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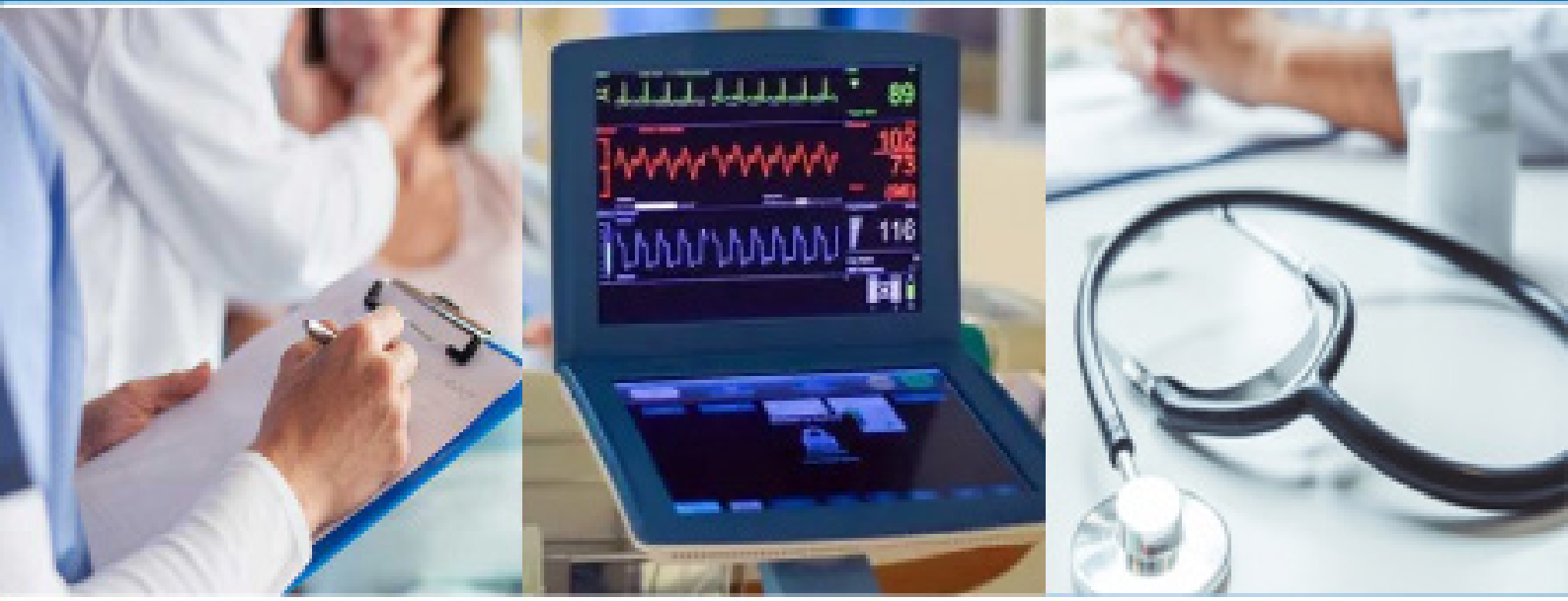

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Our Journal, The Intercontinental Journal of Internal Medicine (ICJIM), started its publication life by publishing its first issue in February 2023, with an experienced editorial staff consisting of experienced and high-level academicians.

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Sincerely Yours,

Prof. Aydın ÇİFCİ
Editor

The Intercontinental Journal of
Internal Medicine

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Original Article

Evaluation of mineralization balance in patients with hypoparathyroidism

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ABSTRACT

Aims: Surgical complications play a major role in the etiology of hypoparathyroidism. Calcium and phosphorus metabolisms are disrupted by hypoparathyroidism. As a result, bone mineralization is impaired and may cause many pathologies. In clinical practice, parathyroid transplantation is not possible in every patient. In this study, we aimed to evaluate whether it would be possible to prevent the complications caused by hypoparathyroidism with mineral-supplemented medical therapy, even if we could not replace the lost parathyroid tissue.

Methods: A total of 79 individuals with hypoparathyroidism (parathormone levels below the reference range for more than one year) secondary to thyroidectomy admitted to our hospital were included in the study. Calcium, phosphorus, alkaline phosphatase (ALP), vitamin D, and creatinine levels were recorded in the last three controls. The relationship between parathormone levels, mineral levels, and ALP, which is an indicator of bone turnover, was analyzed.

Results: The mean calcium value was 8.57±0.90 and the mean phosphorus value was 4.46±0.99 in individuals diagnosed as hypoparathyroid with biochemical data. When the relationship between parathormone and the average of the last three calcium values, the relationship between the average phosphorus value, and the relationship between ALP and vitamin D were examined, no significant difference was found ($p<0.05$). When the relationship between the calcium phosphorus product and its effect on bone mineralization was examined, the mean calcium phosphorus product was 37.64±7.37, and no statistically significant difference was found with parathormone level ($p<0.05$).

Conclusion: Preservation of parathyroid tissue is important for calcium-phosphorus metabolism. Although loss of parathyroid tissue is irreversible, it may be possible to prevent complications with mineral supplementation. As long as calcium and phosphorus balance are maintained externally, bone turnover will be preserved, along with many pathologies caused by hypocalcemia. No matter how low the parathormone level is, the bone mineralization problem caused by hypoparathyroidism can be reduced or even eliminated with mineral levels normalized with medical treatment.

Keywords: Hypoparathyroidism, bone mineralization, hypocalcemia

INTRODUCTION

Hypoparathyroidism is an endocrinologic disorder characterized by congenital or acquired deficiency or absence of parathormone (PTH) secretion, resulting in multisystemic pathologies affecting calcium-phosphorus metabolism. Its prevalence has been found to be 0.37% in the USA and 0.22% in Europe. In Turkey, its prevalence is unknown.[1] The diagnosis is made by biochemical methods and the measurement of serum PTH levels. In the absence of PTH, ionized calcium levels decrease; PTH levels should be controlled in cases of hypocalcemia.[2]

The most common cause of hypoparathyroidism is iatrogenic, secondary to neck surgery. In particular, hypoparathyroidism develops in approximately 10% of patients as a result of complications secondary to thyroidectomy. While 8.3% of these are transient, permanent PTH deficiency occurs in 1.7%. However, these rates have been found to be lower in clinics with more frequent thyroid surgery.[3]

As a result of hypoparathyroidism, serious complications may develop as a result of electrolyte disorders such as calcium deficiency and high phosphate levels. All patients with calcium level below 8 mg/dl should be treated. The aim of treatment is to increase calcium levels through calcium and vitamin D supplements.[4] Although not yet proven, gene therapy has recently attracted attention among treatment options. Parathyroid transplantation is another treatment option.[5] Another proven treatment is the use of PTH analogs; however, this treatment can be used if there is no response to vitamin D and calcium. The goal of treatment should be to maintain calcium levels just below the reference value; however, the dose may be increased if the patient describes symptoms. Phosphorus and magnesium levels should also be

kept within reference limits. The calcium-phosphorus product should be below 55 to prevent metastatic calcifications.[6]

Since hypoparathyroidism causes low bone turnover, it may lead to osteoporosis; bone mineralization is impaired, and the risk of bone fracture increases. In our study, we aimed to determine the conditions affecting bone mineralization in individuals with hypoparathyroidism and to draw attention to what should be done to minimize these conditions.

METHODS

Ethics

The study was initiated after the decision of the Yozgat Bozok University Clinical Ethics Committee 2017-KAEK-189_2022.11.10_07. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Institutional approval was obtained before the study.

Design

The study was planned as a retrospective cross-sectional study.

Patients

All data were collected after ethics committee approval.

Inclusion Criteria

Adult individuals admitted to our hospital between 2017 and 2022 and diagnosed with hypoparathyroidism secondary to thyroidectomy were included in the study.

Exclusion Criteria

Individuals with known renal failure, a diagnosis of obesity, endocrine pathology that may cause osteoporosis, and drug use that may affect bone turnover were excluded.

Methods

Age, gender, creatinine, PTH, calcium, phosphorus, and ALP values were recorded. Calcium values were averaged by recording the last three calcium measurements in order to reflect accurate results. The calcium-phosphorus product was calculated.

Statistical Analysis

The SPSS program was used for statistical analysis of the data. Categorical measurements were summarized as number and percentage, and continuous measurements were summarized as mean and standard deviation. The normal distribution of the measurements was evaluated by the Shapiro Wilk and Kolmogorov Smirnov tests. Statistical differences between independent variables were evaluated with the Student-t test and one-way ANOVA tests for parametric data and Mann-Whitney U and Kruskal-Wallis tests for nonparametric data. A paired t test was used for statistical evaluation of parametric data between dependent variables. Pearson and Spearman correlation analyses were used for correlation evaluations between two measurements for parametric and nonparametric data, respectively.

RESULTS

The study included 79 individuals with PTH values below the reference range (reference range: 15-65 pg/mL). Five (6.32%) of the individuals were male, and 74 (93.67%) were female. The minimum age was 29 years, the maximum age was 75 years, and the mean age was 49.62±11.60 years. PTH, calcium, phosphorus, ALP, and vitamin D levels and their statistical relationships were calculated (Table and Figure).

When PTH measurements were compared with calcium and phosphorus products, it was observed that PTH level had no statistically significant effect on the product of calcium and phosphorus levels (p=0.70), mean phosphorus level (p=0.37) and mean calcium value (p=0.21).

Table . The relationship between PTH, Ca, P, ALP, and vitamin D values of individuals

	Minimum	Maximum	Mean	Reference values	Comparison with PTH
Ca value	6.10 mg/dl	10.27 mg/dl	8.57 ± 0.90	8.8-10.6 mg/dl	p = 0.70
P value	1.80 mg/dl	7.80 mg/dl	4.46 ± 0.99	2.5-4.5 mg/dl	p = 0.37
Ca X P	19.80	61.75	37.64 ± 7.37	Ca X P < 55	p =0.21

PTH: parathormone, Ca: calcium, P: phosphorus, ALP: alkaline phosphatase, p<0.05 not significant

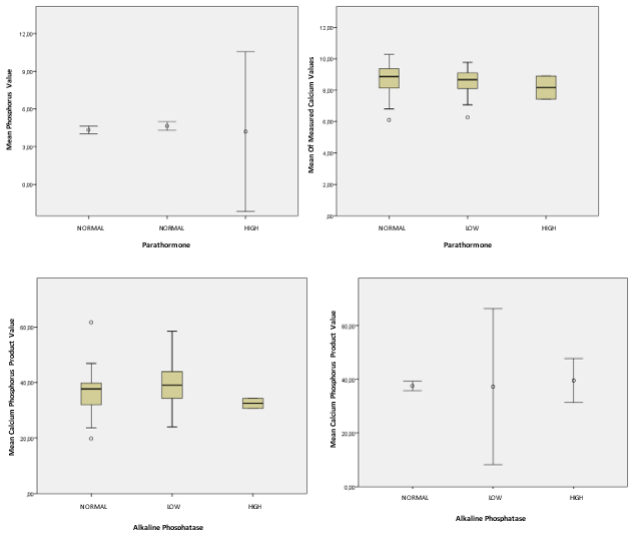

Figure. Parathormone, phosphore, calcium; alkalin phosphatase, calcium phosphatase graphics

Calcium and phosphorus levels can be regulated externally, even if the patient has hypoparathyroidism. Although the loss of parathyroid tissue in these patients requires continuous external medical treatment, it was also shown that it can be kept as regular as a healthy individual with medical treatment.

There was no statistically significant correlation between measured ALP levels and calcium phosphorus products (p; 0.866). Similarly, no statistically significant correlation was found between PTH levels and ALP measurements (p; 0.131). This indicates that the reason for this situation is due to the calcium and phosphorus values that were tried to be normalized with the treatment.

In the comparison between PTH levels and vitamin D levels, no statistically significant difference was observed when the values were grouped as low, medium, and high (p value; 0.681).

In other analyses, no statistical correlation was found between creatinine value and mean calcium value, mean phosphorus value, and calcium phosphorus product value (p values=0.692, 0.281, and 0.439, respectively). Because the creatinine values of all patients were within the reference range.

The result shows that kidneys in the reference range can support regulation and do not disrupt calcium-phosphorus balance.

All the patients were receiving hormone replacement therapy because of the thyroidectomy. However, the euthyroid state of the patients periodically deteriorated during follow-up. When the results of that period were examined, no statistically significant difference was found between the mean calcium and phosphorus levels and the calcium-phosphorus product values of hypothyroid and non-hypothyroid patients (p values 0.606, 0.599, and 0.404, respectively). Again, the result shows that calcium-phosphorus metabolism is completely in the hands of the individual in these patients, and we can preserve bone mineralization as much as possible with treatment compliance.

DISCUSSION

Hypoparathyroidism, one of the complications of thyroid surgery, is observed at a lower rate in experienced surgeons. It is very important to minimize this complication, which is preventable in some patients, considering that patients will receive lifelong medical treatment.[7] Hypoparathyroidism secondary to thyroid surgery was found to be a high etiologic factor in our patients, in accordance with the literature. In the study by Karakoç et al.[8] transient hypocalcemia was found in 63% of thyroidectomized patients. It was reported that the remaining 37% of patients needed lifelong medical treatment. In our study, transient hypoparathyroidism was ruled out because there were patients who had been receiving hypoparathyroidism treatment for at least one year.

There are many mechanisms that regulate calcium-phosphorus balance and, thus, the musculoskeletal system. The parathyroid gland is one of them and is very important. Loss of the parathyroid gland causes disruption of calcium and phosphorus metabolism.[9] Another major system that provides this balance is renal regulation.[10] Our data shows that there is no statistically significant relationship between the glomerular filtration rate and calcium phosphorus values. Because the creatinine values and glomerular filtration rates of all our patients were within the normal range. Thus, we were able to evaluate the effect of parathyroid tissue more clearly by ignoring renal regulation. Another system is the gastrointestinal system; its proper and effective functioning is especially important for the effectiveness of the treatment. Kartal et al.[11] showed how malabsorption and previous gastrointestinal surgeries can cause osteoporosis.

In a study by Demir et al.[12] it was observed that the use of teriparatide in the treatment of osteoporosis reduced the risk of fracture formation, and the importance of parathormone in osteoporosis and osteoporosis-related fractures was emphasized. Since we aimed to see the effect of the parathyroid gland only by eliminating other factors as much as possible in our study, patients with renal failure were not included in our study, and patients with known diseases affecting the gastrointestinal system, surgery, and patients taking medication were not included. However, it was observed that the calcium doses required by patients with the same PTH levels were different, even though standardization was attempted. Because many factors, including body mass index, age, and absorption levels, affect calcium and phosphorus levels. For this reason, patients should be given calcium and vitamin D replacement based on the target ranges of the Turkish Society of Endocrinology and Metabolism (TEMD); it was observed that not everyone's needs are the same due to the different doses of drugs used by our patients. Pregnancy is also an example; the increased PTH-relasing peptide cannot function in the absence of parathyroid tissue; higher doses of treatment are required to meet the increased need for pregnancy.[13]

Options for the treatment of hypoparathyroidism are being developed because the need for lifelong medical treatment is exhausting for patients in every sense. Issues such as parathyroid tissue auto transplantation or donor transplantation with immunosuppression support are widely discussed in the scientific community.[14] Kanımdan et al.[15] obtained very successful results in this regard in their studies on rats. Idiz et al.[16] suggested that severe hypocalcemia attacks could be prevented with auto transplantation; however, it was reported that this was not possible in every center, and cryopreservation laboratories were needed. In another study, it was concluded that functional parathyroid gland conjugates could be produced by 3D printing. Many such methods have been tried.[17] However, today, instead of these treatments, which have very limited applicability, deficient mineral-assisted therapy is applied. All our hypoparathyroid patients receive medical treatment. They use calcium and vitamin D as medical treatments. Since the patients were under medical treatment, the mean values of calcium 8.57±0.90 (n: 8.8-10.6) and phosphorus 4.46±0.99 (n: 2.5-4.5) were found to be normal or close to the normal range. Yüksel et al.[18] examined the factors affecting hypocalcemia after thyroidectomy and concluded that vitamin D should be corrected preoperatively.[18] An example of this is a case in which a patient with pseudohypoparathyroidism improved with vitamin D replacement.[19] In our study, in order to eliminate the vitamin D factor, calcium and phosphorus values measured when vitamin D was in the reference range were included in all our patients.

In our study, no significant correlation was found between the PTH value and both calcium, phosphorus, and calcium phosphorus products ($p<0.05$). The reason for this was thought to be the fact that all patients were under treatment, and these improvements were achieved with external calcium and vitamin D treatment. However, in the case of hypoparathyroidism, low calcium and high phosphorus levels are expected to result in disturbances in calcium-phosphorus balance.[20] In our study, it was observed that the effect of hypoparathyroidism on bone mineral disorders could be prevented by correcting calcium-phosphorus metabolism with external medical treatment; however, it is still not possible to completely replace the lost tissue.

Limitations of the study: Retrospective nature and lack of confirmation by bone densitometry or bone biopsy as bone mineralization indicators.

CONCLUSION

We may face loss of parathyroid tissue as a complication of thyroidectomy. Our study shows that the preservation of parathyroid tissue is, of course, important. However, it is equally important that calcium-phosphorus metabolism be kept in balance with appropriate treatment in these patients. Thus, complications due to hypoparathyroidism can be minimized. Although it is not possible to completely cure the deficiency of the parathyroid gland in adequately

treated hypoparathyroid patients, bone mineralization can be preserved to a great extent.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ethical Committee of Yozgat Bozok University (Date: 10.11.2022, Decision Number: 2017-KAEK-189_2022.11.10_07).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article

Bone density in patients with nonfunctional adrenal incidentaloma

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ABSTRACT

Aims: Adrenal incidentalomas (AI) are adrenal masses that are detected incidentally in imaging studies performed for different reasons in people who do not have any complaints suggestive of adrenal gland disease. The overall prevalence, approximately just over 4%, increases with age. AI is detected in approximately 10% of people over the age of 70. In this context, we thought that CT imaging, which is already used in the diagnosis and follow-up of AI, can contribute to the evaluation of muscle and bone mass without creating additional costs.

Methods: In this retrospective study, 39 patients who were followed up with nonfunctional adrenal incidentaloma (NFAI) by the endocrinology department and 30 healthy individuals with normal adrenal imaging in the abdominal CT examination as the control group were included. Patients with chronic diseases or drug use that may affect bone and muscle mass, and individuals in the postmenopausal period were excluded in this study. Endocrine tests performed to exclude autonomous cortisol secretion, pheochromocytoma and primary hyperaldosteronism; VMA and fractionated metanephrines in 24-hour urine, cortisol values after 1 mg dexamethasone suppression test, baseline serum dehydroepiandrosterone sulfate (DHEAS) levels and plasma aldosterone (ng/dl)/renin (ng/ml/hour) ratio were measured. Autonomous cortisol production was excluded in patients with serum cortisol below 1.8 mcg/dl after 1 mg dexamethasone suppression.

Results: 39 patients with NFAI and 30 healthy volunteers participated in the study. In the NFAI group, 69.2% (n=27) were female and 30.8% (n=12) were male. In the healthy control group 63.3% (n=19) of the people were female and 37.7% (n=11) were male. There was no statistically significant difference between the two groups in terms of gender (p=061). The mean age of the NFAI group is 43 and the mean age of the control group is 49, and there was no statistically significant difference in age between the two groups (p=0.06).

Conclusion: No decrease was found in BMD and paravertebral muscle mass values in the measurements made at L1-3 vertebral level with CT in NFAI patients. Further studies are needed in a larger patient population where the results are evaluated together with the femur and vertebral BMD measurements by DXA method, and muscle strength and performance are evaluated in addition to muscle mass in terms of sarcopenia.

Keywords: Adrenal incidentaloma, bone-mineral density, nonfunctional adrenal incidentalomas, NFAI

INTRODUCTION

Adrenal incidentalomas (AI) are adrenal masses that are detected incidentally in imaging studies performed for different reasons in people who do not have any complaints suggestive of adrenal gland disease. The overall prevalence, approximately just over 4%, increases with age. AI is detected in approximately 10% of people over the age of 70.[1]

Mild cortisol excess (MCE), previously called "subclinical Cushing's syndrome (SCS)", is observed in 15-30% of cases, although most of them are dysfunctional, without the typical clinical features of hypercortisolism.[1] Comorbidities such as type 2 diabetes mellitus and hypertension are common in AI cases. It is thought that this low-grade cortisol excess may be associated with various comorbid conditions (hypertension, type 2 diabetes mellitus, obesity, dyslipidemia, and osteoporosis).[1-3]

There are studies indicating in adipocytokines levels may be associated with insulin resistance. Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) index, and cardiovascular risk factors in nonfunctional adrenal incidentalomas (NFAI) patients.[4,5]

Intermittent cortisol and mineralocorticosteroid hormone secretion that cannot be detected by routine tests in NFAI patients may be a cause of increased cardiovascular risk, and may even have effects on bone and muscle mass.

There are studies showing that in addition to a decrease in BMD in patients with adrenal incidentaloma and subclinical hypercortisolism, the trabecular bone score (TBS), which is an indicator of increased bone quality and fracture risk, decreases.[6]

On the other hand, is there a negative effect on bone and muscle mass in individuals with NFAI? Our current knowledge is insufficient in answering this question. Therefore, in our study, we aimed to measure bone mineral density and muscle mass quantitatively with CT in cases with NFAI. In this context, we thought that CT imaging, which is already used in the diagnosis and follow-up of AI, can contribute to the evaluation of muscle and bone mass without creating additional costs.

METHODS

In this retrospective study, 39 patients who were followed up with NFAI by the endocrinology department and 30 healthy individuals with normal adrenal imaging in the abdominal CT examination as the control group were included. The study was initiated with the approval of the Kırıkkale University Medical Faculty Clinical Researches Ethics Committee (Date: 26.06.2019 Decision No: 2019.06.23). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients with chronic diseases or drug use that may affect bone and muscle mass, and individuals in the postmenopausal period were excluded in this study.

Endocrine tests performed to exclude autonomous cortisol secretion, pheochromocytoma and primary hyperaldosteronism; VMA and fractionated metanephrines in 24-hour urine, cortisol values after 1 mg dexamethasone suppression test, baseline serum dehydroepiandrosterone sulfate (DHEAS) levels and plasma aldosterone (ng/dl)/renin (ng/ml/hour) ratio were measured. Autonomous cortisol production was excluded in patients with serum cortisol below 1.8 mcg/dl after 1 mg dexamethasone suppression.

Hounsfield unit (HU), absolute contrast washout rate and tumor size were noted.

Calcium, phosphorus, albumin, alkaline phosphatase, parathormone, 25-OH Vitamin D, urea, creatinine, hormone profiles, results of endocrinological dynamic tests, ESR and CRP levels were taken retrospectively from the hospital information system.

The measurements were calculated from CT images.

Bone densities and muscle masses were calculated from the CT images of the patient and control groups by area measurement (millimeter square mm^2) method.

ROI (Region of interest) was selected to cover 2/3 of the corpus area in axial sections at the level of L1 vertebra, bone density (HU) was measured without including the bone cortex in the area (Figure 1).

Fat-containing tissues were removed from the paravertebral area (Figure 2a) in axial sections at the level of the L3 vertebra (Figure 2b), and the lean muscle tissue area was measured (Figure 2c).

Statistical Analysis

Statistical analyzes were performed using the Statistical Package for the Social Science' (SPSS 16.0) program. Descriptive statistics were signified as mean ± standard deviation for numerical variables and as numbers and percentages for nominal variables. Kolmogorov Smirnov and ShapiroWilks tests were used to investigate the normal distribution in numerical variables. In the comparison of two independent groups for a numerical variable, the t-test (students' t-test) was used in the independent groups according to whether they fit the normal distribution or not, and the Mann Whitney-U test was used in those who

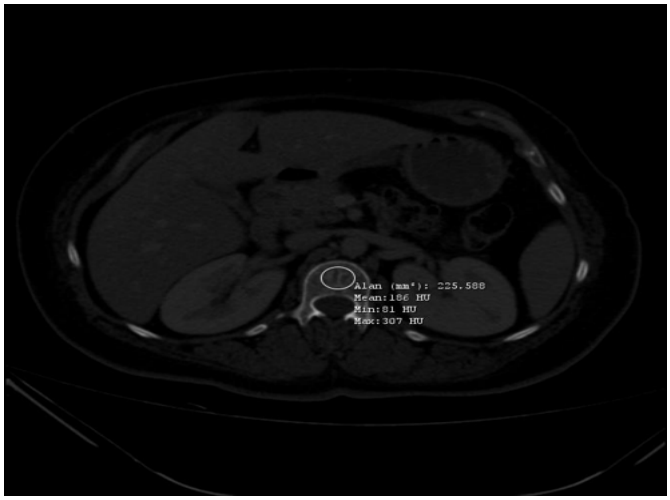

Figure 1. Bone density measurement at L1 vertebra level

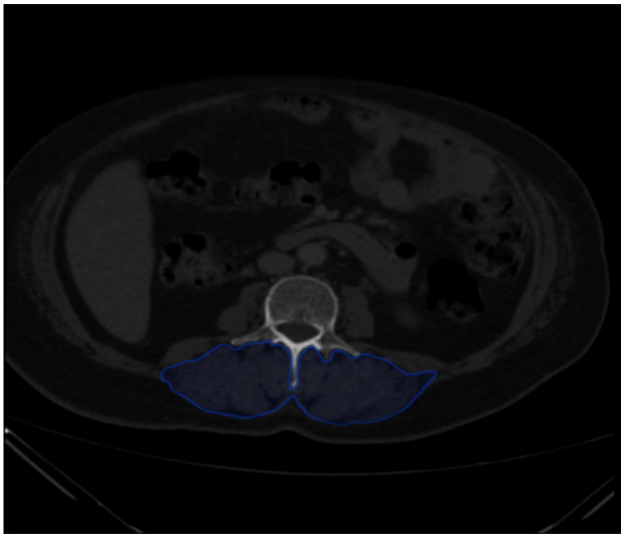

Figure 2a. Paravertebral area measurement at L3 vertebra level

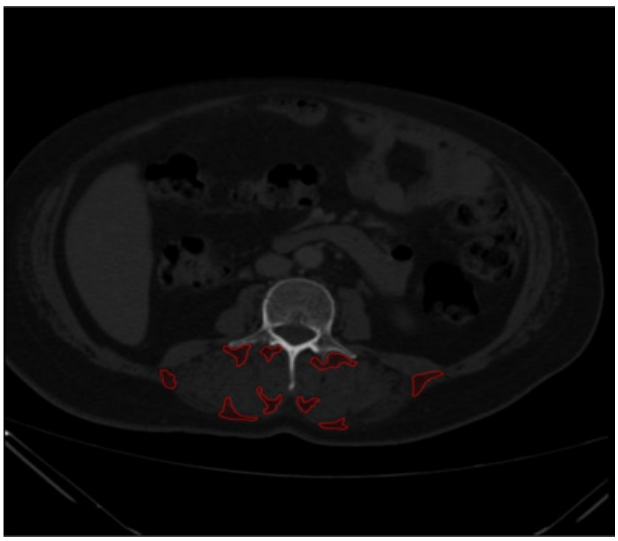

Figure 2b. Fatty tissue within the paravertebral muscles

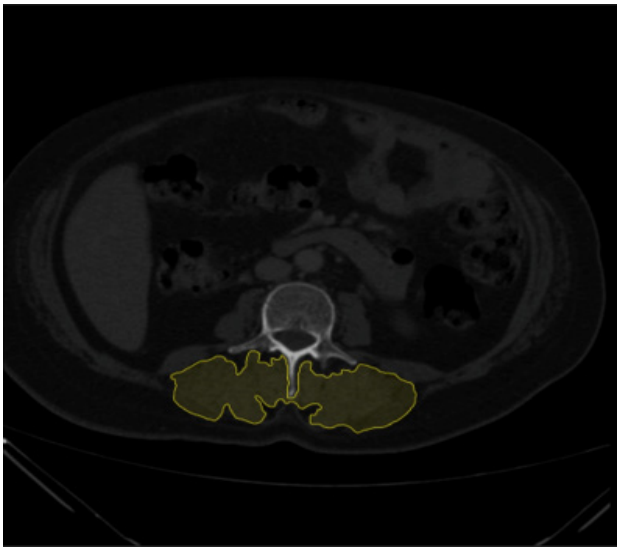

Figure 2c. Fat tissue removed paravertebral muscle tissue

did not fit in with the normal distribution. Chi-square (ChiSquare) test was used to compare nominal variables between groups. Spearman's correlation analysis was used while investigating the relationship between two numerical variables. P<0.05 was considered statistically significant.

RESULTS

39 patients with NFAI and 30 healthy volunteers participated in the study. In the NFAI group, 69.2% (n=27) were female and 30.8% (n=12) were male. In the healthy control group 63.3% (n=19) of the people were female and 37.7% (n=11) were male. There was no statistically significant difference between the two groups in terms of gender (p=061). The mean age of the NFAI group is 43 and the mean age of the control group is 49, and there was no statistically significant difference in age between the two groups (p=0.06) (Table 1a and Table 1b).

There was no significant difference between the groups in serum PTH, Vit D, calcium, phosphorus, albumin, urea, creatinine, sodium, potassium, cortisol, 24-hour urine VMA, normetanephrine/Metanephrine, plasma renin activity, and aldosterone levels (Table 2).

Table 1a. The two group comparisons of demographic characteristics, bone and muscle mass

		NFAI group n=39	Control group n=30	
Age; years		43 (34-50)	49 (28-50)	P=0.064
Sex	Female	27 (69.2%)	19 (63.3%)	P=0.61
	Male	12 (30.8%)	11 (37.7%)	
Bone mass (HU)		205 (102-277)	169 (101-306)	P=0.358
Muscle mass (mm2)		4329 (3289-6687)	4627 (3314-43262)	P=0.506

Table 1b. Demographic characteristics of NFAI and control group

		NFAI group n=39	Control group n=30	
Age, years		43 (34-50)	49 (28-50)	P=0.064
Sex	Female	27 (69.2%)	19 (63.3%)	P=0.61
	Male	12 (30.8%)	11 (37.7%)	

HU: Hounsfield unit

The BMD and muscle mass were similar in both NFAI patients and controls (Table 3).

The mean BMD value in the NFAI group was 205 HU, while it was 169 HU in the control group (p=0.358). The mean muscle mass area was 4329 mm^2 in the NFAI group and 4627 mm^2 in the control group (p=0.506). No correlation was found between muscle and bone measurements and biochemical parameters (Table 4).

Table 2. Comparison of study groups in terms of biochemical parameters

	Study group n=39	Control group n=30	
PTH	38 (22-56)	50.5 (4.2-138)	P=0.384
Vitamin D, ng/ml	12 (2.9-51)	13 (3.2-23)	P=0.691
Calcium, mg/dl	9.4 (8.4-10.3)	9.75 (8.5-10.8)	P=0.231
Phosphorus, mg/dl	3.3 (2.6-4.5)	3.1 (2.3-4.2)	P=0.046
Albumin, g/dl	4.5 (3.6-5.4)	4.7 (3.8-5.5)	P=0.55
Urea, mg/dl	25 (12-38)	25 (17-51)	P=0.433
Creatinine, mg/dl	0.7 (0.5-1.1)	0.7 (0.3-1.1)	P=0.106
Sodium, mmol/L	139 (136-144)	140 (137-145)	P=0.057
Potassium, mmol/L	4.6 (3.5-5.5)	4.4 (3.2-5.3)	P=0.085
Cortisole, ug/dl	11 (3.4-19.8)		
Urine VMA, mg/day	4.55 (2-25)		
Urine metanephrine ug/day	119.5 (27-220)		
Plasma Renin activity, ng/ml/h	1.2 (0.2-7)		
Aldosterone, ng/dl	9.7 (4.6-40)		

Table 3. Muscle and bone mass values of NFAI and control group

	NFAI group n=39	Control group n=30	
Bone mass (HU)	205 (102-277)	169 (101-306)	P=0.358
Muscle mass (mm^2)	4329 (3289-6687)	4627 (3314-43262)	P=0.506

HU: Hounsfield unit

DISCUSSION

In this study, it was indicated that BMD and paravertebral muscle mass measurements made at the L1-3 vertebra level of patients with NFAI were not different from the control group. To our knowledge, this is the first study to quantitatively compare CT with BMD and muscle mass measurements of these two groups.

Glucocorticoids negatively affect bone metabolism through their receptors and ligands on osteoblasts, osteocytes and osteoclasts. Cortisol excess causes differentiation of mesenchymal progenitor cells preferentially to adipocytes, a decrease in the number of osteoblasts, an increase in osteoblast apoptosis and osteoclastogenesis.[7] Bone density loss and osteoporosis are important complications of glucocorticoid excess. However, initial studies reported that BMD measurements in patients with adrenal incidentaloma with autonomic cortisol secretion were not different from controls. In more recent studies, it has been shown that patients with adrenal incidence and subclinical hypercortisolism have a decrease in BMD value, an increase in fracture risk, and a decrease in TBS, which is an indicator of bone quality. Even moderate cortisol excess may have negative effects on bone mineral density (BMD) and bone quality. Moreover, in

Table 4. The correlations between muscle and bone measurements and biochemical parameters

		Age	Ca	P	Alb	D Vit	PTH	Urea	Crea tine	Na	K	Cor	VMA	Meta nefrin	Renin	Ald
Bone	r	-.38	-.2	-.27	-.41*	-.24	.153	-.06	.007	-.29	-.22	-.01	.201	-.05	-.21	.15
	p	.02	.30	.114	.015	.346	.673	.714	.965	.090	.197	.978	.287	.771	.23	.39
	n	39	36	35	35	17	10	39	38	35	35	30	30	28	32	32
Muscle	r	.37*	-.22	-.02	-.03	.034	-.69*	.042	.190	.273	-.05	-.01	.074	.319	-.17	-.18
	p	.022	.199	.905	.869	.896	.025	.797	.253	.112	.766	.959	.699	.098	.33	.32
	n	39	36	35	35	17	10	39	38	35	35	30	30	28	32	32

Ca: calcium, P: phosphorus, Alb; albumin, Vit D; vitamin D, PTH: parathormone, sKrea: serum creatine, Na: sodium, K: potassium, Cor: cortisole, VMA: vani mandelic acid, Ald: aldosterone

a study, it was reported that TBS was lower in patients with mild cortisol excess compared to patients with NFAI while BMD was similar. Even moderate cortisol excess may have negative effects on bone mineral density (BMD) and bone quality. Moreover, in a study, it was reported that TBS was lower in patients with mild cortisol excess compared to patients with NFAI while BMD was similar.[6-11]

Aldosteron direct effects on bone metabolism through mineralocorticoid receptors. In addition, hyperaldosteronism may cause an increase in extravascular volume, leading to urinary calcium and magnesium excretion and secondary hyperparathyroidism. Moreover, hyperaldosteronism may cause increased oxidative stress by decreasing alpha-1 anti-protease activity and increasing lymphocyte hydrogen peroxide production.[6-11]

Possible reasons for the differences in the results of these studies may be the differences in the criteria used for the diagnosis of mild cortisol excess in the studies, genetic differences, differences in male-female distribution, and gonadal status. In our study, cases with mild cortisol excess were not included. This may be why BMD measurements were similar between the NFAI and control groups. In addition, the effects of cortisol excess on skeleton may differ depending on individual sensitivity to cortisol. The GR polymorphism, changes in co-activator and co-repressor levels, and local cortisol production as a result of 11-beta hydroxysteroid dehydrogenase type 1 activity may be possible causes of this difference. The majority of these studies, which show a decrease in bone mineral density, deterioration in bone quality, and an increased risk of fracture in individuals with adrenal incidental and mild cortisol excess, were conducted in a similar patient population by the same author group. Apart from this, the possible reasons for the differences in the results of the studies in the early period may be the differences in the criteria used for the diagnosis of mild cortisol excess in the studies, the differences in the male-female distribution and gonadal status.[7-10]

There is a positive feedback vicious circle relationship between inflammatory cytokines such as IL-6 and tumor necrosis factor-alpha (TNF-α) in sarcopenia. Sarcopenia may be associated with metabolic syndrome and hyperinsulinemia.[12] The relationship between osteoporosis and metabolic syndrome is controversial, with some studies reporting an association and others not.[13-15]

It has been reported that the increase in proinflammatory cytokines such as TNF-α, IL-6, in patients with NFAI may cause subclinical inflammation and insulin resistance.[13] Increased inflammatory cytokines and insulin resistance are conditions associated with sarcopenia.[12] It has been suggested that increased cortisol in patients with Ai may lead to a decrease in muscle mass.[6] It has also been shown that excess aldosterone causes a decrease in skeletal muscle mass in women.[17] However, the number of studies examining the change in body composition in the adrenal incidentaloma patient group is very few. In a recent study, changes in body composition were investigated by DXA method in patients with adrenal incidentalomas with NFAI and mild cortisol excess and control group. There was no difference between the groups in terms of body composition. However, it has been shown that there is a significant relationship between AI and metabolic syndrome, with an increase in both total fat and body fat index.[18]

In our study, muscle mass was measured only in the paravertebral region and there was no difference between the groups. Measurements were not taken with the DXA method or the bioimpedance method. Again, muscle strength and performance were not evaluated.

Limitations of the study: Our study was conducted in a small patient population.On the other hand, BMD measurements of the femur and vertebrae were not made with the DXA method. Muscle mass was measured only in the paravertebral region, measurements were not taken from other regions. Also, muscle strength and muscle performance were not evaluated for sarcopenia.

CONCLUSION

As a result, no decrease was found in BMD and paravertebral muscle mass values in the measurements made at L1-3 vertebral level with CT in NFAI patients. Further studies are needed in a larger patient population where the results are evaluated together with the femur and vertebral BMD measurements by DXA method, and muscle strength and performance are evaluated in addition to muscle mass in terms of sarcopenia.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Kırıkkale University Medical Faculty Clinical Researches Ethics Committee (Date: 26.06.2019, Decision No: 2019.06.23).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article

In asthma patients: relationship between symptom control, quality of life, and the beck anxiety scale

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ABSTRACT

Aims: Asthma is a chronic disease characterized by recurrent airway obstruction. It affects the quality of life of patients and can lead to anxiety and other psychological disorders. In this study, we aimed to find out how asthma affects patients' quality of life and psychological state by using the SF-36 quality of life scale and the Beck anxiety scale (BAS) in patients diagnosed with asthma.

Methods: 222 patients diagnosed with asthma in our outpatient clinics were included in the study. Patient demographic characteristics and respiratory function test parameters were recorded. Outcomes were determined by assessing asthma control status with the asthma control test (ACT), patients' emotional state with the BAS, and quality of life with the SF-36.

Results: According to ACT, 37.8% of patients were uncontrolled, 33.8% were partially controlled, and controlled 28.4%. The distribution in terms of asthma classification: 29.8% were mild intermittent, 5% mild persistent, 35.1% moderate persistent and 40.1% severe persistent. When comparing between ACT groups in relation to the SF-36 quality of life scale; physical function ($p<0.001$), physical role difficulties ($p<0.001$), emotional role difficulties ($p<0.001$), vitality ($p<0.001$), mental health ($p<0.001$), social function ($p<0.001$), pain ($p<0.001$), and general health ($p<0.001$). There was a difference between the groups ACT in relation to BAS ($p<0.001$).

Conclusion: We believe that when regulating the medical treatment of asthma patients, not only their respiratory functions but also their quality of life and psychological status should be evaluated, and measures should be taken to improve the quality of life and psychological disorders.

Keywords: Asthma, SF-36 quality of life scale, Beck anxiety scale

INTRODUCTION

Asthma, characterized by recurrent airway obstruction, is one of the most common chronic respiratory diseases. It affects millions of people around the world, can occur in all age groups, affects the quality of life of patients, and is therefore a global public health problem.[1]

Nowadays, the main goal of asthma treatment is to control asthma symptoms and improve the quality of life of asthma patients. In monitoring asthma patients, history, physical examination, asthma control test (ACT) and pulmonary function tests (PFT) are performed. In practice, ACT helps us regulate treatment by determining the degree of asthma control in a short time.[2,3]

Studies have shown that asthma symptoms negatively affect a person's quality of life and mood at the same time.

The impact of the disease on the physical, psychological, and social functions of daily living is assessed with quality-of-life surveys.[4,5] A multidimensional assessment can be made with the medical outcomes study short form-36 health survey questionnaire (SF-36), which is a common survey used to measure quality of life in chronic patients.[6]

The Beck anxiety scale (BAS), a scale that provides information about the patient's psychological and emotional state is commonly used in clinical assessment and research.[7]

In our study, the relationship between ACT and SF-36 and the BAS, which reflects the physical, emotional, social, and psychological dimensions of the disease, was investigated in patients treated in our outpatient clinics with a diagnosis of asthma.

METHODS

In our study, 222 patients who were diagnosed as asthma by Policlinics of Chest Diseases in Ankara Training and Research Hospital were prospectively evaluated under written approval of themselves and Ethical Committee. The study was approved by the ethics committee of Ankara Training and Research Hospital with date/no: 10.5.2023/1291. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Patients with chronic respiratory and other chronic systemic diseases except asthma who did not consent to participate were not included in the study. Demographic characteristics,

treatments used, and number of emergency department visits were examined. Income levels were classified as low, middle, and high income levels using 2023 data from the Turkish Institute of Statistics.

Spirometry measurements were performed according to the acceptance and repeatability criteria using Sensor Medics VMax spectra 229, Bilthoven, The Netherlands.

Asthma control status was assessed with ACT, and patients' physical, psychological, and social functioning and quality of life were measured with SF-36 quality of life scale and BAS.

Asthma Control Test

ACT is a valid and reliable test. It is a questionnaire consisting of 5 main items that allow assessment of disease control itself, the extent to which asthma interferes with daily activities, the frequency of asthma symptoms during the day and night, and the need for emergency medication.[8-10] In our study, ACT was administered by a physician in a face-to-face interview. According to the total score, 25 points were considered control, 20-24 points were considered partially control, and <19 points were considered uncontrolled.

SF-36 Quality of Life Scale Questionnaire

SF-36 is a self-assessment scale of patients. The SF-36 questionnaire (Medical Outcomes Survey Short Form-36) its Turkish version was translated by Fidan et al. was used to assess patients' quality of life, and The SF-36 questionnaire was given to the patients and they were asked to complete it themselves before the examination. The survey questionnaire SF-36 consists of 8 main headings and 36 questions: physical functions, physical role difficulties, pain, general health, vitality, social functions, emotional role difficulties, mental health. Separate scores are obtained for each subscale and the person's current health status is assessed. The subscale scores range from 0 to 100, with a high score indicating good health.[11]

Beck Anxiety Scale

The BAS is a self-report scale designed to measure somatic, emotional, cognitive, and motivational components. It is a screening questionnaire commonly used in clinical practice and research that allows patients to provide information about themselves and to indicate some of the symptoms they experience when they are anxious or fearful. 0-7 scores indicates minimal anxiety, 8-15 scores indicates mild anxiety, 16-25 scores indicates moderate anxiety, and 26-63 scores indicates severe anxiety.[7]

Statistical Analysis

The study data were analyzed using IBM SPSS Version 23 for Windows (IBM Statistical Package for Social Sciences). Descriptive statistics for categorical variables were presented as numbers and percentages. The comparison of categorical variables was performed using the "Pearson Chi-Square Test" and "Fisher's Exact Test." The normality distribution of numeric variables was assessed using either the "Kolmogorov-Smirnov" or "Shapiro-Wilk" tests. Descriptive statistics for numeric variables were presented as mean (±) standart deviation for parametric variables and as median (min-max) for non-parametric variables. For the comparison of multiple groups, One-Way ANOVA and the Kruskal-Wallis test were used for parametric and non-parametric numeric variables, respectively. The Bonferroni-Tukey correction test was applied to elucidate pairwise differences among multiple groups. Statistical significance levels were considered as $p<0.05$ and were further interpreted as $p<0.001$.

RESULTS

The mean age of patients participating in the study was 50.9±15.3 years and 51.8% were female gender. 25.7% of the patients were smokers. 73% of the patients were married, and 23.9% were literate. In terms of income, middle level income was most frequently detected, it was 59%. According to ACT, 37.8% of patients were uncontrolled, 33.8% were partially controlled, and controlled 28.4%. It was found that 71.6% of women and 28.4% of men were admitted to the emergency department because of asthma. The distribution in terms of asthma classification: 29.8% were mild intermittent, 5% mild persistent, 35.1% moderate persistent and 40.1% severe persistent. The median follow-up time for asthma was 3 years, and irregular follow-up was observed in 60.4% of patients. Demographic, clinical characteristics, SF-36 quality of life scale and Beck anxiety scale results according to asthma severity were shown Table 1. Regarding educational status, it was found that educational level was lower in subjects with moderate and severe asthma, while educational level was higher in subjects with normal and mild asthma ($p<0.001$). In terms of income level, it was found that the income level of individuals with normal asthma severity was higher than that of the other groups ($p<0.001$). While non-smokers formed the majority in the group with normal and mild asthma severity, the number of smokers was higher in the group with moderate and severe asthma ($p<0.001$). Gastroesophageal reflux was found more frequently in the group with moderate and severe asthma severity ($p<0.001$). The rate of emergency department admissions was found to increase with increasing asthma severity ($p<0.01$).

According to the severity of asthma (normal, mild, moderate, and severe), no statistically significant difference was found between groups in terms of FEV_1 value ($p=0.090$). No statistically significant difference was found between ACT groups (not controlled, partially controlled, controlled) in terms of FEV_1 value ($p=0.239$). FEV_1 was lower in women (2.4 vs. 3.5, $p<0.001$). Characteristics of pulmonary function tests in relation to asthma control status was shown Table 2.

When comparing between ACT groups in relation to the SF-36 quality of life scale; physical function ($p<0.001$), physical role difficulties ($p<0.001$), emotional role difficulties ($p<0.001$), vitality ($p<0.001$), mental health ($p<0.001$), social function ($p<0.001$), pain ($p<0.001$), and general health ($p<0.001$). There was a difference between the groups ACT in relation to BAS ($p<0.001$). It was observed that as asthma control decreased, SF-36 scores decreased and BAS scores increased. SF-36 quality of life scale and Beck anxiety scale results according to asthma control test were shown Table 3.

According to asthma classification (intermittent, mild persistent, moderate persistent, severe persistent), there was a difference between groups in all characteristics of SF-36 (Table 4). Looking at all the subscores of the quality of life scale SF-36, we find that the scores decrease with increasing asthma class. While the decrease in scores is evident in the moderately persistent group, the severely persistent group is the group with the lowest scores on the SF-36 quality of life scale.

Table 1. Demographic, clinical characteristics, SF-36 quality of life scale and Beck anxiety scale results according to asthma severity

	Normal (n=58)	Mild (n=74)	Moderate (n=55)	Severe (n=35)	p
Age, years	48.3±16.6	47.2±14.9	54.5±11.3	57.6±16.4	**0.001**[1]
Gender, M/F (%M)	21/37 (36.2%)[a]	53/21 (71.6%)[b]	26/29 (47.3%)[a]	15/20 (42.9%)[a]	<0.001[2]
Marital Status					
•Single	9 (15.5%)	11 (14.9%)	2 (3.6%)	2 (5.7%)	
•Married	45 (77.6%)	47 (63.5%)	46 (83.6%)	24 (68.6%)	**0.024**[2]
•Widowed	4 (6.9%)	16 (21.6%)	7 (12.7%)	9 (25.7%)	
Education Level					
•Illiterate	4 (6.9%)[a]	9 (12.2%)[a,b]	18 (32.7%)[c]	11 (31.4%)[c]	
•Literate	6 (10.3%)[a]	23 (31.1%)[b]	17 (30.9%)[b]	7 (20%)[b]	
•Primary school	9(15.3%)[a]	11 (14.9%)[a]	10 (18.2%)[a]	13 (37.1%)[a]	**<0.001**[2]
•Middle school	7 (12.1%)[a]	16 (21.6%)[a]	5 (9.1%)[a]	1 (2.9%)[a]	
•High school	16 (27.6%)[a]	12 (16.2%)[b]	4 (7.3%)[b]	3 (8.6%)[b]	
•University	16 (27.6%)[a]	3 (4.1%)[b]	1 (1.8%)[b]	0 (0%)[b]	
Income Level					
•Low	4 (6.9%)[a]	10 (13.5%)[a,b]	25 (45.5%)[c]	10 (28.6%)[b,c]	
•Middle	22(37.9%)[a]	57 (77%)[b]	29 (52.7%)[a,c]	25 (71.4%)[b,c]	**<0.001**[2]
•High	32 (55.2%)[a]	7 (9.5%)[b]	1 (1.8%)[b]	0 (0%)[b]	
Pulmonary Function Test					
•FEV1	3.2±0.9	2.9±0.8	2.8±0.6	2.9±0.9	0.090[1]
•FEV1/FVC	0.79±0.03	0.79±0.03	0.78±0.02	0.77±0.03	<0.001[1]
Asthma Control Status					
•Uncontrolled	0 (0%)[a]	6 (8.1%)[a]	43 (78.2%)[b]	35 (100%)[c]	
•Partial control	9 (15.5%)[a,b]	54 (73%)[c]	12 (21.8%)[b]	0 (0%)[a]	<0.001[2]
•Total control	49 (84.5%)[a]	14 (18.9%)[b]	0 (0%)[c]	0 (0%)[c]	
Asthma Follow-up Duration, years	1.5 (1-6)	3 (1-6)	4 (1-8)	4 (1-6)	**<0.001**[3]
Smoking Status:					
•Non-smoker	50 (86.2%)[a]	60 (81.1%)[a]	21 (38.2%)[b]	12 (34.3%)[b]	
•Smoker	6 (10.3%)[a]	13 (17.6%)[a]	22 (40%)[b]	16 (45.7%)[b]	**0.001**[2]
•Former smoker	2 (3.4%)[a,b]	1 (1.4%)[b]	12 (21.8%)[c]	7 (20%)[a,c]	
Reflux, yes/no (yes%)	30/28 (51.7%)[a]	41/33 (55.4%)[a,b]	42/13 (76.4%)[b]	27/8 (77.1%)[b]	0.007[2]
Hospitalization due to asthma, yes/no (yes%)	0/58 (0%)[a]	1/73 (1.4%)[a]	29/26 (52.7%)[b]	33/2 (94.3%)[c]	**0.001**[2]
SF 36 Features					
•Physical function	100 (0-100)	70 (35-100)	50 (0-85)	0 (0-50)	<0.001[3]
•Physical role difficulty	100 (0-100)	100 (0-100)	0 (0-0)	0 (0-0)	<0.001[3]
•Emotional role difficulty	100 (0-100)	100 (0-100)	0 (0-100)	0 (0-0)	<0.001[3]
•Vitality	100 (0-100)	62.5 (20-90)	45 (0-70)	10 (0-50)	<0.001[3]
•Mental health	96 (0-100)	64 (20-88)	48 (8-72)	20 (0-56)	<0.001[3]
•Social function	100 (0-100)	75 (50-100)	50 (25-62.5)	0 (0-50)	<0.001[3]
•Pain	100 (0-100)	77.5 (65-100)	55 (42.5-65)	0 (0-55)	<0.001[3]
•General health	95 (0-1000)	65 (30-90)	35 (5-75)	0 (0-35	<0.001[3]
Beck Anxiety Scale					
•Normal	55 (94.8%)[a]	57 (77%)[b]	1 (1.8%)[c]	0 (0%)[c]	
•Light	1 (1.7%)[a]	9 (12.2%)[a,b]	9 (16.4%)[b]	0 (0%)[a,b]	0.001[2]
•Middle	1 (1.7%)[a]	8 (10.8%)[a]	16 (29.1%)[b]	3 (8.6%)[a,b]	
•Severe	1 (1.7%)[a]	0 (0%)[a]	29 (52.7%)[b]	32 (91.4%)[c]	

[1]One Way ANOVA [2]Pearson Chi-Square test [3]Kruskal Wallis test The upper character, which is different from the upper characters in the other column, shows the difference between the groups according to the row.

Table 2. Characteristics of pulmonary function tests in relation to asthma control status

	Not controlled (n=84)	Partially controlled (n=75)	Controlled (n=63)	p
FEV1	2.85±0.8	2.9±0.8	3.1±0.9	0.239[1]
FEV1/FVC	0.78 (0.72-0.84)	0.79 (0.74-0.94)	0.8 (0.72-0.94)	0.001[2]

[1]One-Way ANOVA [2]Kruskal Wallis test

Gastroesophageal reflux (GER) was found in 63.1% of patients and was similarly frequent in both genders. When the SF-36 characteristics were assessed according to the presence of GER; while there was no difference between the groups in physical function, mental health and pain (p=0.146, p=0.062 and p=0.057, respectively), physical role difficulties, emotional role difficulties, vitality, social function and general health (p=0.001, p=0.002, p=0.042, p=0.003, p=0.011). It was found that SF-36 values were lower in GER group.

Table 3. SF-36 Quality of life scale and Beck anxiety scale results according to asthma control test

	Not controlled (n=84)	Partially controlled (n=75)	Controlled (n=63)	p
SF 36 Features	47.5 (0-85)	75 (30-100)	100 (0-100)	<0.001[1]
•Physical function	0 (0-100)	100 (0-100)	100 (0-100)	<0.001[1]
•Physical role difficulty	0 (0-100)	100 (0-100)	100 (0-100)	<0.001[1]
•Emotional role difficulty	20 (0-70)	60 (20-100)	90 (0-100)	<0.001[1]
•Vitality	28 (0-72)	64 (20-100)	88 (0-100)	<0.001[1]
•Mental health	50 (0-75)	75 (50-100)	100 (0-100)	<0.001[1]
•Social function	55 (0-77.5)	77.5 (42.5-100)	100 (0-100)	<0.001[1]
•Pain	25 (0-70)	65 (25-100)	95 (0-100)	<0.001[1]
•General health				
Beck anxiety scale				
•Normal	5 (6%)[a]	49 (65.3%)[b]	59 (93.7%)[c]	
•Light	8 (9.5%)[a]	9 (12%)[a]	2 (3.2%)[a]	
•Middle	17 (20.2%[a]	10 (13.3%)[a]	1 (1.6%)[b]	<0.001[2]
•Severe	54 (64.3%[a]	7 (9.3%)[b]	1 (1.6%)[b]	

[1]Kruskal Wallis test [2]Pearson Chi-square test The upper character, which is different from the upper characters in the other column, shows the difference between the groups according to the row.

Table 4. SF-36 quality of life scale and Beck anxiety scale results according asthma classification

	Intermittent (n=44)	Mild persistent (n=11)	Moderate persistent (n=78)	Severe persistent (n=89)	p
SF 36 Features					
Physical function	100 (0-100)	95 (85-100)	73 (0-100)	50 (0-85)	<0.001[1]
Physical role difficulty	100 (0-100)	100 (50-100)	100 (0-100)	0 (0-100)	<0.001[1]
Emotional role difficulty	100 (0-100)	100 (67-100)	100 (0-100)	0 (0-100)	<0.001[1]
Vitality	100 (0-100)	80 (50-100)	63 (15-95)	35 (0-70)	<0.001[1]
Mental health	100 (0-100)	80 (48-100)	64 (20-88)	36 (0-72)	<0.001[1]
Social function	100 (0-100)	100 (75-100)	75 (0-100)	50 (0-63)	<0.001[1]
Pain	100 (0-100)	100 (100-100)	78 (0-100)	55 (0-65)	<0.001[1]
General health	95 (0-100)	95 (75-100)	65 (0-90)	25 (0-75)	<0.001[1]
Beck anxiety scale					
Normal	42 (95.5%)[a]	11 (100%)[a,b]	59 (75.6%)[b]	1 (1.1%)[c]	<0.001[2]
Light	0 (0%)[a]	0 (0%)[a]	10 (12.8%)[a]	9 (10.1%)[a]	
Middle	1 (2.3%)[a]	0 (0%)[a,b]	8 (10.3%)[a,b]	19 (21.3%)[b]	
Severe	1 (2.3%)[a]	0 (0%)[a]	1 (1.3%)[a]	60 67.4%)[b]	

[1]Kruskal Wallis test [2]Pearson Chi-square test

DISCUSSION

In our study, patients with severe persistent asthma formed the majority (40.1%). It has been reported that the quality of life of asthma patients may deteriorate significantly when symptoms are severe.[4,12,13]

Studies have reported that the majority of asthma patients were under "partially controlled".[13] In our study, 33.8% of patients were found to be under partially controlled.

In our study, a close relationship was found between ACT and SF-36 and BAS, whereas no relationship was found between ACT and FEV_1. In the study conducted by Bozkurt et al, no significant relationship was found between ACT and PFT. Other studies show that ACT is closely related to patients' quality of life and mood as well as asthma control.[12] ACT is a practical and reliable questionnaire to determine the degree of asthma control. GINA emphasizes that symptom control should be given at least as much importance as respiratory function testing in asthmatics.[1,10,13-16] In our study, PFT, ACT, SF-36 , and the Beck anxiety scale were used in our patients and their relationships with each other were investigated. The fact that in our study, BAS scores were higher and SF-36 scores were lower for quality of life in uncontrolled patients according to ACT results suggests that asthma patients should also be assessed for mood and treated in this regard.[6,17,18]

Trzcincka et al.[17] also mentioned inadequate asthma control in patients with low Beck anxiety scale. Janson et al.[19] found no evidence that patients with diagnosed asthma suffer more frequently from anxiety and depression than patients without asthma.

GER is often associated with asthma and leads to worsening of asthma control. It is important to question GER in asthma patients. Asthma control is facilitated by treating reflux, which greatly affects quality of life. Similar to the study by Bozbaş et al. we found that SF-36 values were lower in patients with GER in our study.[4,13]

In our study, the SF-36 scale scores decreased and BAS increased in patients admitted to the emergency department. Osman et al.[20] have shown that the quality of life of asthma patients deteriorates even when their symptoms are mild. Assessment of emotional state at routine examinations should be considered as part of treatment, especially in patients with low FEV_1 scores and frequent visits to the emergency department, as this affects quality of life.

Study Limitations

Although the study was prospective, it was not possible to show the change in quality of life and BAS as a result of changes in the treatment process of the patients because it was cross-sectional. The results of this study may not be representative of the entire asthma population because of the relatively small number of patients.

CONCLUSION

ACT should be used for asthma diagnosis because it is simple and easy to apply in the clinic. A strong correlation between ACT and quality of life and mood was found. In patients diagnosed with asthma, efforts should be made to improve quality of life by assessing the patient's psychological and physical functioning in addition to medical therapies.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara Training and Research Hospital Clinical Research Ethics Committee. (Date: 10.5.2023, Decision No: 1291).

Informed Consent: All patients signed and free and informed consent form.

Reviewer Evaluation Process: Externally peer-reviewed.

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

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

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Original Article

The place of ultrasonographic imaging in the follow-up of *Helicobacter pylori* infection after diagnosis and treatment

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ABSTRACT

Aims: The objective of this prospective study was to determine the USG findings of antral gastritis caused by *Helicobacter pylori (H. pylori)* infection and to determine the role of ultrasonographic imaging in the follow-up after diagnosis and treatment of this infection.

Methods: This prospective study included patients who were showing symptoms and signs of *H. pylori* infection and were diagnosed with *H. pylori* infection by endoscopic biopsy between November 2022 and October 2023.

The gastric wall thickness was measured and recorded while the patient was in supine position from the anterior wall of the antrum just to the right of the midline using the left lobe of the liver as an acoustic window.

Results: After evaluation of the biopsy samples taken during endoscopic examination, the participants were categorized into 3 groups. The antrum wall thickness was significantly higher in group 2 patients compared to the other two groups. However, no statistically significant difference was found between group 1 and group 3 (group 1-2 $p<0.05$, group 1-3 $p=0.234$, group 2-3 $p<0.05$). The diagnostic value of gastric antrum wall thickness for the diagnosis of H. pylori infection was statistically significant in the ROC curve analysis test with an AUC value of 0.933 within the 95% confidence interval, $p<0.001$.

Conclusion: Our results suggest that USG can detect gastritis caused by *H. pylori* infection and therefore USG may be useful in the follow-up of these patients after diagnosis and treatment.

Keywords: *Helicobacter pylori*, ultrasonography, antral gastritis

INTRODUCTION

Helicobacter pylori (*H. pylori*) is an infectious agent that colonizes in the human stomach, infecting more than half of the world's population, usually causing antral gastritis. However, in some cases, it can cause the development of gastroduodenal diseases such as peptic ulcer, gastric adenocarcinoma and lymphoid tissue lymphoma associated with the gastric mucosa.[1-4] While the incidence varies from region to region, it is one of the most common chronic infectious agents worldwide.[5] The most important risk factors include poor hygiene conditions, low socioeconomic status, crowded environment, contaminated water and food consumption.[6,7] Moreover, albeit not conclusive, the high prevalence in crowded living environments suggests fecal-oral transmission.[8] While the majority of people infected with *H. pylori* develop gastritis, the gastric antrum is the first and most common site of inflammation. Several invasive and non-invasive diagnostic methods are used for the diagnosis of this infection, but none of them is recognized as the gold standard in clinical practice.[9] With effective and long-term treatment, it is possible to eradicate more than 90% of H. pylori.[10]

The inflammation caused by *H. pylori* infection results in thickening of the gastric wall including the mucosal and submucosal layer.[11] The most significant sign of gastrointestinal diseases on radiologic imaging is in most cases increased wall thickness. Following recent technical advances, ultrasonography (USG) has become more important for the diagnosis of different gastrointestinal diseases. USG offers a significant advantage over endoscopy and contrast radiography for its ability to assess changes around the area under examination. In addition, USG provides more detailed information on intestinal wall layers than cross-sectional examinations.[12] Other advantages include easy accessibility, absence of radiation and generally no requirement for pre-procedural preparation.

The objective of this prospective study was to determine the USG findings of antral gastritis caused by *H. pylori* infection and to determine the role of ultrasonographic imaging in the follow-up after diagnosis and treatment of this infection.

METHODS

The study was conducted with the approval of Siirt University Non-invasive Ethics Committee (Date: 2023, Decision No: 80519). We obtained an informed consent form from all patients for procedure. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This prospective study included patients who were showing symptoms and signs of *H. pylori* infection and were diagnosed with *H. pylori* infection by endoscopic biopsy between November 2022 and October 2023. The control group included patients with dyspeptic complaints but without *H. pylori* infection or any gastric pathology on endoscopic biopsy. Patients scheduled for endoscopic examination were referred to our radiology unit before the procedure and an experienced radiologist, who was unaware of the clinical features of the patients, performed transabdominal ultrasonography. Demographics such as age, gender, BMI and smoking history were obtained. Patients younger than 18 years of age, with any known systemic disease, with a prior history of drug use for *H. pylori* infection, who received any systemic antibiotic treatment in the last 3 months, with any known history of malignancy, with a history of gastric surgery, diagnosed with inflammatory bowel disease and with ulcer, malignancy or lymphoma detected during endoscopic procedure were excluded from the study.

Under normal conditions, visualization of the entire stomach is not possible with transabdominal ultrasonography. We therefore preferred the gastric antrum as the measurement site, which is more easily visualized behind the left lobe of the liver and in front of the body of the pancreas. The gastric wall thickness was measured and recorded while the patient was in supine position from the anterior wall of the antrum just to the right of the midline using the left lobe of the liver as an acoustic window (Image). Patients diagnosed with *H.pylori* infection by endoscopic biopsy were initiated on appropriate dose and duration of medical treatment. All patients received a classical 14-day triple therapy protocol consisting of PPI 2×40 mg/day + amoxicillin-clavulanic acid 2×1000 mg/day + clarithromycin 2×500 mg/day. Patients with a history of drug allergy or who were intolerant to the treatment were excluded from the study. After treatment, the same radiologist re-measured the gastric antrum wall thickness using the previous measurement technique and recorded the results. All measurements were performed on a Samsung RS80 EVO (Samsung Medison Co., Ltd., Seoul, Korea) RDUS device using a linear probe with a frequency of 14 MHz.

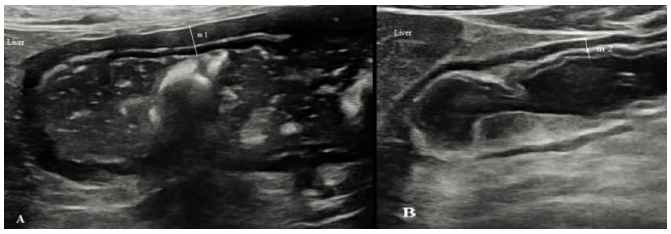

Image: The gastric antrum of a patient with epigastic pain who was diagnosed with H.pylori after endoscopic biopsy is shown by transabdominal ultrasonography before (Picture A) and after treatment (Picture B). The patient had increased antral wall thickness (m1=7.6 mm) which regressed after appropriate treatment (m2=4.3 mm).

Statistical Analysis

SPSS 20.0 program (Statistical Package for the Social Sciences, Chicago, IL) was used for data analysis. During the evaluation of the study data, the conformity of continuous variables to normal distribution was examined by Shapiro-Wilk test. Student's t test was used for paired independent group comparisons and one-way ANOVA was used for comparisons of more than two groups followed by TUKEY test for intergroup differences. The relationship between categorical variables was addressed using Pearson correlation coefficient. The significance level for statistical results was considered as $p<0.05$.

Receiver-operating-characteristic (ROC) curve analysis was used to estimate the diagnostic value of gastric antrum wall thickness in patients with *H. pylori* infection. For the prediction of different models, area under the curve (AUC), cut-off, sensitivity and specificity values were determined.

RESULTS

After evaluation of the biopsy samples taken during endoscopic examination, the participants were categorized into 3 groups. Group 1 included 82 cases without *H. pylori* infection or any pathology on biopsy, group 2 included 122 cases with *H. pylori* infection on biopsy, and group 3 included 109 cases with *H. pylori* infection on biopsy who received treatment and were followed up after treatment.

Demographics such as age, gender, BMI, smoking history and antral wall thickness of the 3 groups were compared (Table 1).

Table 1. Comparison of Intergroup Demographics

Parameter	Group 1 (n=82)	Group 2 (n=122)	Group 3 (n=109)	p
Age, y	39.7±13.2	41.8±13.2	42.1±12.3	.382
Female, n (%)	38(46.3)	64(52.5)	55(50.4)	.800
Male, n (%)	44(53.7)	58(47.5)	54(49.6)	.906
BMI, kg/m²	24.9±3.5	24.1±4.6	24.3±4.6	.351
Smoking, packs/y	12.5±12.9	15.1±16.4	14.1±14.9	.473

SD; Standard deviation, y; year, BMI; Body mass index

No significant difference was found between the groups in terms of age, gender, BMI and smoking habits. Anova was performed to test whether there was a significant intergroup difference in antral wall thickness and the test showed a significant difference between the groups. Tukey test was used to determine the direction of the difference. The antrum wall thickness was significantly higher in group 2 patients compared to the other two groups. However, no statistically significant difference was found between group 1 and group 3 (group 1-2 $p<0.05$, group 1-3 $p=0.108$, group 2-3 $p<0.05$)

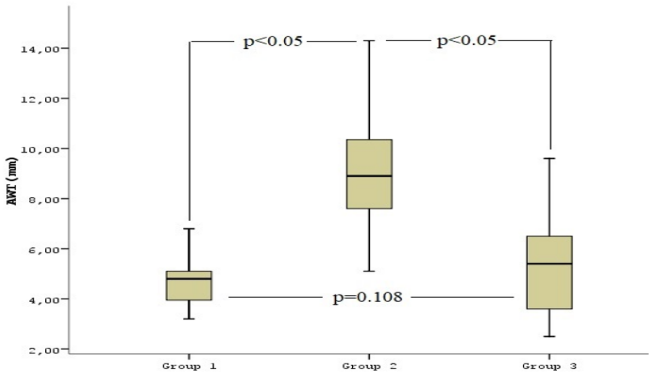

Figure 1. Box plots show the antral wall thickness (AWT) values between group 1 (control group), group 2 (patients with H. pylori before treatment) and group 3 (patients with H. pylori after treatment). The horizontal lines inside each box represent the mean values and the bottom and top rows of each box the minimum and maximum values respectively

(Figure 1 and Table 2).

Table 2. Comparison of antral wall thickness (AWT) values in groups 1, 2 and 3

	Group 1 (n=82)	Group 2 (n=122)	Group 3 (n=109)	p
AWT (mm)±SD	4.76±1.02	9.13±2.11	5.28±1.75	<0.05[a]
Group 1 ve Group 2				<0.05[b]
Group 1 ve Gorup 3				0.108[b]
Group 2 ve Group 3				<0.05[b]

[a]p<0.05 was considered statistically significant (one-way ANOVA).
[b]p<0.05 was considered statistically significant (one-way ANOVA with a post hoc Tukey test).

The diagnostic value of gastric antrum wall thickness for the diagnosis of *H.pylori* infection was statistically significant in the ROC curve analysis test with an AUC value of 0.946 within the 95% confidence interval, p<0.001 (Figure 2).

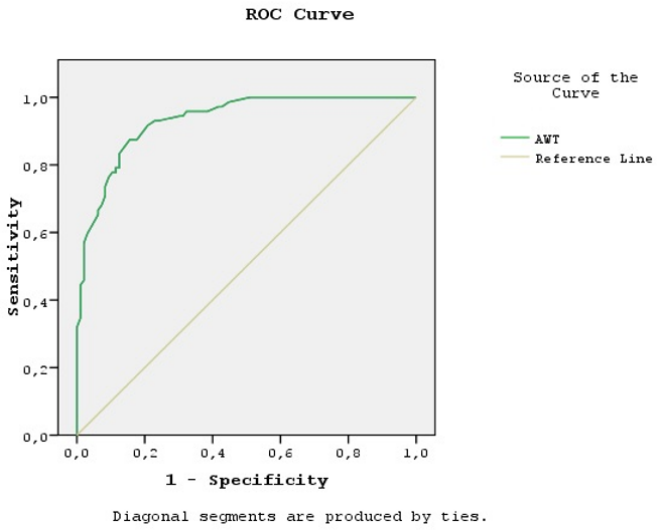

Figure 2. Receiver operating characteristics (ROC) analysis curve of antral wall thickness (AWT) in the diagnosis of *H. pylori* infection

Optimal diagnostic accuracy was determined at values selected for the best odds ratio.

DISCUSSION

The objective of this study was to present transabdominal ultrasonographic findings that may be useful in the diagnosis and treatment of *H. pylori* infection. We hope that confirmation of these results may help in the follow-up of the infection after diagnosis and treatment.

The most common cause of gastric wall thickening is *H. pylori* gastritis.[13] Along with recent technical advances, it is now possible to detect various morphologic features of the gastric walls by USG. Many studies have reported the antrum as the most suitable gastric region for sonographic examination.[1-16] While there is no clinical symptom specific to *H. pylori* infection, the most common symptoms include epigastric pain, dyspeptic complaints, feeling of hunger, bad breath or burning sensation in the stomach. Eradication of the infection is achievable with appropriate treatment which results in a significant reduction of the disease.[11] *H. pylori* infection induces inflammatory changes in the gastric mucosa. Initially, there is involvement of the deep mucosal layer and superficial muscularis mucosa, resulting in gastritis. Due to chronic exposure and high acid environment over time, inflammation spreads to the muscularis mucosa and results in thickening of this layer.[11,17] In their study, Cakmakci et al. found that both the antral wall and mucosal layer increased on sonographic examination in patients with *H. pylori* infection.[11] Consistent with the literature, patients with *H. pylori* infection in our study also had significantly thicker antral wall structure compared to the control group.

Invasive and non-invasive methods are used for the diagnosis of *H. pylori* infection. None of these tests can make a definitive diagnosis. Therefore, at least dual combinations of these tests are recommended for diagnosis, where applicable.[18] Non-invasive methods include urea breath test, serological tests and stool antigen screening. Urea breath test is a reliable non-invasive method to detect urease activity. This test is important as it shows active infection, is rapid and evaluates the response to treatment at an early stage. The most important disadvantages are its high cost and decreased diagnostic value after prior use of antibiotics, proton pump inhibitors or bismuth compounds.[19,20] Serologic tests are a method for detecting antibodies produced by the immune system against the infection by ELISA (enzyme-linked immunosorbent assay). The most important advantages of this method are that it is fast, cheap and easily accessible, while its drawback is poor capacity to detect eradication after treatment.[21] Stool antigen testing is an easy and inexpensive test based on the detection of bacterial antigen in stool by ELISA. It is used to assess eradication after diagnosis and treatment. However, cross-reaction with other *Helicobacter* species in the digestive system constitutes its most important disadvantage.[21] Invasive methods are based on the culture, histopathologic examination, PCR (polymerase chain reaction) and urease tests of the material taken after the endoscopic procedure. Culture is one of the most reliable diagnostic methods that allows the determination of bacterial characteristics and antibiotic susceptibility. Biopsy material is cultivated on a selective medium. However, the long isolation period, laborious and expensive nature are the most important disadvantages.[21-23] Histopathologic examination allows histopathologic study of materials taken from different parts of the stomach. This high sensitive test may give false-negative results in the presence of insufficient bacteria or if the material is taken from the wrong place.[21] The urease test is a method where biopsy material is placed in urea-containing medium to indirectly demonstrate that *H. pylori* produces urease. It is a rapid and reliable test with low post-treatment sensitivity.[24] The polymerase chain reaction is an easy and rapid method that can detect the presence of bacteria even with very small amounts of biopsy specimens. However, an important disadvantage is that it cannot be used in every laboratory.[21,22]

As mentioned above, each test for the detection of *H. pylori* comes with its own advantages and disadvantages. The choice of test for each patient is based on factors that may affect the results of the test, such as cost, clinical status, differences in test performance and antibiotic use.[25] Therefore, given that sonography is a non-invasive, safe, inexpensive and practical examination method, we believe that our sonographic findings will have a significant contribution to the diagnosis of *H. pylori* infection.

Thickening of the gastric wall is the most determinant finding of gastritis and has been demonstrated to improve after appropriate treatment.[9] In this study, we observed that the antrum wall thickness decreased in the control sonographs after appropriate treatment administered to

patients with *H. pylori* infection and there was no statistically significant difference with the control group. From this perspective, we suggest that sonography may have an important role not only in the diagnosis but also in the post-treatment control and follow-up of the infection. Also, to our knowledge, our study is the first to evaluate post-treatment eradication by trasabdominal ultrasonography.

Our study shows that the antrum wall thickness can have a diagnostic power to differentiate patients with *H. pylori* infection with 85% sensitivity and 73% specificity when a cut-off value of 6.9 mm is taken.

Our study had several limiting factors. Firstly, due to the small number of patients, our results should be supported by prospective and controlled studies with a larger patient population. Second, our study was conducted on Caucasian participants from a specific region, so it may not be generalizable to populations of different origins. Third, some of the demographics such as age, gender, height that may affect wall thickness and atrophic changes in the gastric wall that may develop as a result of chronic inflammation due to *H. pylori* infection were not considered in this study. Fourth, a uniform treatment protocol is applied to all patients to eliminate treatment variability.

CONCLUSION

Our results suggest that USG can detect gastritis caused by *H. pylori* infection and therefore USG may be useful in the follow-up of these patients after diagnosis and treatment. As sonography is particularly fast and easily accessible, it can prevent delays in treatment and some unnecessary examinations.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was conducted with the approval of Siirt University Non-invasive Ethics Committee (Date: 2023, Decision No: 80519).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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

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Review

Non-diabetic hypoglycemia

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ABSTRACT

Glucose is the main substrate utilized by the brain, and therefore numerous counterregulatory mechanisms exist to maintain plasma glucose concentration. This makes it rare for hypoglycemia to develop in people who are not taking hypoglycemic drugs, such as insulin or sulfonylureas, for diabetes. The symptoms of hypoglycemia are nonspecific. The presence of Whipple's triad is necessary for diagnosis. When symptoms occur spontaneously, the patient can be evaluated for hypoglycemia. If this is not possible, then a 72-hour fasting test or a mixed meal tolerance test can be performed to create conditions for symptoms to occur. Non-diabetic hypoglycemia is mainly divided into two main groups: insulin-mediated (hyperinsulinism) and insulin-independent. The main causes of hypoglycemia due to endogenous hyperinsulinism are insulinoma and islet cell hyperplasia (nesidioblastosis), post-bariatric surgery, and autoimmune hypoglycemia with the presence of anti-insulin antibodies. Other important causes of hypoglycemia include hypoglycemic drugs, non-islet cell tumors, hormonal deficiencies (primary adrenal insufficiency, anterior pituitary insufficiency), and critical illnesses (liver/kidney failure). In this article, we provide an overview of the pathogenesis and treatment of hypoglycemia.

Keywords: Hypoglycemia, non-diabetic hypoglycemia, insulinoma, nesidioblastosis, postprandial reactive hypoglycemia

DEFINITION OF HYPOGLYCEMIA

Hypoglycemia is a decreasing in plasma glucose concentration enough to cause symptoms. Even when blood glucose is within biochemical norms, rapid and sudden decreasing may cause symptoms. As a result, the definition of hypoglycemia includes the presence of low serum blood glucose, the presence of symptoms, and the improvement of symptoms with glucose intake. Hypoglycemia is usually defined by a plasma glucose concentration below 70 mg/dL; however, there may be no obvious signs and symptoms until the plasma glucose concentration falls below 55 mg/dl. The Whipple triad has been used to define hypoglycemia since 1938.[1] Symptomatic hypoglycemia is clinically diagnosed using the Whipple triad.[2]

The Whipple's triad should be present in cases of true hypoglycemia:

Classic Whipple Triad

1.Symptoms and signs of hypoglycemia
2.A plasma glucose level of 55 mg/dl or less
3.Disappearance of symptoms with glucose administration

Hypoglycemia is a condition frequently encountered in the community during diabetes mellitus treatment. It is rare in older children and adults not receiving diabetes mellitus treatment and may be because of various or multiple etiologies.[2] In healthy individuals, symptoms of hypoglycemia usually develop when the mean plasma glucose is <55 mg/dl. If plasma glucose is <60 mg/dl, it is suspicious; if it is 55 mg/dl, it should be investigated.

Hypoglycemia is rare in people without diabetes mellitus who are not taking hypoglycemic drugs due to the good physiologic efficiency of the counterregulatory mechanisms, i.e., the counter-regulatory system. However, non-diabetic hypoglycemia constitutes a class of endocrine emergencies that should be examined.

SYMPTOMS OF HYPOGLYCEMIA

In the presence of hypoglycemia, the counterregulatory system shows very good physiologic activity.[3] When plasma glucose falls below 70 mg/dl, activation of the counterregulatory system begins, and below 60 mg/dl, increased autonomic activation occurs and symptoms become prominent. Severe symptoms are usually seen when plasma glucose falls below 50 mg/dl. There is a consensus that the threshold for hypoglycemia is 55 mg/dl, but what is important is not the threshold but the association of low blood glucose levels with accompanying clinical symptoms. Hypoglycemia is mostly associated with the following symptoms:[4]

1. Adrenergic symptoms

Symptoms associated with an increased catecholaminergic response, such as sweating, tremors, and palpitations

2. Neuroglycopenic symptoms

Symptoms ranging from dysarthria, confusion, epilepsy, visual and behavioral impairment, and coma caused by a decrease in cerebral glucose concentration

Increased adrenergic activation usually results in minor symptoms, including mild-to-moderate hypoglycemia. Symptoms may vary between individuals, but each individual experiences a similar episode. If plasma glucose decreases even further, glucose entry into the nervous system, especially the brain, is reduced, resulting in neuroglycopenic symptoms. Major symptoms occur, including severe hypoglycemia. ECG changes may also occur in severe hypoglycemia, and QT prolongation may be observed.[5] Hypoglycemia may be asymptomatic or silent, and it is common and often asymptomatic, especially in cases of non-diabetic acute coronary syndrome. Silent hypoglycemia has been associated with silent cardiac ischemia. Silent hypoglycemia is associated with a significantly higher frequency of ventricular extrasystole or non-sustained ventricular tachycardia in patients with acute coronary syndrome.[6] Table 1 shows the minor and major symptoms and signs observed in hypoglycemia. Table 2 shows adrenergic and neuroglycopenic symptoms and signs. Figure 1 shows the glycemic threshold for counterregulatory hormones and the onset of changes in hypoglycemia symptoms in response to hypoglycemia in non-diabetic subjects.[7]

Table 1. Minor and major symptoms and findings in hypoglycemia

Minor Hypoglycemia	Major Hypoglycemia
(The person can handle it himself)	(The person needs someone else's help)
- Feeling of hunger	- Confusion
- Tachycardia, Palpitation	- Cognitive changes
- Shaking, Sweating	- Personality changes
- Paleness	- Coordination difficulty
- Restlessness	- Diplopia
- Dizziness	- Headache
- Defect of vision	- Disorientation
- Tiredness	- Loss of consciousness
- To yawn	- Coma

Table 2. Adrenergic and neuroglycopenic symptoms and findings

Adrenergic	Neuroglycopenic
- Paleness	- Diplopia
- Tremor	- Lethargy
- Irritability	- Difficulty concentrating
- Anxiety	- Confusion
- Tachycardia	- Behavior change
- Palpitations	- Paresthesia
- Sweating	- Fainting
- Weakness	- Convulsion
- Feeling of hunger	- Coma
- Nausea	- Death

ETIOLOGY OF NON-DIABETIC HYPOGLYCEMIA

There are many etiologic factors involved in non-diabetic hypoglycemia. They are generally divided into two main groups:[8]

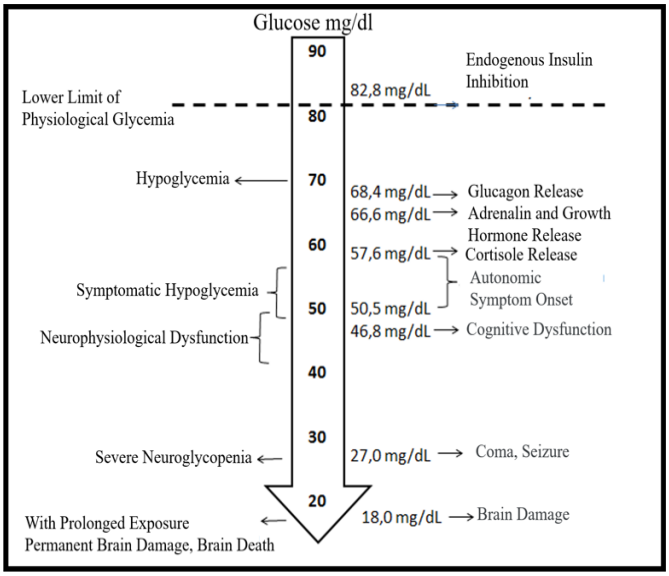

Figure 1. Glycemic threshold for counterregulatory hormones and baseline values of changes in hypoglycemia symptoms in response to hypoglycemia in non-diabetic individuals

1.Insulin-mediated nondiabetic hypoglycemia (hyperinsulinism)

2.Insulin-independent nondiabetic hypoglycemia

Insulin-mediated nondiabetic hypoglycemia is characterized by hyperinsulinism. It is divided into endogenous and exogenous causes. Endogenous causes include insulinoma and islet cell hyperplasia (nesidioblastosis), post-bariatric surgery, and autoimmune hypoglycemia with the presence of anti-insulin antibodies. Exogenous causes are iatrogenic hyperinsulinism and include hyperinsulinemia resulting from the intake of exogenous insulin or insulin secretagogues (sulfonylureas and glinides) in a healthy person, especially factitious hyperinsulinism.

Insulin-independent hypoglycemia; alcohol, visceral insufficiency (liver/kidney failure), critical illness, primary adrenal insufficiency, anterior pituitary insufficiency, severe sepsis, cerebral malaria, anorexia nervosa, cachexia, glycogen storage disease, gastric surgery, mesenchymal tumors with high insulin-like growth factor-2 (IGF-2) levels, autoimmune hypoglycemia with the presence of anti-insulin receptor antibodies, and drugs that cause hypoglycemia. Table 3 lists the causes of nondiabetic hypoglycemia, and Table 4 lists the drugs that may cause or trigger hypoglycemia.

CLASSIFICATION OF NON-DIABETIC HYPOGLYCEMIA

There are two types of non-diabetic hypoglycemia; fasting hypoglycemia and reactive hypoglycemia.[9,10] Table 5 shows the types of non-diabetic hypoglycemia and possible causes.

1. Fasting Hypoglycemia (Postabsorptive)

Occurs in the morning when a meal is skipped or in the time frame of 5 hours after a meal, may be associated with a disease.

2. Reactive Hypoglycemia (Postprandial)

Occurs several hours after eating, usually within 1-4 hours after a meal.

Traditionally, non-diabetic hypoglycemic disorders are classified in this way. This classification has been criticized as being unhelpful diagnostically. This is because some causes of hypoglycemia, such as insulinoma, may present

Table 3. Causes of non-diabetic hypoglycemia

Hypoglycemia with high insulin levels	Hypoglycemia with normal or low insulin levels
Endogenous Causes	**Non-pancreatic Tumors**
• Insulinoma	• Tumors with increased IGF-2 secretion or more frequent precursors (Doege-Potter syndrome)
• Nesidioblastosis	➢ Fibrosarcoma
• Reactive hypoglycemia (hyperinsulinism)	➢ Hemangiopericytoma
• Autoimmune hypoglycemia	➢ Hepatocellular carcinoma
➢ Anti-insulin antibody (Hirata disease)	• Liver-associated malignancies
• Post-bariatric surgery associated hyperinsulinism	➢ Multiple metastases
• Ectopic insulin secretion of non-pancreatic tumors	➢ Hepatocellular carcinoma
• Genetics (congenital hyperinsulinism)	• Medicines
➢ Monogenic causes	• Alcohol
- Beckwith-wiedemann syndrome	➢ Especially excessive drinking -binge drinking-
- Perlman syndrome	• Critical illnesses
- Simpson-Golabi-Behmel syndrome	➢ Liver failure
- Kabuki syndrome	➢ Heart failure
- Sotos syndrome	➢ Kidney failure
- Timothy syndrome	➢ Sepsis
- Costello syndrome (HRAS gene mutation)	➢ Cerebral malaria
- Ondine syndrome	➢ Anorexia nervosa
- Usher type 1c syndrome	➢ Cachexia
- Congenital glycosylation disorder	➢ Malnutrition
➢ Insulin receptor mutation	• Hormone deficiencies
➢ Beta cell insulin secretion regulation gene mutations	➢ Cortisol insufficiency (peripheral adrenal insufficiency)
➢ Channel anomalies	➢ Growth hormone deficiency (hypopituitarism)
- ABCC8 mutation (most common)	➢ Glucagon deficiency
➢ Congenital metabolism errors	➢ Adrenalin deficiency
- Congenital fructose intolerance	• Autoimmune hypoglycemia
- Exercise induced hyperinsulinemia (autosomal dominant)	➢ Anti-insulin receptor antibody
Exogenous Causes	• Early dumping syndrome
• Accidental, covert, or malicious hypoglycemia (iatrogenic or factitious)	➢ After bariatric surgery
➢ Bound to exogenous insulin	- Gastric bypass surgery (roux-en-y operation) – especially
➢ Bound to sulfonylureas or glinides	- Sleeve gastrectomy
• Medications used for therapeutic purposes	➢ Gastrectomy (total or partial)
➢ Tramadol	➢ Esophagectomy (total or partial)
➢ Methadone	➢ Fundoplication (gastroesophageal reflux or hiatal hernia operation)
➢ Cinacalcet	➢ Vagotomy (stomach ulcer treatment)
➢ Topiramate	➢ Pyloroplasty (pyloric stenosis treatment)
➢ Quinolone	• Toxic substances
• Physiological	➢ Toxic hypoglycemic syndrome
➢ pregnancy	- Ake fruit
	• Genetics
	➢ Congenital metabolism errors
	- Glycogen storage disease
	- Fatty acid oxidation disorders
	- Gluconeogenesis disorders
	- Organic aciduria
	- Biotin sensitive multiple carboxylase deficiency
	• Physiological
	➢ Heavy exercise
	➢ Very prolonged hunger

Table 4. Drugs that may cause or trigger hypoglycemia	
- Insulin	- Cinacalcet
- Insulin secretagogues (especially sulfonylureas, meglitinides)	- Ciprofloxacin
- Sulfonamides	- Chloramphenicol
- Tramadol	- Ketoconazole
- Methadone	- Oxytetracycline
- Topiramate	- Isoniazid
- Tyrosine kinase inhibitors	- PAS
- Quinolones (especially 3rd and 4th generations; moxifloxacin, levofloxacin, more rarely ciprofloxacin)	- Ethionamide
- Tigecycline	- P-aminobenzoate
- Anti-malarial drugs (quinine, hydroxychloroquine)	- Acetaminophen
- Derivatives of artemisinin (artesunat, artemeter)	- Indomethacin, propoxyphene, Phenylbutazone
- Quinidine	- MAOI
- Salicylate	- Fluoxetine
- Disopyramide	- Imipramine
- Cibenzoline	- Lithium
- Pentamidine	- IGF-1
- Glucagon (during endoscopy)	- Gabapentin
- Angiotensin converting enzyme inhibitors	- Mifepristone
- Angiotensin receptor blockers	- Heparin
- Non-selective beta-blockers	- 6-Mercaptopurine
	- Trimethoprim-sulphamethoxazole

Table 5. Types of non-diabetic hypoglycemia and possible causes	
Type of Non-diabetic Hypoglycemia	**Possible Causes**
Fasting hypoglycemia	• Tumors or similar formations; tumors that secrete insulin in the pancreas -insulinoma- or hyperplasia -nesidioblastosis-, increased IGF-2 secretion from non-pancreatic tumor • Medicines • Alcohol; especially binge drinking • Serious diseases; those affecting the liver, heart, or kidneys • Serious diseases; those affecting the liver, heart, or kidneys • Low levels-deficiencies of contrainsular hormones such as cortisol, growth hormone, glucagon, or epinephrine • Carbohydrate enzyme defects • Autoimmune (insulin antibodies, insulin receptor antibodies) • Factitious hypoglycemia • Toxic substances; for example, ake fruit causing toxic hypoglycemic syndrome
Reactive hypoglycemia	• Presence of pre-diabetes or risk of diabetes; increased endogenous insulin after meals due to insulin resistance – hyperinsulinemia • Food passes very quickly into the small intestine after stomach surgery. • Rarely, hypoglycemia due to inherited metabolic diseases
* Adapted from reference no 9	

with both postabsorptive and postprandial hypoglycemia. Factitious hypoglycemia may present with symptoms that occur irregularly, independent of food intake. A more useful approach for clinicians is a classification based on clinical features (Table 6). People who appear healthy are likely to have different hypoglycemic disorders than those who are ill.[9]

DIAGNOSTIC APPROACH TO NON-DIABETIC HYPOGLYCEMIA

The diagnostic approach should be started by confirming Whipple's tirade.[11] In patients with Whipple's tirade, non-pancreatic causes should be excluded. Renal, hepatic, and cardiac failure, cortisol and growth hormone deficiency, alcohol intake, drug use, recent surgery, especially bariatric surgery, and psychiatric history should be obtained in detail. It should be borne in mind that the incidence of factitious hypoglycemia is high among healthcare workers.

Blood tests should be evaluated during symptomatic episodes. If hypoglycemia is detected during the symptom, blood samples are taken for tests, and glucose, insulin, c-peptide, proinsulin, and beta-hydroxybutyrate values are examined.[11] Blood tests largely distinguish hypoglycemia caused by endogenous (or exogenous) insulin from hypoglycemia caused by other mechanisms.[10]

In patients who define the Whipple triad but in whom a spontaneous hypoglycemia episode cannot be observed, interventions aimed at triggering hypoglycemia may be performed. The most important tests that can be performed for this purpose are the 72-hour prolonged fasting test and the mixed meal tolerance test.[10] The oral glucose tolerance test (OGTT) is not recommended as a trigger test in the diagnosis of non-diabetic hypoglycemia.[12] There are opinions that limiting the prolonged fasting test to 48 hours is also sufficient to reach the diagnosis.[13] A prolonged fasting test is recommended to determine fasting hypoglycemia, and a mixed meal tolerance test is recommended to confirm postprandial hypoglycemia. Since prolonged fasting test may require fasting for up to 72 hours, this test should be performed in a hospital setting to reduce the risk of hypoglycemia development.[10]

Table 6. Classification of hypoglycemia in adults based on clinical features

Healthy Appearing Individuals	Sick Appearing Individuals
•Medicines	•Medicines
• Insulin or insulin secretagogues	• Insulin or insulin secretagogues
• Alcohol	• Alcohol
• Other drugs	• Other drugs
• Accidental, latent or malicious hypoglycemia	• Critical illnesses
• Endogenous hyperinsulinism	• Hepatic, renal or cardiac failure
- Insulinoma	• Sepsis
-Functional beta cell disorders (Nesidioblastosis)	• Malnutrition
-Non-insulinoma pancreatogenous hypoglycemia	- Anti-insulin antibody
- Post-gastric bypass hypoglycemia	- Anti-insulin receptor antibody
• Insulin autoimmune hypoglycemia	• Hormone deficiency
- Anti-insulin antibody	• Cortisol
- Anti-insulin receptor antibody	• Glucagon and adrenaline
• Idiopathic postprandial hypoglycemia	• Non-islet cell tumor
• Physiological	
- Pregnancy	
- Exercise	

*Adapted from reference no 10

With symptomatic hypoglycemia, blood tests should be measured simultaneously, and a screening for oral hypoglycemic agents (sulfonylureas and meglitinides) should be performed if possible. The glucose response can then be monitored every 10 minutes for 30 minutes with 1 mg intravenous (IV) glucagon stimulation, which strengthens the diagnosis.[2] If the blood glucose level increases more than 25 mg/dl at the end of 30 minutes, these patients have sufficient glycogen storage, and the result is in favor of insulinoma. The absence of an elevation in glucose level indicates that hypoglycemia is due to poor hepatic glycogen reserve/liver failure.[11,14] These tests differentiate hypoglycemia due to hyperinsulinism (endogenous and exogenous) from other causes.[2] Insulin has an anti-ketogenic effect, and plasma beta-hydroxybutyrate levels in insulinomas remain below 2.7 mmol/L during prolonged fasting.[8] In addition, urea and electrolytes, liver function tests, and early morning cortisol; if uncertain, then a short ACTH stimulation test may be performed, and IGF-1 levels, IGF-2 levels if there is a history of weight loss and malignancy, insulin-insulin receptor antibodies may be ordered for differential diagnosis if insulin levels are elevated and partially suppressed c-peptide is present.[8]

The main pathophysiologic feature of endogenous hyperinsulinism is inappropriately high insulin secretion when plasma glucose concentration drops to hypoglycemic levels. In the presence of hypoglycemia-related symptoms, signs, or both, endogenous hyperinsulinism is documented if plasma concentrations of glucose are less than 55 mg/dl (3 mmol/L), insulin is at least 3 mU/L (18 pmol/L), C-peptide is at least 0.6 µg/L (0.2 nmol/L), and proinsulin is at least 5.0 pmol/L.[10] Table 7 shows the differential diagnosis of symptomatic hypoglycemia in prolonged fasting, and Figure 2 shows the diagnostic algorithm for spontaneous hypoglycemia.

48-72 Hour Fasting Test (Prolonged Fasting Test)

The patient must be hospitalized for the test. The patient can consume calorie-free, caffeine-free beverages and should continue normal activity during the test. Unnecessary medications should be discontinued.[11,15] Fingertip capillary blood glucose measurement is performed until the blood glucose value reaches 60 mg/dl; close symptomatic follow-up of the patient is necessary.[11,15] Plasma insulin, c-peptide, proinsulin, and beta-hydroxybutyrate samples should only be sent for analysis in samples with plasma glucose concentrations of less than 60 mg/dl. Fasting is terminated when the plasma glucose concentration falls below 45 mg/dl and the patient has symptoms and/or signs of hypoglycemia (or 72 hours without symptoms). Alternatively, if the Whipple triad has been previously documented with certainty, fasting may be terminated when the plasma glucose concentration is below 55 mg/dl without symptoms or signs.[11] If hypoglycemia

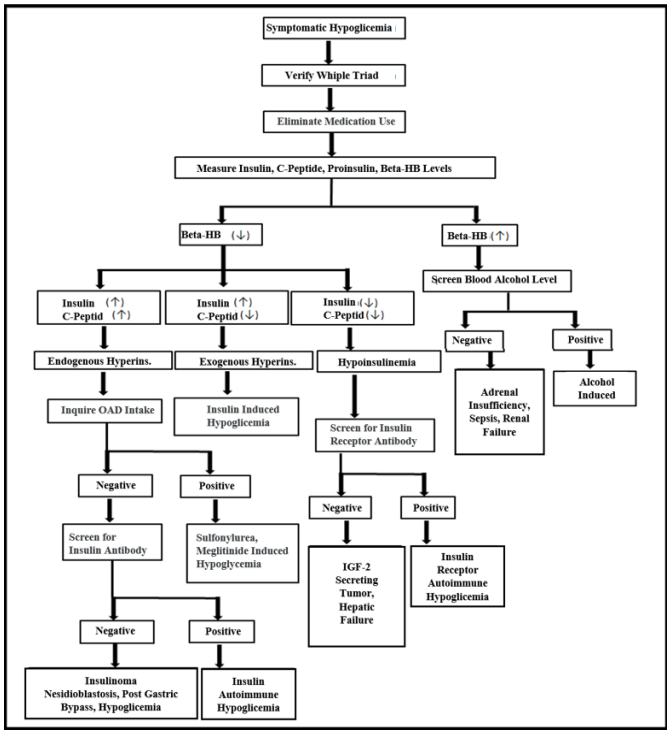

Figure 2. Diagnostic algorithm for spontaneous hypoglycemia
*Beta-HB: Beta-Hydroxybutyrate, *Adapted from reference no. 11

Table 7. Differential diagnosis of fasting hypoglycemia (glucose <55 mg/dl)

Insulin (mU/L)	C-peptide (µg/L)	Proinsulin (pmol/L)	Sulfonylurea	Antibody	Beta-HB (mmol/L)	Glucose response to glucagon (mg/dl)	Diagnosis
↑ ≥3	→ <0.6	→ <5	-	-	→ <2.7	↑ >25	Exogenous insulin intake
↑ ≥3	↑ ≥0.6	↑ ≥5	-	-	→ <2.7	↑ >25	Insulinoma, NIPHS, PGBH
↑ ≥3	↑ ≥0.6	↑ ≥5	+	-	→ <2.7	↑ >25	Sulfonylurea purchase
↑ ≥3	↑ ≥0.6	↑ ≥5	+	+ (Insulin)	→ <2.7	↑ >25	Insulin autoimmune syndrome
→ <3	→ <0.6	→ <5	-	+ (Insulin receptor)	→ <2.7	↑ >25	Insulin receptor autoimmune syndrome
→ <3	→ <0.6	→ <5	-	-	→ <2.7	↑ >25	IGF-2 secreting tumor

* NIPHS: Non-insulinoma pancreatogenous hypoglycemia syndrome, PGBH: Post-gastric bypass hypoglycemia

occurs at the end of the test, 1 mg of IV glucagon is given, and the response in glucose levels is observed. Insulin antibodies can also be measured, but they do not necessarily need to be measured during hypoglycemia.[11]

Mixed Meal Tolerance Test (MMTT)

In postprandial hypoglycemia, a mixed meal tolerance test is an appropriate option. Non-essential medications should be discontinued. After an overnight fast, patients are given a non-liquid meal that typically triggers symptoms of hypoglycemia, called a "mixed meal". A meal determined according to the total caloric need of the patient and corresponding to 25-30% of the daily caloric intake; 50% of the calories are carbohydrates, 33% fat, and 17% protein, and the person is asked to eat the meal in 10 minutes.[16] It is more rational to use a mixed meal that the patient reports cause symptoms.[15] Blood sample is collected for plasma glucose, insulin, c-peptide, and proinsulin before and at 15, 30, 60, 90, and 120 minutes, and at 3, 4, and finally 5 hours after eating.[17] The patient is observed for the development of symptoms. The samples mentioned above are sent for analysis only if glucose is <60 mg/dl.[11,15] If hypoglycemia develops at the end of the test, 1 mg of IV glucagon is given, and the response in blood glucose can be monitored as recommended in the 72-hour fasting test.[11]

Imaging

When insulinoma is suspected, imaging procedures are meaningful only after biochemical confirmation of hyperinsulinemic hypoglycemia. Contrast-enhanced abdominal computed tomography (CT) and abdominal magnetic resonance imaging (MRI) with pancreatic protocols are appropriate imaging options.[11] However, it is not possible to localize almost 30% of neuroendocrine tumors with conventional imaging modalities such as ultrasound, CT, and MRI. Endoscopic ultrasonography is a more sensitive and successful method of detecting the insulinoma focus.[18] The combination of nuclear imaging methods and positron emission tomography (PET)/CT is also a sensitive method for the identification of most insulinomas. 68Ga-DOTA-TATE-PET/CT can be considered an adjunctive imaging study when all imaging procedures are negative and a minimally invasive surgical approach is planned.[19] If clinical symptoms and findings are clearly suggestive of an insulinoma, intraoperative Doppler ultrasonography at the time of resection seems to be the simplest but most sensitive diagnostic method to localize the mass.[20] In selected cases, selective arterial calcium stimulation (SACST) and hepatic venous sampling are effective and safe minimally invasive methods for insulinoma localization and can be used when noninvasive techniques fail.[21]

NON-DIABETIC HYPOGLYCEMIA IN APPARENTLY HEALTHY INDIVIDUALS

Hypoglycemia is a rare metabolic emergency in non-diabetic individuals. Its incidence rate in individuals admitted to hospitals was found to be 0.26% in one study.[22] The rates of plasma glucose levels below 50 mg/dl and 40 mg/dl were found to be 13 and 8 per 10,000, respectively.[23] While hospital admission was to the emergency department with a rate of more than 90%, the cases with plasma glucose levels below 50 mg/dl were listed as follows from most to least frequent: renal disease 32%, sepsis 30%, alcohol 21%, pneumonia 16%, liver disease 16%, congestive heart failure 16%, factitious hypoglycemia 11%, and cancer 5%. In another prevalence study, adrenal insufficiency (34%) and prediabetes (24%) were found to be the most common causes of non-diabetic hypoglycemia in patients followed up in endocrinology clinics. Factitious hypoglycemia was 16%, iatrogenic hypoglycemia 10%, insulinoma 6%, alcohol 2%, and criminal hypoglycemia 1%.[24]

Insulinoma

Insulinoma is a rare neuroendocrine tumor that leads to excessive insulin release and consequently causes symptoms of hypoglycemia in patients, with an annual incidence of 4 per 1 million people. However, it is the most common neuroendocrine tumor of the pancreas. Most occur sporadically, but they may also be associated with multiple endocrine neoplasia type-1 (MEN-1) syndrome. Sporadic insulinomas are typically smaller than 2 cm (90% of cases), solitary (90% of cases), and benign (90% of cases).[25] The most common cause of hyperinsulinemic hypoglycemia in adults is insulinoma. Neuroglycopenic attacks during food deprivation are a typical clinical feature of patients with insulinoma.[26]

Insulinomas are characterized by episodes of hypoglycemia that are normally associated with fasting but may also occur postprandially. If suspected, early referral to a specialized center for testing and confirmatory diagnosis is appropriate because the cure rate with surgical treatment is quite high in the majority of cases.[27]

Non-Insulinoma Pancreatogenous Hypoglycemia Syndrome (NIPHS) - Nesidioblastosis -

Non-insulinoma pancreatogenous hypoglycemia syndrome (NIPHS) is a rare syndrome characterized by pancreatic beta cell hypertrophy leading to endogenous hyperinsulinism and bouts of neuroglycopenia resulting from increased beta cell function.[11] It manifests itself with increased autonomic insulin secretion and a consequent decrease in blood glucose. It is observed in approximately 0.5% to 7% of patients with hyperinsulinemic hypoglycemia.[28] In adults, nesidioblastosis is extremely rare and is mostly diagnosed in adolescence and middle age.[26] NIPHS in adults was formerly referred to as "nesidioblastosis" and was characterized by an increase in the number and volume of beta cells, as in childhood.[29] However, the incidence of NIPHS has started to increase relatively, especially with the increase in bariatric surgical procedures, and has taken its place among the chronic complications of gastric bypass surgery.[28] The clinical features of adult-onset nesidioblastosis can be predominantly determined by postprandial hyperinsulinemic hypoglycemia, a negative 72-hour fasting test, negative preoperative localization studies for insulinoma, and a positive SACST.[26]

Post-Gastric Bypass Hypoglycemia (PGBH)

The incidence of obesity is increasing day by day, and bariatric surgery is becoming an important treatment option for individuals with obesity. Hypoglycemia after bariatric surgery is one of the possible complications of treatment. This condition may present with symptoms and signs ranging from mild hypoglycemic symptoms and signs to neuroglycopenia. The incidence is higher pos-gastric bypass compared to other procedures.

Postprandial hyperinsulinemic hypoglycemia after bariatric surgery is a rarely reported metabolic complication of bariatric surgery and is most commonly associated with Roux-en-Y gastric bypass (RYGB). A consensus has begun to emerge that the main cause is changes in glucose kinetics and changes in gastrointestinal and pancreatic hormone levels involved in glucose homeostasis due to anatomical changes after bariatric surgery.[30] After RYGB, functional increases in insulin secretion occur as a result of increased glucose sensitivity of the beta cell and increased fasting and postprandial secretion of incretin hormones, especially GLP-1.[31]

Postprandial hyperinsulinemic hypoglycemia seen after RYGB surgery has historically been referred to as "late dumping syndrome". This is distinct from the so-called "early dumping syndrome", which is common after RYGB and usually occurs within minutes to 1 hour after ingestion of high-calorie-dense foods (especially refined sugars and fats).[30] Early dumping, a consequence of rapid emptying of food into the jejunum due to surgically altered anatomy, is characterized by vasomotor symptoms (flushing, tachycardia), abdominal pain, and diarrhea. Late dumping is a form of "reactive hypoglycemia". It occurs 1-3 hours after a meal and is the result of an intense insulin response to hyperglycemia caused by the rapid absorption of simple sugars from the proximal small intestine.[32]

However, animal studies have shown an increase in first-phase insulin secretion, pancreatic hyperplasia, improvement in islet cell structure, a marked increase in beta cell mass, a slight increase in the ratio of beta cell area to total pancreatic area, and an increase in the number of small islet cells closely associated with exocrine ducts post-gastric bypass surgery.[33] However, Meier et al.[34] compared the cellular changes in individuals with PGBH after partial pancreatectomy with the pancreas of obese and lean individuals in an autopsy study and sought an answer to the questions of whether beta cell area and beta cell formation increased and beta cell apoptosis decreased in patients with hypoglycemia after PGBH. At the end of the study, it was observed that beta cell area did not increase in individuals with PGBH compared with obese and even lean control subjects. Consistent with this finding, it was found that there was no increase in beta cell formation (islet neogenesis and beta cell replication) or a decrease in beta cell loss in individuals with PGBH.[34] As a result, the view that beta cell hyperplasia seen in individuals with PGBH is actually a relative concept and is due to beta cell hyperplasia that has already developed over the years to compensate for hyperinsulinemia while obesity develops in individuals has prevailed. This view is supported by the finding that hypoglycemia is not completely resolved in individuals with PGBH, even if beta cell mass is reduced by partial pancreatectomy.[35]

Typically, presentation with post bariatric hypoglycemia first occurs 1 year or more postoperatively, with symptoms usually occurring 1 to 3 hours after a meal. Symptomatic hypoglycemia occurring very early in the postoperative period (<6 to 12 months), in a fasting state, or 4 hours after caloric intake is not typical, and other causes of hypoglycemia should be considered in the presence of these conditions.[35] It should be kept in mind that rare cases of NIPHS and insulinoma may also be seen post-gastric bypass.[36,37]

Dumping Syndrome

Dumping syndrome includes gastrointestinal and vasomotor symptoms that occur after eating a meal. Early dumping syndrome occurs 15 minutes to 1 hour after ingestion of food. The symptoms that follow are mainly related to the gastrointestinal tract and are caused by osmotically driven fluid shifts from the blood into the lumen. Symptoms of late dumping syndrome occur 1 to 3 hours after a meal and include mainly vasomotor symptoms. They are caused by reactive hypoglycemia caused by an increase in insulin secretion that overcompensates for the glucose load delivered to the portal circulation. A number of peptides and vasoactive substances contribute to the pathogenesis of both types of dumping: neurotensin, vasoactive intestinal peptides, catecholamines, serotonin, and substance P.[38]

Both dumping syndromes can be seen after bariatric surgical procedures, and the prevalence is close to 10%. It can occur after both sleeve gastrectomy and gastric bypass surgeries, but is significantly more common post-gastric bypass.[38] Early dumping syndrome may also occur after total or partial gastrectomy, total or partial esophagectomy, fundoplication, gastroesophageal reflux or hiatal hernia operation, vagotomy operation for gastric ulcer treatment, or pyloroplasty operation for pyloric stenosis treatment. In addition, signs and symptoms such as postprandial reactive

hypoglycemia, early satiety, and diarrhea may be observed in patients with normal gastric anatomy due to primary accelerated gastric emptying and have been defined as Middleton syndrome.[39]

In Dumping syndrome, symptoms usually improve with regulation of nutrition. There are publications indicating that alpha-glucosidase inhibitors may also be beneficial.

Autoimmune Hypoglycemia

Autoantibodies against insulin cause hyperinsulinism and ultimately hypoglycemia through the inappropriate dissociation of insulin-antibody complexes. Conversely, autoantibodies directed against the insulin receptor cause hypoinsulinemic hypoglycemia by direct stimulation of insulin receptors. Postprandial hypoglycemia is usually observed.[11]

Insulin Autoimmune Syndrome

Insulin autoimmune syndrome (IAS) is a condition to be kept in mind in patients with very high insulin levels and no evidence of insulinoma. It is characterized by spontaneous hypoglycemia, elevated insulin levels, and increased circulating insulin antibodies, and the imaging modalities used to diagnose insulinoma are completely normal. Compared to insulinoma cases, very high insulin levels are observed and are mostly above 1000 mlU/ml.[40] It is a form of immune-mediated hypoglycemia that develops in the presence of a predisposing genetic predisposition, especially with the effect of a triggering factor such as a drug or viral infection. It is thought that there is a strong association, especially with drugs containing the sulfhydryl group, and methimazole stands out in terms of causing IAS among drugs containing this group.[41] Drugs that may lead to IAS are listed in Table 8. There are also publications showing an association of IAS with some autoimmune diseases and plasma cell dyscrasias.[40]

In approximately 80% of patients with IAS, hypoglycemia resolves spontaneously after less than 3 months without any special treatment other than prevention of drug exposure, but persistent hypoglycemia may also be observed in some patients. In drug-induced cases, treatment consists of discontinuation of the responsible drug, small and frequent feedings six or more times a day, and a low-carbohydrate diet. For hypoglycemia, alpha-glucosidase inhibitors (acarbose, miglitol) may help by reducing glucose uptake in the intestines and preventing postprandial excess insulin secretion by beta cells. If hypoglycemia persists, high-dose steroid therapy (prednisolone 30-60 mg/day), immunosuppressive therapy (azathioprine or 6-mercaptopurine), or plasmapheresis may be considered. In addition, rituximab, an anti-CD20 monoclonal antibody, suppresses insulin autoantibodies by blocking de novo antibody responses and can be used in treatment.[41,42] Somatostatin analogs, diazoxide, and even pancreatectomy have been proposed as strategies to reduce insulin release with variable results.[41]

Insulin Receptor Autoimmune Syndrome

Autoantibodies to the insulin receptor are rare and typically cause severe insulin resistance and hyperglycemia, a condition referred to as type B insulin resistance. Rarely, antibodies against the insulin receptor can also cause hypoglycemia.[43-45]

However, in one quarter of patients with type B insulin resistance, autoimmune-mediated hypoglycemia may develop during the clinical course. In some patients with autoantibodies to the insulin receptor, pure hypoglycemia may occur without any evidence of insulin resistance or hyperglycemia. In such cases, the mechanism of hypoglycemia is insulin receptor agonism.[43] The association with systemic autoimmune diseases, especially systemic lupus erythematosus, is very high and is more common in women.[43,44] Mixed connective tissue disease is another common autoimmune association. The presence of antibodies directed against the insulin receptor has also been shown very rarely in malignant cases such as multiple myeloma and Hodgkin lymphoma.[40] Hypoglycemia cases with only insulin receptor autoantibody positivity in the absence of another disease may also be observed.[45]

In the presence of marked hypoglycemia, low insulin and c-peptide levels and concomitant IGF-2 levels within normal limits or low are decisive in the diagnosis. Attacks may be observed as both fasting hypoglycemia and postprandial hypoglycemia.[43,45] Glucorticoids and rituximab are among the recommended treatments. Plasmapheresis also has a role in treatment success. Treatment with immunosuppressive agents, such as azathioprine and cyclophosphamide, may also be used. In most cases, various combinations of these treatment modalities are the most commonly used treatment modalities.[43-45]

Table 8. Drugs that can cause insulin autoimmune syndrome

-	Methimazole
-	Carbimazole
-	Alpha lipoic acid
-	Pyritinol
-	Glutathione
-	Methionine
-	Captopril
-	Hydralazine
-	Procainamide
-	Diltiazem
-	Clopidogrel
-	D-penicillamine
-	Penicillin G
-	Imipenem
-	Isoniazid
-	Hydralazine
-	Alpha-mercaptopropionyl glycine
-	Pantoprazole
-	Omeprazole
-	Tolbutamide
-	Gliclazide
-	Steroids
-	Diclofenac
-	Loxoprofen-sodium
-	Tolperisone hydrochloride
-	Albumin

Factitious Hypoglycemia

Factitious hypoglycemia results from inappropriate use of hypoglycemic agents, such as insulin or oral insulin secretagogues; it may be accidental, covert, or malicious. It is more common in healthcare workers, relatives of those receiving diabetes treatment in the family, or those with a history of psychiatric comorbidity.[11] In covert drug intake, individuals aim to obtain "patient" status. For this purpose, they may accept invasive procedures, including laparotomies and sometimes even resections of the pancreas.[46] Evaluation of plasma levels of sulfonylureas should be performed in every case of hyperinsulinemic hypoglycemia, especially if the patient is likely to have access to the drug at work or in the family.[47] Accidental hypoglycemia, on the other hand, occurs when there are medical treatment errors or medication errors, especially pharmacy errors, for example, incorrectly administering a sulfonylurea for another drug.

In general, individuals with factious disorders tell their story in a dramatic way but are quite vague and inconsistent when asked to provide more details.[48] Factitious hypoglycemia resulting from the surreptitious self-administration of insulin or a hypoglycemic agent is usually manifested by irregularly occurring neuroglycopenic symptoms. A stepwise approach and psychiatric evaluation are necessary to provide appropriate guidance and supportive follow-up.[23]

Hypoglycemia of Non-islet Cell Tumors

Hypoglycemia due to non-pancreatic tumors is rarely seen. These tumors, also called non-islet cell tumors, are often caused by an increase in IGF-2, a peptide that activates the insulin receptor.[49] Ectopic insulin secretion has been reported in a few cases, but most have not been convincingly proven.[50] Nevertheless, extrapancreatic insulin-secreting neuroendocrine tumors with hyperinsulinemic hypoglycemia have been reported very rarely.[51]

Non-islet cell tumor hypoglycemia (NICTH) is most commonly seen in tumors of mesenchymal or hepatic origin, but a wide variety of tumor types can cause large IGF-2 production.[50,52] It can be seen especially frequently in solitary fibrous tumors.[53] Fibrosarcoma, leiomyosarcoma, hemangiopericytoma, and mesothelioma are the most common tumors in which NICTH is found.[50,52] Other reported tumors include adenocarcinomas such as large-cell lung adenocarcinomas, ovarian adenocarcinomas, gastrointestinal stromal tumors, and renal cell carcinoma. In tumors with abnormal IGF-2 gene transcription and gene expression, the precursor of IGF-2, 'big' IGF-2, is hypersecreted with incomplete translation. High circulating IGF-2 activates the insulin receptor and causes hypoglycemia.[49]

The clinical features of NICTH result from recurrent episodes of fasting hypoglycemia and tumor growth and spread. The diagnosis of NICTH includes low glucose levels (serum glucose <55 mg/dl) with concurrent low insulin/proinsulin/c-peptide/β-hydroxybutyrate levels and the absence of positive results in screening for oral hypoglycemic agents.[51] Even when IGF-2 levels are normal, IGF-I levels are suppressed, and therefore the IGF-2:IGF-1 ratio increases above the normal molar ratio of 3:1 and frequently approaches or exceeds 10:1.50 Especially in benign solitary fibrous tumors, response to treatment is good, and hypoglycemic attacks end after complete resection.[53]

TOXIC HYPOGLYCEMIA

Alcohol-Induced Hypoglycemia

Alcohol is an important cause of fasting hypoglycemia. It is a rare phenomenon in normal, healthy individuals. It is more common in malnourished individuals, binge drinkers, accidental children, diabetics using insulin or oral drugs, Addison's disease, pituitary insufficiency, and hyperthyroidism. Alcohol may especially exacerbate insulin and sulfonylurea-induced hypoglycemia.[54]

The liver is the key to glucose homeostasis. Numerous drugs, including alcohol, can alter intrahepatic pathways vital for normal glucose production by the liver, resulting in hypoglycemia.[55] Hepatic autoregulation and neurohumoral mechanisms play a role as glucose counterregulatory mechanisms to prevent hypoglycemia and during hypoglycemia. Hepatic autoregulation primarily involves glycogenolysis and gluconeogenesis. One of the main factors contributing to the development of hypoglycemia with alcohol consumption is the inhibitory effect of alcohol on gluconeogenesis. This effect depends on the amount of alcohol consumed and the underlying nutritional status of the individual. In a healthy person with normal glycogen reserves, alcohol has rarely been shown to cause hypoglycemia within 8-12 hours (overnight fasting). However, acute alcohol intake after fasting for 3 to 4 days can cause severe and prolonged hypoglycemia in healthy individuals. Individuals with diabetes, impaired liver function, and malnutrition are at higher risk.[54]

Toxic Hypoglycemic Syndrome

Toxic hypoglycemic syndrome is a condition that is more common in tropical regions, occurs especially as a result of ingestion of unripe ake fruit, and may have a mortal course.[56] In this toxic condition, known as "Jamaican vomiting disease", clinical symptoms may include excessive vomiting, altered mental status, and hypoglycemia. Severe cases have been reported to cause seizures, hypothermia, coma, and death.[57]

Hypoglycin A protein found in unripe fruit inhibits gluconeogenesis, causing depletion of glycogen storage and leading to hypoglycemia. Medical treatment is primarily supportive treatment with intravenous fluids and dextrose.[56] Figure 3 shows unripe and ripe ake fruit.

Figure 3. Immature and ripe ake fruit

Postprandial Reactive Hypoglycemia

Postprandial hypoglycemia describes the timing of hypoglycemia (within four hours after meals) and is not a diagnosis in itself.[12] Postprandial hypoglycemia that occurs after food intake is called reactive hypoglycemia.[58] Many conditions may be associated with postprandial hypoglycemia.[12,39]

The term postprandial syndrome is used to describe a disorder observed in individuals with satiety symptoms suggestive of hypoglycemia but without concomitant biochemical evidence of hypoglycemia, usually seen after ingestion of a high-carbohydrate meal, and in whom symptoms disappear after dietary change.[12]

Reactive hypoglycemia is a phenomenon that may be affected by exaggerated insulin release and insulin resistance. The presence or absence of insulin effects in the development of reactive hypoglycemia is related to the duration and

mechanism of hypoglycemia. It is simply divided into late and early reactive hypoglycemia.

Late reactive hypoglycemia usually occurs as part of the insulin resistance syndrome and may be caused by delayed insulin secretion and thus delayed activation of GLUT-4. Inhibition of first-phase insulin secretion may result in late reactive hypoglycemia due to an exaggerated relative increase in second-phase insulin secretion.[58]

Early reactive hypoglycemia occurs in the first 1-2 hours of glucose loading. It may result from accelerated gastric emptying or an exaggerated incretin effect. It is also possible that accelerated gastric emptying leads to an increase in incretin.[39] This is partly mediated by the gut hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) and contributes to early hypoglycemia by causing excessive insulin exocytosis and, in addition, an inadequate response to hypoglycemia by suppressing GLP-1 glucagon.[39,58]

The basis of treatment in individuals with reactive hypoglycemia is a reduced glycemic load and a low glycemic index diet. Low-glycemic-index diets provide significantly lower plasma glucose, serum insulin, and plasma GLP-1 levels during the postprandial period. In such individuals with postprandial autonomic symptoms, avoiding foods high in glucose, consuming foods high in fiber, frequent (every three hours) small meals or snacks, and a regular exercise regimen may significantly contribute significantly to symptom relief. If dietary modification is not successful in reducing symptoms, trying alpha-glucosidase inhibitors to delay carbohydrate absorption and thus reduce the insulin response to a meal may be helpful for some individuals.[12]

TREATMENT

There is a relative increase in the mortality rate among individuals with non-diabetic hypoglycemia. More commonly, an increase in the rate of traffic accidents due to cognitive dysfunction and fatal arrhythmias, such as prolonged QT, may be observed and affect morbidity.[22] Therefore, it is important to raise blood glucose rapidly in cases of hypoglycemia. Emergency treatment of hypoglycemia should be performed with carbohydrate intake if possible or with parenteral glucose if not possible.[15]

Acute Treatment of Hypoglycemia

Treatment depends on the severity of symptoms and the patient's ability to tolerate oral intake. Glucose can be given orally to a patient with conscious neuroglycopenic symptoms. 10-20 grams of glucose are given, and symptoms are monitored. Sugar cubes, glucose tablets, and fruit juices such as orange juice are suitable options. One cube of sugar contains 2.5 grams of glucose, and 4-8 cubes of sugar are consumed quickly. Fast-acting glucose tablets contain 4-5 grams of glucose, and 3-5 are consumed. One glass of orange juice is 200 cc and contains 29 grams of glucose. After 15 minutes, the blood glucose measurement is repeated, and if it is below 70 mg/dl, the treatment is repeated. If there is brain fog or loss of consciousness, IV dextrose treatment should be administered. 50 cc (1 ampoule) IV of 50% dextrose, followed by 10% dextrose infusion at a rate of 100 cc/hour to prevent recurrent episodes of hypoglycemia, is the appropriate treatment option. 1 mg IV, intramuscular or subcutaneous glucagon, or a single dose of 3 mg intranasal glucagon are also among the recommended treatments.[11] After hypoglycemia and state of consciousness improve after both oral and parenteral treatment, the patient is given slowly absorbed carbohydrates orally to prevent a recurrence of hypoglycemia.

Patients with severe, prolonged hypoglycemia may develop hypoglycemic coma due to cerebral edema. This is defined as a decreased level of consciousness that persists for >30 minutes despite correction of hypoglycemia. In the presence of such a condition, 40 g IV mannitol in 20% solution, glucocorticoids (e.g., 10 mg IV dexamethasone), or both are administered over 20 minutes.[11] Figure 4 shows the acute treatment of hypoglycemia.

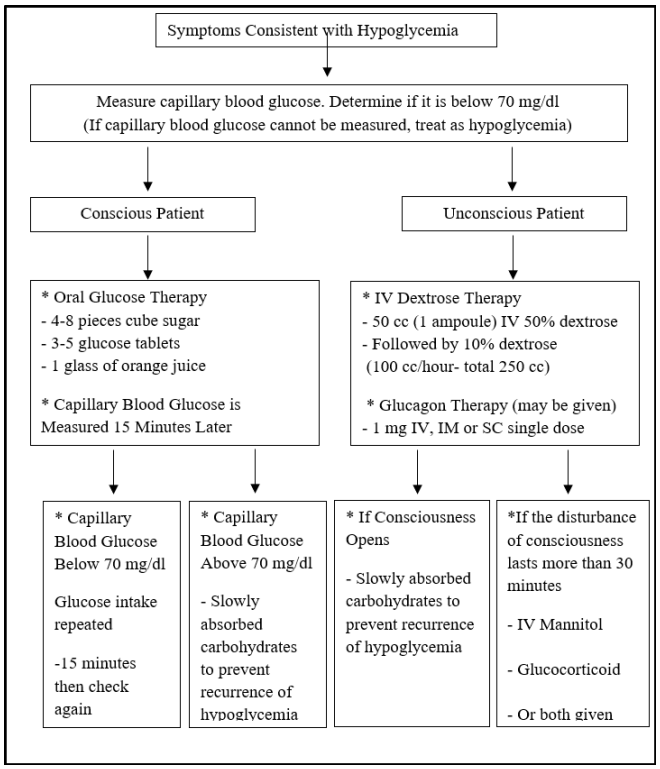

Figure 4. Approach to acute treatment of hypoglycemia

Long-Term Management of Hypoglycemia

The underlying cause should be considered, and the long-term management of hypoglycemia should be tailored accordingly. The management of hypoglycemia should take into account patient well-being and patient preferences and tailor treatment to the specific hypoglycemic disorder. Most hypoglycemic disorders require specialized treatment, such as surgical excision to treat solitary insulinomas. However, in cases such as postprandial reactive hypoglycemia or post-gastric bypass hypoglycemia, appropriate nutritional therapy advice can help manage daily work and activities.[10]

Regulating Diet for Therapeutic Purposes

Dietary interventions may be helpful in non-insulinoma pancreatogenous hypoglycemia, including in patients with Roux-en-Y gastric bypass hypoglycemia. Frequent feeding and a low-carbohydrate diet are common recommendations. In Roux-en-Y gastric bypass hypoglycemia, restricting carbohydrates, avoiding foods with a high glycemic index and simple sugars, and adding protein and fat to every meal are recommended. Gastrostomy tube feeding may be considered in patients with hypoglycemia after the Roux-en-Y gastric

bypass who are resistant to dietary changes.[2]

Medical Treatment

If resection is not possible or as a temporary measure in individuals with hyperinsulinism, medical treatment with alpha-glucosidase inhibitors, calcium channel blockers, diazoxide, or somatostatin analogs may be used.

Alpha-glucosidase inhibitors delay the digestion of ingested carbohydrates, resulting in lower blood glucose concentrations after meals. Acarbose can be used to reduce hyperinsulinism and hypoglycemia after the Roux-en-Y gastric bypass. Calcium channel blockers may help treat hypoglycemia by inhibiting glucose-stimulated insulin secretion from pancreatic beta cells; Verapamil 80 mg twice daily has been reported in the literature, but other agents such as diltiazem and nifedipine have also been used. Diazoxide inhibits insulin secretion by opening ATP-dependent potassium channels in the pancreatic beta cell. Diazoxide is given orally at 3-8 mg/kg/day every 8-12 hours up to 1200 mg/day. Somatostatin analogs (octreotide and lanreotide) inhibit insulin secretion when given in high doses, but may not be as effective as diazoxide. Octreotide is given as a subcutaneous injection, ranging from 100 micrograms twice daily to 1500 micrograms daily, while the longer-acting lanreotide is given monthly. Chemotherapy can be used to treat insulinomas and non-islet cell tumors when necessary. Radiotherapy may also be performed in non-islet cell tumors.[2] Especially in the presence of malignant insulinomas, treatments such as chemoembolization, radiofrequency ablation, radical mass reduction (debulking) surgery, verapamil treatment, octreotide treatment, and chemotherapy can be applied.[59]

CONCLUSION

Non-diabetic hypoglycemia is an important condition that may develop due to a variety of different etiologic factors and should be treated rapidly due to its noisy clinic. Especially untreated fasting, hypoglycemia may lead to severe neuroglycopenia sequelae and even death. Insulinoma is usually a small, solitary, intrapancreatic, benign tumor. It is usually sporadic. However, it may also be associated with MEN-1. The main treatment for insulinoma is surgery. Reactive hypoglycemia is a milder form of hypoglycemia seen in the postprandial period. Untreated reactive hypoglycemia causes discomfort, but leaves no sequelae. Lifestyle changes are recommended and form the basis of treatment. In hypoglycemic conditions that need to be rapidly detected and treated in endocrine emergencies, it is absolutely necessary to investigate the cause after normoglycemia is achieved with emergency treatment.

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Review

Diagnosis and treatment of hepatic encephalopathy - review

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ABSTRACT

Hepatic encephalopathy is observed in patients with liver dysfunction. Therefore, chronic liver disease patients are more affected. Due to reduced liver function, neurotoxins generated by damaged intestinal flora reach the brain. Hepatic encephalopathy can be classified according to the degree of symptoms. Ammonia concentration is thought to be important in pathogenesis. Its early phases can be diagnosed with a variety of tests. And it is possible to resolve and eliminate hepatic encephalopathy with imaging and treatment.

Keywords: Ammonia, cirrhosis, hepatic encephalopathy, liver

INTRODUCTION

Liver cirrhosis can be an outcome of variable causes, such as high alcohol consumption, non-alcoholic fatty liver disease, or viral infections. After an inflammation phase, the liver parenchyma transforms into the fibrosis state, which is followed by the compensated state. The symptomatic period of the disease is the decompensated state,[1] which can cause palpable fluid accumulation in the abdomen and bacterial peritonitis.[2] Liver cirrhosis is a pathological result of chronic liver disease, even though primary cause of cirrhosis is hepatocytes' continuous life-and-death cycle.[3] This cirrhotic process causes deceleration of metabolism in which ammonia is converted to urea. As a result, the ammonia increases in circulation.[4] Hepatic encephalopathy is a complication of cirrhosis, which is responsible for the majority of hospitalizations.[5] It is important to make a differential diagnosis from other neurological and psychological situations which may be present in elders with co-morbid diseases in patients with chronic liver dysfunction and is considered a reversible situation. Toxic substances that accumulate in the brain negatively impact on perception and attention. Sleep patterns are also disrupted.[7] Neurotoxins from the intestine reach the brain due to a damaged liver and are demonstrated to be responsible for the symptoms. Although high ammonia levels are expected, it is not thought to be a predictor factor of the severity of the disease.[8] In this review we aimed to highlight the current approaches to hepatic encphalopaty.

MECHANISM OF HEPATIC ENCEPHALOPATHY

In terms of mechanism, when the liver cannot fully perform, ammonia and other substances accumulate in the brain, causing the volume of astrocytes to expand, which increases oxidative stress. These negative changes disrupt the interaction between the astrocyte and other neurons, and the symptoms increase dramatically. The transport of glutamine to the mitochondria also causes an increase in ammonia production.[9] According to the Trojan horse hypothesis, glutamine transported to the mitochondria triggers the formation of reactive oxygen species and ammonia, which causes an increase in glutamate and glutamine. The process results in a decrease in oxidative phosphorylation capacity. Ammonia has an important role in the impairment of mitochondrial functions. Ammonia causes pH alterations, and although this blocks the later stages of the autophagy process, it leads to the breakdown of mitochondria because it is ubiquitous.[9]

STAGING OF HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy is observed at a scale from minimal hepatic encephalopathy to overt encephalopathy depending on the extent of damage caused.[10] This is known as the West Haven Criteria.[11] Minimal hepatic encephalopathy (MHE) is mostly used to describe changes that can be distinguished by tests. Thus, neurophysiological changes may not affect the consciousness. The lack of awareness, decreased attention, decreased ability to perform tasks, sleep disturbance, anxiety and euphoria are among the prominent features of stage one. Along with minimal hepatic encephalopathy, stage one also described as covert hepatic encephalopathy because of lack of overt encephalopathic features. However, this does not mean that it should not be treated. On the contrary, the patient should be intervened at this stage, as it is a precursor to advanced stages.[12]

In stage two, lethargy or apathy, time disorientation, personality changes, inappropriate behavior, dyspraxia-

planning impairment, and flapping tremor may be observed. Stage two has distinguishing features from stage one by confusing at least three of the following: months, day of the month, day of the week, season, and year. Temporary disorientation distinguishes stage two from stage three, which features prominent hepatic encephalopathy symptoms. In stage three, disorientation is expected to be permanent. There are a semi-dazed state and unusual behaviors. Disorientation increased, and disorientation in spatial perception advanced beyond stage two. At this point, it is possible to report at least three of the spatial parameters incorrectly, such as country, state (or region), city or place. In stage four, the stage of coma is reached and there is no response to painful stimuli. Thus, a patient with hepatic encephalopathy is classified and described according to Table.[11]

Table. Hepatic encephalopathy classification - an example: HE, type C, stage 3 classified as recurrent, precipitous

Type	Stage		Progress	Spontaneous or precipitated
A	MHE	Covert	Episodical	Spontaneous
	1		Recurrent	
B	2	Overt		Precipitated
C	3		Persistant	
	4			

Generally, the pathogenesis is based on three types: In type A, an encephalopathy secondary to acute liver failure is expected. Type B is used to describe hepatic encephalopathy secondary to the presence of portosystemic shunts. In type C, there is a hepatic encephalopathy secondary to cirrhosis.[13]

TESTS AND IMAGING

There are some scoring tests, especially for MHE and stage 1 hepatic encephalopathy. The Psychometric Hepatic Encephalopathy Score (PHES) test is considered the gold standard,[14] assessing psychomotor speed and visuospatial coordination, which is thought to detect neuropsychological deficits in latent hepatic encephalopathy.[15] It includes five widely validated tests: Number connection test (NCT)-A, NCT-B, line tracing test, digit symbol test and serial dotting test (SDT).[16,17] The main problem with this test is that it takes 20-30 minutes to complete, which makes it unpractical. The critical flicker frequency (CFF) test is a neurophysiological test that evaluates the patient's ability to discriminate flickering light using a glasses-shaped device and has been widely validated[18,19] and is comparable to the PHES test.A value below 38 Hz is recommended for detecting latent hepatic encephalopathy.[20] The test is easy to accomplish but the device is expensive. Some tests, such as the stroop test, may also be useful. The stroop test reflects frontal region activity. If the color and the color expressed by the word are not the same, measurement is made based on the patient's reaction.[21] In the animal naming test (ANT), fluency in meaning is analyzed by having as many animal names as possible uttered in one minute. An environment isolated from external factors is required. If the patient pauses for 15 seconds before the extinction of one minute, a clue is given with the name of an animal, and the patient is allowed to continue the test.[22]

In hepatic encephalopathy, neuronal loss and manganese accumulation can lead to bilateral, reversibly symmetrical globus pallidus and substantia nigra T1 hyperintensity. An increase in glutamate and glutamine peaks is expected as a result of hyperammonemia. Cerebral edema may also be observed in hepatic encephalopathy. Cytotoxic edema is expected in acute hepatic encephalopathy, and vasogenic edema is expected in chronic hepatic encephalopathy. However, mixed-type edema is expected later. Preservation of perirolandic areas and the occipital cortex is an important finding in differentiating hepatic encephalopathy from hypoxic-ischemic encephalopathy.[23]

DIFFERENTIAL DIAGNOSIS

If overt hepatic encephalopathy and acute confusional state are considered, diabetic symptoms such as hypoglycemia and ketoacidosis, alcohol intoxication, Wernicke's withdrawal symptoms, drugs such as benzodiazepines, opiates, electrolyte disorders, neuroinfections, psychiatric disorders, intracranial hemorrhage, organ failure, dementia and conditions such as brain lesions must be excluded.[11]

TREATMENT

Constipation plays an important role in the development of hepatic encephalopathy. Therefore, as the transition period without digestion is prolonged, toxic metabolites can be reabsorbed and, cause an increase in ammonia. Lactulose and lactitol are considered first-line treatments because they accelerate the passage.[24]

As portal hypertension increases in the liver, spontaneous portosystemic shunts (SPSS) may occur. Splenorenal shunts, especially those located to the left of the spleno-porto-mesenteric junction ("left side") are most associated with recurrent hepatic encephalopathy.[25,26] Shunt obliteration is among the treatment options because it blocks the passage of ammonia.[24] Transjugular intrahepatic portosystemic shunt (TIPS) is a procedure to reduce portal hypertension. For refractory variceal bleeding and refractory ascites, a stent is placed between the portal vein and the hepatic vein. Therefore, the portal venous flow is shunted directly to the systemic circulation. Thus, it reduces bleeding and ascites and indirectly helps to prevent hepatic encephalopathy.[27,24]

Due to the disruption of intestinal flora in liver cirrhosis, probiotics are growing in popularity and significance. In hepatic encephalopathy, probiotics can be used to regulate the disrupted intestinal flora.[28] Also, there are some studies that suggest fecal microbiota transplantation (FMT) is effective in reducing cognitive impairment and the number of hospitalizations in cirrhotic patients. However, it has not been proven yet that further studies should be followed.

L-ornithine L-aspartate (LOLA): L-ornithine and L-aspartate contain amino acids involved in metabolic pathways that produce urea and glutamine.[24] Ornithine is involved as both an activator and substrate in urea production and aspartate stimulates the synthesis of glutamine, which acts as a substrate in urea production. As a result, ammonia levels are reduced through the liver.[29]

Rifaximin is thought to reorganize the intestinal microbiota, as concluded in a recent study. Bacterial composition and diversity are considered beneficial as it prevents impaired bowel regulation, which is an important cause of hepatic encephalopathy.[30]

CONCLUSION

Hepatic encephalopathy should be considered as a preventable symptom. In cases of possible liver failure where hepatic encephalopathy is considered, differential diagnoses should be carefully evaluated with the principle that "non est morbus, ibi est patientes estote": There are no diseases, there are patients. Healthcare providers should be alert for the early stages of hepatic encephalopathy, and awareness of early diagnosis and treatment should be increased.

ETHICAL DECLARATIONS

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Case Report

An uncommon side effect: amiodarone-related hypothyroidism in a patient with negative thyroid autoantibodies

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ABSTRACT

Amiodarone is an antiarrhythmic drug frequently used in cardiac dysrhythmias. One of the most important side effects of amiodarone is thyroid dysfunction. Amiodarone-induced thyrotoxicosis (AIT) and amiodarone-induced hypothyroidism (AIH) can occur depending on individuals' iodine status and previous thyroid disease. In this case, we aimed to present the hypothyroidism that developed in a patient with negative thyroid autoantibodies after amiodarone use.

Keywords: Amiodarone, levothyroxine, hypothyroidism

INTRODUCTION

Amiodarone is one of the antiarrhythmic drugs used in cardiac rhythm disorders.[1] However, there are limitations of usage due to its iodine content.[2] One of the side effects of amiodarone is dysfunction of thyroid glands.[3] Amiodarone-induced thyrotoxicosis (AIT) or amiodarone-induced hypothyroidism (AIH) may occur depending on the iodine status of individuals and previous thyroid disease history.[4]

Although AIH is more frequently seen in female patients with positive thyroid autoantibodies, it has been reported in autoantibody-negative patients in the literature. There is limited data on the prognosis of these patients in the literature. With this case report, we aimed to describe the challenges in the management of AIH in a patient with comorbidities.

CASE

A 75-year-old female patient was admitted to our internal medicine clinic with muscle weakness, and edema in the extremities and periorbital region that had increased in the last 3 months. In her medical history, she was under medication of furosemide for congestive heart failure and subcutaneous insulin for diabetes mellitus. She also had a history of one hemodialysis session a few months ago for ultrafiltration in the intensive care unit (ICU). After discharge from the ICU, 200 mg amiodarone treatment was started for supraventricular tachycardia. She had no history of alcohol or smoking.

In physical examination, she had bilateral edema in the lower extremities, on the dorsal face of the hand, and in the periorbital region. The head and neck examinations were normal, and the thyroid glands were non-palpable. In her chest examination, rales and rhonchi were present prominently on the right lung. Her heart and abdominal examinations were normal. Her blood pressure was 130/70 mmHg, and her pulse rate was 64 beats/minute. Her oxygen saturation was normal. Her electrocardiogram was in normal sinus rhythm. Her laboratory findings were as follows: creatinine: 4.7 mg/dL, BUN: 52 mg/dL PH: 7.38, HCO_3: 23.8 mEq/L, PCO_2: 38.7 mm/Hg, Hb: 8.5 g/dL platelet count:264000. TSH: 85.5 uIU/L (reference range: 0.35-4.94), triiodothyronine (T3): 0.67 pg/mL (reference range: 1.71-3.71), and T-thyroxine (T4): 0.46 (reference range: 0.58-1.64). Thyroid function tests were normal four months ago. Her thyroid autoantibodies were negative. Her thyroid ultrasound imaging (USG) showed a heterogeneous appearance with decreased echogenicity which suggests thyroiditis (**Figure 1**).

She was diagnosed with amiodarone-related hypothyroidism. After cardiology consultation amiodarone treatment was stopped, and diltiazem treatment was started with levothyroxine replacement. During follow-up, she needed oxygen therapy despite intensive diuretic treatment. Because of her critical condition, we started hemodialysis with ultrafiltration for excessive volume load (**Figure 2**).

DISCUSSION

In treating dysrhythmias such as supraventricular tachycardia, atrial fibrillation, and atrial flutter, amiodarone is usually chosen.[5] As a result of the high iodine content and long half-life of this substance, it also affects the thyroid tissues.[6]

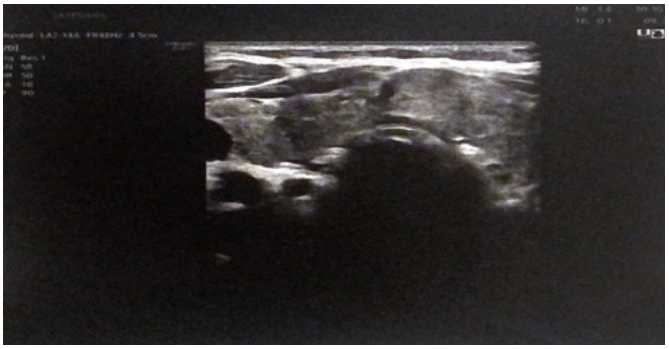

Figure 1. Thyroid ultrasound of the patient after the use of amiodarone. Thyroid gland parenchyma has a heterogeneous appearance with decreased echogenicity. Thyroiditis

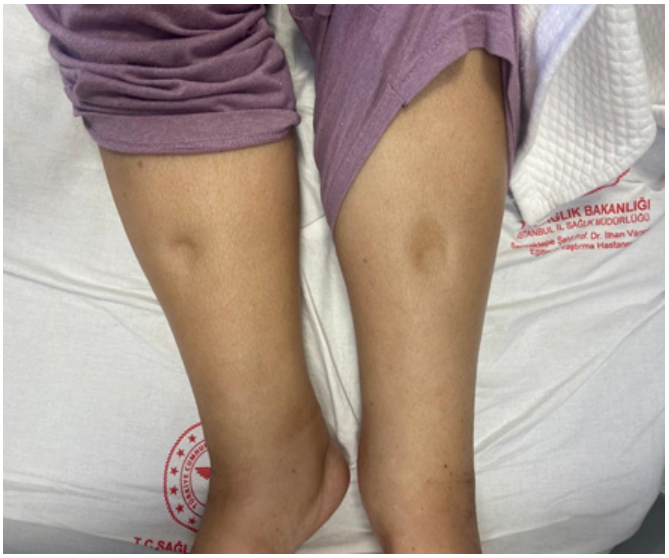

Figure 2. Rough and hard +3 edema in the lower extremities that does not respond to medical treatment

The high level of iodide released through the metabolism of amiodarone inhibits thyroid hormone release and biosynthesis (Wolff-Chaikoff effect). AIH is thought to be a result of iodine's inability to escape the Wolf-Chaikoff effect, especially in Hashimoto's disease.[7] Amiodarone discontinuation in AIH is not always necessary. It was recommended to start levothyroxine replacement therapy without discontinuing the amiodarone, especially for uncontrolled dysrhythmias.[8] Since our patient's dysrhythmia was managed with beta-blockers and her existing co-morbid diseases, we stopped amiodarone medication to control the hypothyroidism earlier.

The basal TSH level is important before starting amiodarone treatment. TSH elevation during treatment could be a sign of AIH . Increased levels of TSH in the first three months may not be useful because it may also occur in euthyroid patients. On the other hand, a significant elevation (>20 uIU/L) in the early period is usually a sign of thyroid disease.[9] In this case, before the start of amiodarone treatment, her TSH levels were within the normal range. A significant increase in TSH after only the first month of treatment provided evidence of the diagnosis. Thyroid autoantibodies increase the risk of development of AIH.[10] It was also reported that women are at higher risk than men.[11] This situation is supported by the fact that the patient in our patient is a woman. However, her thyroid autoantibodies were negative. This reflects the significance for us to pay attention to the development of AIH in the group of patients who do not have autoantibodies. Martino et al. showed in a study of 28 AIH patients, that 70% of autoantibody-positive patients developed persistent hypothyroidism, whereas 10% of autoantibody-negative patients developed persistent hypothyroidism.[12] Before starting amiodarone therapy, it is advised to check the patient's thyroid autoantibodies, TSH, T4, and T3 levels in the serum.[9] By doing so, the risk of AIH can be recognized in patients at early stages and prevented without resulting in permanent hypothyroidism. Before starting treatment, we can determine the patient's thyroid condition with USG, which can be helpful when observing signs of permanent hypothyroidism after amiodarone cessation. Our patient's thyroid USG was compatible with thyroiditis (**Figure 1**). A comparison could not be possible, hence she had not thyroid USG before starting amiodarone treatment.

CONCLUSION

The indications for starting amiodarone treatment should be clearly defined. Because hypothyroidism may disrupt the compensatory mechanisms of patients with comorbid diseases such as congestive heart failure and chronic renal failure. Thus, by closely observing these patients, these complications may be prevented.

ETHICAL DECLARATIONS

Informed Consent: Written consent was obtained from the patient.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: The author declare that they have all participated in the design, execu-tion, and analysis of the paper, and that they have approved the final version.

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