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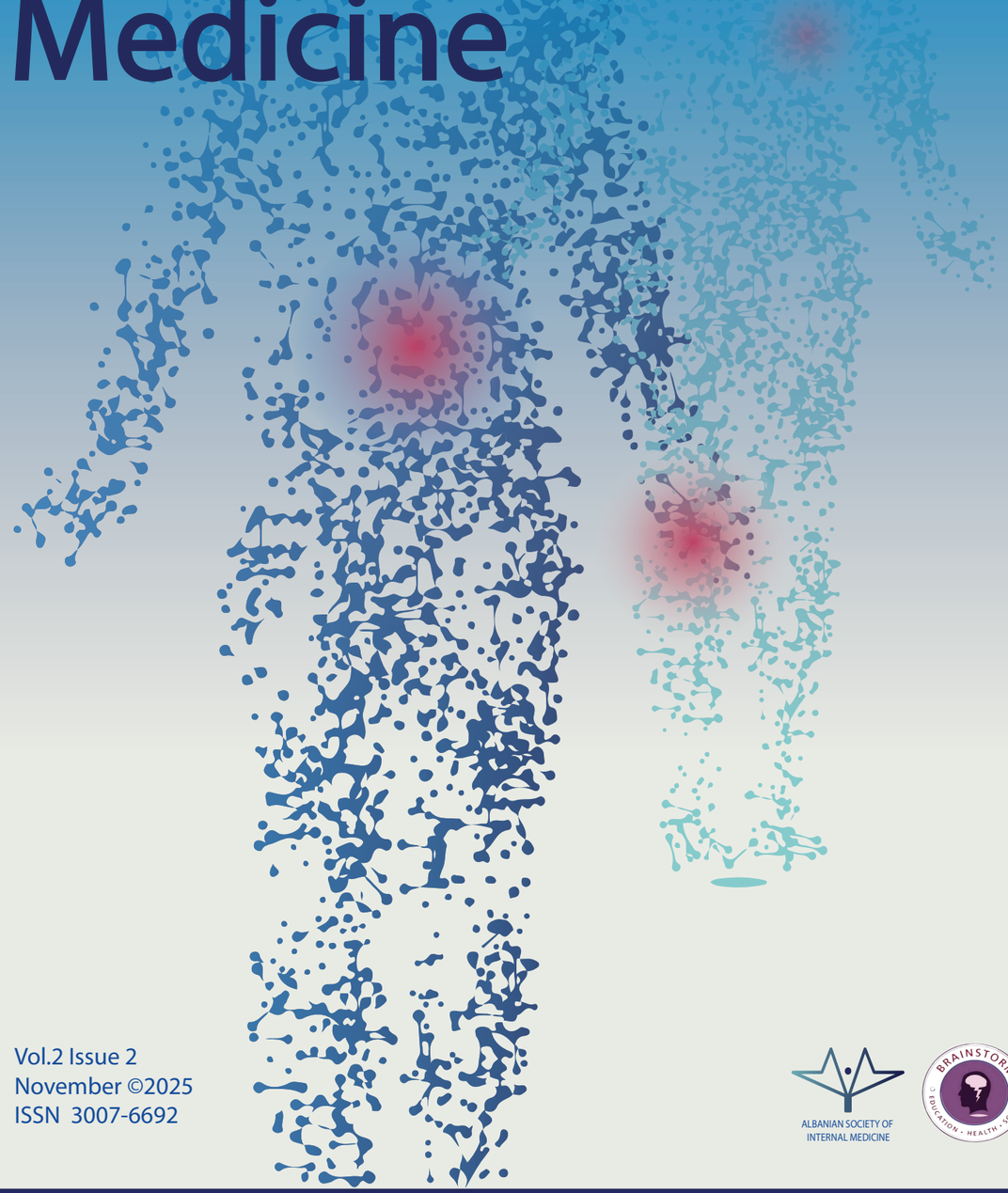
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TABLE OF CONTENTS

ENDOCRINE HYPERTENSION: AN UNDERRECOGNIZED BUT TREATABLE CAUSE OF SECONDARY HYPERTENSION 6

Ergita Nelaj 7

BREAST CANCER AWARENESS, FINDINGS FROM A CROSS-SECTIONAL STUDY AMONG ALBANIAN WOMEN 8

Albana Shahini, Bledi Kreka, Altin Malaj 8

FOUR-YEAR SINGLE-CENTER EXPERIENCE IN TREATING PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA IN ALBANIA 24

Bledi Kreka, Enkeleida Çuedari, Flutura Proko, Anila Pema, Albana Shahini, Alma Idrizi, Manika Kreka, Arvin Dibra 24

THE EMERGENCE OF SALT REDUCTION AS A NATIONAL HEALTH PRIORITY IN ALBANIA 34

Ledio Çollaku, Margarita Gjata, Eneida Hoxha, Artenca Çollaku, Elizana Petrela 34

GASTROINTESTINAL INVOLVEMENT IN SYSTEMIC SCLEROSIS: CORRELATION WITH IMMUNOLOGICAL ACTIVITY – A RETROSPECTIVE OBSERVATIONAL STUDY 43

Valbona Duraj, Entela Shkodrani, Jona Isaku, Juarda Gjonbrataj, Artur Zoto, Artur Kollcaku 43

PLEUROPULMONARY MANIFESTATIONS OF ANKYLOSING SPONDYLITIS: A LITERATURE REVIEW 50

Eugerta Dilka, Valbona Duraj, Klara Ziu, Luljeta Hoxha 50

THE INTESTINAL MICROBIOME AS A NOVEL THERAPEUTIC TARGET IN THE INTEGRATED MANAGEMENT OF CARDIO-RENAL-METABOLIC SYNDROME 58

Irida Kecaj, Ergita Nelaj, Ilir Gjermeni, Kei Xhixhabesi, Ina Refatllari, Sonila Gozhita, Margarita Gjata 58

"THE SILENT DEATH OF THE PITUITARY": PATHOPHYSIOLOGY AND CLINICAL IMPACT OF SHEEHAN'S SYNDROME 71

Puhizë Osmanaj 71

AN UNUSUAL PRESENTATION OF ANTI-GLOMERULAR BASEMENT MEMBRANE (GBM) DISEASE WITH SEVERE ANEMIA 83

Ariana Strakosha, Amantia Imeraj, Vilma Çadri, Nevi Pasko 83

EXFOLIATIVE PSORIATIC ERYTHRODERMA: A CALL FOR HELP AND ATTENTION 90

Diana Muja, Migena Gega, Valbona Zeneli 90

ALCOHOLIC CARDIOMYOPATHY: A CASE REPORT PRESENTATION 97

Sonil Marko, Irena (Çeko) Marko, Eva Duraku, Llukan Rrumbullaku, Ilir Alimehmeti 97

Letter to the Editor

ENDOCRINE HYPERTENSION: AN UNDERRECOGNIZED BUT TREATABLE CAUSE OF SECONDARY HYPERTENSION

Dear Editor,

Hypertension remains a major global health issue, impacting over 1.4 billion people worldwide [1]. While most cases are classified as essential hypertension, about 5–15% are caused by secondary factors, many of which are related to endocrine issues. Endocrine hypertension (EH) is a type of high blood pressure influenced or driven by hormonal imbalances. These conditions typically result from either excessive or insufficient hormone secretion that governs fluid balance, vascular tone, and sodium metabolism. EH is a potentially treatable form of hypertension, but it is often underdiagnosed and undertreated in healthcare. As awareness of its prevalence and cardiovascular risks grows, there is a renewed focus on early detection and targeted management of EH [2].

Among them, primary aldosteronism (PA) has emerged as the most prevalent form, affecting 10–20% of patients with resistant hypertension and up to 6% of those with mild hypertension, with some studies reporting even higher rates [3]. Despite strong evidence, PA remains substantially underdiagnosed. Early and systematic screening using the aldosterone-to-renin ratio (ARR) is recommended for patients with resistant hypertension, spontaneous or diuretic-induced hypokalemia, adrenal incidentalomas, or a family history of early-onset hypertension. Timely identification is critical, as unilateral aldosterone-producing adenomas can be surgically cured, while bilateral adrenal hyperplasia benefits significantly from targeted therapy with mineralocorticoid receptor antagonists, including newer nonsteroidal agents [4].

Other important endocrine causes of hypertension include pheochromocytoma and paraganglioma (PPGL), Cushing's syndrome, and thyroid dysfunction, all of which remain frequently overlooked in clinical practice. PPGLs, though rare, carry substantial morbidity and exhibit a high prevalence of germline mutations, approximately 70%, making genetic counseling a central component of evaluation [5]. Cushing's syndrome, including its subclinical adrenal form, is associated with rapid-onset hypertension, metabolic complications, and increased cardiovascular risk [2]. Thyroid disorders also contribute meaningfully: hyperthyroidism often induces systolic hypertension via increased cardiac output, while hypothyroidism leads to diastolic hypertension through increased vascular resistance [6]. Given these diverse mechanisms, clinicians should incorporate routine thyroid function tests and maintain vigilance for characteristic endocrine features in patients with atypical or difficult-to-control hypertension.

Considering these findings, clinicians should maintain a high index of suspicion for EH in patients with resistant hypertension, early-onset hypertension (<30 years), or specific clinical

features. Early identification not only improves blood pressure control but may also reverse cardiovascular remodeling, such as left ventricular hypertrophy and arterial stiffness.

Looking ahead, the development of multidisciplinary hypertension centers and AI-powered diagnostic tools may enhance the detection and management of EH, ensuring that patients receive personalized, etiology-specific treatments [7].

In conclusion, endocrine hypertension, although often overlooked, represents a clinically significant and highly treatable category of secondary hypertension. In light of the proven benefits of accurate diagnosis and targeted treatment, routine screening in high-risk patients should be encouraged. Strengthening adherence to current guidelines, improving physician awareness, and integrating structured endocrine evaluation into routine hypertension management pathways are essential next steps.

Sincerely,

Ergita Nelaj

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Original Article

BREAST CANCER AWARENESS, FINDINGS FROM A CROSS-SECTIONAL STUDY AMONG ALBANIAN WOMEN.

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ABSTRACT

Background: Breast cancer is the leading cause of death worldwide. Achieving early detection through screening and increasing awareness about risk factors and clinical signs, and symptoms is of vital importance. Studies have indicated that often awareness is not adequate, and screening methods are not accessible or affordable in low-resource settings.

Methods: A cross-sectional study surveyed Albanian women using an online questionnaire. Information was collected on socio-demographics, personal history, and knowledge of breast cancer cases, risk factors, signs and symptoms, as well as screening methods, frequency of examinations, etc. The data was analyzed with Stata 16, looking at uni and bivariate analysis, for three levels of education. Chi-square tests for independence between other characteristics and education were considered significant at a p-value of 0.05.

Results: A total of 455 Albanian women completed the online questionnaire. The mean age of respondents was 39.9±12.4 years, 92% lived in urban settings, and 67% in the capital, Tirana. 70.8% had knowledge of breast cancer in close relatives, and only 9.5% had a history of benign breast disease. Only the number of weekly hours of exercise and age at first breast examination were associated with educational level. Of all the risk factors asked, only giving birth after the age was 30 was associated with education level. None of the lifestyle-related risk factors was associated with education level. Of all the clinical signs and symptoms asked, only the breast lump, the armpit mass, and abrupt changes in the shape of the breast were associated with education level. Awareness of when and at what age to start/conduct breast self-examination, and its frequency, was associated with education level.

Conclusion: The findings are like other studies conducted in low-resource settings on three continents, suggesting inadequate breast cancer awareness. Breast awareness campaigns should target Albanian women of all educational backgrounds at the primary health care level.

Keywords. breast cancer, awareness-raising, socioeconomic conditions, education.

ABSTRAKT

NDËRGJEGJËSIMI PËR KANCERIN E GJIRIT, GJETJET NGA NJË STUDIM CROSS-SECTIONAL MIDIS GRAVE SHQIPTARE

Hyrje. Kanceri i gjirit është shkaku kryesor i vdekjes në mbarë botën. Arritja e zbulimit të hershëm përmes shqyrtimit dhe rritjes së ndërgjegjësimit rreth faktorëve të rrezikut dhe shenjave e simptomave klinike është me rëndësi jetike. Studimet kanë treguar se shpesh ndërgjegjësimi nuk është i mjaftueshëm dhe metodat e shqyrtimit nuk janë të arritshme ose të përballueshme në mjedise me burime të ulëta.

Metoda: Një studim anketoi gratë shqiptare duke përdorur një pyetësor online. U mblodhën informacione mbi socio-demografinë, historinë personale dhe njohuritë për rastet e kancerit të gjirit, faktorët e rrezikut, shenjat dhe simptomat, si dhe metodat e shqyrtimit, frekuencën e ekzaminimeve etj. Të dhënat u analizuan me Stata 16, duke parë analizën uni dhe bivariate, për tre nivele arsimi. Testet Chi katror për pavarësinë midis karakteristikave të tjera dhe arsimit u konsideruan të rëndësishme në vlerën p prej 0.05.

Rezultatet: Një total prej 455 grash shqiptare plotësuan pyetësorin online. Mosha mesatare e të anketuarve ishte 39.9±12.4 vjeç, 92% jetonin në mjedise urbane dhe 67% në kryeqytetin e Tiranës. 70.8% kishin njohuri për kancerin e gjirit tek të afërmit e ngushtë dhe vetëm 9.5% kishin një histori të sëmundjes beninje të gjirit. Vetëm numri i orëve të ushtrimeve javore dhe mosha në ekzaminimin e parë të gjirit ishin të lidhura me nivelet e arsimit. Nga të gjithë faktorët e rrezikut të pyetur, vetëm lindja pas moshës 30 vjeç ishte e lidhur me nivelin e arsimit. Asnjë nga faktorët e rrezikut të lidhur me stilin e jetës nuk ishte e lidhur me nivelin e arsimit. Nga të gjitha shenjat dhe simptomat klinike të pyetura, vetëm noduset e gjirit, masa në sqetull dhe ndryshimet e menjëhershme të formës së gjirit ishin të lidhura me nivelin e arsimit. Ndërgjegjësimi se në cilën moshë dhe kur të ciklit menstrual duhet të fillojë/kryhet vetë ekzaminimi i gjirit dhe frekuenca e tij ishin të lidhura me nivelin e arsimit.

Përfundim. Gjetjet janë të ngjashme me studime të tjera të kryera në mjedise me burime të pakta në tre kontinente, duke sugjeruar ndërgjegjësim të pamjaftueshëm për kancerin e gjirit. Fushatat e ndërgjegjësimit për gjirin duhet të synojnë gratë shqiptare të të gjitha prejardhjeve arsimore në nivelin e kujdesit shëndetësor parësor.

Fjalë kyce: kanceri gjirit, ngritje ndergjegjesimit, kushtet socio ekonomike, edukimi.

INTRODUCTION

Some 2.3 million new cases of breast cancer were diagnosed worldwide in 2022, with over 670 thousand deaths globally [1]. Half of these cases occurred in women with no risk factors other than sex and age. In 95% of the countries, breast cancer is the first or second leading cause of female deaths [2]. In 2022, breast cancer became the second most common type of cancer after lung cancer [3]. The US National Cancer Institute reported an estimated 310 thousand new cases of breast cancer and over 40 thousand deaths, or 6.9% of all cancer deaths in the United States [4]. The European Cancer Information System estimated over 370 thousand new cases of breast cancer in females in the 27 countries of the EU, with over 95 thousand estimated deaths in 2022 [5].

Breast cancer was the leading cause of death for females in Albania in 2022, and the third cause of death for both sexes [6]. WHO also indicated that survival from breast cancer is widely inequitable between and within countries; nearly 80% of deaths from breast and cervical cancer occur in low- and middle-income countries [2]. While the incidence is higher in developed countries, the cases in developing countries are detected at an advanced stage [7-10]. Screening and early detection improve outcomes in breast cancer cases, and several countries [11], including Albania, have initiated pilots in improving screening and early detection of breast cancer, including the use of clinical breast examination and mammography. Breast self-examination is still considered an early detection tool in many countries with limited access to mammography or high costs [8] that are not covered by national screening schemes.

In developed countries, breast self-examination is not seen as reliable or beneficial [8, 12,13], but it is largely regarded as beneficial in many developing countries in low-resource settings. Numerous articles published advocate for more to be done in raising breast awareness to curb the preventable mortality linked to breast cancer. Studies conducted to assess breast awareness and evaluate the impact of education across Africa [11, 14-18], Asia [7,19-28], and Europe [12, 13, 29, 30] advocate for targeted training programs that have an impact on increasing breast awareness, health behavior, and health service utilization. These studies look at breast awareness in low-resource settings [10, 21, 31], risk factors linked to breast cancer, and health behavior and utilization patterns in women of different age groups and backgrounds. A recurring theme is the need to strengthen breast awareness and support health education measures on risk factors and a healthy lifestyle.

Knowledge of breast cancer risk factors and regular testing through imaging, clinical, or self-examination methods play an important role in early detection and treatment. As such, assessing awareness levels and healthy behaviors might bring insights into what population groups would need to benefit from more awareness campaigns or education programs. In this study, we look at the awareness of Albanian women of reproductive age on breast cancer, its risk factors, factors linked to lifestyle, awareness of screening procedures, and their frequency.

MATERIALS AND METHODS

The study population was the Albanian women aged 16-80 residing in the capital Tirana, other districts, and abroad. The study was a cross-sectional study with convenience sampling, with respondents contacted through a social media account. Respondents were approached either directly by the principal investigator or relatives who had previously visited a private clinic where screening procedures for breast cancer were completed. The respondents received a link to the study page that provided more information on the survey (in Albanian) and explained the reasons and importance of the responses. We have no information on the number of people who received the invitation link but refused to respond.

Data collection was done online making use of Google forms, with questions determined to ask information on socio-demographics (age, education level, residence, province), personal history, and knowledge of breast cancer (knowledge of breast cancer in close relatives, chest radiation at a young age, use of oral contraceptives, history of benign breast disease, and hormone replacement therapy). We also asked the respondents about risk factors (menstruation before age of 12, late menopause, giving birth after age 30, and not having given birth to a child). Another group of questions focused on lifestyle-related risk factors (low activity, obesity, age over 40, lack of breastfeeding, smoking, alcohol consumption, stress, high consumption of red meat or fatty food, low consumption of vegetables and fruits, etc.). knowledge of clinical signs and symptoms of breast cancer was also assessed by asking of breast lumps, masses under the armpit, bleeding discharges of the nipple, changes of the nipple and breast skin, changes on the shape of the breast etc. the last block of questions was linked to perceived risks of mammography, biopsy, as well as the best time to have examinations of the breasts and when was the age of first exam.

The study received the approval of the ethical committee of the Medical University on January 2024. No information that could be used to identify the respondents was collected or stored in any way. The data was entered directly through self-reporting and analyzed with Stata 16. The analysis focused on univariate frequencies, bivariate analysis of all variables with education level, and looking at chi-square tests of independence between the variables. Associations for which the p-value was 0.05 or less were considered statistically significant and were further investigated for the strength of the association and multivariate analysis modelling. The results were displayed as both numbers and percentages, keeping missing values in the tables for reporting purposes.

RESULTS

A total of 455 Albanian women living in Albania and abroad participated in the study and completed the self-reported questionnaire online. Mean age was 39.9±12.4 years. Of all of them, 66% were married, and 92% lived in urban settings. 67% of them lived in Tirana, and only 5.7% responded from abroad. The socio-demographic characteristics are displayed in Table 1.

Table 1. Socio-demographic characteristics

Characteristics		Education				p-value
		Middle	*Uni*	*Postgrad*	*Total*	
Marital Status	*Single*	14 (18.9%)	56 (31.3%)	57 (28.2%)	127 (27.9%)	0.080
	Married	51 (68.9%)	114 (63.7%)	135 (66.8%)	300 (65.9%)	
	Other	9 (12.2%)	9 (5.0%)	10 (5.0%)	28 (6.2%)	
Urbrur	*Rural*	18 (24.3%)	7 (3.9%)	10 (5.0%)	35 (7.7%)	0.000
	Urban	56 (75.7%)	172 (96.1%)	192 (95.0%)	420 (92.3%)	
Residence	*Abroad*	4 (5.4%)	9 (5.0%)	13 (6.4%)	26 (5.7%)	0.018
	Districts	32 (43.2%)	43 (24.0%)	49 (24.3%)	124 (27.3%)	
	Tirana	38 (51.4%)	127 (70.9%)	140 (69.3%)	305 (67.0%)	

In terms of personal history and knowledge of disease, the only characteristics that were significantly linked to education level were hours of activity per week and age at first breast exam. The personal history of disease and characteristics of other health-related items are listed in Table 2.

Table 2. History, knowledge of disease, and other characteristics**.**

Characteristics		Education				p-value
		Middle	***Uni***	***Postgrad***	***Total***	
History of cancer in the family	Yes	21 (28.4%)	44 (24.6%)	66 (32.7%)	131 (28.8%)	0.220
	No	51 (68.9%)	135 (75.4%)	136 (67.3%)	322 (70.8%)	
	NA	2 (2.7%)	0 (0.0%)	0 (0.0%)	2 (0.4%)	
OC uses 5 years plus	*Yes*	5 (6.8%)	9 (5.0%)	12 (5.9%)	26 (5.7%)	0.846
	No	68 (91.9%)	169 (94.4%)	190 (94.1%)	427 (93.8%)	
	NA	1 (1.4%)	1 (0.6%)	0 (0.0%)	2 (0.4%)	
Hormone Replacement Therapy	*Yes*	2 (2.7%)	8 (4.5%)	4 (2.0%)	14 (3.1%)	0.353
	No	70	168	198	436	

		(94.6%)	(93.9%)	(98.0%)	(95.8%)	
	NA	2 (2.7%)	3 (1.7%)	0 (0.0%)	5 (1.1%)	
History of Benign Disease	*Yes*	8 (10.8%)	17 (9.5%)	18 (8.9%)	43 (9.5%)	0.844
	No	63 (85.1%)	161 (89.9%)	184 (91.1%)	408 (89.7%)	
	NA	3 (4.1%)	1 (0.6%)	0 (0.0%)	4 (0.9%)	
High Radiation on the Chest/Breast	*Yes*	1 (1.4%)	8 (4.5%)	3 (1.5%)	12 (2.6%)	0.148
	No	70 (94.6%)	170 (95.0%)	199 (98.5%)	439 (96.5%)	
	NA	3 (4.1%)	1 (0.6%)	0 (0.0%)	4 (0.9%)	
Do you think mammography radiation may cause cancer?	*Yes*	14 (18.9%)	22 (12.3%)	30 (14.9%)	66 (14.5%)	0.067
	No	27 (36.5%)	107 (59.8%)	105 (52.0%)	239 (52.5%)	
	NA	33 (44.6%)	50 (27.9%)	67 (33.2%)	150 (33.0%)	
Which diagnostic method is more accurate?	*ECHO*	32 (43.2%)	76 (42.5%)	82 (40.6%)	190 (41.8%)	0.249
	MRI	21 (28.4%)	78 (43.6%)	91 (45.0%)	190 (41.8%)	
	NA	21 (28.4%)	25 (14.0%)	29 (14.4%)	75 (16.5%)	
Do you think biopsy increases the risk of cancer by spreading it?	*Yes*	18 (24.3%)	37 (20.7%)	32 (15.8%)	87 (19.1%)	0.106
	No	33 (44.6%)	102 (57.0%)	122 (60.4%)	257 (56.5%)	
	NA	23 (31.1%)	40 (22.3%)	48 (23.8%)	111 (24.4%)	
Do you suffer from other diseases?	*Yes*	13 (17.6%)	28 (15.6%)	21 (10.4%)	62 (13.6%)	0.140
	No	53 (71.6%)	142 (79.3%)	171 (84.7%)	366 (80.4%)	
	NA	8 (10.8%)	9 (5.0%)	10 (5.0%)	27 (5.9%)	
If in menopause, how many kg did you gain?	*< 2*	4 (5.4%)	2 (1.1%)	4 (2.0%)	10 (2.2%)	0.282
	2-4	7 (9.5%)	14 (7.8%)	9 (4.5%)	30 (6.6%)	
	5-9	9 (12.2%)	13 (7.3%)	16 (7.9%)	38 (8.4%)	
	>=10	6 (8.1%)	2 (1.1%)	9 (4.5%)	17 (3.7%)	
	NA	48	148	164	360	

		(64.9%)	(82.7%)	(81.2%)	(79.1%)	
How many hours per week do you exercise?	*<2*	12 (16.2%)	36 (20.1%)	37 (18.3%)	85 (18.7%)	0.000
	2-7	18 (24.3%)	83 (46.4%)	96 (47.5%)	197 (43.3%)	
	>=8	32 (43.2%)	32 (17.9%)	39 (19.3%)	103 (22.6%)	
	NA	12 (16.2%)	28 (15.6%)	30 (14.9%)	70 (15.4%)	
Do you use an IUD	*Yes*	1 (1.4%)	11 (6.1%)	5 (2.5%)	17 (3.7%)	0.082
	No	71 (95.9%)	165 (92.2%)	196 (97.0%)	432 (94.9%)	
	NA	2 (2.7%)	3 (1.7%)	1 (0.5%)	6 (1.3%)	
Did you ever use IVF	*Yes*	2 (2.7%)	3 (1.7%)	5 (2.5%)	10 (2.2%)	0.827
	No	68 (91.9%)	165 (92.2%)	185 (91.6%)	418 (91.9%)	
	NA	4 (5.4%)	11 (6.1%)	12 (5.9%)	27 (5.9%)	
At what age did you have your first exam	*< 20*	5 (6.8%)	13 (7.3%)	4 (2.0%)	22 (4.8%)	0.006
	20-29	11 (14.9%)	42 (23.5%)	66 (32.7%)	119 (26.2%)	
	30-39	37 (50.0%)	63 (35.2%)	76 (37.6%)	176 (38.7%)	
	>=40	12 (16.2%)	19 (10.6%)	17 (8.4%)	48 (10.5%)	
	NA	9 (12.2%)	42 (23.5%)	39 (19.3%)	90 (19.8%)	

The data shows that 70.8% of respondents have knowledge of breast cancer in close relatives, but only 5.7% have used oral contraceptives for longer than 5 years. Only 3.1% have used hormonal therapy after menopause, and only 9.5% have a history of benign breast disease. Only 2.6% reported a history of high radiation on the chest when young. The responses to additional questions on beliefs are interesting. 14.5% believe mammography can cause cancer, and both ultrasound and mammography are equally the best screening methods. 19.1% believe that a biopsy taken to diagnose can cause the spread of the disease. 13.5% suffer from other illnesses (metabolic or hormonal). The mean weight gain reported after menopause was 6.2±5.7 (median 5kg). The median number of hours exercising per week was 4. Of all the ob-gyn-related risk factors, only giving birth after the age of 30 was significantly associated with education. Table 3 shows the ob-gyn-related risk factors.

Table 3. OB-GYN-related risk factors increase the risk of breast cancer

Characteristics		Education				p-value
		Middle	***Uni***	***Postgrad***	***Total***	
Started menstruating before 12 years	*Yes*	19 (25.7%)	33 (18.4%)	50 (24.8%)	102 (22.4%)	0.318
	No	53 (71.6%)	138 (77.1%)	149 (73.8%)	340 (74.7%)	
	NA	2 (2.7%)	8 (4.5%)	3 (1.5%)	13 (2.9%)	
Late menopause (after age 55)	*Yes*	9 (12.2%)	20 (11.2%)	22 (10.9%)	51 (11.2%)	0.975
	No	52 (70.3%)	123 (68.7%)	140 (69.3%)	315 (69.2%)	
	NA	13 (17.6%)	36 (20.1%)	40 (19.8%)	89 (19.6%)	
Giving birth after age 30	*Yes*	22 (29.7%)	95 (53.1%)	109 (54.0%)	226 (49.7%)	0.000
	No	47 (63.5%)	65 (36.3%)	79 (39.1%)	191 (42.0%)	
	NA	5 (6.8%)	19 (10.6%)	14 (6.9%)	38 (8.4%)	
Giving birth to a child increases the risk of cancer	*Yes*	4 (5.4%)	3 (1.7%)	5 (2.5%)	12 (2.6%)	0.210
	No	60 (81.1%)	159 (88.8%)	174 (86.1%)	393 (86.4%)	
	NA	10 (13.5%)	17 (9.5%)	23 (11.4%)	50 (11.0%)	

It seems that Albanian women are not aware that early menses and late menopause are risk factors for breast cancer, with 74.4% and 69.2% saying no, respectively. Opinions are split on whether giving birth after the age of 30 is a risk factor for breast cancer (48.7% saying yes), and only 2.6% reported that giving birth to a child increases the risk of cancer.

When asked about lifestyle-related risk factors to breast cancer, the responses are shown in Table 4. Only breastfeeding seems to be associated with education levels, with only 4.2% responding that breastfeeding can increase the risk of breast cancer.

Table 4. Lifestyle-related breast cancer risk factors

Characteristics		Education				p-value
		Middle	*Uni*	*Postgrad*	*Total*	
Low Activity	*Yes*	37 (50.0%)	108 (60.3%)	118 (58.4%)	263 (57.8%)	0.438
	No	33 (44.6%)	67 (37.4%)	79 (39.1%)	179 (39.3%)	
	NA	4 (5.4%)	4 (2.2%)	5 (2.5%)	13 (2.9%)	
Obesity	*Yes*	43 (58.1%)	103 (57.5%)	116 (57.4%)	262 (57.6%)	0.983
	No	29 (39.2%)	73 (40.8%)	82 (40.6%)	184 (40.4%)	
	NA	2 (2.7%)	3 (1.7%)	4 (2.0%)	9 (2.0%)	
Age over 40 years	*Yes*	49 (66.2%)	92 (51.4%)	110 (54.5%)	251 (55.2%)	0.072
	No	22 (29.7%)	81 (45.3%)	86 (42.6%)	189 (41.5%)	
	NA	3 (4.1%)	6 (3.4%)	6 (3.0%)	15 (3.3%)	
Breastfeeding	*Yes*	2 (2.7%)	13 (7.3%)	4 (2.0%)	19 (4.2%)	0.031
	No	66 (89.2%)	160 (89.4%)	191 (94.6%)	417 (91.6%)	
	NA	6 (8.1%)	6 (3.4%)	7 (3.5%)	19 (4.2%)	
Smoking and Alcohol	*Yes*	53 (71.6%)	138 (77.1%)	150 (74.3%)	341 (74.9%)	0.839
	No	17 (23.0%)	37 (20.7%)	45 (22.3%)	99 (21.8%)	
	NA	4 (5.4%)	4 (2.2%)	7 (3.5%)	15 (3.3%)	
Stress	*Yes*	63 (85.1%)	168 (93.9%)	185 (91.6%)	416 (91.4%)	0.120
	No	9 (12.2%)	9 (5.0%)	14 (6.9%)	32 (7.0%)	
	NA	2 (2.7%)	2 (1.1%)	3 (1.5%)	7 (1.5%)	
High consumption of red meat	*Yes*	41 (55.4%)	87 (48.6%)	101 (50.0%)	229 (50.3%)	0.467
	No	27 (36.5%)	82 (45.8%)	85 (42.1%)	194 (42.6%)	
	NA	6 (8.1%)	10 (5.6%)	16 (7.9%)	32 (7.0%)	
Low-vegetable diet	*Yes*	40 (54.1%)	81 (45.3%)	93 (46.0%)	214 (47.0%)	0.417

	No	31 (41.9%)	91 (50.8%)	97 (48.0%)	219 (48.1%)	
	NA	3 (4.1%)	7 (3.9%)	12 (5.9%)	22 (4.8%)	
High-fat diet	*Yes*	47 (63.5%)	106 (59.2%)	108 (53.5%)	261 (57.4%)	0.293
	No	23 (31.1%)	69 (38.5%)	83 (41.1%)	175 (38.5%)	
	NA	4 (5.4%)	4 (2.2%)	11 (5.4%)	19 (4.2%)	

The majority (57.8%) are aware that low physical activity might lead to breast cancer and similarly think that obesity is a risk factor too. 55.2% responded that age over 40 is a risk factor, while 74.9% responded that smoking or alcohol is a risk factor for breast cancer. Over 91% responded that stress is a risk factor, and 57.4% that a high-fat diet is a risk factor. About half responded that red meat and a low-vegetable diet may be a risk factor.

When asked about recognizing the clinical signs and symptoms of breast cancer, the respondents confirmed that a breast lump (71.2%) and an armpit mass (70.8%) could be related to breast cancer. 65.9% of them also reported that a sudden change in the shape of the breast may be related to breast cancer. The rest of the signs were not significantly linked to the level of education. Table 5 shows the distribution of signs and symptoms by education level.

Table 5. Clinical signs and symptoms of breast cancer

Characteristics		**Education**				**p-value**
		Middle	***Uni***	***Postgrad***	***Total***	
Nodus	*Yes*	43 (58.1%)	128 (71.5%)	153 (75.7%)	324 (71.2%)	0.002
	No	31 (41.9%)	44 (24.6%)	39 (19.3%)	114 (25.1%)	
	NA	0 (0.0%)	7 (3.9%)	10 (5.0%)	17 (3.7%)	
Mass under armpit	*Yes*	43 (58.1%)	124 (69.3%)	155 (76.7%)	322 (70.8%)	0.004
	No	29 (39.2%)	47 (26.3%)	39 (19.3%)	115 (25.3%)	
	NA	2 (2.7%)	8 (4.5%)	8 (4.0%)	18 (4.0%)	
Bleeding or discharge from nipple	*Yes*	39 (52.7%)	105 (58.7%)	132 (65.3%)	276 (60.7%)	0.140
	No	28 (37.8%)	62 (34.6%)	56 (27.7%)	146 (32.1%)	
	NA	7 (9.5%)	12 (6.7%)	14 (6.9%)	33 (7.3%)	

Pulling of nipple inwards	*Yes*	32 (43.2%)	80 (44.7%)	105 (52.0%)	217 (47.7%)	0.126
	No	37 (50.0%)	84 (46.9%)	76 (37.6%)	197 (43.3%)	
	NA	5 (6.8%)	15 (8.4%)	21 (10.4%)	41 (9.0%)	
Wound around the nipple	*Yes*	34 (45.9%)	94 (52.5%)	103 (51.0%)	231 (50.8%)	0.701
	No	32 (43.2%)	74 (41.3%)	76 (37.6%)	182 (40.0%)	
	NA	8 (10.8%)	11 (6.1%)	23 (11.4%)	42 (9.2%)	
Redness of the breast skin	*Yes*	29 (39.2%)	103 (57.5%)	96 (47.5%)	228 (50.1%)	0.112
	No	36 (48.6%)	70 (39.1%)	83 (41.1%)	189 (41.5%)	
	NA	9 (12.2%)	6 (3.4%)	23 (11.4%)	38 (8.4%)	
Abrupt changes in the size of the breast	*Yes*	39 (52.7%)	114 (63.7%)	127 (62.9%)	280 (61.5%)	0.158
	No	30 (40.5%)	59 (33.0%)	56 (27.7%)	145 (31.9%)	
	NA	5 (6.8%)	6 (3.4%)	19 (9.4%)	30 (6.6%)	
Abrupt changes in the shape of the breast	*Yes*	41 (55.4%)	117 (65.4%)	142 (70.3%)	300 (65.9%)	0.021
	No	28 (37.8%)	56 (31.3%)	44 (21.8%)	128 (28.1%)	
	NA	5 (6.8%)	6 (3.4%)	16 (7.9%)	27 (5.9%)	

Lastly, the study participants responded to the best time to have a breast examination. Almost half responded that the best time to have a clinical examination by a doctor and nurse was after age 40 (45.7%), 54.5% said that after 40 years of age is the best time to have a mammography examination, and 61.8% reported that the best time to start breast self-examination is after the age of 20 years old. Details are shown in Table 6.

Table 6. Best time for breast examinations

Characteristics		**Education**				**p-value**
		Middle	***Uni***	***Postgrad***	***Total***	
When is the best time to start the breast exam by the doctor or midwife?	*After 20 yr*	19 (25.7%)	47 (26.3%)	61 (30.2%)	127 (27.9%)	0.431
	After 25 yr	15 (20.3%)	53 (29.6%)	52 (25.7%)	120 (26.4%)	
	After 30 yr	40 (54.1%)	79 (44.1%)	89 (44.1%)	208 (45.7%)	

When is the best time to start mammography?	*After 20 yr*	11 (14.9%)	25 (14.0%)	24 (11.9%)	60 (13.2%)	0.895
	After 30 yr	26 (35.1%)	56 (31.3%)	65 (32.2%)	147 (32.3%)	
	After 40 yr	37 (50.0%)	98 (54.7%)	113 (55.9%)	248 (54.5%)	
When is the best time to start self-breast exams?	*After 20 yr*	37 (50.0%)	107 (59.8%)	137 (67.8%)	281 (61.8%)	0.002
	After 30 yr	22 (29.7%)	60 (33.5%)	50 (24.8%)	132 (29.0%)	
	After 40 yr	15 (20.3%)	12 (6.7%)	15 (7.4%)	42 (9.2%)	
When is the best time to do a self-breast exam in the menstrual cycle?	*1 wk after menses*	47 (63.5%)	138 (77.1%)	156 (77.2%)	341 (74.9%)	0.046
	1 mo after menses	27 (36.5%)	41 (22.9%)	46 (22.8%)	114 (25.1%)	
How often should a breast cancer self-examination be performed?	*Each month*	31 (41.9%)	65 (36.3%)	89 (44.1%)	185 (40.7%)	0.046
	Quarterly	43 (58.1%)	114 (63.7%)	113 (55.9%)	270 (59.3%)	

Some 74.9% of respondents said the best time for an examination is 1 week after menstruation starts, and 59.3% of respondents said self-examination is best done quarterly. The mean age at first breast examination was 31.8±9.24 years.

DISCUSSION

The study population was heavily populated by university graduates who had additional training (master's and PhD degrees). Only 16% had less than a university degree. The overall majority with a residence in Tirana and otherwise in urban settings indicates that the findings of this study cannot be extrapolated to the rest of the Albanian women. Nonetheless, the information collected through this study, the first in Albania, will help understand some of the focus areas where health information efforts might be of value.

The study findings seem to suggest that the awareness of breast cancer is not adequate. Similar findings came from other studies in the UAE Emirates [23], Saudi Arabia[28], Oman[16], Cameroon[18], Gaza[26], Bangladesh[32], Pakistan[25], and Türkiye[29].

Several studies suggest that health education or awareness campaigns need to be planned, initiated, and supported, either for health personnel or women, as part of primary health care settings [12, 17-20, 24- 27, 30, 33- 36].

Our study suggests that breast awareness is not related to education level or achievements; hence, our suggestion is that when the Ministry of Health in Albania initiates country health education campaigns on breast cancer, the campaign should focus on all, irrespective of socio-demographic backgrounds. The only clinical signs and symptoms linked to education

level were the presence of lumps or masses and changes in the shape of the breast. In this case, the higher the level of education completed, the larger the percentage of respondents who responded positively. As the age of start of self-examination and the frequency were relatively high, the suggestion would be to focus on women of lower education for further health education sessions on the clinical signs and symptoms.

The health education can be integrated into the primary health care, and informative materials can be produced and distributed in the large network of primary health care facilities across Albania. Negative beliefs on the dangers of mammography or biopsy will need to be addressed, while establishing a national screening program for women as part of the health insurance scheme [10,11,25, 33, 35].

CONCLUSIONS

The breast awareness campaign should target Albanian women of all educational backgrounds at the primary health care level. Awareness is not always related to education level or achievements, so it is mandatory to include health education in school programs and to extend informative materials and hands-on training in the primary health care system. A national screening program helps to bring technology not only to large and important cities but also to most rural areas where the facilities are almost nonexistent.

Conflicts of interest: The authors declare that they have no conflicts of interest.

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Original Article

FOUR-YEAR SINGLE-CENTER EXPERIENCE IN TREATING PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA IN ALBANIA

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ABSTRACT

Introduction: Non-Hodgkin Diffuse Lymphomas are known for their high responsiveness and effectiveness to chemotherapy compared to other indolent lymphomas. The combination of Doxorubicin, Vincristine, Cyclophosphamide, and Prednisone has been the standard treatment for many years. Today, with modern therapies, significant progress has been made in treating more than 50% of cases. Treatment with the anti-CD20 monoclonal antibody rituximab has dramatically improved the prognosis for patients with aggressive NHL.

Aim: Evaluation of FPS (Progression Free Survival), CR (Complete Response), and PR (Partial Response) for patients diagnosed with Diffuse Large B-cell Lymphoma (DLBCL) in our patient group.

Materials and Methods: We followed up 57 patients all treated at the Oncology Service. These patients diagnosed with DLBCL have been treated from January 2019 to January 2022. We have analyzed patients' data for whom the minimal time from the end of treatment has been at least 24 months. We have measured the time since the beginning of treatment until relapse of disease or the patient's death. We have used the Cheson 1999 criteria to evaluate the response of treatment.

Results:57 patients were enrolled and followed up in this study. Among our patients, the majority were CD 20 +**.** Many patients have been diagnosed in stage 2. Most relapses happened within the first 24 months; only two relapses happened after 24 months. Relapse-free disease interval is seen in at least 32 patients, more than 24 months and over 40 months in 12 patients at the time of evaluation.

Conclusion: In general, progression-free survival (PFS) seems to be 50 % and 28 % respectively, for R-CHOP and CHOP. Overall survival is over 5 years in patients treated with rituximab. We've been using rituximab IV or sc for more than 12 years in our hospital. This study was conducted in order to establish a registry in the framework of a NASRI project as well.

Keywords. complete response, partial response, progression disease, progression-free survival, non-Hodgkin Lymphoma, Diffuse Large B-cell Lymphoma

PËRVOJA KATËRVJEÇARE E NJË QENDRE TË VETME NË TRAJTIMIN E PACIENTËVE ME LIMFOMË DIFUZE TË QELIZAVE TË MËDHA B (DLBCL), NË SHQIPËRI

ABSTRAKT

Hyrje. Limfomat difuze non-Hodgkin karakterizohen nga efikasiteti i lartë i trajtimit me kemioterapi, krahasuar kjo me limfomat e tjera indolente. Kombinimi i Doxorubicinës, Vincristinës, Cyclofosfamidit dhe Prednisonit ka qenë trajtimi standard për shumë vite. Në ditët e sotme, në epokën e trajtimeve moderne është arritur një progres i rëndësishëm në trajtimin e tyre në më shumë se 50% të rasteve klinike. Trajtimi me antikorpe monoklonale anti-CD20, si rituximabi, ka ndryshuar në mënyrë dramatike prognozën e pacientëve që vuajne nga NHL (Non-Hodgkin Lymphoma) agresive gjatë dy dekadave të fundit.

Qëllimi. Vlerësimi i FPS (Mbijetesa pa Progres e Sëmundjes), CR (Përgjigja e plotë) dhe PR (Përgjigje e Pjesshme) për pacientët e diagnostikuar me Limfomë Difuze me Qeliza B (DLBCL) në grupin e pacientëve tanë.

Materiali dhe Metodat. Ne ndoqëm 57 pacientë, të gjithë të trajtuar në Shërbimin e Onkologjisë. Këta pacientë të diagnostikuar me DLBCL janë trajtuar nga janari 2019 deri në janar 2022. Terapia anti CD 20 + (Rituximab) është perdorur ne vetem 28 pacientë. Ne kemi analizuar të dhënat e pacientëve për të cilët koha nga fundi i trajtimit ka qenë të paktën 24 muaj. Ne kemi matur kohën që nga fillimi i trajtimit deri në rikthimin e sëmundjes ose vdekjen e pacientit. Për vlerësimin e përgjigjes janë përdorur kriteret e Cheson 1999.

Rezultatet. 57 pacientë u regjistruan dhe u ndoqën në këtë studim. Në mesin e pacientëve tanë pjesa më e madhe, karakterizohej CD20.+. Shumica e pacientëve janë diagnostikuar në stadin II. Shumica e recidivave ndodhën brenda 24 muajve të parë, vetëm dy rikthime ndodhën pas 24 muajsh. Intervali i sëmundjes pa rikthim vërehet në të paktën 32 pacientë më shumë se 24 muaj dhe mbi 40 muaj në 12 pacientë në kohën e vlerësimit.

Përfundimi. Mbijetesa pa Progres e Sëmundjes është 50% dhe 28% për R-CHOP dhe CHOP. Në vendin tonë prej më shumë se 12 vitesh pacientët trajtohen me rituximab me adminsitrim intravenoz ose subkutan. Ky studim u realizua edhe në kuadrin e një projekti të NASRI-t për krijimin e një regjistri kombëtar.

Fjalë kyçe. përgjigje e plotë, përgjigje e pjesshme, sëmundje progresive, mbijetesë pa progress, NHL: Limfoma Non-Hodgkin, DLBCL: Limfoma Difuze me qeliza të mëdha B

INTRODUCTION

Non-Hodgkin lymphomas account for 2–3% of all malignancies in developed countries. They cover a range of neoplasms from slow-growing to aggressive tumors, the latter having a rapidly fatal course. The age-specific incidence increases throughout life. Their cause remains unknown, but environmental factors, virus infections, and genetic abnormalities are

all considered important. The clinical presentation of non-Hodgkin lymphoma varies widely. Many patients seek medical attention because of a tumor mass, which may be nodal or extranodal. General symptoms such as weight loss, fever, infections, and lethargy are common and may be the first signs. Often, patients have widespread disease with bone marrow involvement at diagnosis.

Non-Hodgkin Diffuse Lymphomas are characterized by high efficacy of chemotherapy treatment compared to other indolent lymphomas. The combination of Doxorubicin, Vincristine, Cyclophosphamide, and Prednisone has been the standard treatment for many years. Nowadays, in the era of modern treatments, there has been great progress in treating more than 50% of clinical cases. Treatment with the monoclonal antibody anti-CD20 (rituximab) was first approved for indolent lymphomas in progress since 1997, and it has dramatically improved patient outcomes, significantly changing the prognosis for patients suffering from aggressive NHL in the last two decades.

Non-Hodgkin lymphoma (NHL) is classified into more than 30 types based on the type of lymphocyte involved: B lymphocytes (B cells) or T lymphocytes (T cells). Non-Hodgkin lymphoma is also categorized by other factors, including whether it is aggressive (fast-growing) or indolent (slow-growing). Nearly 90 percent of non-Hodgkin lymphoma cases originate in B cells.

The most Common forms of B-cell non-Hodgkin lymphoma include: Diffuse large B-cell lymphoma (DLBCL), Follicular lymphoma, Mantle cell lymphoma (MCL), Marginal zone lymphoma, Mucosa-associated lymphoid tissue (MALT) lymphoma, Splenic marginal zone B-cell lymphoma. Less common forms of B-cell lymphoma include: Burkitt lymphoma, Lymphoplasmacytic lymphoma

Our topic of interest is **Diffuse large B-cell lymphoma (DLBCL), which seems to be** the most common type of non-Hodgkin lymphoma in the United States, Europe, and all over the world.

DLBCL accounts for about 30 percent of all cases. It is most often diagnosed in older adults. DLBCL is aggressive and may spread quickly. It may be found not only in the lymph system, but as a primary disease elsewhere in the body, including the gastrointestinal tract, testes, breasts and brain.

Subtypes of DLBCL include: Primary mediastinal B-cell lymphoma is often found in the mediastinum, the area of the chest cavity between the lungs. This type of lymphoma, which is more common in young women, may produce fast-growing tumors that may encompass the mediastinum cavity and press on the airways and blood vessels.

Primary central nervous system (CNS) lymphoma originates in the brain or spinal cord and may be found in patients with acquired immunodeficiency syndrome (AIDS) or those whose immune systems may be compromised, including organ transplant patients. When primary CNS lymphoma originates in the eye, it is called ocular lymphoma.

Symptoms of DLBCL may include swelling caused by enlarged lymph nodes in the neck, underarms, or groin. The swelling may or may not be painless. Other symptoms may include coughing or difficulty swallowing, night sweats, fever, swollen face, weight loss, and fatigue.

Treatments for DLBCL may include chemotherapy, targeted therapy, and sometimes radiation therapy. Surgery may be required in some cases to remove obstructive tumors (1) Non-Hodgkin Diffuse Lymphomas are characterized by high efficacy of chemotherapy treatment, compared to other indolent lymphomas. The combination of Doxorubicin, Vincristine, Cyclophosphamide, and Prednisone has been the standard treatment for many years. The addition of Rituximab to this regimen in the early 2000s to treat DLBCL produced better outcomes for patients (2,3). Six cycles of CHOP in combination with eight cycles every 21 days remains the standard despite the various attempts to test more dense treatment (4, 5), maintenance rituximab, and more cycles. Today, there is at least a 50% curability rate with modern treatment (6). Rituximab, a chimeric anti-CD20 antibody, was initially approved in 1997 for relapsed low-grade NHL. Rituximab binds to a surface protein, called CD20, located on mature B cells. Once bound, the antibody activates the body's immune system, which then attacks the cancer cells (7). Our study aims to evaluate FPS, CR, and PR for patients diagnosed with DLBCL in our patient group.

METHODOLOGY

This is a retrospective study involving 57 patients diagnosed and treated at our Service from January 2019 to January 2022. We included patients whose follow-up period since the end of treatment was at least 24 months. We measured the time from the start of treatment until disease relapse or patient death. The response to treatment was evaluated using the Cheson 1999 criteria. The results were assessed in July 2024.

We have excluded from our study:

- Patients with Lymphoblastic Lymphomas and Burkitt Lymphomas
- Patients who have not tolerated at least 2 first cycles of treatment (side effects or treatment interruptions for other reasons)
- Patients who have not had a minimal IHC panel documented

The diagnosis is confirmed after the lymph node biopsy result or bone marrow biopsy when necessary. The minimal IHC panel included CD20, Ki-67, CD19, and CD21. Only one patient was CD20 negative (-). Staging was performed using total body CT, measuring LDH levels, CBC (Complete Blood Count), and LFT. Extra nodal metastases were documented. Lesions larger than 7 cm were considered bulky. Treatments included chemotherapy, CHOP, R-CHOP 21, and CVP. Due to shortages, Rituximab was used in the treatment of 28 patients. CVP was administered to an elderly patient with multiple comorbidities. Radiotherapy was used palliatively in 22 patients, 10 of whom had bulky nodal lesions.

RESULTS

57 patients, 16 - 77 years old, have been diagnosed with DLCBL during the time of this study in our Service. The mean age was 55,1. In this group, 52,6 % were females and 47,4% males.

Table 1. Distribution of patients according to the stage of the disease

Classification	Stage	
IA	1	1.8%
IE	8	14.0%
II	7	12.3%
IIA	5	8.8%
IIB	1	1.8%
IIE	13	22.8%
III	4	7.0%
IIIA	2	3.5%
IIIB	1	1.8%
IIIE	2	3.5%
IV	6	10.5%
IVE	7	12.3%
Total	57	100.0%

In Table 1 is seen that many patients have been diagnosed in stage 2.

Table 2. The frequency of extra nodal manifestations

Classification	Extra nodal manifestations	
Breast	1	1.8%
Parotid glandule	1	1.8%
Liver	2	3.5%
Ileum	2	3.5%
Jejunum	2	3.5%
Bones	1	1.8%
Skin	1	1.8%
Pectoral muscles	1	1.8%
Naso pharynx	1	1.8%
Negative	28	49.1%
Pericardium& Pleural	1	1.8%
Pericardium	1	1.8%
Pulmonary and hepatic	1	1.8%
Pulmonary	1	1.8%

Pulmonary and bones	1	1.8%
Kidney and maxillary site	1	1.8%
Gastric	8	14.0%
Gastric and pancreatic	1	1.8%
Gastric and pulmonary	1	1.8%
Testicular	1	1.8%
Total	**57**	**100.0%**

In Table 2 is shown that 49,1% of patients present with no extra nodal manifestations ($p< 0.0001$)

Table 3. PS frequency (Performance Status Frequency)

Classification	**PS**	
0	6	10.5%
1	28	49.1%
2	22	38.6%
3	1	1.8%
Total	57	100.0%

Table 4. Chemotherapy regimen treatment in our patients

1 CHOP	2	3.5%
3 CHOP	2	3.5%
4 CHOP	7	12.4%
4 CVP	1	1.7%
4 RCHOP	4	7.0%
5 CHOP	4	7.0%
5 RCHOP	1	1.7%
6 CHOP	7	12.4%
6 RCHOP	19	33,.3%
8 CHOP	6	10.5%
8 RCHOP	4	7.0%
Total	**57**	**100.0%**

Table 5. Frequency of Relapse

Classification	RELAPSE

No relapse	**32**	**56.1%**
Death	3	5.2%
Multifocal	13	22.8%
CNS relapse	3	5,3%
Breast	1	1.8%
Bone	2	3,5%
Spinal cord	1	1.8%
Secondary cancer	2	3,5%
Total	57	100.0%

Table 6. Frequency of Response

Classification	RESPONSE

CR (COMPLETE RESPONSE)	36	63.2%
PD (PROGRESSIVE DISEASE)	3	5.3%
PR (PARTIAL RESPONSE)	11	19.2%
RD (REFRACTORY DISEASE)	3	5.3%
SD (STABLE DISEASE)	4	7 %
Total	57	100.0%

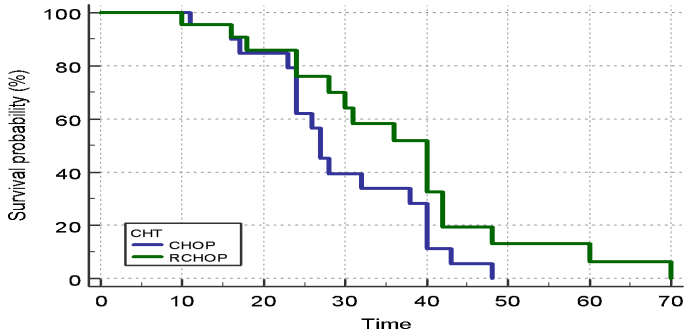
Table 6 shows that PET (Positron Emission Tomography) was performed in only 4 patients, and Complete Molecular Response was measured in 2 patients.

Table 7. Frequency of Second-Line Therapy

Classification X	SECOND LINE TREATMENT

No data	2	3.5%
No second-line treatment	**41**	**71.9%**
Second-line treatment	11	19.3%
Second-line treatment and alive	2	3,5 %
Second-line treatment (CHOP)	1	1.8%
Total	57	100.0%

Graph 1: Progression Free Survival according to Chemotherapy regimen



In Graph 1, it is shown that there is a light significance (p =0,005)
RCHOP is more effective than CHOP treatment

Graph 2: Patients' relapse-free survival.



In Graph 2, it is seen that 56% of patients were relapse-free at least after 24 months, and a considerable percentage more than 24 months.

57 patients were enrolled and followed in this study. Most of our patients were CD20+. Many were diagnosed at stage 2(see Table 1). Two patients developed secondary cancers, respectively, in the 30th and 40th months of follow-up. Most relapses occurred within the first 24 months; only two relapses happened after 24 months (see Graph 2). The relapse-free interval was observed in at least 32 patients for more than 24 months, and in 12 patients for over 40 months at the time of evaluation. Response evaluation using PET was possible in 4 patients (abroad), and in two of them, complete metabolic response was observed (see Table 6). A total of 25 patients experienced relapse, accounting for 43,8% of the cohort (see Table 5). Relapse was seen in 2 patients with stage II, 4 with stage IIE, 3 with stage III, 5 with stage IV, and 5 with stage IVE. Complete response to treatment was observed in 36 patients, representing 63,2% (see Table 6). Primary resistance to treatment was identified in 3 patients (5,3%). RCOP proved to be more effective than CHOP treatment (see Graph 1).

DISCUSSION

Treatment with CHOP in DLBCL has been used in patients since 1980 and beyond. It has been the standard treatment for aggressive Non-Hodgkin Lymphoma. This protocol achieved 5-year survival rates of 30-40% in our patients. In 30% of patients, there was no treatment response, or the disease progressed rapidly soon after treatment. The FDA approved the combination of anti-CD20 with the CHOP scheme (R-CHOP) in 2006 for the treatment of malignant lymphomas with diffuse large B-cell lymphoma (DLBCL), based on recent studies GELA/ LNH 98.5, MinTde E4494/SWOG, which demonstrated efficacy for patients both under and over 60 years of age.

One of our study's limitations is the method used to evaluate treatment response, due to the absence of PEC-CT examination in our service, which is a standard imaging technique for NHL. This exam was only performed privately on 4 patients. The slight statistical significance favoring the RCHOP combination over CHOP is because rituximab was used in only 28 patients.

CONCLUSION

Progression-free survival (PFS) was 50% for R-CHOP and 28% for CHOP. In our country, we have been using rituximab via intravenous or subcutaneous administration for over 10 years, with satisfactory results for our DLBCL patients.

Conflicts of interest: The authors declare that they have no conflicts of interest.

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Original Article

THE EMERGENCE OF SALT REDUCTION AS A NATIONAL HEALTH PRIORITY IN ALBANIA

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ABSTRACT

Background. Albania is confronting a significant public health problem based on its historical diet: excessive salt consumption. As a leading cause of hypertension and cardiovascular disease, excessive salt intake has spurred a national movement in the direction of prevention-based health initiatives. This article explores Albania's emerging position in the fight against salt, looking at the process of transformation from traditional dietary patterns to the development of an organized public health response.

Current Position & Strategies. Historically characterized by a high-salt cuisine, Albania is now at a policy development and sensitization critical point. No studies have been made so far regarding salt consumption, except for placing labels for salt content visibly, and some vague publicity for salt reduction, no WHO guidelines have been implemented. Current statistics, including a study we made in Tirana that validated levels of consumption well beyond recommendations (11,8g salt/day), have accelerated the national debate and left action a necessity.

Conclusion & Future Direction. The future requires a multi-faceted approach. Albania's strategy now must coalesce into a strong, mandatory national program. Future priorities include establishing stronger regulatory management of the food industry, implementing clear and transparent front-of-pack labeling, and launching sustained, mass-media public education campaigns. The goal is to implement a cultural shift in eating habits, with salt reduction as a pillar of national cardiovascular disease prevention for a healthier future.

Keywords. Salt reduction, WHO guidelines, Eating habits

EMERGJENCA E REDUKTIMIT TË KRIPËS SI NJË PRIORITET NACIONAL PËR SHËNDETIN PUBLIK NË SHQIPËRI.

ABSTRAKT

Hyrje. Shqipëria po përballet me një problem të rëndësishëm të shëndetit publik bazuar në dietën e saj historike: konsumin e tepërt të kripës. Si një shkak kryesor i hipertensionit dhe sëmundjeve kardiovaskulare, marrja e tepërt e kripës ka nxitur një lëvizje në drejtim të iniciativave shëndetësore të bazuara në parandalim. Ky artikull shqyrton pozicionin në zhvillim të Shqipërisë në luftën kundër kripës, duke parë procesin e transformimit nga modelet tradicionale të të ngrënit në formimin e një përgjigjeje të organizuar të shëndetit publik.

Pozicioni & Strategjitë Aktuale. Historikisht e karakterizuar nga një kuzhinë me shumë kripë, Shqipëria tani është në një pikë kritike të zhvillimit të politikave dhe sensibilizimit. Deri më tani nuk janë bërë studime në lidhje me konsumin e kripës, dhe përveç vendosjes së etiketave për përmbajtjen e kripës në mënyrë të dukshme, dhe një publiciteti të dobët mediatik, nuk janë zbatuar udhëzime të OBSH-së në lidhje me këtë alarm global. Statistikat aktuale, përfshirë një studim që ne bëmë në Tiranë ku vërtetoi nivelet e konsumit përtej rekomandimeve (11,8g kripë/ditë), kanë përshpejtuar debatin kombëtar dhe e kanë lënë veprimin një domosdoshmëri.

Përfundimi & Drejtimi i Ardhshëm. E ardhmja kërkon një qasje shumëplanëshe. Strategjia e Shqipërisë tani duhet të shkojë drejt në një program të fortë dhe të detyrueshëm kombëtar. Prioritetet e ardhshme janë vendosja e një menaxhimi më të fortë rregullator në industrisë ushqimore, zbatimi i etiketimit të qartë në pjesën e përparme të paketimit dhe promovimi i fushatave të qëndrueshme edukuese publike. Qëllimi është të zbatohet një ndryshim kulturor në zakonet e të ngrënit, me reduktimin e kripës si një shtyllë e rëndësishme në parandalimin kombëtar të sëmundjeve kardiovaskulare për një të ardhme më të shëndetshme.

Fjalë kyç. Reduktimi i kripës, udhëzimet e OBSH-së, zakonet e të ngrënit

INTRODUCTION

Hypertension is a global alert

HBP (high blood pressure) is the leading risk of death in the world [1]. Unfortunately, worldwide, blood pressure levels are predicted to increase further, particularly in developing countries. In 2018, chronic diseases took the lives of 43 million people globally, accounting for 75% of the total deaths that year, and this is projected to rise to 53 million in 2030 [2].

Among these chronic disease-related fatalities, cardiovascular (CV) diseases were responsible for 44% of them [2]. High dietary salt intake is a significant contributor to elevated blood pressure [3]. Evidence from diverse sources spanning animal, epidemiology, and human intervention studies demonstrates the association between salt intake and HBP [4]. Daily sodium intake varied considerably across population groups, according to the Intersalt study [6], from a low of 4 g salt/d (sodium: 1.56 g/d, 68 mmol/d) among the Alaskan Inuit to 27 g

salt/d (sodium: 10.6 g/d, 460 mmol/d) in the Akita prefecture in northeastern Japan. It has been estimated that salt intakes in Belgium, Denmark, and the Netherlands were between 8 and 9 g/d, and in Finland, Italy, and Portugal, were between 9 and 12 g/d [6]. These results resonate with local trends observed in neighboring Balkan countries, such as Montenegro (11.5 g/day) [7], Slovenia (10.9 g/day) [8], and Greece (9.54 g/day) (9), which suggest a similar dietary pattern of reliance on salt-preserved traditional foods, processed meat, and widespread use of discretionary salt.

Recent intervention studies have found decreases in cardiovascular events following reductions in dietary sodium [10]. Salt intake is high in most countries and, therefore, strategies to lower salt intake could be an effective means to reduce the increasing burden of HBP and the associated cardiovascular disease. Effective collaborative partnerships between governments, the food industry, scientific organizations, and healthcare organizations are essential to achieve the WHO (World Health Organization)-recommended population-wide decrease in salt consumption to less than 5 g/day [11]. In the milieu of increasing cardiovascular disease worldwide, particularly in resource-constrained low- and middle-income countries, salt reduction is one of the most cost-effective strategies to combat the epidemic of HBP, associated cardiovascular disease, and improve population health [11]. Almost all European countries have conducted population studies to estimate the daily salt consumption.
In various studies, 24 h urinary sodium was significantly associated with BP as well as the increase in BP with age [6, 12]. National programs that reduce dietary salt consumption, including labelling changes and reformulation of products, are very cost-effective [11]. Lowering salt intake by 5.8 g was associated with a 3.1 mmHg decrease in SBP (systolic BP) [13].
Most recently, a global analysis indicated that 8.5 million deaths could be avoided over 10 years (2006–2015) by salt-reducing initiatives alone, and the estimated cost/person of implementing this was reported to be between $0.04–$0.32. [14]
There is strong evidence from trials that following a lower sodium diet reduces both average systolic (-3.3mmHg) and diastolic blood pressure (-2.2mmHg), compared with a higher sodium diet. Every 1000mg reduction in sodium is associated with a 2.8mmHg lowering of systolic and 1.7mmHg lowering of diastolic blood pressure [15]. The effect of sodium reduction on blood pressure is more pronounced in individuals with high blood pressure [15]. DASH (interventional Investigation) was a feeding study with randomization to DASH or control diets with high, medium, and low sodium intake (roughly 3300, 2400, and 1500 mg/day on average) for 30 days. It found a graded reduction in blood pressure with lower sodium versions of both diets (6.7 mmHg among those on the control diet and 3.0 mmHg among those on the DASH diet), with a stronger effect among those with hypertension at baseline, but also in normotensive persons [13]. Furthermore, it was also found that populations with low average daily salt intakes had low BP and very little or no increase in BP with age.

Alarming statistics in Albania

In Albania, in 2021, non-communicable diseases accounted for 66% of all deaths. Among females, stroke and ischemic heart disease were the top leading causes of death with 291 and 256 per 100000 population, respectively [5]. Hypertension is one of the main risk factors for cardiovascular diseases, accounting for almost two-thirds of all strokes and half of all ischemic heart diseases. The overall mortality rate from CVD (SIZ, Stroke, Hypertensive Heart Disease) in 2021 was estimated at 497 deaths per 100,000 inhabitants. The demographic transition experienced over the last three decades has inevitably led to a significant change in the epidemiological profile of the Albanian population, characterized by a noticeable shift towards non-communicable diseases, particularly cardiovascular diseases, cancer, chronic respiratory diseases, and diabetes. The main risk factors in the Albanian population consist of hypertension (the main risk factor, accounting for about 34% of overall mortality), food-related risks (second, accounting for about 23.4% of overall mortality), smoking (accounting for about 20% of overall mortality), followed by alcohol (4.92%) [5]

A Deep-Rooted Taste

Albanian cuisine enjoys a reputation for strong and pronounced tastes. Salt has long been a basic seasoning; sprinkled generously while cooking, it was also often added automatically at the table. This "culture of salt" is deeply rooted in the country's culinary as well as social traditions. Recently, though, a more critical public health focus has been the deliberate reduction of dietary sodium. There has been a growing body of evidence that directly relates excessive salt intake to adverse cardiovascular events, increasingly informing both clinical guidance and public discourse.

The following analysis attempts to outline Albania's path toward dealing with this major health issue. It looks into the current public health policies, determines the persistent cultural and pragmatic barriers to behavior modification, and considers possible ways to change this food habit. In addition, it will provide some of the main findings of a recently conducted Tirana survey that quantified both current consumption patterns and established a baseline for continued intervention.

The Invisible Threat: What Does Excess Salt Do?

Sodium, a primary component of dietary salt (NaCl), is an essential electrolyte involved in critical physiological processes, including fluid balance, neuromuscular function, and cellular homeostasis. The estimated minimum physiological requirement for adults is approximately 550 mg of sodium (24 mmol) per day [16, 17].

However, chronic consumption of sodium more than physiological needs disrupts systemic regulation. The primary mechanism involves osmotic fluid retention to dilute elevated serum

sodium concentrations. This increases intravascular volume, leading to elevated cardiac preload and a consequent rise in systemic blood pressure.

Sustained hypertension is a major modifiable risk factor for numerous serious pathologies, including:

- Acute coronary syndromes and myocardial infarction
- Cerebrovascular accidents (stroke)
- Chronic kidney disease and progressive renal impairment
- Reduced bone mineral density and osteoporosis
- Increased risk of gastric carcinoma

In alignment with cardiovascular risk reduction, the World Health Organization (WHO) recommends a maximum daily intake of less than 5 grams of salt (equivalent to approximately 2000 mg of sodium) [15]. Despite this, global surveillance data indicate that the average population consumption frequently exceeds this recommendation by more than twofold—a pattern of excess also observed in Albania.

Policies and Initiatives: A Shift Towards Change

Until recently, salt reduction was rather a subjective issue than systemic in Albania. However, the recent few years have witnessed a visible difference.

So far, in our country, no studies have been conducted in the population to accurately determine salt consumption by measuring urinary sodium excretion in 24-hour urine. It has also been achieved, in cooperation with the Ministry of Health, to place labels for salt content visibly. Negotiations have been made with large food industry producers to reduce the amount of salt, but there have been no results. No significant campaigns have been conducted in the population on the importance of reducing salt in the diet.

Despite all this, challenges are still the norm. A widespread informal economy and home food production make monitoring and regulation difficult. Furthermore, changing consumption patterns is a lengthy process.

The Tirana Study: A Snapshot of the Current Reality

To get a clearer view of how widespread the problem is in an urban Albanian context, we conducted an observational study in the country's capital city, Tirana. The study involved estimating as closely as possible the average salt intake of the urban adult population with the best means available: 24-hour urine collection. The technique has been described as the "gold standard" since it measures the quantity of sodium the body is passing out and provides a very reliable estimate of intake.

Methodology: A total of 150 adults between the ages of 18 and 75 from the Tirana region were randomly selected. Participants were instructed to pass all urine during a period of 24 hours in special containers. The volume and sodium content (Na) of the sample were measured. Salt excretion was subsequently calculated from a standard formula (g NaCl = mmol $Na^+ \times 0.05844$).

RESULTS: An Alarming Readout

The findings of our research show a worrisome, but not surprising, snapshot of our eating habits.

1. Excessive Average Consumption: The mean 24-hour sodium excretion was found to be 202.54 mmol/day with an SD of 93.56. If this is converted to actual salt consumption, then residents of Tirana are consuming an average of 11.8 grams of salt per day (SD 5.48). This is more than double the WHO recommendation (5g/day) and implies that the cardiovascular system of the population is undergoing a very high degree of overload.

2. Gender Difference: The study found a statistically significant difference between the genders. Urinary sodium excretion among men was 223.85 mmol/day (SD 106.51) and for women was 190.80 mmol/day (SD 83.96). This would amount to a salt intake of 13.08 grams/day in men and 11.09 grams/day in women. The difference was statistically significant at P-value 0.045. This can be due to social factors, diet, or even body size and metabolic variation.

3. Age and Salt Consumption: To our surprise, our research failed to find any statistically significant correlation between salt consumption and age. Consumption increased slightly with age; however, this trend was not statistically significant. This suggests that the habit of excessive salt consumption exists in all age groups, as opposed to specifically the older age groups.

4. Body Mass Index (BMI) and Salt: Perhaps the most striking finding from the study was the positive correlation between Body Mass Index (BMI) and salt intake. Analysis showed a weak positive, but highly statistically significant association ($r=0.183$, $p=0.001$). This suggests that as BMI increases (i.e., heading in the direction of overweight or obese categories), so does the level of salt intake. This association is troubling because it illustrates a common pattern of bad eating: a high-calorie, unhealthy-fat, processed-food diet (which tends to be high in salt as well as fat), leading to weight gain and increased cardiovascular risk.

Implications and The Future

Our findings in Tirana are not figures; they reflect a health reality that must be immediately addressed. An average of 11.8 grams of salt per day exposes close to the entire adult population to a high risk for the development of hypertension and its complications.

What needs to be done?

1. Continuous Education: The awareness campaigns must be intensified and targeted, particularly towards the risk groups (men, overweight individuals).

2. Industry Collaboration: Work with bakeries and producers of common food products (e.g., white bread, white cheese, sausage industry) to gradually reduce salt content so the public can acclimatize to altered flavor.

3. Family Doctors' Role: Family physicians are on the ground and can play a crucial role in advising and screening patients on salt intake.

4. Making Easy Choices: On an individual level, each of us can start by removing the saltshaker from the table, reducing the amount of salt used in cooking by a third, replacing it with herbs and spices, and reading food labels carefully to choose lower-sodium alternatives.

CONCLUSION: A Long Journey Towards a Better Taste

Reduction of sodium intake in Albania requires a continuous and multi-faceted public health approach. Ultimately, success will depend on a gradual cultural shift away from associating traditional flavor with high salt content and toward appreciation of the natural tastes of food, accented by healthier seasoning choices.

Data from the Tirana study provides a critical and reliable evidence base that confirms the need for intervention. The findings are unequivocal and concerning; yet this presents a clear mandate for action rather than any cause for pessimism. It is a direct call to action for policymakers, the food industry, and the public.

The reduction of dietary salt is not a sacrifice of flavor or tradition but is rather an investment towards long-term health. It's a modification that preserves the enjoyment of food while significantly mitigating the risk of chronic disease, enhancing both life expectancy and quality of life.

While science provides the evidence, the responsibility for implementation rests with everyone. The time to act to take strategic steps in protecting health at a population level is now.

Conflicts of interest: The authors declare that they have no conflicts of interest.

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Original Article

GASTROINTESTINAL INVOLVEMENT IN SYSTEMIC SCLEROSIS: CORRELATION WITH IMMUNOLOGICAL ACTIVITY – A RETROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Background. Gastrointestinal involvement is a frequent complication of systemic sclerosis, contributing to morbidity and mortality. Standardized approaches for assessment remain limited in low-resource settings**.**

Objective. To describe gastrointestinal involvement in Albanian systemic sclerosis patients, evaluate correlations with immunological markers, and compare findings with international data.

Methods: Retrospective review of 75 systemic sclerosis patients treated at the University Hospital Center "Mother Teresa," Tirana (2018–2022); complete data available for 62 patients. Gastrointestinal symptoms were assessed using the UCLA SCTC GIT 2.0 questionnaire. Clinical, laboratory, and selective endoscopic evaluations were performed. ANA, ENA, and Anti-Scl-70 antibodies were measured. Follow up every six months.

Results. Esophageal involvement was most frequent (90%), followed by intestinal involvement (40–70%). Oral manifestations: xerostomia (32%), microstomia, microcheilia. Dysphagia 25%, reflux 36%, GERD 32%, esophageal inflammation 39%. Gastric: gastroparesis 39%, GAVE 3.2%. Duodenal erosions 21.2%, malabsorption 26%. ANA+ 90%, ENA+ 78%, Anti-Scl-70+ 71%, all significantly correlated with Gastrointestinal involvement ($p<0.05$).

Conclusion. GI involvement in Albanian systemic sclerosis patients mirrors international patterns. ANA, ENA, and Anti-Scl-70 positivity are associated with Gastrointestinal manifestations. Systematic assessment using clinical, immunological, and selective endoscopic evaluation is feasible in low-resource settings. Prospective studies and local validation of symptom scoring tools are recommended.

Keywords. systemic sclerosis, gastrointestinal involvement, ANA, Anti-Scl-70, immunological activity

MANIFESTIMET GASTROINTESTINALE NË SKLEROZËN SISTEMIKE: KORRELACIONI ME AKTIVITETIN IMUNOLOGJIK – STUDIM RETROSPEKTIV

ABSTRAKT

Hyrje. Manifestimet gastrointestinale janë një komplikacion i shpeshtë i sklerozës sistemike, duke kontribuar në morbiditet dhe mortalitet. Qasjet standarde për vlerësim mbeten të kufizuara në vende me burime të pakta diagnostike.

Qëllimi. Të përshkruhen manifestimet gastrointestinale tek pacientët shqiptarë me sklerozë sistemike, të vlerësohen korrelacionet me treguesit imunologjikë dhe të krahasohen me të dhënat ndërkombëtare.

Metoda. U realizua një rishikim retrospektiv i 75 pacientëve me sklerozë sistemike të trajtuar në Qendrën Universitare të Spitalit "Nënë Tereza", Tiranë (2018–2022); të dhëna të plota ishin të disponueshme për 62 pacientë. Simptomat GI u vlerësuan me pyetësorin UCLA SCTC GIT 2.0, ndërsa u kryen ekzaminime klinike, laboratorike dhe endoskopike selektive. U matën antitrupat ANA, ENA dhe Anti-Scl-70. Pacientët ndiqeshin çdo gjashtë muaj.

Rezultate. Përfshirja ezofageale ishte më e shpeshta (90%), e ndjekur nga ajo intestinale (40–70%). Manifestimet orale përfshinin xerostomia (32%), microstomia dhe microcheilia, ndërsa 23% plotësonin kriteret për sindromën e Sjogren-it. Manifestimet ezofageale: dysphagia 25%, odynophagia 18%, reflux 36%, GERD 32%, strictures 28%, inflamacion 39%. Manifestimet gastrike përfshinin gastroparezë 39%, gastritis 30%, erosive gastritis 27%, ulcer gastrik 16%, dhe GAVE 3.2%. Në zorrët e vogla: erozionet duodenale 21.2%, malabsorbim 26%, mungesë e vitaminës B6 28%, mungesë e vitaminës B12 31%, anemi 32%, dysmotility intestinale 13%, dhe SIBO 12%. Koloni/anorektumi përfshinte dysmotility 15%, sindromin e zorrëve irritabile 21%, dhe disfunksion të sfinkterit anal 3%. Antitrupat ANA ishin pozitiv në 90% të pacientëve, ENA në 78%, dhe Anti-Scl-70 në 71%, të gjitha duke treguar korrelacion të ndjeshëm me manifestimet gastrointestinale ($p<0.05$).

Përfundimi. Manifestimet gastrointestinale tek pacientët shqiptarë me sklerozë sistemike pasqyrojnë modelet ndërkombëtare. Pozitiviteti i ANA, ENA dhe Anti-Scl-70 lidhet me shfaqjen e manifestimeve gastrointestinale. Vlerësimi sistematik duke përdorur ekzaminime klinike, imunologjike dhe endoskopike selektive është i realizueshëm edhe në mjedise me burime të kufizuara. Rekomandohen studime prospective dhe validimi lokal i instrumenteve për vlerësimin e simptomave.

Fjalë kyçe. sklerozë sistemike, manifestime gastrointestinale, ANA, Anti-Scl-70, aktivitet imunologjik

INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune connective tissue disease with microvascular injury, fibrosis, and multi-organ involvement [1–4]. Gastrointestinal (GI) complications occur in >90% of patients and impact prognosis and quality of life [5–7]. Esophageal dysmotility, gastroparesis, malabsorption, and colonic dysmotility are most frequent [8–10]. Immunological markers such as ANA, ENA, and Anti-Scl-70 often correlate with disease activity and organ involvement [11-13]. Data from low-resource countries are scarce, where access to endoscopy and imaging may be limited [14]. This study evaluates the prevalence, patterns, and immunological correlations of GI manifestations in Albanian SSc patients.

MATERIALS AND METHODS

This retrospective observational study included 75 patients with systemic sclerosis (SSc) treated between 2018 and 2022 at the Rheumatology Clinic and Consultation Center, University Hospital Center "Mother Teresa," Tirana. Complete data were available for 62 patients and were analyzed for this study.

Gastrointestinal (GI) involvement was assessed using the UCLA SCTC GIT 2.0 questionnaire, in conjunction with a clinical evaluation of the oral cavity, esophagus, stomach, small intestine, and colon/anorectum. Fibrogastroscopy was performed when clinically indicated. Patients were followed every six months according to international guidelines [5, 16], which included clinical assessments, laboratory tests, symptom scoring, and selective endoscopic evaluations [5, 16] evaluations [5, 16]. Small intestinal bacterial overgrowth (SIBO) was assessed based on breath testing, which was systematically performed.

Immunological assessment included testing for antinuclear antibodies (ANA), extractable nuclear antigen (ENA) profile, and anti-Scl-70 antibodies in all patients. Additional tests, such as rheumatoid factor (RF), anti-dsDNA, ANCA, and complement levels, were performed as clinically indicated.

Statistical Analysis

Descriptive statistics were used for demographic and clinical variables. Categorical variables were compared using Chi-square tests, and continuous variables were compared using t-tests. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 62 patients were analyzed, of whom 92% were female. The mean age was 48.2 years (men 56.2, women 49.5), with the most frequent age group being 56–65 years (39%). Male patients exhibited 38% higher gastrointestinal (GI) involvement compared to females.

Oral manifestations were common, with xerostomia and salivary gland fibrosis each present in 32% of patients, and Sjogren's syndrome in 23%. Esophageal involvement was the most frequent, including dysphagia in 25%, odynophagia in 18%, reflux in 36%, GERD in 32%, strictures in 28%, and esophageal inflammation in 39%. Gastric involvement included gastroparesis in 39%, gastritis in 30%, erosive gastritis in 27%, gastric ulcers in 16%, and GAVE in 3.2%. Small intestinal manifestations comprised duodenal erosions in 21.2%, malabsorption in 26%, vitamin B6 deficiency in 28%, vitamin B12 deficiency in 31%, anemia in 32%, intestinal dysmotility in 13%, and small intestinal bacterial overgrowth (SIBO) in 12%. Colonic and anorectal involvement, though less frequent, included dysmotility in 15%, irritable bowel syndrome in 21%, and anal sphincter dysfunction in 3%. Indirect manifestations such as muscle atrophy, altered intestinal reflexes, and dysmotility may contribute to functional GI impairment even in asymptomatic patients. Regarding immunological markers, ANA positivity was observed in 90% of patients, ENA in 78%, and Anti-Scl-70 antibodies in 71%. All three markers showed a significant correlation with GI involvement, with p-values of 0.01, 0.03, and 0.01, respectively.

Figure 1 illustrates the overall prevalence of GI manifestations across different organ systems, highlighting the predominance of esophageal and gastric involvement. These findings emphasize the importance of systematic assessment and monitoring, including both clinical evaluation and selective endoscopic examination, even in low-resource settings.

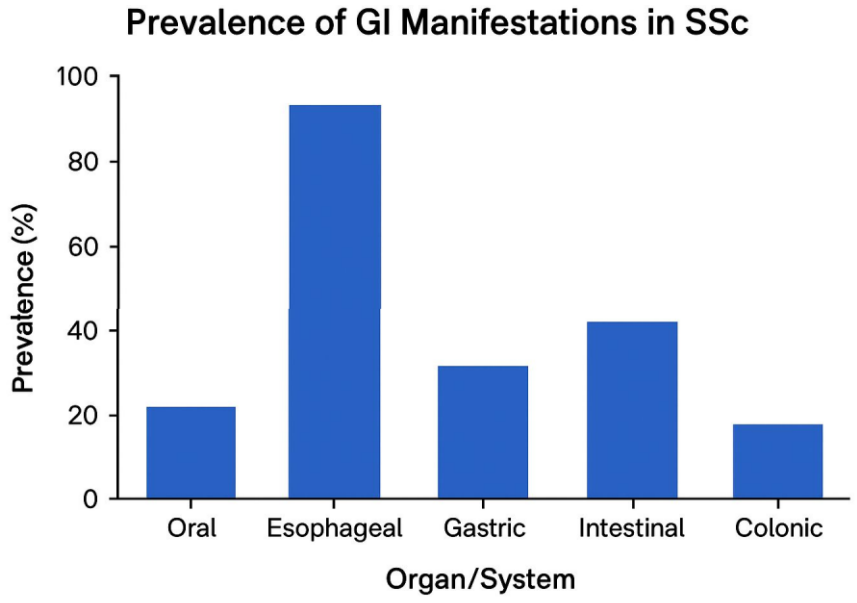


Figure 1. **T**he overall prevalence of GI manifestations across different organ systems.

DISCUSSION

Gastrointestinal (GI) involvement is highly prevalent among Albanian patients with systemic sclerosis (SSc), with esophageal manifestations, particularly dysmotility and gastroesophageal reflux, being the most frequent. This finding is consistent with data from European and US cohorts, which report esophageal involvement in up to 70–90% of patients with SSc [8,9,17]. The predominance of esophageal manifestations underscores the importance of early recognition and monitoring, as delayed diagnosis may lead to complications such as strictures, Barrett's esophagus, and significant nutritional deficiencies. Our study demonstrated significant correlations between autoantibody profiles, namely ANA, ENA, and anti-Scl-70, and the presence of GI manifestations. These results align with prior international literature, indicating that specific immunological patterns may predispose patients to more severe or extensive GI involvement [11,12,18]. In particular, anti-Scl-70 positivity has been previously associated with diffuse cutaneous SSc and increased risk of esophageal dysmotility, suggesting a possible pathogenic link between autoimmunity and gastrointestinal fibrosis. The UCLA SCTC GIT 2.0 questionnaire was used in this cohort to provide a structured evaluation of GI symptoms, including reflux, bloating, diarrhea, and constipation. Although this instrument is widely validated internationally, local cultural and linguistic validation is recommended to ensure accuracy and relevance of patient-reported outcomes in the Albanian population. Such validation would improve symptom assessment, enhance patient monitoring, and allow for better comparability with other cohorts [5,16].

From a clinical management perspective, systematic follow-up is essential. We recommend follow-up visits every six months, supplemented by selective fibrogastroscopy based on symptom severity or progression. Even in low-resource settings, this approach enables timely detection of esophageal complications and allows for earlier intervention, including dietary modifications, prokinetic therapy, and endoscopic management where indicated [5,16].
Although this study provides important insights into GI involvement in Albanian SSc patients, the relatively small sample size (n=62) and female predominance (92%) may limit the generalizability of the findings. Therefore, larger, multicenter studies are needed to confirm these observations and improve representativeness. Future research should also integrate comprehensive biomarker analysis, nutritional assessments, and detailed immunological profiling to elucidate pathogenic mechanisms, identify patients at higher risk for severe GI involvement, and guide individualized therapy.

CONCLUSIONS

Gastrointestinal involvement is common in Albanian SSc patients, particularly esophageal manifestations, and mirrors patterns seen internationally. ANA, ENA, and anti-Scl-70 positivity correlate with GI symptoms. Structured symptom assessment and selective endoscopic evaluation are feasible even in low-resource settings. Future studies should focus on local validation of symptom scores and prospective analyses to improve monitoring and management.

Conflicts of interest: The authors declare that they have no conflicts of interest.

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PLEUROPULMONARY MANIFESTATIONS OF ANKYLOSING SPONDYLITIS: A LITERATURE REVIEW

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ABSTRACT

Ankylosing spondylitis is a chronic seronegative spondyloarthropathy, which results in ankylosis of the spine and sacroiliac joints, although involvement is also seen in large and small joints. AS is a chronic, multisystem inflammatory disease of unknown etiology. *HLA-B27* is the gene with the strongest association. Although classically thought of as a spinal disease, it can also involve other organs, such as the eyes, lungs, and heart. Pleuroparenchymal involvement is uncommon and is seen in the later stages of the disease. Pulmonary involvement in AS is usually in the form of upper lobe fibrocavitary disease

Keywords: Ankylosing spondylitis, pleuropulmonary, HRCT

MANIFESTIMET PLEUROPULMONARE TË SPONDILITIT ANKILOZANT: RISHIKIM LITERATURE.

ABSTRAKT

Spondiliti ankilozant është një spondiloartropati kronike seronegative, e cila rezulton në ankilozë të shtyllës kurrizore dhe nyjeve sakroiliake, megjithëse përfshirja vërehet edhe në nyje të mëdha dhe të vogla. AS është një sëmundje inflamatore kronike multisistemike me një etiologji të panjohur. HLA-B27 është geni me lidhjen më të fortë. Edhe pse klasikisht mendohet si një sëmundje e shtyllës kurrizore, ajo mund të përfshijë organe të tjera si sytë, mushkëritë dhe zemra. Përfshirja pleuroparenkimale është e pazakontë dhe shihet në fazat e mëvonshme të sëmundjes. Përfshirja pulmonare në AS zakonisht është në formën e sëmundjes fibrokavitare të lobit të sipërm.

Fjalë kyçe. Spondiliti ankilozant, pleuropulmonare, HRCT

I. Ankylosing spondylitis.

Ankylosing spondylitis (AS) (less commonly known as Bechterew disease or Marie-Strümpell disease) is a chronic seronegative spondyloarthropathy, which results in fusion (ankylosis) of the spine and sacroiliac (SI) joints, although involvement is also seen in large and small joints (1), with the major histocompatibility antigen HLA B27 (2). Traditionally, it was thought there was a male predilection of 3:1 or more. The disease usually manifests in young adults, with the first symptoms becoming evident in the third decade, although up to 18% of cases manifest in the second decade (1). AS is a chronic, multisystem inflammatory disease of unknown etiology (3). Patients are rheumatoid factor (RF) negative, hence seronegative. *HLA-B27* is the gene with the strongest association. Other possibly contributing genes include *ERAP-1*, *IL23R*, and TNF-associated genes (4). Diagnosis requires showing sacroiliitis on imaging or spine inflammation using MRI. Treatment is with nonsteroidal anti-inflammatory drugs (NSAIDs) and/or tumor necrosis factor inhibitors or interleukin-17 (IL-17) inhibitors and physical measures that maintain joint flexibility (5).

Although classically thought of as a spinal disease, it can involve other organs such as the eyes, lungs, and heart (6). Systemic manifestations of ankylosing spondylitis occur in approximately 25% of patients (7).

II. Pleuropulmonary manifestations of ankylosing spondylitis

Ankylosing spondylitis, a chronic multisystem inflammatory disorder, can present with articular and extra-articular features. It can affect the tracheobronchial tree and the lung parenchyma (8).

Pleuroparenchymal involvement is uncommon and is seen in the later stages of the disease or may follow an asymptomatic clinical course (9,10), and the rate of abnormal findings increases with increased duration of AS (3). The lung parenchymal involvement generally occurs many years after the onset of arthritic changes (11).

Pulmonary involvement can be both direct and indirect: Direct involvement is via the development of interstitial lung disease. Indirect involvement occurs when joints of the thoracic cage, such as the costovertebral joints, become fused; thus, movement is limited, and chest wall compliance is reduced (12).

The most frequently seen symptoms are upper lobe fibrobullous disease, interstitial lung disease, pleural thickening, pleural effusion, and the formation of mycetoma (9,13). Less often, emphysema, pneumothorax, and cor pulmonale have been reported (13). Upper lobe cavitary lesions are late complications secondary to fungal and mycobacterial infections (14, 15).

These changes seen in AS were observed using X-rays, respiratory function tests, bronchoalveolar lavage, and transbronchial biopsy in previous studies (9). HRCT changes have been described in more recent studies; however, these studies have involved only a

small number of patients. The highest number of patients included in these studies was 55 (16). In addition, fewer HRCT findings were evaluated (3).
Respiratory complications also include obstructive sleep apnea (8).

II.1. The most frequently seen pleuropulmonary manifestations are:

a. *Apical fibrobullous disease*. Ankylosing spondylitis is a common cause of pulmonary apical fibrocystic disease; early involvement may be unilateral or asymmetrical, but most cases eventually consist of bilateral apical fibrobullous lesions, many of which are progressive with coalescence of the nodules, formation of cysts and cavities, fibrosis, and bronchiectasis (8).
Upper lobe fibrobullous disease is the most common lung manifestation described in 1.3% to 30% of patients with ankylosing spondylitis (17,18).
Bilateral apical scarring is believed to be the earliest pulmonary manifestation (18). Apical/upper lobe predominant interstitial lung disease with small cystic spaces (in ~1% of patients) (19).
Pulmonary fibrosis is a rare manifestation of ankylosing spondylitis, which may be complicated by infection and haemorrhage, and determines the dismal prognosis of these patients (20).
b. *Mycobacterial or fungal superinfections* of the upper lobe cysts and cavities occur commonly. Aspergillus fumigatus is the most common pathogen isolated, followed by various species of mycobacteria. The prognosis of patients with fibrobullous apical lesions is mainly determined by the presence, extent, and severity of superinfection (8).
c. *Chest wall restriction*. The restrictive ventilator defect may develop because of either fusion of costovertebral joints and ankylosis of the thoracic spine or anterior chest wall involvement (11). The most common thoracic finding in ankylosing spondylitis (AS) is ankylosis of the costovertebral joints with severe limitation of chest expansion, inducing a restrictive syndrome. Pleural and pulmonary fibrosis can occur during the disease (21). The lung is involved in up to 30% of patients with chest wall restriction, and upper lobe fibrosis is the commonest (13,22).
d. *Apical pleural thickening* in ankylosing spondylitis is common in association with apical fibrobullous disease (23). Pleural disease is otherwise rare (24).
e. *Pleural effusion* is extremely rare (18). Pleural effusion occurs in autoimmune connective tissue diseases as a part of the inflammatory component. It could also be due to serositis related to ankylosing spondylitis (25). Pleural effusion due to connective tissue disease (CTD) develops secondary to increased capillary permeability due to immune or non-immune inflammation (26).
Pleural effusion is often associated with apicobullous disease (27). Isolated pleural effusion may be seen in patients with AS without a simultaneous apical fibrobullous involvement of the lungs, and it responds well to corticosteroid (28).
f. A recent survey has suggested that in the absence of ankylosing spondylitis, the presence of *HLA B27* may be associated with an increased frequency of pleurisy and spontaneous pneumothorax (29). There is a higher risk of pneumothorax in patients with AK, and it may be recurrent in some (11).

II.2. Epidemiology of pleuropulmonary manifestations

Lung parenchymal involvement is reported in different studies with a small number of cases, ranging in frequency ratios (3).
The rate of pleuroparenchymal involvement has been reported in various small clinical studies to be 0%-85% in X-ray or high-resolution computed tomography (HRCT) studies

(9,10,13,16,18,30-38). The incidence of pleuropulmonary involvement shows a big variation in the literature, probably as a result of selection biases (2).
Pulmonary manifestations are rare, causing upper lobe fibro cavitary disease (18). These have a significant variation in the literature (39). Dudley-Hart et a1 (40) reported two patients with a history of pleurisy, and one of them had a pleural effusion in 1950. Zorab has reported one tuberculous and one non-tuberculous pleural effusion among 53 cases of ankylosing spondylitis in 1962 (29). Crompton et al noted bilateral pleural calcification in 255 patients with ankylosing spondylitis, unrelated to tuberculosis or asbestos exposure in 1974 (41). Kinnear and Shneerson had reported only pleural effusion without apical involvement (42). These effusions were bilateral (18) or unilateral (39,42) and recurrent (42,43). There were pleural effusions coexistent with pericardial effusion in some cases (44). Spencer et al described bilateral pleural thickening in one out of 200 patients with ankylosing spondylitis (45). The temporal relationship between activity in the spinal and pleural disease or the response to treatment was not observed (24).

II.3. Diagnosis of pleuropulmonary manifestations

Chest radiographic findings may mirror the severity of clinical involvement (8).
Computed tomography is useful in delineating the extent of pleural thickening, bullous changes, volume loss, parenchymal fibrosis, and bronchiectasis, as well as identifying or excluding intracavitary pulmonary mycetoma (22).
HRCT is useful to evaluate early lung parenchymal changes in patients with AS (3). HRCT examination of the lungs may show the presence of parenchymal micronodules, parenchymal bands, subpleural bands, interlobular and intralobular septal thickening, irregular interfaces, ground glass opacities, consolidation, mosaic pattern, bronchial wall thickening, bronchial wall dilatation, thickening, emphysema, rib cage asymmetry, honeycomb appearance, structural distortion, apical fibrosis, and other additional findings (3). Cavitation is uncommon and was reported in only 0.45 patients in one series (41).
There is no correlation between the radiological extent of the disease (spinal changes and pulmonary involvement) and any of the haematological or biochemical parameters measured (30).
Pleural effusion developed in AS patients is usually exudative with a normal pH and glucose values. Inflammatory cells, including eosinophils, have been identified in cytological examination (26, 46). Other than involvement of the pleura, pleural effusion can be secondary to the drugs (sulfasalazine therapy) used for treatment of AS (47) or bilateral transudative effusion due to involvement of the heart (48,49).
It can be diagnosed via exclusion of other etiologies such as parapneumonic effusion, tuberculosis, and malignancies. Pleural biopsies can be performed and mainly result in chronic inflammation (50).
Pulmonary function test results are nonspecific and generally parallel the severity of parenchymal involvement. Restrictive ventilatory impairment can develop in patients with ankylosing spondylitis because of either fusion of the costovertebral joints and ankylosis of the thoracic spine or anterior chest wall involvement (8).

II.4. Treatment of pleuropulmonary manifestations

No treatment has been shown to alter the clinical course of apical fibrobullous disease. Although several anti-inflammatory agents, such as infliximab, etanercept, and adalimumab, are being used to treat ankylosing spondylitis, their effects on pulmonary manifestations are unclear (8).

The treatment of AS-associated pleural effusion is not well documented (50). Pleural effusion resolves spontaneously in some cases. However, systemic or local steroids or phenylbutazone had been effective in the pleural effusion (51), as recurrence may be a prominent feature of the disease, as in our case. Systemic prednisolone (30 mg daily) (42), local administration of steroids (20 mg prednisolone locally to the pleural cavity after complete drainage of the effusion) (51), or phenylbutazone (200 mg daily) (43) had been successfully used in the treatment of pleural effusion (2).

II.5. Prognosis of pleuropulmonary manifestations

Pulmonary parenchymal disease is typically progressive, and cyst formation, cavitation, and fibrosis are seen in advanced cases (8).

CONCLUSION

Ankylosing spondylitis, beyond its skeletal involvement, may be associated with significant pleuropulmonary manifestations that usually appear in the later stages of the disease and often remain clinically silent for a long time. The most frequent pulmonary finding is apical fibrobullous disease, which may be complicated by fungal or mycobacterial superinfections and can markedly worsen prognosis. High-resolution computed tomography is the most sensitive imaging modality for the early detection of pulmonary abnormalities and should be considered in patients with long-standing disease or respiratory symptoms. Early recognition and a multidisciplinary approach are essential to optimize management and improve patient outcomes.

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Review Article

THE INTESTINAL MICROBIOME AS A NOVEL THERAPEUTIC TARGET IN THE INTEGRATED MANAGEMENT OF CARDIO-RENAL-METABOLIC SYNDROME

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ABSTRACT

The group of cardio-renal-metabolic diseases, encompassing chronic kidney disease, obesity, type 2 diabetes mellitus, atherosclerotic cardiovascular diseases, and heart failure, represents a significant global health challenge, contributing substantially to the increasing burden of morbidity and cardiovascular mortality.

In recent years, considerable attention has been directed toward the relationship between the intestinal microbiota and the host organism, as studies have revealed the essential metabolic role of the intestinal microbiome and its impact on immune dysregulation within the gastrointestinal tract. The intestinal microbiome functions as an endocrine organ, producing bioactive metabolites such as short chain fatty acids (SCFAs), trimethylamine N-oxide (TMAO), and bile acids, which directly and indirectly influence inflammation, metabolic function, and intestinal barrier integrity. Furthermore, the microbiome modulates immunological and hormonal mechanisms of the host, mediating bidirectional communication between the gut and key organs, including the heart, kidneys, and metabolic systems.

This review examines the intricate relationships between the intestinal microbiome, the cardiovascular system, renal function, and metabolism. It highlights the critical roles of the gut cardiovascular, gut renal, and gut metabolic axes in the pathogenesis and progression of multisystem diseases encompassed within the cardio-reno-metabolic syndrome, while also discussing innovative therapeutic strategies. Modulation of the intestinal microbiome represents a promising opportunity for the prevention and personalized management of metabolic diseases and their cardiovascular and renal complications, thereby addressing a critical global public health concern.

Keywords: Intestinal microbiome, microbial metabolites, dysbiosis, cardio-renal-metabolic syndrome, therapeutic targets.

MIKROBIOMA E ZORRËS SI NJË OBJEKTIV I RI TERAPEUTIK NË MENAXHIMIN E INTEGRUAR TË SINDROMËS KARDIO-RENO-METABOLIKE

ABSTRAKT

Grupi i sëmundjeve kardio-reno-metabolike, që përfshin Sëmundjen Kronike të Veshkave, Obezitetin, Diabetin Mellitus tip 2, Sëmundjen Kardiovaskulare Aterosklerotike dhe Insuficiencën Kardiake, përbën një sfidë të rëndësishme globale shëndetësore, duke kontribuar në rritjen e barrës së sëmundshmërisë dhe vdekshmërisë kardiovaskulare.

Në vitet e fundit, lidhja ndërmjet mikrobiotës intestinale dhe organizmit pritës ka tërhequr vëmendje të konsiderueshme, pasi studimet kanë evidentuar rolin metabolik thelbësor të mikrobiomës intestinale si dhe efektet e saj në disbalancimin imun të traktit gastrointestinal. Mikrobioma intestinale vepron si një organ endokrin, duke prodhuar metabolitë bioaktivë si acide yndyrore me zinxhir të shkurtër (SCFA), trimetilaminë N-oksid (TMAO) dhe acide biliare, të cilët ndikojnë në mënyrë direkte dhe indirekte në inflamacion, funksionin metabolik dhe integritetin e barrierës intestinale. Gjithashtu, mikrobioma ndikon në mekanizmat imunologjikë dhe hormonalë të organizmit, duke ndërmjetësuar komunikimin bidireksional mes zorrëve dhe organeve kryesore si zemra, veshkat dhe sistemi metabolik.

Në këtë përmbledhje, analizohen ndërveprimet komplekse midis mikrobiomës intestinale, sistemit kardiovaskular, funksionit renal dhe metabolizmit. Artikulli thekson rëndësinë e boshtit zorrë - sistem kardiovaskular, boshtit zorrë - veshka dhe boshtit zorrë – metabolizëm, si rrugë kyçe në patogjenezën dhe progresionin e sëmundjeve multisistemike brenda sindromës kardio-reno-metabolike, si dhe eksploron qasjet terapeutike inovative. Modifikimi i mikrobiomës intestinale paraqet një mundësi premtuese për parandalimin dhe menaxhimin e personalizuar të sëmundjeve metabolike dhe ndërlikimeve të tyre kardiovaskulare dhe renale, duke adresuar kështu një problematikë kritike në shëndetin publik global.

Fjalë kyçe: Mikrobioma intestinale, metabolitë mikrobiomikë, disbioza, sindroma kardio-reno-metabolike, objektiva terapeutike.

INTRODUCTION

Cardiovascular Kidney Metabolic (CKM) syndrome affects multiple organ systems, contributing to complications such as kidney failure, cognitive decline, MASLD, sleep apnea, and increased cancer risk (1). However, its greatest impact is on cardiovascular disease (CVD), which drives most of the associated morbidity and premature mortality (1). CKM disrupts vascular integrity, promotes atherogenesis, and impairs myocardial function, leading to higher risks of coronary heart disease, stroke, heart failure, peripheral artery disease, atrial fibrillation, and sudden cardiac death (1, 2). Since 2008, the AHA and NHLBI have promoted the term “Cardio Reno Metabolic Syndrome” to highlight the need for integrated management of cardiovascular, renal, and metabolic diseases (3). In October 2023, the AHA officially recognized “Cardiovascular Kidney Metabolic Syndrome” as a unified clinical entity, emphasizing the shared pathophysiology of heart disease, kidney disease, type 2 diabetes, and obesity, and urging a reassessment of current strategies for cardiovascular risk prediction and prevention (1). CKM syndrome is stratified into five progressive stages: stage 0, absence of CKM risk factors; stage 1, excess or dysfunctional adiposity; stage 2, presence

of metabolic risk factors such as hypertriglyceridemia, hypertension, diabetes mellitus, and metabolic syndrome; stage 3, subclinical cardiovascular disease within the CKM context; and stage 4, manifest clinical cardiovascular disease in CKM syndrome (1). Importantly, the current classification excludes the liver, an organ central to metabolic dysfunction. MASLD, and its progressive form MASH, are strongly associated with insulin resistance and obesity, and directly affect cardiovascular and renal health. Thus, we propose expanding the framework to Cardiovascular Kidney Hepatic Metabolic (CRHM) syndrome to better capture these inter-organ interactions (4).

In Albania, as in many other countries, this syndrome is an increasing public health challenge due to the high rates of cardiovascular, renal, and metabolic diseases. Implementing an integrated, multidisciplinary approach to CKM/CRHM syndrome management offers hope for better treatment outcomes and preventive measures across these interconnected disease areas. Recent research highlights the crucial role of the intestinal microbiota in host metabolism and immune regulation. Beyond maintaining health, it contributes to the development of diseases such as hypertension, atherosclerosis, heart failure, chronic kidney disease, type 2 diabetes, and obesity (5, 6). The gut microbiota is a diverse and dynamic community of trillions of microbes, bacteria, viruses, fungi, and archaea that inhabit the gastrointestinal tract (7). It supports host health through digestion, vitamin synthesis, and immune modulation (8). Metabolically, it processes nutrients via two main pathways: saccharolytic fermentation of carbohydrates into SCFAs, and proteolytic fermentation of proteins into SCFAs and potentially harmful byproducts like ammonia and indoles, especially relevant in kidney dysfunction (9). Acting like an endocrine organ, the gut microbiome communicates with the host via immune pathways and both metabolite-dependent and independent mechanisms. Key microbial products, such as TMAO, SCFAs, and bile acids, regulate various physiological processes, underscoring the microbiome's central role in systemic health and disease (5).

Pathophysiological Impact of the Microbiome and Its Metabolites in Cardio-reno-Metabolic Diseases

The gut microbiota varies significantly between individuals, influenced by environmental factors, genetics, and lifestyle. It includes archaea, bacteria, and eukarya, with bacteria mainly *Firmicutes* and *Bacteroidetes* making up over 90% of the population (10). Advances in sequencing and bioinformatics have enabled deeper insight into these microbes and their roles in cardiometabolic disease (11). The gut microbiota influences systemic health through complex signaling pathways. Microbial molecules like LPS and peptidoglycans cross the intestinal barrier and activate innate immunity via pattern recognition receptors (PRRs). When gut barrier integrity is impaired, these signals can also affect vascular endothelial cells directly (12). Beyond structural components, microbiota affects distant organs through bioactive metabolites like TMA/TMAO, SCFAs, and bile acids (13, 14). These metabolites interact with hormones such as ghrelin, leptin, GLP-1, and PYY, and influence the parasympathetic nervous system, thereby regulating glucose homeostasis and metabolic syndrome pathways (15). Cardio-renal-metabolic (CKM) syndrome involves intertwined metabolic, cardiovascular, and renal dysfunctions, manifesting as hypertension, heart failure, dyslipidemia, abdominal obesity, insulin resistance, hyperglycemia, hyperuricemia, and chronic kidney disease.

Gut Microbiota and Hypertension

Hypertension is the leading modifiable risk factor for cardiovascular disease and a key clinical target. Evidence shows that the gut microbiota significantly regulates blood pressure: germ-free animals exhibit higher blood pressure, highlighting the microbiota's role (16). In angiotensin II–induced hypertensive mice show gut dysbiosis characterized by reduced diversity and increased Firmicutes/Bacteroidetes ratio (17). Antibiotics have lowered blood pressure in resistant hypertension patients, indicating a microbial influence (18). Additionally, higher levels of butyrate-producing *Odoribacter* are linked to lower blood pressure in overweight pregnant women (19). Microbial metabolites like short-chain fatty acids (SCFAs) regulate blood pressure by interacting with host G protein-coupled receptors such as GPR41 and Olfr78. Olfr78 activation causes vasoconstriction and raises blood pressure, while GPR41 promotes vasodilation and lowers it (20). The gut microbiota also influences vascular regulation by modulating enteric and sympathetic nervous systems, affecting neuronal signaling and lymphocyte movement in the gut (21). Therapeutically, probiotics, particularly strains within the genus *Lactobacillus*, have demonstrated beneficial effects in blood pressure reduction, as evidenced by recent meta-analytical data (22).

Microbiota-Driven Mechanisms in Atherosclerosis and Ischemic Heart Disease

Both intestinal and oral microbiota contribute to atherosclerosis and cardiovascular disease (CVD). Bacterial DNA has been found in atherosclerotic plaques, supporting a microbial role in plaque formation and stability (11). Patients with unstable plaques show altered fecal microbiota, including reduced *Roseburia*, increased pro-inflammatory peptidoglycan production, and lower anti-inflammatory carotenoids (23). Animal studies reveal that gut microbiota affects infarct size and cardiac function, with probiotics like *Lactobacillus plantarum* and *L. rhamnosus* GR-1 providing cardioprotection by reducing hypertrophy and preventing heart failure (24). A key mechanism involves microbial metabolism of dietary choline and carnitine into trimethylamine (TMA), which the liver converts to trimethylamine N-oxide (TMAO). High plasma TMAO levels are linked to increased risks of myocardial infarction, stroke, and sudden cardiac death, with the highest quartile showing a 2.5-fold greater incidence of major cardiovascular events over three years, independent of other risk factors (14, 25). TMAO also promotes plaque instability, rupture, and thrombosis by affecting platelet calcium signaling (26). Targeting microbial enzymes to lower TMAO is a promising therapeutic approach in CVD (27).

Gut Microbiota and Heart Failure

The gut hypothesis of heart failure postulates that diminished cardiac output and systemic congestion lead to ischemia and edema of the intestinal mucosa. This compromised intestinal barrier function facilitates bacterial translocation and elevates circulating endotoxin levels, thereby perpetuating chronic systemic inflammation in heart failure patients. Clinical evidence indicates that individuals with heart failure accompanied by peripheral edema exhibit increased endotoxin concentrations and heightened inflammatory cytokine levels, both of which are significantly reduced following diuretic therapy. Additionally, these patients display alterations in intestinal microbiota composition alongside increased intestinal permeability (28). The microbial metabolite trimethylamine N-oxide (TMAO) is markedly elevated in patients with heart failure and serves as a prognostic biomarker independent of conventional risk factors, correlating with an increased risk of clinical deterioration and

mortality (14, 28). Experimental studies utilizing animal models have demonstrated that a choline-enriched diet elevates TMAO levels and exacerbates ventricular remodeling, myocardial fibrosis, and progression of heart failure via activation of the TGF-β/Smad3 signaling pathway (27). Nonetheless, the therapeutic potential of targeting microbial TMA production to mitigate heart failure development or improve clinical outcomes in humans remains to be conclusively determined.

Gut Microbiota and Dyslipidemia

Emerging evidence demonstrates that the gut microbiota plays a mechanistic role in modulating host lipid profiles, showing associations with serum triglycerides and high-density lipoprotein (HDL) cholesterol levels, independently of body mass index and underlying metabolic conditions (28, 29). Microbial metabolites, notably secondary bile acids, regulate lipid and glucose metabolism via activation of nuclear and membrane receptors such as the farnesoid X receptor (FXR) and G protein-coupled receptor 131 (GPR131). Additionally, trimethylamine N-oxide (TMAO) exerts proatherogenic effects by impairing cholesterol transport and disrupting bile acid metabolism (29). Furthermore, hepatic genetic modulation of flavin-containing monooxygenase 3 (FMO3), the enzyme responsible for TMA oxidation, significantly influences plasma lipid metabolism and circulating lipid concentrations, underscoring its critical role in maintaining lipid homeostasis (30).

Gut Microbiota and Obesity and Type 2 Diabetes Mellitus (T2DM)

The gut microbiota plays a critical role in the pathophysiology of obesity, type 2 diabetes mellitus (T2DM), and metabolic regulation through the production of key metabolites, including short-chain fatty acids (SCFAs) and bile acids (BAs). Alterations in the microbial community, characterized by an increased Firmicutes-to-Bacteroidetes ratio and a reduction in butyrate-producing bacteria, have been consistently associated with obesity and T2DM (31). SCFAs mediate their effects via G protein-coupled receptors GPR41 and GPR43, modulating inflammatory responses, glucose homeostasis, and secretion of hormones such as glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) (31). Concurrently, microbiota-mediated metabolism of bile acids influences host energy balance by activating the farnesoid X receptor (FXR) and Takeda G protein-coupled receptor 5 (TGR5), with dysregulated bile acid profiles linked to insulin resistance and obesity (28, 32). Notably, bariatric surgery induces significant modifications in both the gut microbiota composition and bile acid pools, which contribute to improvements in glucose and lipid metabolism. Moreover, fecal microbiota transplantation from post-bariatric surgery patients to murine models has demonstrated protective effects against adiposity gain (28, 32).

Gut Microbiota and Hyperuricemia

The intestinal microbiota plays a pivotal role in purine metabolism and the regulation of serum uric acid levels. Gut microorganisms produce key enzymes such as uricase, allantoinase, and allantoicase, which facilitate the degradation of uric acid and reduce purine absorption within the intestinal tract, thereby mitigating the progression of hyperuricemia. Additionally, intestinal urate transporters, including ATP-binding cassette sub-family G member 2 (ABCG2) and glucose transporter 9 (GLUT9) are modulated by commensal gut bacteria and are crucial for uric acid secretion and homeostasis. This interplay underscores a

significant mechanistic link between the gut microbiome and the pathogenesis of hyperuricemia (33).

Gut Microbiota and Chronic Kidney Disease

Chronic kidney disease (CKD) is frequently accompanied by dysbiosis of the intestinal microbiota, which contributes to increased production of ammonia via microbial urease activity. This ammonia production compromises the integrity of the intestinal epithelial barrier, facilitating translocation of uremic toxins and bacterial DNA into systemic circulation, thereby exacerbating systemic inflammation (28,34). Among the microbial-derived toxins, indoxyl sulfate and p-cresyl sulfate are particularly noteworthy due to their association with cardiovascular complications and insulin resistance; these toxins accumulate as a result of impaired renal clearance and are poorly removed by conventional dialysis modalities (34). A principal source of indoxyl sulfate is the enzymatic activity of tryptophanases expressed by intestinal Bacteroides species, with modulation of these bacteria significantly impacting systemic toxin levels. Additionally, trimethylamine N-oxide (TMAO), another gut microbiota-derived metabolite, accumulates in CKD patients and correlates with disease progression and elevated mortality risk (28, 35). Collectively, these findings highlight the intestinal microbiota and its metabolites as promising therapeutic targets in CKD management, complementing advancements in dialysis techniques (28).

Gut Microbiota and the Potential for Novel Therapeutic Interventions

Advances in understanding the role of the gut microbiota have stimulated considerable interest in harnessing its therapeutic potential for disease management. Given the microbiota's influence on multiple physiological systems, modulating its composition presents a promising strategy to prevent or ameliorate various disorders. Consequently, numerous clinical studies are investigating approaches aimed at microbiota manipulation to improve metabolic and cardiovascular health (Figure 1).

- **Gut Microbiota-Modifying Preparations: Evaluating the Effects of Probiotics, Prebiotics, and Symbiotics on Metabolic Health**

Prebiotics, probiotics, and symbiotics represent distinct but complementary strategies to modulate the intestinal microbiota. Prebiotics non-digestible fermentable fibers such as inulin and fructooligosaccharides promote the growth of beneficial microbial populations and have demonstrated positive effects on insulin resistance. Probiotics, primarily composed of bacterial genera *Lactobacillus* and *Bifidobacterium*, have shown efficacy in stabilizing glucose metabolism in patients with type 2 diabetes mellitus. However, challenges related to the viability of probiotics during gastrointestinal transit necessitate advanced delivery methods, such as microencapsulation, to enhance their therapeutic potential. Symbiotics, which combine probiotics with prebiotics, aim to facilitate the colonization and metabolic activity of beneficial microbes and are under investigation as promising agents for diabetes and metabolic disease management (36).

- **Fecal Microbiota Transplantation**

Fecal microbiota transplantation (FMT) involves the transfer of fecal material from healthy donors to recipients to restore a balanced microbial ecosystem. While FMT is established in treating recurrent *Clostridioides difficile* infections with cure rates exceeding 80%, emerging evidence suggests its potential utility in cardiometabolic diseases. Allogeneic FMT from metabolically healthy donors to obese patients with metabolic syndrome has been shown to enhance hepatic and peripheral insulin sensitivity independent of weight loss. This intervention also increases microbiota richness and diversity, notably boosting populations of butyrate-producing bacteria such as *Roseburia*, which are linked to improved glucose homeostasis. Despite these promising outcomes, concerns about safety persist, including the risk of transmitting endotoxins or pathogens, warranting caution and further research. An alternative under consideration involves transplantation of defined microbial consortia rather than whole fecal material to mitigate these risks (37).

- **Bacteriophages**

Bacteriophages, viruses that specifically infect bacteria, offer a targeted approach to modulate the microbiota and treat antibiotic-resistant infections by lysing pathogenic bacterial cells without disrupting the host's microbial environment. Nonetheless, bacterial resistance mechanisms including CRISPR-Cas systems and spontaneous mutations can limit phage efficacy. Furthermore, the acidic gastric environment may impair phage viability, necessitating precise identification of bacterial targets and optimized delivery systems for clinical effectiveness (38).

- **Genetic Modification of Intestinal Bacteria**

Recent advances in genetic engineering have enabled the development of modified probiotics capable of delivering therapeutic molecules. Engineered bacterial strains have been employed experimentally to treat conditions such as colitis, diabetes, obesity, and infectious diseases. For instance, *Lactobacillus jannaschii* has been genetically altered to express cyanovirin-N, a protein that reduced simian immunodeficiency virus infection by up to 63% in rhesus monkeys. Additional engineered therapies include bacterial expression of synthetic immunoregulatory proteins and targeted protein delivery systems, representing innovative avenues in microbiome-based treatment modalities (39).

- **Psychobiotics**

Psychobiotics, encompassing probiotics, prebiotics, postbiotics, and symbiotics, modulate the gut-brain axis and exert effects on mental health. These agents operate via immunoregulatory pathways, neuroendocrine signaling, and vagal nerve stimulation to influence emotional and cognitive processes, while also attenuating inflammation associated with depression. Psychobiotics show therapeutic promise for neurodegenerative and psychiatric disorders, although robust clinical trials are necessary to validate their efficacy and safety in human populations (40).

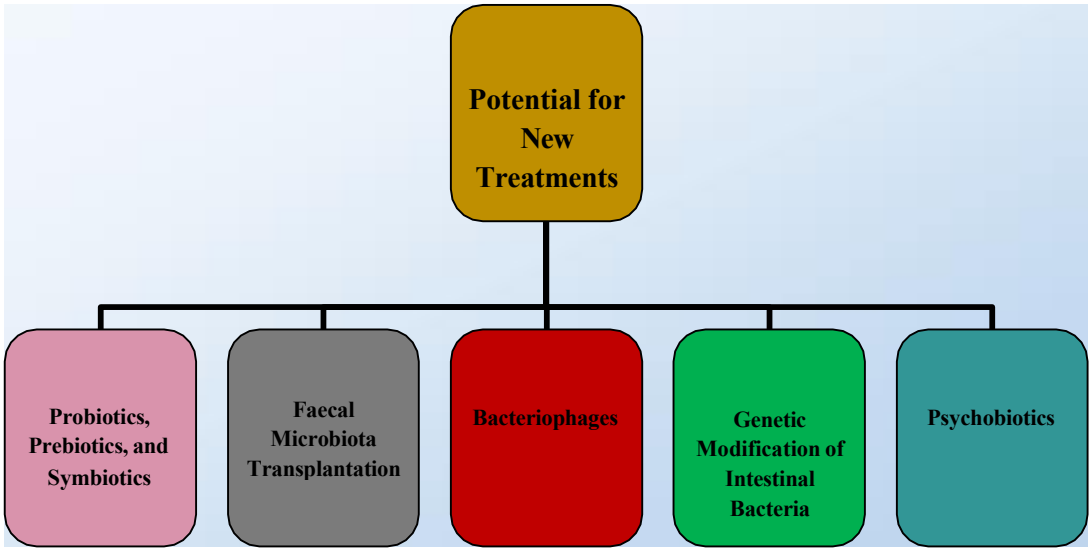


Figure 1. Gut microbiota and the potential for new treatments

Current Limitations in Understanding and Therapeutic Challenges

Although strong links exist between gut microbiota, microbial metabolites, and cardiovascular disease (CVD), definitive mechanistic proof of a causal role in atherosclerosis and its complications remains limited. Many studies, including antibiotic trials and fecal microbiota transplants, lack precise identification of the responsible microbes, metabolites, and molecular pathways. Bridging these gaps requires integrative mechanistic research alongside large prospective cohorts to clarify causality and inform targeted microbiota-based therapies.

Therapeutic modulation of microbiota shows promise but faces challenges such as identifying effective bacterial strains for complex diseases, accounting for disease phenotype and location, and addressing variable clinical responses. Most evidence stems from animal models, with human translational relevance still uncertain.

Advancing mechanistic understanding and therapeutic accuracy requires sophisticated in vitro models like chemostats that mimic native microbial ecosystems. However, microbiota-based therapies, especially those using genetically modified organisms (GMOs), raise safety and regulatory concerns—such as horizontal gene transfer and ecological risks from environmental release. Containment methods, including auxotrophic bacterial strains unable to survive outside the host, help mitigate these risks. Bacteriophage therapies also face challenges like functional loss and need careful adaptation to host environments. These complexities highlight the need for strong collaboration between researchers and regulators to develop frameworks ensuring safe, effective, and ethical use of microbiota-targeted treatments.

CONCLUSIONS AND RECOMMENDATIONS FOR THE FUTURE

Extensive research in animals and humans shows that intestinal microbiota profoundly impacts health and disease development. Culture-independent methods reveal the microbiome's complexity and diverse bacterial metabolites, which regulate key physiological processes. These metabolites and their host receptors offer promising targets for treating cardiometabolic diseases. Modulating microbiota through diet, probiotics, prebiotics, or enzyme inhibitors can beneficially influence host metabolism. Future personalized medicine may use microbial metabolite levels as biomarkers to tailor therapies, similar to glucose or cholesterol monitoring. These strategies offer promising advances in preventing, diagnosing, and treating cardiometabolic syndromes.

Conflicts of interest: The authors declare that they have no conflicts of interest.

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Review Article

"THE SILENT DEATH OF THE PITUITARY": PATHOPHYSIOLOGY AND CLINICAL IMPACT OF SHEEHAN'S SYNDROME

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ABSTRACT

Sheehan's syndrome, also called postpartum hypopituitarism, is a condition characterized by necrosis and impaired function of the anterior pituitary gland, typically resulting from severe blood loss during or shortly after childbirth. Its low incidence, prolonged course with nonspecific clinical manifestations, and higher prevalence among women in underdeveloped or developing countries often contribute to a delayed diagnosis. This condition is marked by reduced secretion of all anterior pituitary hormones, leading to clinical features such as failure of lactation in the postpartum phase to amenorrhea, and infertility. The diagnosis of Sheehan's syndrome is established through hormonal assays, dynamic stimulation tests, and imaging studies of the pituitary gland. Treatment consists of lifelong hormone replacement therapy.

Keywords. Sheehan's syndrome, postpartum hypopituitarism, pituitary necrosis, pituitary hormones, and empty sella.

"VDEKJA E HESHTUR E HIPOFIZËS": FIZIOPATOLOGJIA DHE NDIKIMI KLINIK I SINDROMËS SHEEHAN

ABSTRAKT

Sindroma e Sheehan-it, e quajtur edhe hipopituitarizëm pas lindjes, është një gjendje e karakterizuar nga nekroza dhe funksioni i dëmtuar i gjëndrës së hipofizës anteriore, që zakonisht rezulton nga humbja e rëndë e gjakut gjatë ose menjëherë pas lindjes së fëmijës.

Incidenca e ulët, ecuria e zgjatur me manifestime klinike jo specifike dhe prevalenca më e lartë tek gratë në vendet e pazhvilluara ose në zhvillim, shpesh kontribuojnë në një diagnozë të vonuar. Kjo gjendje karakterizohet nga sekretimi i zvogëluar i të gjitha hormoneve të hipofizës anteriore, duke çuar në karakteristika klinike të tilla si dështimi i laktacionit në fazën pas lindjes deri në amenorre dhe infertilitet. Diagnoza e sindromës së Sheehan-it vendoset përmes analizave hormonale, testeve dinamike të stimulimit hormonal dhe studimeve imazherike të gjëndrës së hipofizës. Trajtimi konsiston në terapi zëvendësuese hormonale gjatë gjithë jetës.

Fjalë kyçe. sindroma Sheehan, hipopituitarizmi pas lindjes, nekroza e hipofizës, hormonet e hipofizës dhe sella turcica e zbrazët.

INTRODUCTION

The pituitary gland is a classical endocrine gland, in the narrow sense that its special function is the production, release, and storage of hormones (1). Despite being very small and described as a "pea-sized gland", its importance in the organism is significant. It is in a part of the sphenoid bone, called the ''sella turcica", lying under the hypothalamus. Divided into two parts, the anterior and posterior pituitary, the anterior pituitary communicates with the hypothalamus via a specialized network of blood vessels called the hypothalamo-pituitary portal system. In contrast, the posterior pituitary communicates with the hypothalamus via a neural pathway (2). The hypothalamus releases several hormones specific to its connections with the anterior pituitary (Table 1).

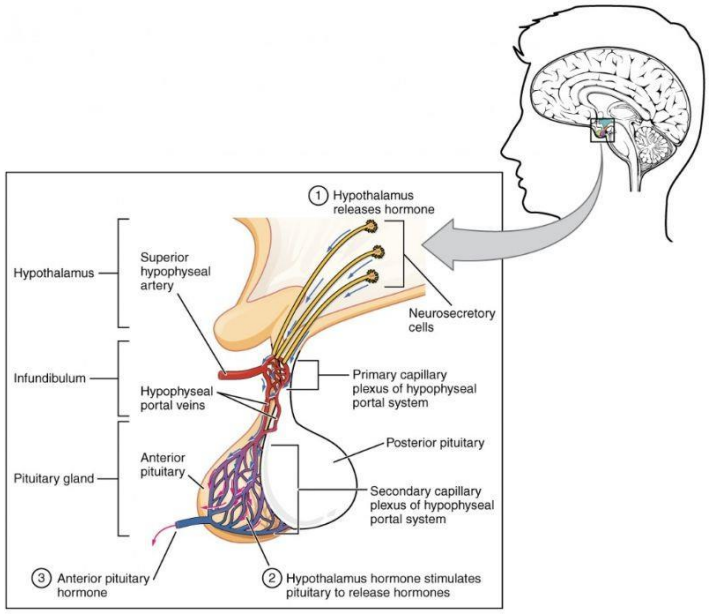


Figure 1. The hypothalamus produces separate hormones that stimulate or inhibit hormone production in the anterior pituitary. Hormones from the hypothalamus reach the anterior pituitary via the hypophyseal port.

Source: Adapted from StatPearls [Internet]. Endocrine Emergencies. Treasure Island (FL): StatPearls Publishing; 2024. Available from https://www.ncbi.nlm.nih.gov/books/NBK595005/ figure/ch9endocrine.F9.4/. Open-access content distributed under the terms of the Creative Commons Attribution 4.0 International License (CC BY 4.0) (https:// creativecommons.org/licenses/by/4.0/).

Pituitary gland size increases by approximately 0.08 mm per week during pregnancy. The pituitary gland enlarges throughout pregnancy but typically should not exceed 10 mm during most of this period. Postpartum pituitary size, up to 12 mm, is considered within normal limits (3). Sheehan's syndrome is caused by severe pituitary damage due to ischemic necrosis following significant postpartum hemorrhage (4). First described by Harold Leeming Sheehan in 1937, the condition often remains undiagnosed for decades, leaving patients without appropriate treatment (5).

Table 1. Hormonal signaling from the hypothalamus to target organs via the anterior pituitary.

Hypothalamus	Hormone	Pituitary (Adenohypophysis)	Pituitary Hormone	Target Organ
GnRH	Gonadotropin-Releasing Hormone	Anterior Lobe	FSH/LH	Gonads
CRH	Corticotropin-Releasing Hormone	Anterior Lobe	ACTH	Adrenal Cortex
TRH	Thyrotropin-Releasing Hormone	Anterior Lobe	TSH	Thyroid
PRH	Prolactin-Releasing Hormone	Anterior Lobe	Prolactin	Mammary Gland
GHRH	Growth Hormone-Releasing Hormone	Anterior Lobe	GH	Liver (+ body)

This article presents a review of the existing scientific literature on Sheehan's syndrome, drawing from relevant and reliable studies. For the literature search, major databases such as PubMed, Scopus, and Web of Science were consulted, including publications up to May 2025. Original articles, case reports, clinical studies, and systematic reviews were selected to summarize information on the etiology and pathogenesis of the disease, clinical presentation, diagnosis, differential diagnosis, treatment options, and prognosis. All sources referenced in the paper are cited in the References section.

Epidemiology.

Sheehan's syndrome is an endocrine disorder that is relatively rare in developed countries but remains a significant concern in underdeveloped and developing regions (6). A systematic study conducted at a tertiary care hospital identified Sheehan's syndrome as the leading cause of panhypopituitarism, accounting for 57.14% of cases (7).

Data from several studies indicate an incidence of 5.1 cases per 100,000 births in developed countries (8). In contrast, a study from India found that 3% of women over the age of 20 had

Sheehan's syndrome, with over half having delivered at home (9). Similarly, a study from Nigeria reported 11 cases, with an average age of 35.1 years at the time of diagnosis, around 6.9 years later between the inciting postpartum hemorrhage and diagnosis (10).

Etiology and Pathophysiology

During pregnancy, the pituitary gland undergoes hypertrophy in response to increased functional demands associated with fetal development (11). The primary factor driving its enlargement is the proliferation of lactotroph cells in response to elevated estrogen levels (12). The increase in estrogen during pregnancy comes mainly from the placenta, which converts androgens to estrogens from the adrenal cortex of the mother and fetus through the enzyme aromatase (13).

The enlargement of the pituitary gland during pregnancy is not accompanied by a proportional increase or expansion of its vascular network, which supplies the gland with blood. As a result, any condition that impairs blood flow or reduces oxygen delivery through these vessels places the pituitary at significant risk of ischemia and subsequent necrosis.

Conditions that may reduce perfusion to the anterior pituitary primarily involve severe postpartum hemorrhage but can also include prolonged maternal hypotension even in the absence of active bleeding (14,15).

Complicated births, such as multiple births, placental abnormalities, trauma during birth, uterine atony, and various coagulation disorders, are all factors that can be accompanied by large losses of blood volume, causing severe hypovolemia, and in some cases, ischemia of organs such as the anterior pituitary, leading to the so-called "Sheehan's Syndrome" (Table 2) (16,17).

Due to the nonspecific and gradual onset of symptoms, this disease is frequently diagnosed months or even years after onset; however, certain signs related to impaired hormone production can appear immediately.

Table 2. Risk factors of hemorrhage during labor.

Risk factors of hemorrhage during labor
Multiple pregnancy
Placental abnormalities
Trauma during birth
Uterine atony
Coagulation disorders

Clinical Presentation

Early signs of the disease

- Agalactia (Failure to produce breast milk) - due to lack of prolactin.
- Extreme fatigue, dizziness, and hypotension - due to lack of ACTH, the adrenal glands do not stimulate the production of cortisol, which under normal conditions is essential for maintaining blood pressure, coping with physical stress, and regulating metabolism through gluconeogenesis.
- Amenorrhea (absence of menstruation) results from insufficient FSH and LH levels, which inhibit ovarian follicle maturation, estrogen production, ovulation, and progesterone secretion by the corpus luteum, ultimately leading to anovulation and menstrual cycle cessation.
- Loss of secondary sexual characteristics (such as lack of pubic and axillary hair) - because of the lack of the hormones FSH, LH, through their influence on the production of estrogen and androgens (from the ovaries), and the lack of the hormone ACTH through its influence on the production of androgens (from the adrenal glands).
- Cold, pale, and reduced skin elasticity occurs due to deficiencies in TSH and cortisol, which affect metabolism, peripheral circulation, and connective tissue integrity (18,19,20).

These symptoms are often overlooked due to their nonspecific presentation, mistakenly attributed to the physiological adaptation of the mother's body after childbirth, a situation that leads to the appearance of later signs (Table 3).

Late signs of the disease

- Low libido and inability to get pregnant again - due to the decrease in FSH and LH, which affects the decrease in energy, function, and sexual desire.
- Hypoglycemia - due to the decrease in ACTH and cortisol, respectively, which leads to impaired gluconeogenesis by the liver.
- Pale skin - from lack of ACTH, leading to reduced stimulation of melanin production.
- Mood swings with depression and/or anxiety - from lack of TSH (decreased T3 and T4), lack of FSH and LH (decreased estrogen), and lack of ACTH (decreased cortisol), through their influence on metabolic processes in the brain and neurotransmitters that regulate emotions and stress coping.
- Anemia - because of a lack of TSH and estrogen, which normally stimulate the production of erythropoietin and bone marrow and improve iron absorption.

- Hyponatremia - lack of ACTH, which reduces cortisol, in severe cases can also affect the secondary reduction of aldosterone, thus causing hypotension, hyponatremia, and thirst (21, 22, 23).

Table 3. Early and Late Manifestations of Pituitary Hormone Deficiency.

Early Manifestations	Late Manifestations
Agalactia	Low libido
Extreme fatigue	Infertility
Dizziness	Hypoglycemia
Hypotension	Pale skin
Amenorrhea	Mood swings (depression and/or anxiety)
Loss of secondary sexual characteristics	Anemia
Cold, pale, and reduced skin elasticity	Hyponatremia

Diagnosis

The diagnosis of Sheehan's syndrome is established through a combination of disease history, physical examination, laboratory testing, and brain imaging such as MRI and CT (24).

According to the history of the disease, the patients reported heavy bleeding during or shortly after labor, lack of milk secretion, extreme fatigue, lack of menstrual cycle, decreased libido, and dizziness.

On examination, the skin appears cold, dry, and pale, and there's a lack of axillary and pubic hair, which is sometimes accompanied by a decrease in breast mass.

Laboratory tests reveal decreased levels of all anterior pituitary hormones: ACTH, FSH, LH, TSH, GH, and prolactin, accompanied by reduced cortisol, estrogen, T3, and T4 concentrations. (25). Other signs supporting the diagnosis are anemia, hypoglycemia, and hyponatremia (26).

Stimulation tests

To understand the levels of pituitary function, the so-called stimulation tests are used, which, in a state of normal functioning, stimulate the relevant organs to produce corresponding substances (27). These include the insulin stimulation test, which normally stimulates GH and cortisol; however, in Sheehan's disease, the hormones are absent due to the pituitary's failure to produce them.

TRH test: This test is used to stimulate the release of TSH and prolactin, but in Sheehan's disease, the response to these hormones is absent.

GnRH test: Under normal conditions, it would stimulate FSH and LH; however, in this case, the response is absent (28, 29).

Brain imaging

On postpartum MRI and CT imaging, due to enlargement of the pituitary gland, especially from the proliferation of prolactin-producing cells, the pituitary gland appears enlarged still. Following severe postpartum hemorrhage, the pituitary gland may exhibit inflammation and fluid accumulation. An enlarged appearance on imaging does not indicate increased functional pituitary tissue but rather reflects surrounding edema (30).

In the later phase (>6 months), the pituitary gland suffers a shrinkage due to necrosis, leaving an atrophic remnant on imaging (Fig. 2), called an empty sella or empty pituitary fossa, thus presenting permanent damage to the pituitary gland; the now empty space is filled by CSF, which can be seen on imaging (Fig. 3) (31,32, 33).

MRI is the gold standard, while CT is only used if MRI is contraindicated or unavailable.

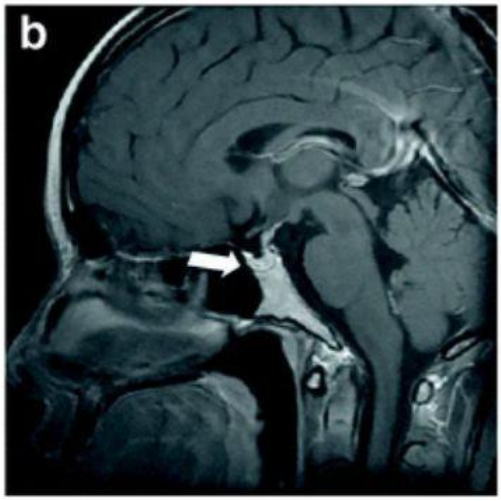


Figure 2. *Diminution in the pituitary gland size, observed 6 months postpartum. The white arrow indicates the pituitary gland*.

Source: Adapted from Matsuzaki S. et al., BMC Pregnancy and Childbirth (2017). Open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC BY 4.0). DOI: 10.1186/s12884-017-1380-y

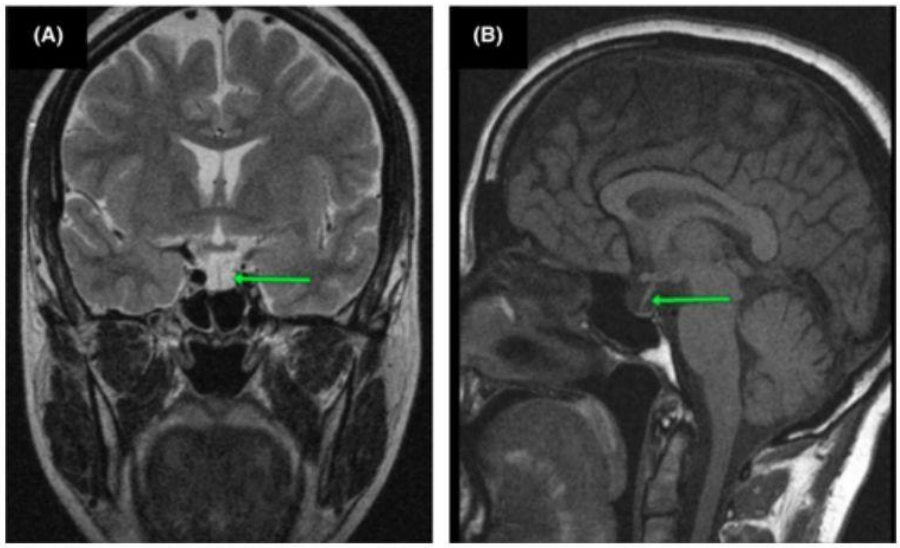


Figure 3*. Magnetic resonance imaging of sella. The arrow shows a CSF-filled sella with a thin rim of pituitary tissue and pituitary stalk, indicating an empty sella. (A) T2 coronal section, (B) T1 sagittal section. CSF, cerebrospinal fluid.*

Source: Adapted from Alamri M, et al. "A rare case of Sheehan's syndrome presenting with hyponatremia and hypoglycemia." Clinical Case Reports (2023). Open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC BY 4.0). DOI: 10.1002/ccr3.8521

Differential diagnosis

Early-stage differential diagnoses include macroadenomas, cysts, lymphocytic hypophysitis, infiltrative disorders, and pituitary apoplexy. (34)

In the late stages, Sheehan syndrome can be confused with diseases such as primary empty sella syndrome, non-Sheehan hypopituitarism due to radiation, Addison's disease, and postpartum depression (35).

Treatment

Treatment consists of lifelong replacement of deficient pituitary hormones to maintain physiological function (Table 4) (36, 37).

- For ACTH deficiency, corticosteroids such as hydrocortisone or prednisolone are prescribed in a regulated dose.
- For TSH deficiency, T4 (levothyroxine) is prescribed.
- For FSH/LH deficiency, estrogen and progesterone are administered if the patient has not yet reached menopause.

- For GH deficiency, when it is documented via stimulation tests, rhGH/somatropin is given, especially in cases of extreme fatigue, muscle wasting, or decreased bone density. To prevent adrenal crisis, we must make sure that adrenal insufficiency is treated before GH.

Table 4. Treatment of Sheehan's syndrome

Deficient Hormone	Prescribed Medication
ACTH	Corticosteroids
TSH	Levothyroxine
FSH/LH	Estrogen and Progesterone
GH	rhGH/somatropin

Prognosis and outcome

If diagnosed early, Sheehan's syndrome has a very good prognosis with hormone replacement therapy. In case of late detection, patients may face numerous problems resulting from the lack of appropriate hormones, leading to a poor prognosis with possible consequences, including death from adrenal crisis and multiorgan failure.

CONCLUSION

Sheehan's syndrome remains a significant issue in underdeveloped and developing countries due to multiple factors: limited professional awareness, particularly in primary care; poor socio - economic conditions; geographical and financial barriers to essential medical evaluations; restricted access to obstetric care; underreporting of postpartum hemorrhage and the lower socio - cultural status of women, who often perceive the symptoms as normal postpartum changes.

Timely recognition of Sheehan's syndrome, along with appropriate referral and early diagnosis, allows for restoration of the lost hormonal functions and can reduce or even completely prevent long-term complications.

Conflicts of interest: The authors declare that they have no conflicts of interest.

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Case Report

AN UNUSUAL PRESENTATION OF ANTI-GLOMERULAR BASEMENT MEMBRANE (GBM) DISEASE WITH SEVERE ANEMIA

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ABSTRACT

Background: Anti–glomerular basement membrane (anti-GBM) disease is a rare autoimmune small-vessel vasculitis classically characterized by rapidly progressive glomerulonephritis and pulmonary hemorrhage. Anemia is frequently observed but is usually mild to moderate and secondary to inflammation or bleeding. Severe anemia as the initial and predominant manifestation is distinctly uncommon and may lead to diagnostic delay.

Case presentation: We report the case of a 21-year-old woman who presented with a three-month history of profound, transfusion-dependent normocytic anemia associated with fever, asthenia, and mild respiratory symptoms, in the absence of initial renal impairment. Extensive hematological, infectious, and autoimmune investigations were unremarkable. Renal function was preserved and urinalysis was not performed at presentation. Several weeks later, the patient developed rapidly progressive acute kidney injury and hemoptysis. Imaging revealed diffuse alveolar hemorrhage, and serological testing demonstrated circulating anti-GBM antibodies. Renal biopsy confirmed crescentic glomerulonephritis with linear IgG deposition along the glomerular basement membrane. Immunosuppressive therapy with high-dose corticosteroids, cyclophosphamide, and plasmapheresis was promptly initiated. After treatment, the patient showed progressive clinical improvement, with a gradual increase and subsequent stabilization of hemoglobin levels and complete resolution of pulmonary manifestations. Despite only partial renal recovery, she required temporary hemodialysis and ultimately underwent successful living-donor kidney transplantation following sustained anti-GBM antibody negativity.

Conclusion: This case highlights severe anemia as an unusual presenting feature of anti-GBM disease and emphasizes the importance of considering small-vessel vasculitis in the differential diagnosis of unexplained anemia. Early urinalysis and immunological testing are crucial to avoid diagnostic delay and to enable timely initiation of life-saving therapy.

Një paraqitje e pazakontë e sëmundjes anti–membranë bazale glomerulare (GBM) me anemi të rëndë

Key words: anemia, anti-glomerular basement membrane disease, small vessel vasculitis, rapidly progressive glomerulonephritis, pulmonary hemorrhage

NJË PARAQITJE E PAZAKONTË E SËMUNDJES ANTI–MEMBRANË BAZALE GLOMERULARE ME ANEMI TË RËNDË

ABSTRAKT

Hyrje Sëmundja anti–membranë bazale glomerulare (anti-GBM) është një vaskulit autoimun i rrallë i enëve të vogla te gjakut, i karakterizuar në mënyrë klasike nga glomerulonefriti me progresion të shpejtë dhe hemorragjia pulmonare. Anemia vërehet shpesh, por zakonisht është e lehtë deri e moderuar dhe dytësore ndaj inflamacionit ose gjakderdhjes. Paraqitja me anemi të rëndë si manifestimi fillestar dhe dominues është dukshëm e rrallë dhe mund të çojë në vonesë diagnostike.

Paraqitja e rastit: Raportojmë rastin e një paciente 21-vjeçare që u paraqit me histori tre mujore të anemisë së rëndë normocitare normokromike, të varur nga transfuzionet, e shoqëruar me temperatur, asteni dhe simptoma respiratore të lehta, në mungesë të dëmtimit fillestar të funksionit renal. Ekzaminimet e gjera hematologjike, infektive dhe autoimune rezultuan pa gjetje patologjike. Funksioni renal ishte i ruajtur por analiza e urinës nuk u krye në momentin e paraqitjes. Pas disa javësh, pacientja zhvilloi dëmtim akut renal me progresion të shpejtë dhe hemoptizi. Ekzaminimet imazherike evidentuan hemorragji alveolare difuze, ndërsa testimi serologjik tregoi praninë e antitrupave qarkullues anti-GBM. Biopsia renale konfirmoi glomerulonefrit me kreshente dhe depozitim linear të IgG përgjatë membranës bazale glomerulare. U fillua menjëherë terapi imunosupresive me kortikosteroide me dozë të lartë, ciklofosfamid dhe plazmaferezë. Pas trajtimit, pacientja shfaqi përmirësim klinik progresiv, me rritje graduale deri ne stabilizim të niveleve të hemoglobinës, si dhe resolvim të plotë të manifestimeve pulmonare. Nga pikepamja renale pacientja ju nenshtrua trajtimit dialitik te perkoheshem i cili u pasua nga nje rekuperim i pjeseshem i funskion renal dhe mbas 1,5 vitesh iu nënshtrua me sukses transplantitt renal nga dhurues i gjallë pas negativizimit të qëndrueshëm të antitrupave anti-GBM.

Konkluzioni: Ky rast thekson aneminë e rëndë si një paraqitje të pazakontë të sëmundjes anti-GBM dhe nënvizon rëndësinë e përfshirjes së vaskuliteve të enëve të vogla në diagnozën diferenciale të anemive të pashpjeguara. Kryerja e hershme e analizës së urinës dhe testimi imunologjik janë thelbësore për të shmangur vonesën diagnostike dhe për të mundësuar fillimin në kohë të terapisë shpëtuese për jetën.

Fjalët kyçe: anemi, sëmundja anti–membranë bazale glomerulare, vaskulit i enëve të vogla,

glomerulonefrit me progresion të shpejtë, hemorragji pulmonare

INTRODUCTION

Anti–glomerular basement membrane (anti-GBM) disease, previously known as Goodpasture syndrome, is a rare but potentially life-threatening autoimmune vasculitis characterized by renal and pulmonary involvement. The disease is mediated by circulating anti-GBM antibodies directed against the non-collagenous (NC1) domain of the α3 chain of type IV collagen, a crucial component of the glomerular and alveolar basement membranes. Anti-GBM disease has an estimated prevalence of 1–2 cases per million population and presents a bimodal age distribution, with incidence peaks in the third and sixth decades of life. Although no well-defined risk factors have been identified, environmental and host-related factors such as smoking, inhalation of hydrocarbons, and a personal or family history of autoimmune disease have been implicated as potential triggers.

Clinically, patients may present with constitutional symptoms, including fever, malaise, weight loss, and arthralgia. Renal involvement, which occurs in more than 90% of cases, typically manifests as rapidly progressive crescentic glomerulonephritis, characterized by acute deterioration of renal function and nephritic urinary sediment. Pulmonary involvement is observed in approximately 30–60% of patients and is most commonly due to alveolar hemorrhage, presenting with hemoptysis, although in some cases it may manifest abruptly as life-threatening diffuse alveolar hemorrhage.
Mild anemia is a usual finding in anti-GBM disease, as in other small vessel vasculitis, and is usually attributed to systemic inflammation, pulmonary hemorrhage, and macrohematuria. However, severe anemia as the initial and predominant clinical manifestation is distinctly uncommon and may result in significant diagnostic delay.

Here, we report the case of a young female patient who presented with a three-month history of profound anemia, in whom the classical renal and pulmonary features of anti-GBM disease became evident only later in the disease course. This case highlights the importance of considering small vessel vasculitis, such as anti-GBM disease, in the differential diagnosis of unexplained severe anemia and underscores the value of early urinalysis and immunological testing to enable timely diagnosis and prompt initiation of immunosuppressive therapy.

CASE PRESENTATION

We present the case of a 21-year-old caucasian woman with no relevant past medical history and no family history of renal or autoimmune disease. She had been an active smoker during the previous year. Since October 2023, she developed recurrent episodes of hyperpyrexia (up to 39°C), alternating with subfebrile temperatures (37.2–37.3°C), associated with progressive and severe asthenia, pallor, dry cough, and profuse sweating. After approximately two months of persistent symptoms, laboratory investigations performed in January 2024 revealed severe normocytic normochromic anemia (Hemoglobin 3.9 g/dL), prompting urgent referral to the Hematology Unit.

Initial diagnostic workup An extensive diagnostic evaluation was performed, including protein and hemoglobin electrophoresis, immunoelectrophoresis, reticulocyte count, complement levels (C3, C4), autoimmune screening (ANA, ANCA including MPO-ANCA and PR3-ANCA, rheumatoid factor, AMA, anti-CCP, anti–double-stranded DNA antibodies), tumor markers (CEA, CA 19-9, CA 15-3, alpha-fetoprotein), and serological testing for hepatitis B and C viruses, HIV-1/2, cytomegalovirus, and Toxoplasma gondii. All investigations were unremarkable. Bone marrow aspiration and immunophenotyping excluded hematological malignancy or bone marrow failure syndromes.

Transthoracic echocardiography and cardiologic evaluation resulted in normal. Upper gastrointestinal endoscopy excluded gastrointestinal bleeding, showing only hyperemic duodenal bulb mucosa and a hiatal hernia.
At that time, renal function was preserved (serum creatinine 0.6 mg/dL, urea 26.2 mg/dL), and renal ultrasonography revealed kidneys of normal size and echogenicity with no evidence of obstruction or chronic parenchymal disease. Unfortunately, urinalysis was not performed at presentations.
Since no clear etiology of such severe anemia was found, the patient proceeded with follow-up and was treated with subsequent red blood cell transfusions, remaining transfusion-dependent for several weeks.

DIAGNOSIS

In March 2024, during a follow-up hematology consultation, a rapid deterioration of renal function was detected in a few days (Creatinine 0.6→ 5.08 mg/dL; Urea 26,2→ 118 mg/dL) associated with worsening of pulmonary symptoms with hemoptysis leading to urgent admission to our Nephrology Unit.
On admission, clinical and laboratory findings were consistent with a reno-pulmonary syndrome, characterized by rapidly progressive acute kidney injury with macroscopic hematuria, active nephritic urinary sediment, subnephrotic-range proteinuria, and pulmonary hemorrhage confirmed at chest contrast-enhanced computed tomography (CT) which showed bilateral pulmonary parenchymal opacities with a diffuse ground-glass pattern, more pronounced in the right lung, consistent with diffuse alveolar hemorrhage.
Based on the clinical presentation, anti–glomerular basement membrane (anti-GBM) disease was strongly suspected. Urgent serological testing confirmed the presence of circulating anti-GBM antibodies, subsequently corroborated by immunoblot analysis. The diagnosis was confirmed by renal biopsy, which showed on light microscopy revealed crescentic glomerulonephritis with fibrocellular crescents involving most sampled glomeruli and disruption of Bowman's capsule, without significant interstitial fibrosis or tubular atrophy. Immunofluorescence microscopy demonstrated strong, diffuse linear IgG deposition along the glomerular basement membranes in all evaluable glomeruli, with a corresponding linear pattern for both kappa and lambda light chains. IgA, IgM, C3, and C1q staining were negative. These findings were diagnostic of anti-GBM disease and concordant with the serological results.

Treatment and follow-up

Given the fulminant presentation and high mortality associated with anti-GBM disease, immunosuppressive therapy was initiated immediately. The patient received high-dose intravenous methylprednisolone (1g daily for three consecutive days), followed by oral prednisone at 1 mg/kg/day associated with intravenous cyclophosphamide (500 mg ev every two weeks) and therapeutic plasmapheresis.
During hospitalization, clinical conditions improved with a slow but progressive increase in hemoglobin levels; pulmonary manifestations progressively resolved, as corroborated by radiologic improvement. Unfortunately, despite preserved residual diuresis, renal function initially continued to deteriorate, necessitating the initiation of renal replacement therapy. The patient underwent twice-weekly maintenance hemodialysis from April to August 2024. Subsequently, a gradual but partial recovery of renal function was observed, allowing discontinuation of dialysis. At follow-up, the patient has remained dialysis-free for approximately 18 months, with stable chronic kidney disease stage 4 under conservative management. During this period, circulating anti-GBM antibodies remained persistently negative, and no recurrence of pulmonary hemorrhage was documented.
Following immunosuppressive treatment, hemoglobin levels stabilized and remained within the therapeutic target range under erythropoietin support.

DISCUSSION

Anti–glomerular basement membrane (anti-GBM) disease is a rare autoimmune vasculitis characterized by rapidly progressive glomerulonephritis and, in a subset of patients, pulmonary hemorrhage. Despite its well-described clinical triad, the initial presentation may be heterogeneous, leading to diagnostic delay and adverse renal outcomes. This case illustrates an uncommon presentation of anti-GBM disease, in which severe anemia represented the predominant and earliest clinical manifestation, preceding overt renal and pulmonary involvement by several months.

Anemia is frequently observed in anti-GBM disease and is typically multifactorial, resulting from systemic inflammation, urinary blood loss, and overt or occult alveolar hemorrhage. However, profound anemia as the initial and isolated manifestation is distinctly uncommon. In the present case, the patient experienced a three-month history of transfusion-dependent anemia before the development of rapidly progressive renal failure and clinically manifested alveolar hemorrhage. During this early phase, renal function was preserve contributing to a delay in recognizing the underlying process.

Pulmonary involvement in anti-GBM disease may be clinically overt or subclinical. Occult alveolar hemorrhage can lead to significant iron loss and anemia even in the absence of massive hemoptysis or acute respiratory failure. In our patient, early respiratory symptoms were present but nonspecific, and imaging initially suggested an interstitial pattern, underscoring how pulmonary hemorrhage may be misinterpreted as infectious or inflammatory lung disease.

Renal involvement ultimately followed a fulminant course, with rapid progression from normal renal function to dialysis-dependent kidney failure. Early initiation of immunosuppressive therapy, including high-dose corticosteroids, cyclophosphamide, and plasmapheresis, is the cornerstone of anti-GBM disease management and is associated with

improved patient survival. In this case, despite prompt treatment after diagnosis, the patient required maintenance hemodialysis, although a partial and transient recovery of renal function allowed discontinuation of renal replacement therapy for approximately 18 months. This fluctuating course reflects the severe initial glomerular injury demonstrated by crescentic glomerulonephritis on renal biopsy.

This case emphasizes several important clinical lessons. First, small vessel vasculitis, such as anti-GBM disease, should be considered in the differential diagnosis of unexplained severe anemia, especially when accompanied by systemic symptoms. Second, early urinalysis and immunological testing are essential to avoid diagnostic delay. Finally, although renal prognosis remains poor in advanced disease, timely diagnosis and appropriate long-term management can allow stabilization and recovery of extra-renal manifestations.

CONCLUSIONS

Severe unexplained anemia may represent an early manifestation of small vessel vasculitis, such as anti-GBM disease, and should prompt diagnostic evaluation particularly in the presence of systemic symptoms.
Immunosuppressive therapy can lead to rapid and sustained correction of anemia, highlighting hemoglobin as a potential marker of disease activity. Early urinalysis and immunological testing are essential to avoid diagnostic delay and improve outcomes.

Conflicts of interest: The authors declare that they have no conflicts of interest.

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Case Report

EXFOLIATIVE PSORIATIC ERYTHRODERMA: A CALL FOR HELP AND ATTENTION

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ABSTRACT

Erythroderma is an erythema in more than 90% of the body surface and represents a dermatological emergency with extensive erythematous skin and scaling. First described by Von Hebra in 1868, erythroderma represents a rare cutaneous inflammatory state with associated dysfunction of both the skin barrier and metabolic processes. Most cases result from pre-existing and chronic dermatoses such as eczema and psoriasis. Untreated, the patient may succumb to multisystem organ failure and high-output heart failure secondary to cutaneous volume loss. We present a case of Exfoliative Psoriatic Erythroderma as a patient's first presentation of psoriasis in the eighth decade of life, with no dermatological history, who started with erythrodermic psoriasis, developing a systemic inflammatory response, which was treated with methotrexate with good response. Erythrodermic psoriasis is a severe and rare variant of psoriasis vulgaris, the condition of which can be fatal. The objective of presenting this case is to call attention to this rare entity.

Keywords: Psoriasis; Erythroderma; rare entity; dermatological emergency; treatment; prognosis.

ERITRODERMIA PSORIATIKE EKSFOLIATIVE; NJË THIRRJE PËR NDIHMË DHE VËMENDJE

ABSTRAKT

Erythrodermia është një eritemë në më shumë se 90% të sipërfaqes së trupit dhe përfaqëson një urgjencë dermatologjike. E përshkruar për herë të parë nga Von Hebra në vitin 1868, erythroderma përfaqëson një gjendje të rrallë inflamatore të lëkurës me disfunksion të barrierës kutane dhe proceseve metabolike. Shumica e rasteve rezultojnë nga dermatoza të meparshme dhe kronike si ekzemat dhe psoriaza. Nëse nuk trajtohet, pacienti mund të vdesë nga insuficenca multiorganore dhe insuficenca kardiake. Ne prezantojmë një rast klinik të Erythrodermës Psoriatike Exfoliative si paraqitja e parë e psoriasisit ne një pacient në

dekadën e tetë të jetës, pa histori dermatologjike, qe fillon me psoriasis erythrodermike, duke zhvilluar një përgjigje inflamatore sistemike, me një përgjigje relativisht të mire ndaj terapise sistemik me metotreksat. Erythrodermia Psoriatike është një variant i rëndë dhe i rrallë i psoriasis vulgaris, e cila mund të rezultoje dhe ne fatalitet. Qëllimi i prezantimit të këtij rasti është risjellja ne vëmendje e këtij entiteti të rrallë dermatologjik.

Fjale kyce: Psoriasis; Eritroderma; entitet i rralle; urgjence dermatologjike trajtimi; prognoza.

INTRODUCTION

The annual incidence of erythroderma is estimated to be 1–2 per 100,000 population in Europe, with a male preponderance (6). Erythroderma may be present at birth or may develop acutely or insidiously. Erythroderma is a manifestation of severe skin dysmetabolism, reported in severe forms of a range of diseases that can be broadly categorized into congenital, infective, inflammatory, immunobullous, neoplastic, iatrogenic, and idiopathic causes (7). Many diseases are associated with erythroderma, but most cases result from pre-existing and chronic dermatoses, such as psoriasis or eczema. The pathogenesis of erythroderma is poorly understood. Psoriasis is an autoimmune, inflammatory skin disease characterized by various variants, including plaque psoriasis, guttate psoriasis, erythrodermic psoriasis, and pustular psoriasis. These variants share three clinical features in common: erythema, thickening, and scaling (1,2,3). Erythrodermic psoriasis, in turn, has an incidence of approximately 2%, representing a severe variant that constitutes a dermatological emergency (5). Patients develop coalescent erythema, scaling, and exfoliation, affecting 90% of the body surface. The course of this dermatosis, as well as its prognosis, will depend on the severity, age group, presence of additional infections, and treatment adherence (4). The objective of presenting this case is to review the current and timely treatment of this rare entity and to bring attention to this “could be” fatal dermatosis.

CLINICAL CASE

An 82-year-old man, at least 10 years on treatment with antihypertensive medications, was diagnosed with benign prostatic hyperplasia 3 years ago on treatment with tamsulosin. No history of previous dermatosis. History of smoking with 20 cigarettes per day. He came with a condition of two months’ evolution, characterized by intermittent fever, chest pain, and dyspnea. He received non-dermatological consultation and treatment with intramuscular steroids and antibiotics for a presumable infection of the urinary tract, with no response. After two weeks, dermatosis was added to the trunk, which spread to the scalp and extremities, palms, and soles. The examination revealed a generalized dermatosis that spared only the mucosa; characterized by diffuse erythema, desquamation with whitish scaling, in a few areas with erythematous-scaly plaques of whitish scaling, in the rest of the skin and annexes, nails were involved too. (Fig.1,2,3,4,5,6)





Figure1 et 2. Diffuse erythema, desquamation, and whitish scaling in both hands and feet.





Figure 3 et 4. Whitish scaling, diffuse erythema of legs and arms, bilateral subungual hyperkeratosis.





Figures 5 et 6. Diffuse erythema, whitish scaling in the face, head, and trunk

The patient had a fever of 38 °C with leukocytosis of 15,700 mm^3, with neutrophils 76%, the blood chemistry showed no alterations. Systemic inflammatory response syndrome and erythroderma were integrated. The skin biopsy reported epidermis with psoriasiform hyperplasia, mild spongiosis, neutrophil infiltrate in the superficial layers, and parakeratosis, papillary dermis with dilated vessels and intense chronic inflammation. (Fig.7) With a broad differential diagnosis and no previous history of psoriasis, the diagnosis of EP in this patient was particularly challenging. In this case, a correlation of subtle pathology and clinical history led to the diagnosis of EP.

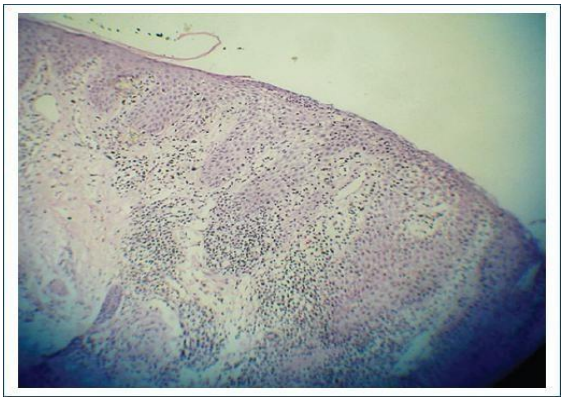


Figure 7. Epidermal psoriasiform hyperplasia with mild spongiosis, neutrophil infiltrate, parakeratosis; in papillary dermis with dilated vessels.

Treatment for EP includes adequate hydration, topical steroids, and vitamin D analogs, management of associated infections, and immunosuppression for uncontrolled symptoms. Methotrexate at a dose of 12.5 milligrams was started weekly for 3 months at a reduced dose, along with folic acid 5 mg once a week, emollients, and soap substitutes. The patient showed good skin improvement after one month. Liver function tests and blood counts remained normal. Follow-up was scheduled for 3 months, continuing topical treatment with emollients, 20% urea in thick skin areas, and topical corticosteroids. The patient is currently being followed up by the dermatology service.

DISCUSSION

Erythrodermic psoriasis is a rare and severe variant that affects 1-2% of patients with psoriasis, being the most common cause of erythroderma, responsible for approximately 25% of cases (5). Risk factors for the development of the disease include genetic factors, environmental factors, most involved are smoking, obesity, alcohol consumption, the intake of some drugs such as beta blockers, lithium, antimalarials, streptococcal infection, HIV. In the case here described, smoking and infection of the urinary tract were found to be the triggering factors (8,9). An important trigger for erythrodermic psoriasis is treatment with systemic glucocorticoids or abrupt discontinuation of systemic drugs such as methotrexate or cyclophosphamide (10). The pathogenesis of psoriasis is triggered by activated dendritic cells that produce IL-23 and TNF-α, stimulating the activation of CD4 Th17 lymphocytes and cytotoxic CD8 lymphocytes, which secrete IL-17 and IL-22 that sustain the inflammatory process and generate the epidermal hyperproliferation characteristic of the disease (11). The main clinical manifestation of erythrodermic psoriasis is the appearance of a generalized confluent erythema that affects between 75-90% of the total body surface. It has a rapid onset over several days or a gradual onset over several weeks, followed by exfoliation and desquamation of the skin that develops several days after the appearance of the erythema. The desquamation is usually accompanied by pain, itching, and photosensitivity in the areas with the greatest exfoliation activity. Most patients present nail disorders. The extra-cutaneous manifestations are fever, chills, malaise, tachycardia, arthralgia, and lymphadenopathy (12). The diagnosis should be made by investigating the personal or family history of psoriasis, history of possible triggers for the disease, and coexistence of clinical characteristics, emphasizing a physical explanation of the skin. No serological test confirms the diagnosis of erythrodermic psoriasis, so it is essential to perform a skin biopsy. The histological characteristics that most support the diagnosis of erythrodermic psoriasis were acanthosis, diffuse parakeratosis, diffuse hypogranulosis, and the presence of neutrophils in the epidermis and hypodermis. The histological characteristics in the biopsy were compatible, which confirmed the diagnosis in our case (13). Among the complications of erythrodermic psoriasis, hemodynamic alterations such as peripheral edema, high-output heart failure, shock, or acute renal failure have been described along with the thermoregulatory alterations and infections due to loss of the skin barrier. Being a systemic inflammatory disease, it is associated with several comorbidities, including psoriatic arthritis, uveitis, cardiovascular disease, metabolic and non-alcoholic syndrome (14,15). There is no consensus on the management of erythrodermic psoriasis. The most useful support recommendations are hemodynamic and body temperature monitoring, fluid and electrolyte replacement, nutritional support, treatment of associated infections, skin care with moist dressings, hydration, oatmeal baths, and topical corticosteroids to reduce pain and itching (16). Systemic therapy should be started immediately and should be chosen with respect to severity, patient comorbidities, and drug availability. The recommended first-line therapies are: cyclosporine (with an initial dose of 3 to 5mg/kg/day), which produces significant improvement in the first month and complete remission after one year. Infliximab (with an initial dose of 5mg/kg at week zero, two, and six, followed by 5 mg/kg every 8 weeks) (17,18). Alternative therapy is Methotrexate (with a weekly dose of 7.5mg to 25mg per day with folic acid supplementation 1mg/day), observing improvement after the first weeks of starting treatment (19). In countries with little access to drugs such as cyclosporine, infliximab, or new biologic therapies, like in Albania, either due to high cost or adverse effects, methotrexate and oral corticosteroids have been chosen as a second line. Our case had

a good response with methotrexate, but represents a call for help and attention to this rare entity.

CONCLUSIONS

This case represents an unusual presentation of EP in a patient without a prior history of psoriasis. When patients are critically ill with an erythrodermic rash, it is important to consider EP in the differential diagnosis. Skin biopsy and histological analysis aid in the diagnosis of EP, given the broad differential associated with erythrodermic skin reactions. Our case report may serve as a call for healthcare professionals to be aware of the symptoms and characteristics of exfoliative psoriatic erythroderma, including the need for immediate and appropriate treatment. With accurate treatment and supervision, patients can achieve significant improvement and avoid life-threatening complications.

Conflicts of interest: The authors declare that they have no conflicts of interest.

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Case Report

ALCOHOLIC CARDIOMYOPATHY: A CASE REPORT PRESENTATION

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ABSTRACT

Introduction. Alcoholic cardiomyopathy is a form of acquired cardiomyopathy associated with daily alcohol consumption of more than 80 g/day for a period of over 5 years. According to studies, its pathophysiology includes direct oxidative damage from ethanol and its metabolites, primarily acetaldehyde, as well as activation of the renin-angiotensin-aldosterone system.

Methods. We describe the case of a 35-year-old male patient with a 20-year history of alcohol consumption (AUDIT > 25), who presented to the emergency department with difficulty breathing, oedema, and numbness of the extremities, thoracic and abdominal discomfort, jaundice, and physical weakness.

Discussion: Alcoholic cardiomyopathy is a variant of dilated cardiomyopathy, caused by excessive alcohol use, accompanied by left ventricular enlargement and systolic dysfunction.

Result & Conclusion. This case study clearly shows the correlation between high levels of alcohol use and the development of dilated cardiomyopathy at a young age with multiorgan involvement. This case highlights the importance of a comprehensive evaluation of heart function. Imaging, particularly echocardiography, and the exclusion of alternative structural and ischaemic aetiologies reveal alcohol as the primary cause of this form of cardiomyopathy.

Keywords: Alcoholic cardiomyopathy, alcohol consumption, heart failure, ethanol

KARDIOMIOPATIA ALKOOLIKE: PREZANTIM RASTI KLINIK

ABSTRAKT

Hyrje. Kardiomiopatia alkoolike është një formë e kardiomiopatisë së fituar, e lidhur me konsumin e përditshëm të alkoolit më shumë se 80 g/ditë për një periudhë mbi 5 vjet. Studimet kanë treguar që fiziopatologjia e saj përfshin aktivizimin e sistemit renine-angitensine-aldosteron, si dhe dëmtimin oksidativ drejtpërdrejt nga etanoli dhe metabolitëve të tij kryesisht acetaldehidit.

Metodologji. Prezantim rastit të një pacienti, mashkull 35 vjeç, me një histori 20 vjeçare të konsumit të alkoolit (AUDIT > 25), i cili paraqitet në urgjencë me vështirësi në frymëmarrje, edemë dhe mpirje të anësive, dhimbje torakale dhe abdominale, ikter dhe dobësi trupore.

Diskutime: Kardiomiopatia alkoolike është një variant i kardiomiopatisë dilatuar, i shkaktuar nga përdorimi i ekzagjeruar i alkoolit, shoqëruar me zgjerimi të ventrikulit te majtë dhe mosfunksionimi sistolik.

Rezultate & Përfundime. Ky studim rasti tregon qartë korrelacionin midis niveleve të larta të përdorimit të alkoolit dhe zhvillimit të kardiomiopatisë së dilatuar në një moshë të re me përfshirje të shumë organeve. Ky rast nënvizon nevojën për të kryer një ekzaminim të plotë të funksionit të zemrës. Imazheria, veçanërisht ekokardiografia, dhe përjashtimi i etiologjive alternative strukturore dhe iskemike zbulojnë alkoolin si shkakun kryesor të kësaj forme të veçantë të kardiomiopatisë.

Fjalë kyçe: kardiomiopatia alkoolike, konsumi i alkoolit, insuficenca kardiake, ethanol

INTRODUCTION

Excessive alcohol consumption is a substantial public health concern worldwide, with far-reaching social, economic, and healthcare implications. Estimates suggest that a significant portion of the global population has consumed alcohol at least once since adolescence, highlighting the early and widespread exposure to this substance. In addition to its social and behavioral consequences, alcohol has been linked to multiple medical conditions.[i]

WHO's Global Status Report on alcohol and health, based on 2019 data on the public health impact of alcohol worldwide, shows an estimated 400 million people live with alcohol use disorders globally, and 209 million people live with alcohol dependence. The new report from the WHO highlights that 2.6 million deaths per year were attributable to alcohol consumption, accounting for 4.7% of all deaths. [ii]

From a health perspective, the complications of excessive alcohol use are both mental & physical. They range from psychiatric, gastrointestinal, neurological, and cardiological disturbances. In Western countries, up to 10% of the adult population suffers from an alcoholism-related disease.[iii]

Alcohol is one of the toxic substances frequently consumed globally. Although daily intake of low to moderate amounts of alcohol improves the cardiovascular health of ischemic and non-ischemic patients, chronic and excessive consumption of alcohol could result in progressive cardiac dysfunction and heart failure (HF). Chronic alcohol consumption or abuse is defined as the daily intake of more than 80 g of alcohol for a period of at least five years. [iv]

Alcoholic cardiomyopathy (ACM) is a heart disease caused by long-term alcohol use. It is marked by ventricular dilation and reduced heart function. ACM is a major cause of non-ischemic dilated cardiomyopathy.[v]

Alcohol induces several changes in the myocardial structure (myocyte loss, intracellular organelle dysfunction, and contractile protein alterations). However, the exact pathogenesis of ACM is still unclear. Total alcohol abstinence, together with heart failure treatment drugs,

results in at least partial recovery of the myocyte damage, with a consequent improvement in cardiac function.[vi]

Epidemiological studies investigating the nexus between chronic alcohol abuse and the development of ACM report a reciprocal relationship between chronic alcohol abuse and ACM. In a case-controlled study evaluating the relationship between alcohol consumption and idiopathic dilated cardiomyopathy (DCM), a correlation was demonstrated between patients diagnosed with DCM and a history of alcohol consumption. The incidence of excessive alcohol abuse among the 100 DCM patients was 40% compared to 23% in a control group of 211 healthy individuals.[4]

ACM is a leading cause of non-ischemic dilated cardiomyopathy in the United States. The incidence of alcoholic cardiomyopathy ranges from 1-2% of all heavy alcohol users. It is estimated that approximately 21-36% of all non-ischemic cardiomyopathies are attributed to alcohol. The prevalence of alcoholic cardiomyopathy in addiction units is estimated to be around 21-32 %. Overall data with regards to alcohol induced cardiomyopathy is insufficient and does not illustrate significant available data. The most common age population for ACM is males from age 30-55 with a significant history of alcohol use for more than 10 years. Females constitute roughly 14 % of cases of alcohol induced cardiomyopathy; however, the lifetime exposure required for women to develop alcohol induced cardiomyopathy is less compared to men.[5]

Early reports of clinical manifestations of ACM established by Otto von Bollinger, a German pathologist, indicated structural abnormalities such as left ventricular dilation and hypertrophy, and comorbidities such as delirium tremens and cirrhosis of the liver. Other clinical manifestations reported by William McKenzie include accelerated heart pulse, swelling and enlargement of the veins, poor prognosis with progressive HF, dilated cavities of the heart, and fatty degeneration of the ventricular walls. Having coined the expression ***"Munich beer heart"*** to demonstrate the effect of chronic alcohol abuse on the human heart in the mid-19th century, Bollinger became the first to highlight the clinical manifestations of ACM.[4]

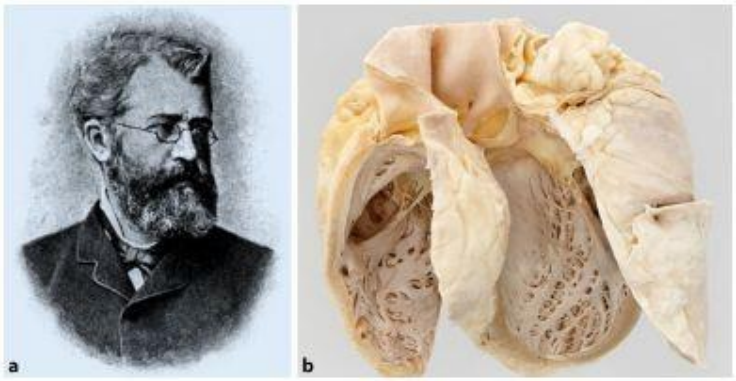


Figure 1: **a** Otto von Bollinger. (© de.wikipedia.org). **b** Munich beer heart.(© Philipp Mansmann in http://www.bayerische-staatszeitung.de/staatszeitung/kultur/detailansicht-kultur/artikel/ bierherz.html)[vii]

The pathogenesis of ACM also involves interaction between genetically related factors, such as HLA subtypes or the alcohol dehydrogenase enzyme allele, as well as non-genetic factors, including thiamine deficiency and exposure to various substances that are directly toxic to

cardiac cells. These structural and intracellular alterations cause activation in compensatory mechanisms in response to cardiac dysfunction, such as the renin-angiotensin-aldosterone system, increased sympathetic signal firing, and an increase in brain natriuretic peptide release.[5]

Chronic heavy alcohol abuse will also increase blood pressure and cause a downregulation of the immune system that could lead to increased susceptibility to infections, which in turn could add to the development of heart failure. Myocardial tissue analysis resembles idiopathic cardiomyopathy or chronic myocarditis. [7]

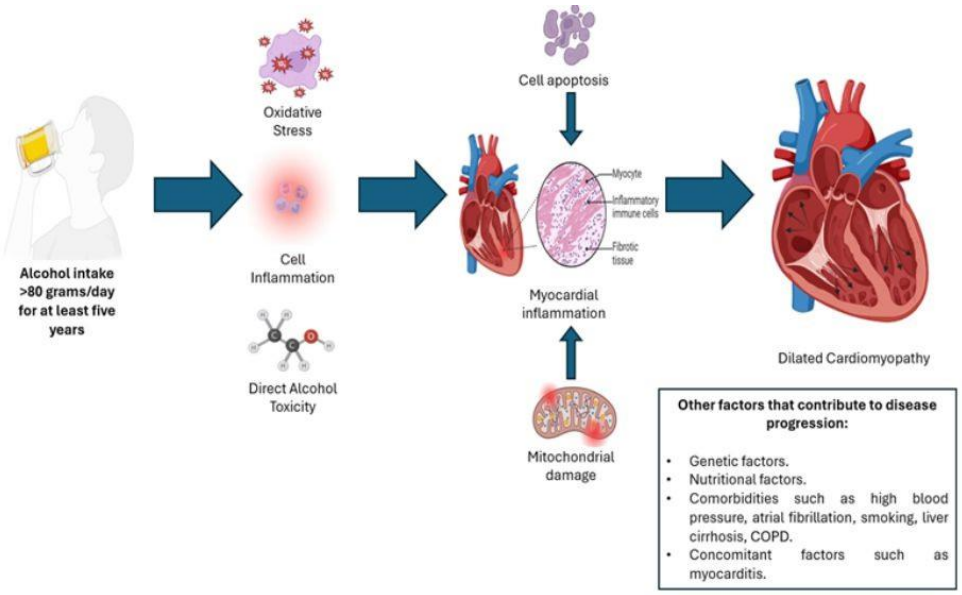


Figure 2: Pathogenic mechanisms of alcohol-induced cardiomyopathy.

Source: Figure created by the author David Fernando Ortiz-Perez, using BioRender.com[1]

Before making this diagnosis, it is essential to exclude other possible causes of dilated cardiomyopathy, such as valvular disease, ischemic heart disease, hypertension, or systemic disorders affecting the cardiac muscle, and to determine the average daily dose consumed by the patient.

Drinks as measures of alcohol are often given in ounces (oz), whereby 1 oz equals 28.35 g or 29.57 ml. Examples for 100 % alcohol in ml of one standard drink in consumed beverages are between 17.6 to 17.76 ml:

- Beer: 12 fluid ounces of 5 % beer = 355 ml fluid = 17.5 ml 100 % alcohol.
- Wine: 5 fluid ounces of 12 % wine = 148 ml fluid = 17.76 ml of 100 % alcohol.
- Distilled spirits: 1.5 fluid ounces of ~40 % liquor = 44 ml = 17.6 ml of 100 % alcohol.[7]

The following diagnostic criteria have been proposed to confirm the alcoholic etiology of cardiomyopathy:

1. History of excessive alcohol consumption: More than 80 grams per day for at least five years.

2. Echocardiographic findings: An increase in the left ventricular end-diastolic diameter exceeding two standard deviations from the normal value and an ejection fraction below 50%.

3. Exclusion of other etiologies: Essential to ensure that myocardial dysfunction is not attributable to valvular, ischemic, hypertensive, or systemic causes.[1]

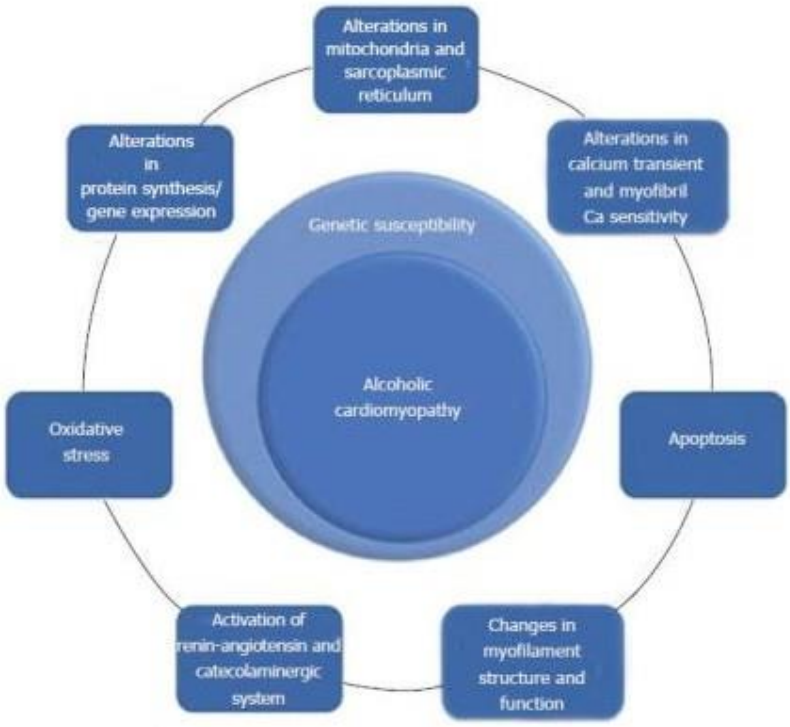


Figure 3: The Pathophysiology of Alcoholic Cardiomyopathy
Common pathophysiologic mechanisms for ACM are oxidative stress, apoptosis, alteration in calcium hemostasis, impaired mitochondrial stress, altered protein synthesis, and changes in myofilament structure and function. Adapted from Guzzo-Merello et al. 2014[viii]

In this context, we report a rare case of early-onset alcoholic cardiomyopathy with multiorgan involvement. A 35-year-old patient with a 20-year history of heavy alcohol use was diagnosed with icterus and admitted to the hospital for further testing.

CASE PRESENTATION

A 35-year-old male patient with no known medical history was admitted to a university hospital for difficulty breathing, edema, and numbness in his limbs, thoracic and abdominal pain, jaundice, and physical weakness. The patient described beginning to consume alcohol at age fifteen and increasing his intake over the past five years. On initial physical examination,

he had severe jaundice of the skin, a heart rate of 90 beats per minute, a blood pressure of 105/60 mmHg, a respiratory rate of 25 breaths per minute, and an oxygen saturation of 96%.

Laboratory examinations showed Azotaemia 66 mg/dl, Creatinine 0.52 mg/dl, Total bilirubin 7.62 mg/dl, AST 178 U/l, GGT 2132 U/l, Amylase 12 U/l, Lipase 112 U/l, LDH 585 U/l, Potassium 2.7 mmol/l, PT 66%, INR 1.33, RBC 3.22*106, Hgb 12 g/dl, Hct 34.6%, Total Protein 5.5, N-proBNP/BNP 4370 pg/ml.

Abdominal ultrasound showed fatty liver with an enlarged size up to 24 cm, with minimal fluid around the liver, hilum, and ansa.

Angio-CT of the abdomen revealed minimal bilateral pleural fluid, with a thickness of 26 mm dexter and 15 mm sinister. Bilateral postero-basal fibrotic bands are applied. Liver with increased steatosis dimensions. Contracted cholecyst with a round lesion 22-18 mm, probable calculus. Bile ducts not distended. Homogeneous pancreas. Both kidneys are without calculus without stasis. Urinary bladder with regular contours. Intestinal loops are not visible. Generalized desiccation of mesenchymal and subcutaneous adipose tissue. Minimal fluid in the pelvis.

ECG: Sinus rhythm with a frequency of 100/min, low QRS voltage in the precordial and extremity leads, and nonspecific repolarization changes are observed.

The patient experienced acute alcohol withdrawal symptoms, including tremor, disorientation, and psychomotor agitation, which peaked 48 hours after being admitted to the hospital. The patient was sent to the Clinical Toxicology Service for alcohol withdrawal management. Reduced BP, reduced O_2sat, and elevated N-proBNP/BNP complicated the patient's overall health.

In echocardiography was observed diffuse hypokinesis of the left ventricle. Dilated left ventricle with a severe decrease in EF = 0.25. Restrictive pattern of left ventricular filling. Mitral regurgitation to advanced. Dilatation of the left and right atrium. Dilated right ventricle. Tricuspid regurgitation to moderate. PsAP 47mmHg. Pericardial fluid in a small circumferential amount.

Because alcohol withdrawal and cardiomyopathy are both life-threatening conditions that require immediate medical attention, the patient's treatment was challenging. Antiepileptic medications, vitamin therapy, and benzodiazepines form the cornerstone of withdrawal management treatment. To treat cardiomyopathy, beta-blockers and diuretics were added to the medication.

DISCUSSION

Alcoholic cardiomyopathy is a variant of dilated cardiomyopathy, caused by excessive alcohol use, accompanied by left ventricular enlargement and systolic dysfunction.[ix]

Current research suggests that alcoholic cardiomyopathy is detected as a result of a deterioration in the patient's overall state and is a co-occurring symptom of alcohol withdrawal syndrome beyond the young age of the patient. The initial clinical therapy of patients identified with ACM should be based on aetiology,[x] and it should be suspected in all patients who exhibit hazardous or harmful alcohol

consumption, and a score of 15 or more (AUDIT Test) indicates the likelihood of alcohol dependence (moderate-severe alcohol use disorder).[xi]

Since the primary etiology of ACM is chronic alcohol intake, the cornerstone of treatment should be total abstinence from alcohol. Abstinence from alcohol improves LV function and relieves pulmonary artery and pulmonary capillary wedge pressure associated with ACM.[4]

A multidisciplinary strategy is vital, addressing not only heart failure management but also alcohol dependence through psychological support, nutritional counseling, and cardiac rehabilitation programs. Early detection and prompt intervention are critical because delays in treatment may reduce reversibility of myocardial injury and significantly worsen long-term outcomes.[1]

CONCLUSION

This case study clearly shows the correlation between high levels of alcohol use and the development of dilated cardiomyopathy at a young age with multiorgan involvement. This case highlights the importance of conducting a thorough examination of heart function. Imaging, particularly echocardiography, and the exclusion of alternate structural and ischaemic aetiologies reveal alcohol as the primary cause of this form of cardiomyopathy. Early identification and thorough care, including alcohol withdrawal management and a multidisciplinary approach, are critical for improving the prognosis and quality of life for affected people.

Conflicts of interest: The authors declare that they have no conflicts of interest.

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