30.02 ± 7.41 months in the UAP group, 30 ± 9.21 months in the NSTEMI group, and 29.86 ± 8.62 months in the STEMI group.

Overall mortality

In the follow-up, death was observed in 70 (7.8%) cases in general. When distributed according to diagnostic groups, there were 22 (6.5%) deaths in UAP cases, 22 (10.7%) in NSTEMI cases, and 26 (7.3%) deaths in STEMI cases.

Mortality rates from cardiovascular and non-cardiac causes

It was determined that 50 (5.5%) cases died due to CV, and 20 (2.2%) cases died due to non-cardiac

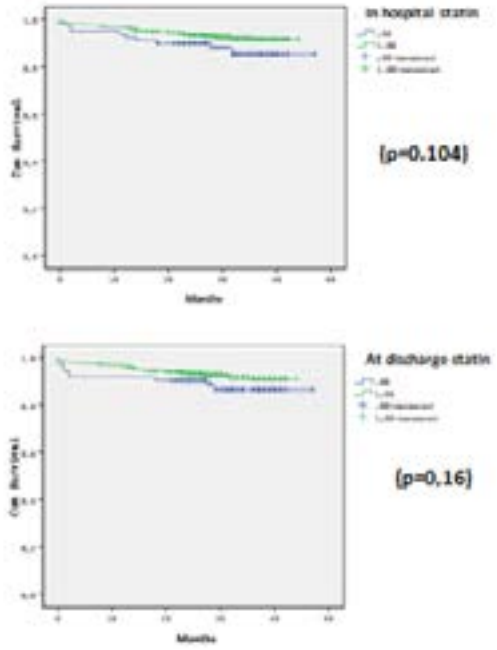

Fig. 1. Relationship between long-term mortality and the use of statins in-hospital and discharge

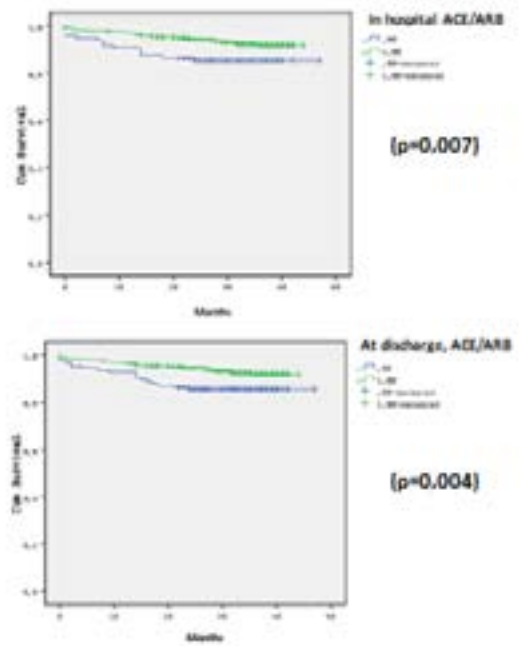

Fig. 2. Relationship between long-term mortality and the use of ACE inhibitors/ARBs

causes. When 50 cases who were found to have died due to CV events are distributed according to their diagnoses, 13 (3.8%) out of 339 cases (mean follow-up of 30.02 ± 7.41 months) with UAP, 19 (9.2%) out of 206 cases (mean follow-up of 30 ± 9.21 months) diagnosed with NSTEMI and 18 (5.1%) out of 356 cases (mean 29.86 ± 8.62 months follow-up) diagnosed with STEMI died. During follow-up, 26% (13) of CV deaths occurred in the UAP group, 38% (19) in the NSTEMI group, and 36% (18) in the STEMI group.

In the follow-up of the cases, death from non-cardiac causes was recorded in 9 (2.7%) cases in the UAP group, in 3 (1.5%) cases in the NSTEMI group, and in 8 (2.2%) cases in the STEMI group (Table 6).

Relationship between long-term mortality and the use of statins, ACE inhibitors/ARBs, and beta-blockers in-hospital and discharge

When evaluated with the Kaplan-Meier curve:

During hospitalization, no reducing effect of statin use on long-term mortality was found (p = 0.14) (Fig. 1). It was detected that long-term mortality was significantly reduced with the use of ACE inhibitor / ARB (p = 0.007) (Fig. 2). It was found that the long-term mortality-reducing effect of beta-blocker use was significant (p = 0.014) (Fig. 3).

At discharge, the statin administration did not significantly affect long-term mortality (p = 0.16) (Fig. 1). However, the administration of ACE/ARB was significantly effective in long-term mortality (p = 0.004) (Fig. 2). It was detected that beta-blocker administration did not have a significant effect in long-te

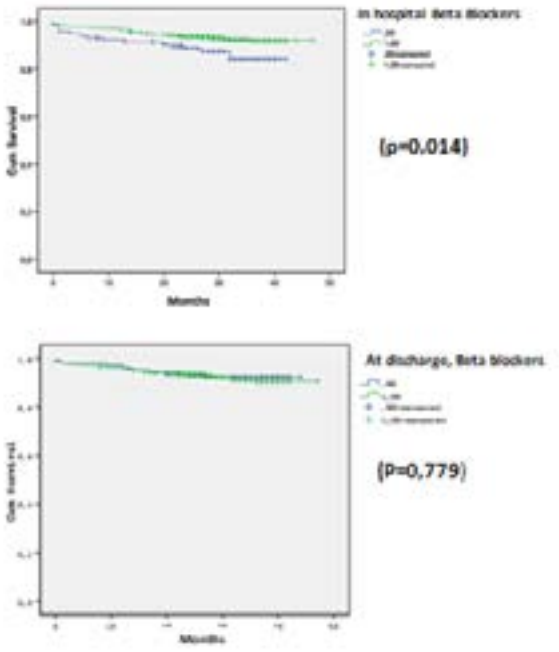

Fig. 3. Relationship between long-term mortality and the use of beta-blockers in-hospital and discharge

DISCUSSION

In this study, 339 (38%) cases diagnosed with UAP, 206 (23%) cases diagnosed with NSTEMI, and 356 (39%) cases diagnosed with STEMI were included in the analysis. In GRACE registry, the cases consisted of 29% with UAP, 30% with NSTEMI and 34% with STEMI. [3] The reasons why the UAP group was found to be proportionally higher in our case is that patients who did not undergo coronary imaging and misdiagnosed as UAP, not actually having ACS, could have been evaluated in the study. Another point is that there were 85 cases whose data could not be reached and therefore were excluded from the analysis, which may have contributed to the higher proportion of those diagnosed with UAP.

In terms of gender distribution, 706 out of 901 patients were male (78.4%), and 195 (21.6%) patients were female. This rate was similar to the rates found in the GRACE, Euro Heart Survey ACS and ENACT studies. [3-5] The gender distribution of the cases in our study reminds us the fact that male gender is an important risk factor for coronary artery disease.

The mean age of the patients was calculated as 57 in the STEMI group and 62 in the NSTEMI and UAP groups. In a study by Tokgözoğlu *et al*., when compared to EUROASPIRE III, the most important difference was that Turkish patients were younger than Europeans, and had higher rates of continued smoking, inactivity, and low HDL after MI. [6]

Among the other values determined in terms of CV disease and risk factors of the cases, the rates of hyperlipidemia, hypertension, diabetes, PCI and CABG history were found to be compatible with GRACE registry. [3]

When CV disease histories were evaluated before hospitalization, it was found that 75% of STEMI cases, 52% of NSTEMI cases and 48% of cases with UAP did not have a previous CV event. Another conclusion that can be drawn from this is that the frequency of ACS can be reduced by disseminating preventive treatments (hypertension, hyperlipidemia, Diabetes. etc) and strategies (weight management, avoiding smoking, avoiding sedantery life sytle, etc).

In the light of the evidences of studies such as HOPE, EUROPA, PEACE, ONTARGET, the effects of Renin Angiotensin System (RAS) blockers used for blood pressure control in primary prevention are clear. [7-9]

Another goal in primary prevention is the treatment of hyperlipidemia. In our study, it was found that 42% of STEMI cases, 53% of NSTEMI cases, and 58% of UAP cases had hyperlipidemia risk factors. These rates are also consistent with the data of the GRACE and Euro Heart Survey ACS study. [3, 4] The average LDL values were found to be 116 mg/dl in the STEMI group, 108 mg/dl in the NSTEMI group, and 113 mg/dl in the UAP group. These values are above the target values recommended by the treatment guidelines. 10 Some researchers, like Rosensen, sugges that there is a change in serum levels of plasma proteins as an acute phase response after MI, a decrease in lipid and lipoprotein levels starts in 24-48 hours and reaches a maximum in 4-7 days, and they return to their true value within 2 months after infarction. 11 This may explain the fact that the mean LDL levels of the cases were not excessively high. In primary prevention studies such as HPS, ASCOTT-LLA, and WOSCOPS, it is known that statins reduce the risk of mortality and major CV events in individuals with high CV risk. [12-14]

In the subgroups, no difference was found between the total cholesterol, HDL and TG values measured at hospitalization with the "post-hoc" evaluation. Mean total cholesterol measured for all groups was 189 ± 48 mg/dl, HDL was 42 ± 11mg/dl, and TG was 178 ± 134 mg/dl.

In a meta-analysis using the data of beta-blocker studies after MI, it was found that the odds ratio decreased by 23% in the long term and by 4% in the short term. 15 In a study by Gottlieb *et al*., involving 70000 patients using metoprolol, atenolol and propranolol, they showed 40% improvement in 2-year survival. 16 Beta-blockers are used in the acute phase of ACS because of their antiarrhythmic and antianginal effects, as well as their infarct-limiting effects. In the COMMIT/CCS study, it is emphasized that i.v. beta-blockers should be administered carefully, especially in patients with a high Killip class. 17 In our study, the rates of in-hospital beta-blocker use in STEMI, NSTEMI and UAP cases were 82%, 89% and 86% respectively. The rates of beta-blocker use during discharge in STEMI, NSTEMI and UAP cases was found 86%, 89% and 81% respectively. While a significant relationship was found between long-term (approximately 30 months) survival and in-hospital use of beta-blockers ($p = 0.01$), no significant relationship was found between use of beta-blockers at discharge and long-term survival ($p = 0.779$). This result suggests that beta-blockers are much more effective in the acute phase of ACS. Failure to use adequate doses and titration at the time of discharge may explain the lack of effect on long-term survival. Moreover, failure to use medications properly after discharge may also be related to the lack of expected long-term benefits. However, there are also publications in the literature showing that there may not be a long-term reduction in mortality with the use of high-dose titrated beta-blockers after ACS. 18

Given the lack of strong randomized controlled trial on the duration of beta-blocker usage in post-MI patients, a more personalized approach should be adopted (based on the LVEF, arrhythmias, etc). If the LVEF is low (< 40%), beta-blockers should be used for longer periods of time. [1, 2] For most of the patients with preserved ejection fraction, the evidence suggests short-term use of beta-blockers to reduce the risk of reinfarction and angina. Nasasra *et al*. evaluated 7392 ACS patients (without heart failure or left ventricular systolic dysfunction) between 2000 and 2016 and found that beta-blockers were prescribed to 6007 cases. The 30-day major adverse cardiac events (MACE) rates were similar in patients using and not receiving beta-blockers at discharge (9.0% and 9.5%, respectively). One-year survival was not significantly different between beta-blockers users and non-users (HR 0.8, 95% CI 0.58 to 1.11, $p = 0.18$). 19 In the GULF-COAST trial (a prospective multicenter cohort of ACS) in-hospital, 6-month and 12-month mortality were studied, in relation to beta blocker use: prior to admission, 24-hour post-admission and on discharge. Patients with LVEF > 40% were included in the study. Prior beta blocker use or its administration in 24 hours decreased in-hospital mortality (OR = 0.25, 95% CI [0.09-0.67]; OR = 0.16, 95% CI [0.08-0.35]; respectively). Beta blocker on discharge lowered 1-month mortality (OR = 0.28, 95% CI [0.11-0.72]), but had a neutral effect on mortality and reinfarction at 6 and 12 months. 20 Further studies are needed to understand the optimal duration of beta-blocker therapy post-MI. The REDUCE SWEDHEART study, which is planned to be completed in 2025, will help answer the questions that come to mind regarding the use of beta blockers in this patient group. [21]

The positive effects of ACE inhibitors/ARBs in ACS cases have been shown in many studies. These positive effects include the Inhibition of ventricular remodeling, improvement of endothelial functions, slowing of atherogenesis process and anti-inflammatory response. In the light of the studies of AIRE (with ramipril), GISSI-3 (with lisinopril), CONSENSUS-II (with enalapril), SAVE (with

captopril), ISIS-4 (with captopril), SMILE (with zofenopril), and TRACE (with trandolapril), it is recommended to start ACE inhibitor therapy in the early period (within 24 hours). 22-28 Angiotensin II receptor-1 blockers (ARB) are recommended as an alternative treatment for patients who cannot tolerate ACE inhibitor therapy. In the VALIANT study (with valsartan), in the CHARM-alternative subgroup (with candesartan), positive effects were demonstrated with the use of ARBs in these patients. [29-31]

In our study, the rates of in-hospital use of ACE inhibitor/ARB group drugs in STEMI, NSTEMI and UAP cases were determined as 87%, 91% and 84% respectively. The rates of administration of ACE inh/ARB to the cases during discharge in STEMI, NSTEMI and UAP cases were determined as 83%, 85% and 81% respectively. The relationship between survival of approximately 30 months and ACE inhibitor/ARB use in hospital and at discharge was significant (p = 0.007 and p = 0.004). This can be explained by the early onset of the hemodynamic regulating effects of RAS blockers (such as reduced afterload, reducing the risk of lung congestion) and the addition of anti-inflammatory, antiatherogenic and remodeling effects in the long term.

Sud *et al*. followed up a total of 165058 patients with a diagnosis of coronary artery disease (mean age 75 years, 65.5% male, 64.7% prescribed RAS blockers) for 4 years. They found that CV death and the frequency of MI or USAP were significantly lower in those receiving RAS blockers. In subgroup analyzes, it was determined that the decrease in MACE was more pronounced in those with a previous history of MI. [32]

As for statins, whose positive effects have been shown in large studies in primary and secondary prevention of coronary artery disease, it was detected that they were used in STEMI, NSTEMI and UAP at rates of 92%, 95%, and 83% respectively, during the in-hospital period, and were prescribed at rates of 89%, 92%, and 86%, respectively, in STEMI, NSTEMI, and UAP patients at discharge. Large statin studies in ACS cases can be listed as PROVE-IT, MIRACLE and A to Z. [33-35] The positive effects of statins in acute coronary syndromes may be related to their LDL-lowering and/or pleiotropic effects. [36] Among these effects are regulation of endothelial functions, anti-inflammatory effects, reduction of matrix metalloproteinase levels and tissue factor expression. In our study, the relationship between long-term survival and statin use in the hospital and at discharge was not found to be significant (p values 0.1 and 0.16, respectively). This may be related to the fact that high-dose statin therapy is not used, especially in the acute period. However, the efficacy and safety of high-dose statin use has been demonstrated in the PROVE-IT, MIRACLE, and A to Z studies. In a meta-analysis involving 26497 patients (including 16 randomized controlled trials), which assess high-intensity and standard statin regimens for efficacy and safety in patients with ACS, high-intensity statin therapy resulted in more clinical benefits regarding MACE compared with standard statin treatment in both Asian (RR = 0.77; 95%CI, 0.61-0.98; P = 0.03) and non-Asian (RR = 0.79; 95%CI, 0.71-0.89; P < 0.0001) patients. 37 The fact that a sufficient number of cases failed to reach the target LDL levels in the long term may be due to treatment non-compliance or treatment inadequacy after discharge, which can be shown as a reason for not detecting a statistical relationship with mortality.

In-hospital mortality rates were reported as 8% in STEMI cases, 5% in NSTEMI cases, and 3% in UAP cases in GRACE registries. [3] In-hospital mortality rates in our study were observed with a frequency of 7.6% in STEMI cases, 2.4% in NSTEMI cases, and 0.6% in UAP cases. In-hospital CV-related death was found to be 7% in STEMI, 2.4% in NSTEMI, and 0.6% in UAP. Among the causes of CV death were pulmonary edema, cardiac arrest, VF, cardiogenic shock and pulmonary embolism. Cardiogenic shock was the leading cause of in-hospital death in STEMI and NSTEMI cases, and according to our records, it accounts for 59% of in-hospital deaths.

In our study, an average of 30-month follow-up data was obtained in all diagnostic groups for long-term mortality assessment. During the follow-up, 70 (7.8%) cases died. When distributed according to diagnostic groups, 22 (6.5%) deaths occurred in UAP cases, 22 (10.7%) deaths in NSTEMI cases, and 26 (7.3%) deaths in STEMI cases. When 50 patients who died due to CV events are distributed according to their diagnoses, 13 (3.8%) of 339 patients were diagnosed with UAP (mean follow-up of 30.02 ± 7.41 months), 19 (9,2%) of 206 patients with NSTEMI (mean follow-up of 30 ± 9.21 months), and 18 (5.1%) of 356 patients with STEMI (mean follow-up of 29.86 ± 8.62 months). During follow-up, 26% (13) of CV-related deaths were seen in the UAP group, 38% (19) in the NSTEMI group, and 36% (18) in the STEMI group. Polonski *et al*. evaluated 13441 cases with MI (8250 STEMI, 5191 NSTEMI cases). In the 2-year follow-up of the cases, the long-term prognosis was

worse in the NSTEMI group. The frequency of death, re-infarction, stroke and CABG was found to be higher in the NSTEMI group ($p < 0.0001$). 38 In their observational study data, Terkelsen *et al*. reported that mortality rates were higher in NSTE-ACS cases than in STEMI cases, and there was a two-fold difference between the groups at the end of 4 years. [39] This difference in the medium and long term may be due to the different patient profiles, as seen in our study, because patients diagnosed with NSTE-ACS are older, and comorbidities such as diabetes and kidney failure are more common in these patients. This difference may be related to the more diffuse atherosclerotic process and the more intense inflammation in these cases. [40, 41]

CONCLUSION

In conclusion, our study, as a retrospective study, clearly demonstrates the clinical approach applied to the cases treated with the diagnosis of ACS in a university hospital clinic. Although it is a point to be criticized that the study is not prospective, it should be noted that in prospective studies it is highly probable that a more ideal treatment or application would be given to the patients. Therefore, the physician will be influenced by the study (bias). However, in this retrospective study, both the pre-hospital and in-hospital period and the following 2-year retrospective follow-up period were presented in a more realistic way without any influence. Obtained mortality, complication and treatment rates proved the truth, and these rates are objective data reflecting daily clinical practice as can be expected.

The most important limitation of our study was that the retrospective data obtained in the study was reliable to the extent which hospital electronic record system, patient file data and telephone feedback from patients allowed. Another limitation is that the study data were obtained from patients who were followed up and treated in the clinic about 15 years ago rather than current ACS patients, and that current drugs (for example, new antiaggregants) and clinical approaches (more widespread use of primary percutaneous coronary intervention) could not be applied to patient groups. Further multi-centered, retrospective and prospective clinical studies, in which current treatment recommendations are applied and more patient populations are included, will contribute to diminish the knowledge gap on this subject.

Authors' Contribution

Study Conception: BA, LMK,; Study Design: BA, LMK,; Supervision: LMK,; Materials: YBA, LMK,; Data Collection and/or Processing: BA,; Statistical Analysis and/or Data Interpretation: YBA, LMK,; Literature Review: BA, ISA,; Manuscript Preparation: BA, ISA and Critical Review: BA, ISA.

Conflict of interest

None declared.

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Comparison of cardiac risk factors in patients with primary nephrotic syndrome and secondary amyloidosis

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ABSTRACT

Objectives: To investigate the risk factors of proteinuria on the development of atherosclerosis in primary nephrotic syndrome and secondary amyloid cases and to determine the differences in these disease groups that are well matched in terms of age, gender, arterial blood pressure levels, glomerular filtration rate and body mass index.

Methods: The patient groups were selected in such a way that the protein levels in the 24-hour urine were exactly the same. 29 patients with nephrotic syndrome, 30 patients with secondary amyloidosis and 30 control groups were included in the study. C-reactive protein, fibrinogen, total cholesterol, triglyceride, low-density lipoprotein, high-density lipoprotein, lipoprotein a, apolipoprotein Al, B, E, glomerular filtration rate and 24-hour protein in the urine were compared between the patient and control groups

Results: In patient groups; total cholesterol, triglyceride, low-density lipoprotein, lipoprotein -a, apolipoprotein A, B, E and fibrinogen levels were found to be very high compared to the control group, while high-density cholesterol levels were lower($p < 0.01$). When both disease groups are compared; total cholesterol, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, apolipoprotein A, B, E levels were higher in the nephrotic syndrome group than in the secondary amyloidosis group($p < 0.05$). However, there was no difference between the patient groups in terms of C-reactive protein, fibrinogen and lipoprotein a levels ($p > 0.05$).

Conclusions: Atherosclerotic risk factors are quite high in proteinuria nephrotic syndrome and secondary amyloid patient groups, and patients with amyloidosis should be closely monitored for other atherosclerotic risk factors in addition to amyloid accumulated in the organs.

Keywords: Nephrotic Syndrome, SecondaryAmyloidosis, Cardiovascular Risk factors

Proteinuria has been shown to be associated with cardiovascular diseases, dyslipidemia, and hypertension. [1] Myocardial infarction risk is increased 5-6 times in patients with nephrotic proteinuria. [2] Proteinuria accelerates atherosclerosis by causing endothelial dysfunction, inflammation, dyslipidemia and hypercoagulability. Nephrotic syndrome is a disease characterized by a tendency to severe proteinuria, hypoalbuminemia, hyperlipidemia, edema and hypercoagulability. For this reason, there are many studies in the literature showing that the risk of atherosclerosis and coronary artery disease increases in Nephrotic syndrome. [3] Secondary amyloidosis is another disease that causes nephrotic proteinuria due to renal involvement. The risk of cardiovascular disease increases due to amyloid deposition, inflammation, and complications of Nephrotic syndrome in amyloidosis. In studies, both

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cardiac and vascular system effects were reported in primary amyloidosis cases. Cardiovascular involvement has been reported at a rate of 54-100% in primary amyloid cases and 10% in secondary amyloid cases. [3-5] There are many publications showing the relationship between Nephrotic syndrome and cardiovascular disease very well. [3, 6, 7] Onthe other hand, there are very few studies on atherosclerotic risk factors in patients with secondary amyloidosis with proteinuria. [8] In our study, we aimed to compare atherosclerotic risk factors between patients with secondary amyloid and Nephrotic syndrome and to investigate the relationship of proteinuria with dyslipidemia and other atherosclerotic risk factors.

METHODS

Thirty patients diagnosed with secondary amyloidosis, 29 patients diagnosed with nephrotic syndrome, and 30 healthy volunteers as the control group were included in the study among the patients investigated for proteinuria in the nephrology outpatient clinic. Demographic characteristics, blood pressure and body mass index (BMI) of the three groups were recorded. Complete blood count at diagnosis, total cholesterol, triglyceride, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), apo-lipoproteinA1 (apo- A1), apo-lipoprotein-B (apo-B), apo-lipoprotein E (apo-E), lipoprotein-(a) [Lp-(a)], C- reactive protein (CRP), fibrinogen, urinalysis and 24-hour urine protein amount and creatinine clearance were calculated. Electrocardiography and chest X-ray were taken. Tissue biopsies were performed with patient consent for the etiology of secondary amyloidosis and nephrotic syndrome. Patients with high blood pressure and taking cholesterol-lowering drugs were not included in the study.

Statistics

Chi-square Test, Analysis of Variance (Post hoc Bonferonni), Spearman Correlation Analysis, Kruskal Wallis Test and Mann Whitney U test were used to evaluate the data. Statistical significance level was taken as $p < 0.05$ in the analyzes.

RESULTS

The secondary amyloidosis group consisted of 12 females and 18 males, with a mean age of 46.5 ± 14.2 years. The nephrotic syndrome group consisted of 12 females and 17 males, with a mean age of 45.3 ± 13.3 years (Tablo 1). The control group consisted of 15 females and 15 males, with a mean age of 45.4 ± 5.7 (37-55) years. In the etiology of secondary amyloidosis was detected Crohn's disease in 1(3%), Rheumatoid arthritis (RA) in 2(7%), Bechet's disease in 3(10%), Bronchiectasis in 4(13%), Tuberculosis in 8(27%), Familial Mediterranean Fever (FMF) in 12(40%) of the cases. In the etiology of nephrotic syndrome was detected focal segmental glomerulonephritis (FSGN) in 4(13%), membranous glomerulonephritis (MGN) in 6(17%), diffuse proliferative glomerulonephritis (DPGN) in 6(20%), membranoproliferative glomerulonephritis (MPGN) in 14(47%) of the cases. There was no statistically significant difference between the three groups in terms of gender, age, smoking and BMI ($p > 0.05$). There was a statistically significant difference between the nephrotic syndrome and control group cases in terms of triglyceride ($p < 0.05$), total cholesterol ($p < 0.001$), albumin, fibrinogen, CRP, LDL-C, HDL-C apo-Al, apo B, apo E, Lp (a) and GFR ($p < 0.01$). There was a statistically significant difference between the nephrotic and control group cases in terms of triglyceride ($p < 0.05$), total cholesterol ($p < 0.00$l), HDL-C, LDL-C, albumin, fibrinogen, CRP, apo-Al, apo B, apo E, Lp (a), and GFR ($p < 0.01$). There was a statistically

Table 1. General Clinical Characteristics of Study Subjects (Mean + standard deviation, $p > 0.05$)

	NS n: 29	AA n: 30	Control n: 30
Age (year)	45.3 ± 13.3	46.5 ± 14.2	45.4 ± 5.7
Female/male	12 / 17	12 / 18	15/ 15
Proteinuria (g/L)	5.0 ± 2.3	5.0 ± 2.1	-
Creatinine (mg/dl)	1.1 ± 0.4	1.0 ± 0.4	0.7 ± 0.3
Cigaret(packet/year)	6 (20.4%)	7 (23.3%)	8 (26.6%)
BMI (kg/m^2)	23.8 ± 4.5	25.1 ± 4.8	24.4 ± 3.8

Table 2. Mean (mean ± standard deviation) and P values of Atherosclerotic Risk Factors among Nephrotic Syndrome. Secondary Amyloidosis and Control Group Cases

	Nephrotic syndrome n: 29	*P* Value	Secondary Amyloid n: 30	*P* Value	Control n: 30
Age (year)	45.3 ± 13.2	> 0.05	46.5 ± 14.2	> 0.05	45.4 ± 5.7
Creatinine (mg/dl)	1.1 ± 0.4	> 0.05	1.0 ± 0.4	> 0.05	0.7 ± 0.3
Albumine (mg/dl)	2.4 ± 0.4	< 0.01	2.3 ± 0.7	< 0.01	4.1 ± 0.3
CRP (mg/dl)	34.1 ± 24	< 0.01	38.6 ± 28.7	< 0.01	3.5 ± 1.5
Fibrinogen (mg/dl)	444.7 ± 221.3	< 0.01	466.4 ± 44.3	< 0.01	211.5 ± 47.5
Total cholesterol (mg/dl)	310.0 ± 85.5	< 0.001	252.0 ± 90.0	< 0.001	145.0 ± 24
Triglyceride (mg/dl)	211.0 ± 68.6	< 0.05	178.2 ± 56.0	< 0.05	10 1.0 ± 25
HDL-C (mg/dl)	44.1 ± 7.5	< 0.01	39.3 ± 14.2	< 0.01	54 ± 11.9
LDL-C (mg/dl)	229.5 ± 84.3	< 0.01	184.3 ± 87.2	< 0.01	78.9 ± 17.3
Lp (a) (mg/dl)	66.1 ± 23.9	< 0.01	60.1 ± 29.7	< 0.01	16.7 ± 6.3
Apo-Al (mg/dl)	119.7 ± 22.6	< 0.01	104.8 ± 30.4	< 0.01	148.5 ± 22.1
Apo-B (mg/dl)	182 ± 49.9	< 0.01	156.5 ± 64.7	< 0.01	61.2 ± 7.7
Apo-E (mg/dl)	6.0 ± 3.03	< 0.01	5.4 ± 1.9	<0.01	4.0 ± 1.4
GFR (ml/min)	83.9 ± 15.2	< 0.01	83.4 ± 16.8	< 0.01	101.3 ± 4 ± 7

significant difference among the cases with amyloid and nephrotic syndrome in terms of triglyceride ($p < 0.05$), total cholesterol ($p < 0.001$), apo-Al, apo B, apo E, HDL-C and LDL-C ($p < 0.01$). There was no significant difference in terms of GFR, albumin, fibrinogen, CRP and Lp (a) ($p > 0.05$, Tablo 2). There was a significant positive correlation between proteinuria and nephrotic syndrome (n: 29) patients in

Table 3. Correlation and P values between Proteinuria and Atherosclerotic Risk Factors in Nephrotic Syndrome, Secondary Amyloid, Secondary Amloid and Nephrotic Syndrome Cases

	Proteinuria (g/L)		
	Nephrotic syndrome	**Secondary Amyloid**	**Secondary Amyloid and Nephrotic Syndrome**
Cr (mg/L)	r = 0.01. $p > 0.05$	r = 0.24. $p >$ o.o5	r = 0.15. $p > 0.05$
Alb (mg/dl)	r = -13. $p > 0.05$	r = -0.49. $p < 0.01$	r = -0.34. $p < 0.01$
CRP (mg/dl)	r = 0.01. $p > 0.05$	r = 0.38. $p > 0.05$	r = 0.22. $p > 0.05$
Fibrinogen (mg/dl)	r = -0.01. $p > 0.05$	r = 0.13. $p > 0.05$	r = 0.08. $p > 0.05$
Total cholesterol (mg/dl)	r = 0.35. $p < 0.05$	r = 0.46. $p < 0.05$	r = 0.54. $p < 0.001$
Triglyceride (mg/dl)	r = 0.28. $p > 0.05$	r = 0.23. $p > 0.05$	r = 0.35. $p < 0.01$
HDL-C (mg/dl)	r = 0.05. $p > 0.05$	r = -0.49. $p > 0.05$	r = 0.10. $p > 0.05$
LDL-K (mg/dl)	r = 0.38. $p > 0.05$	r = 0.38. $p < 0.05$	r = 0.48. $p < 0.001$
Lp (a) (mg/dl)	r = 0.07. $p > 0.05$	r = 0.07. $p > 0.05$	r = 0.02. $p > 0.05$
ApoA1 (mg/dl)	r = 0.18. $p > 0.05$	r = 0.14. $p > 0.05$	r = 0.07. $p > 0.05$
Apo-B (mg/dl)	r = 0.09. $p > 0.05$	r = 0.25. $p > 0.05$	r = 0.30. $p < 0.05$
Apo-E (mg/dl)	r = 0.08. $p > 0.05$	r = 0.38. $p < 0.05$	r = 0.23. $p > 0.05$
GFR (ml/min)			r = 0.15. $p > 0.05$

There is a weak correlation between r (correlation coefficient) = 0.00-0.24, moderate relationship r = 0.25-0.49, strong relationship r = 0.50-0.74, strong relationship r = 0.75-1.

terms of total cholesterol (r = 0.35, $p < 0.05$). There was no relationship between other parameters. There was a significant positive correlation between proteinuria and secondary amyloid (n: 30) group cases in terms of total cholesterol (r = 0.46, $p < 0.05$), LDL-C (r = 0.38, $p < 0.05$) and apo E (r = 0.35, $p < 0.05$. There was no correlation between other parameters. When proteinuria with nephrotic syndrome and secondary amyloidosis group cases (n: 59) were compared, there was a significant positive correlation in terms of total cholesterol (r = 0.54, $p < 0.001$), LDL-C (r = 0.4. 8, $p < 0.001$), triglyceride (r = 0.35, $p < 0.001$) and apo B (r = 0.30, $p < 0.05$). There was a significant negative correlation for albumin (r = -0.34, $p < 0.01$, Tablo 3).

DISCUSSION

The relationship between proteinuria with cardiovascular mortality and morbidity has been known for a long time.9 Proteinuria increases cardiovascular mortality and morbidity 5-85 times due to endothelial dysfunction, lipoprotein metabolism disorder, decrease in GFR, hypercoagulability and inflammation. [1, 2, 10-12] Although cardiovascular mortality and morbidity in nephrotic syndrome is well known [1, 7, 13,] studies showing CV mortality and morbidity in secondary amyloidosis, which can cause nephrotic syndrome are very few. [8] According to our knowledge, there is no study comparing atherosclerotic risk factors in both groups. In our study; in 29 patients with nephrotic syndrome, 30 patients with secondary amyloidosis, and 30 completely healthy people, who were almost equal in terms of age, gender, smoking, BMI and proteinuria, as atherosclerotic risk factors CRP, fibrinogen, total cholesterol, triglyceride, LDL-C, HDL-C, Lp(a), apo Al, apo B and apo E levels were measured. In both disease groups, serum total cholesterol, triglyceride, LDL-C, Lp(a), apo Al, apo B, apo E, CRP and fibrinogen atherosclerotic risk factors were significantly higher than the control group, but serum HDL-C levels were lower. This part of our study shows that proteinuria increases atherosclerotic risk factors and is compatible with studies in the literature. [12, 14] In the second part of our study; When NS and secondary amyloid patients were compared in terms of atherosclerotic risk factors, serum total cholesterol, triglyceride, LDL-C, HDL-C, apo Al, apo B and apo E levels were higher in the group nephrotic syndrome compared to the secondary amyloid group [(total cholesterol, triglycerides, LDL-C, HDL-C, apo Al, apo B and apo E. There was a statistically insignificant increase in serum Lp, (a) level in the nephrotic syndrome group compared to the secondary amyloid group. In the literature, nephrotic syndrome has been studied extensively in terms of atherosclerotic risk factors, cardiovascular diseases and mortality-morbidity. In terms of atherosclerotic lipid levels, our study was compatible with most studies in the literature on nephrotic syndrome atherosclerotic risk factors. [7, 12, 15] Although secondary amyloidosis is more common in our country, studies showing atherosclerotic risk factors are scarce in the domestic and foreign literature. [8] The effect of proteinuria on atherosclerosis and arteriosclerotic risk factors has been known for many years. [6, 16] Our study is one of the few studies that we believe can be very useful in comparing secondary amyloidosis and nephrotic syndrome, showing the effect of atherosclerotic risk factors, the relationship between proteinuria and risk factors, apart from the amyloid material accumulating in the organs in secondary amyloidosis. Many factors play a role in the atherosclerotic process: abnormalities in lipid metabolism, endothelial dysfunction, inflammatory and immunological events. [8, 17] These factors involved in the pathogenesis are also frequently found in patients with nephrotic syndrome. Hyperlipidemia and abnormalities in lipoprotein metabolism have been known in nephrotic syndrome for a long time, and it is known that increased hepatic synthesis and decreased catabolism are responsible for its pathogenesis. [18] Although the importance of blood lipids has been demonstrated, the absence of hyperlipidemia in some of the patients has increased efforts to evaluate other risk factors, and studies conducted for this purpose have shown the importance of inflammatory markers such as high-sensitive CRP, and markers with hemostatic function such as lipoprotein(a), homocysteine, and fibrinogen. All stages of atherothrombosis are characterized by inflammation. It is also a process involving fatty streak formation, early phase of atherogenesis, endothelial cells, inflammatory cytokines and leukocytes. Thrombotic complications in plaque are associated with local and systemic inflammation. It has been determined that high-sensitive CRP levels are associated with myocardial infarction, stroke, peripheral arterial disease and sudden cardiac death. However, if the levels are > 10mg/L in sequential measurements, it is associated with inflammation and it is recommended to be investigated accordingly. [19] In

our study, we found that CRP levels were high, indicating inflammation or infection, in both the secondary amyloidosis and nephrotic syndrome patient groups. The place of lipoprotein (a) in atherosclerosis and its relationship with both coronary and peripheral artery disease have been shown, and previous studies have shown that the levels of lipoprotein (a) increases in patients with nephrotic syndrome. [15, 20] The importance of endothelial dysfunction and inflammation has been increasingly recognized in recent years. The importance of endothelial dysfunction and inflammation has been increasingly recognized in recent years. Serum CRP level is the most studied inflammatory marker, and the relationship between increased levels and cardiovascular events has been shown in various studies. The same relationship has been shown with fibrinogen levels, which is also an acute phase reactant and plays a role in thrombus formation. [21] It has been suggested that endothelial dysfunction in nephrotic syndrome is involved in the atherosclerotic process as well as in protein leakage. The literature on secondary amyloidosis is limited, the studies on cardiac pathologies here were mostly conducted with primary amyloidosis (AL), and both cardiac and vascular system effects were reported. In our country, secondary amyloidosis is frequently seen, and there is not enough data on the changes in the cardiovascular system in this patient group. Although it has been previously reported that mortality is high in patients with renal failure with systemic amyloidosis, information about the causes of mortality is limited. In the study conducted by Sengul *et al*. in patients with secondary amyloidosis undergoing hemodialysis, they found the mortality to be high similar to diabetic patients and found that the most important causes of death were infection first and then cardiovascular causes. In the same study, it was shown that CRP and serum albumin were associated with mortality. [7] In a study by Cengiz *et al*., it was reported that atherogenic lipid and apolipoprotein levels were higher in patients with chronic renal failure (CRF) as a result of secondary amyloidosis than in healthy controls and non-amyloid CRF. [6] Secondary amyloidosis occurs due to underlying rheumatological diseases, chronic infections and inflammatory bowel diseases and is characterized by the accumulation of serum amyloid A (SAA) protein in tissues. Serum amyloid A protein, which is an acute phase reactant and whose level can increase up to 1000 times with inflammatory stimuli, is mainly synthesized in the liver in relation to HDL-C. However, studies conducted in recent years have shown that SAA protein is found in endothelium, atherosclerotic lesions, and smooth muscle cells. SAA protein found in atherosclerotic lesions is thought to play a role in lipid metabolism by causing uptake or excretion of lipids at the cellular level. It is thought that SAA protein may cause remodeling of vascular walls or plaques by causing collagenase synthesis from smooth muscles, apart from lipid metabolism. SAA protein can also affect thrombus formation by disrupting platelet aggregation and adhesion in the endothelium. [22] In our study, lipidprofile in the patient group with amyloidosis, similar to nephrotic syndrome, showed a significantly atherogenic feature compared to the control group. Lipoprotein (a), CRP and fibrinogen levels were higher in both patient groups compared to the control group, and there was no significant difference in the comparison of the patient groups. This may have been due to infections that we could not detect in the patient groups with nephrotic syndrome and secondary amyloidosis, although patients with infections were excluded from the study. In the third part of our study, the relationship between proteinuria and CV risk factors was evaluated. In the nephrotic syndrome group, serum total cholesterol, and among the secondary amyloid (n: 30) groups, total cholesterol, LDL-C and apo E levels were significantly positive, but with serum albumin levels in both patient groups had a negative correlation. There was no relationship between the two groups with other parameters. This difference in secondary amyloidosis could be due to amyloid material accumulating in the vascular structures. Between total (n: 59) cases of total nephrotic syndrome and secondary amyloid groups with proteinuria, in terms of total cholesterol, LDL-C, triglyceride and apo B had significant positive correlation, but there was a significant negative correlation with albumin. There was no relationship between other parameters. In conclusion, atherosclerotic risk factors were significantly higher in patients with proteinuria, nephrotic syndrome due to various causes, and secondary amyloid compared to the control group. In the study of Wencai Jiang *et al*., it was reported that the level of atherosclerosis increases as the level of proteinuria increases. [23] Our study is one of the few studies showing atherosclerotic risk factors in secondary amyloidosis. However, the limitation of our study is the insufficient number of cases. Further studies in larger case groups can give meaningful results.

CONCLUSION

Atherosclerotic risk factors are quite high in nephrotic syndrome and secondary amyloid patient groups with proteinuria, and patients with amyloidosis should be closely monitored in terms of other atherosclerotic risk factors in addition to amyloid accumulating in the organs. In addition, we believe that in diseases progressing with proteinuria, primary disease treatment and atherosclerotic risk factors and proteinuria should also be treated. Multicenter studies with more case series are needed to prove our study.

Authors' Contribution

Study Conception: OC, TA, KC,; Study Design: OC, TA, KC,; Supervision: OC, TA, KC,; Materials: OC, TA, KC,; Data Collection and/or Processing: OC, TA, KC,; Statistical Analysis and/or Data Interpretation: OC, TA, KC,; Literature Review: OC, TA, KC,; Manuscript Preparation: OC, TA, KC and Critical Review: OC, TA, KC.

Conflict of interest

No potential conflicts of interest relevant to this article were reported.

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