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About Editor

Prof Dr. Mehmet Ozaslan

Department of Biology, Gaziantep University, Türkiye

Website: mehmetozaslan.com

E-mail: ozaslanmd@gantep.edu.tr

Language Editor

Lecturer Ceren Dogan

School of Foreign Languages, Necmettin Erbakan University, Türkiye

Email: cerendogan@erbakan.edu.tr

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Abstracts and full-text reports uploaded to the conference system undergo a review procedure. Authors will be notified of the application results in three weeks. Submitted abstracts will be evaluated on the basis of abstracts/proposals. The conference system allows you to submit the full text if your abstract is accepted. Please upload the abstract of your article to the conference system and wait for the results of the evaluation. If your abstract is accepted, you can upload your full text. Your full text will then be sent to at least two reviewers for review. **The conference has a double-blind peer-review process.** Any paper submitted for the conference is reviewed by at least two international reviewers with expertise in the relevant subject area. Based on the reviewers' comments, papers are accepted, rejected or accepted with revision. If the comments are not addressed well in the improved paper, then the paper is sent back to the authors to make further revisions. The accepted papers are formatted by the conference for publication in the proceedings.

Aims & Scope

Compared to other fields, developments and innovations in the fields of medical and health sciences are very fast. In this century, where the human population is rapidly increasing and technology is developing rapidly, health problems are constantly changing and new solutions are constantly being brought to these problems. With the Covid 19 epidemic, it has emerged that a health problem affects all humanity and all areas of life. For this reason, this conference focused on the changes and innovations in the field of Medical and Health Sciences.

The aim of the conference is to bring together researchers and administrators from different countries, and to discuss theoretical and practical issues of Medical and Health Sciences. At the same time, it is aimed to enable the conference participants to share the changes and developments in the field of Medical and Health Sciences with their colleagues.

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Control of Medical Care within the System of Mandatory Health Insurance in Bulgaria

Violeta Chuchulska

Medical University of Plovdiv

Rumyana Stoyanova

Medical University of Plovdiv

Abstract: The aim of the study was to analyze the regulatory framework and the practice of control activities within the system of mandatory health insurance in Bulgaria, carried out by the National Health Insurance Fund (NHIF) and the Regional Health Insurance Funds (RHIFs), with a focus on the mechanisms for controlling medical care and the expenditure of public funds. Methods: A documentary and regulatory analysis was conducted, covering the current legislation, secondary regulatory acts, the National Framework Contract, the NHIF Budget Act, and official strategic and institutional documents related to healthcare control in Bulgaria. Results: The control system is implemented through preliminary, current (on-site/sudden), and subsequent control, planned and unplanned inspections, as well as budgetary and financial mechanisms at both micro- and macro-levels. Patient participation plays a significant role through the Electronic Health Record and the possibility to submit complaints and signals. Despite the well-developed regulatory framework, structural limitations were identified, particularly the shortage of controllers with medical education and the limited capacity for real-time control. Conclusion: The control activities of the NHIF and RHIFs represent a key instrument for ensuring transparency and financial sustainability in the Bulgarian health insurance system. Further improvement requires strengthening human resources capacity and the development of digital control tools.

Keywords: Mandatory health insurance, NHIF, Control of medical care, Financial control.

Introduction

Under conditions of limited resources and increasing public expectations, the control exercised by the National Health Insurance Fund should not be viewed merely as an administrative function, but as a strategic instrument for ensuring the quality, accessibility, and transparency of healthcare services. The subject of the present study is the control mechanisms within the healthcare system in Bulgaria related to the expenditure of public funds by the NHIF. The object of the analysis is the functions of the National Health Insurance Fund as the main institution responsible for exercising control over the use of public financial resources in healthcare.

The aim of this study is to analyze the existing control practices of the NHIF, to identify their weaknesses, and to propose directions for improvement through digitalization, enhanced institutional coordination, and regulatory changes aimed at increasing accountability and preventing abuse. In this context, control should not be considered solely as a sanctioning mechanism, but also as a tool for optimizing management processes, protecting patients' rights, and ensuring the sustainability of public healthcare financing.

Method

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The present study was conducted through a documentary and regulatory analysis of the current legislation in the field of healthcare and mandatory health insurance. The analysis covered the Health Act, the Health Insurance Act, the National Health Insurance Fund Budget Act, secondary regulatory acts, the National Framework Contract for Medical Activities, as well as official strategic and institutional documents related to control activities within the Bulgarian healthcare system. The analysis was aimed at identifying the main forms, mechanisms, and limitations of control over medical care and the expenditure of public funds.

Results and Discussion

Institutional and Regulatory Frameworks for the Control of Public Funds

The regulatory review demonstrated that control in the Bulgarian healthcare system is organized within a multilayered institutional structure based on specific financial and organizational principles aimed at ensuring adequate, accessible, and high-quality medical care for the population. This structure reflects the complex and multi-component nature of the healthcare system, in which medical and non-medical activities operate under different regulatory regimes.

In this context, control in healthcare is established as a systemic mechanism for monitoring, evaluating, and regulating compliance with legal requirements, medical standards, and the efficiency of public resource utilization. As emphasized in scientific literature, the primary objective of control is to ensure quality, safety, and equitable access to healthcare services, while simultaneously limiting abuse, inefficiency, and financial risks within the system (Georgieva et al., 2007).

The findings demonstrated that control functions in healthcare were distributed among several key institutions with clearly defined competences. Central roles are assigned to the Ministry of Health, the Regional Health Inspectorates, the Executive Agency Medical Supervision, the National Health Insurance Fund, the National Audit Office, the Public Financial Inspection Agency, and the National Revenue Agency, each operating within a legally defined scope of authority (Health Act, 2004; Health Insurance Act, 1998). National health policy is formulated and coordinated by the Council of Ministers, which, upon proposal by the Minister of Health, approved the National Health Strategy and national health programs. Legislative and parliamentary oversight was exercised by the National Assembly through its Standing Committee on Health, which participated in the development of legislative initiatives, reviewed the activity and budget reports of the NHIF, and, when necessary, established ad hoc committees to address specific issues (National Assembly, 2023).

With regard to control over the quality of medical care and the protection of patients' rights, the analysis identified the leading role of the Executive Agency Medical Supervision. The agency exercises continuous oversight over the activities and organization of healthcare establishments regardless of their ownership and performs control over the management of public funds, including those allocated for medicinal products fully financed by the state (Executive Agency Medical Supervision, 2023).

Control over the revenue side of the system is carried out primarily by the National Revenue Agency, which is responsible for the collection of mandatory health insurance contributions and exercises control over NHIF revenues through tax audits and inspections (National Revenue Agency, 2023). The National Social Security Institute performs a complementary control function regarding the insurance status of economically active individuals (National Social Security Institute, 2023). Financial control over NHIF expenditure was also exercised by the National Audit Office and the Public Financial Inspection Agency, which monitored the legality, expediency, and effectiveness of public spending (Agency for State Financial Inspection, 2023; National Audit Office, 2023).

Established Control Functions and Powers of the National Health Insurance Fund

The analysis of regulatory documents showed that the National Health Insurance Fund occupied a central position in the system of control over the use of public funds for healthcare services. Its primary control function was directed at monitoring the lawful expenditure of resources derived from mandatory health insurance contributions collected by the National Revenue Agency, as well as at ensuring their targeted and efficient use within the system of mandatory health insurance (NHIF Budget Act, 2025; National Revenue Agency, 2025).

The study identified that the NHIF exercised direct control over its contractual partners-healthcare establishments, pharmacies, and providers of dental care-through inspections focused on the volume, legal basis, and compliance of reported medical activities with the services contracted and reimbursed. This control covered both the medical and financial aspects of provided care and aimed to prevent unjustified payments and deviations from contractual conditions (Health Insurance Act, 1998).

The results of the regulatory analysis also indicated that the control powers of the NHIF were clearly defined within the framework of the current health legislation governing the organization, operation, and financing of the healthcare system in Bulgaria (Health Act, 2004). According to Article 2 of the Health Act, health was defined as a state of physical, mental, and social well-being and was recognized as a national priority to be guaranteed by the state. Within this regulatory context, the control exercised by the NHIF was based on principles such as equal access to healthcare services, prioritization of prevention, protection of vulnerable groups, state participation in healthcare financing, and the guarantee of accessible medical care (Health Act, 2004; Health Insurance Act, 1998).

In this sense, the findings suggest that the control activities of the NHIF extended beyond the scope of purely financial supervision and functioned as an institutional mechanism for the implementation of state health policy and the protection of citizens' constitutional rights to healthcare. Control over the expenditure of public funds was thus established as a key instrument for balancing the financial sustainability of the system with the social and health objectives of mandatory health insurance.

Organizational and Administrative Control Mechanisms

The organizational framework of control within the National Health Insurance Fund was structured around a two-tier governance model comprising a Supervisory Board and a Governor. The Supervisory Board performs key strategic and control functions and includes representatives of the state, employers' organizations, trade unions, and representatives of patient rights organizations. This structure created institutional conditions for the participation of multiple stakeholders in the management and control of public funds in healthcare (Health Insurance Act, 1998).

Within its statutory powers, the Supervisory Board adopted internal regulations governing the activities and structure of the institution, participated in the preparation and approval of the National Framework Contract, adopted the draft annual budget, and approved reports on budget execution and institutional performance. Since 2021, these functions had been complemented by mechanisms aimed at ensuring greater predictability and financial sustainability of the NHIF budget, including the non-payment of activities exceeding the volumes and values specified in the contracts of healthcare establishments (Health Insurance Act, 1998).

Control over the implementation of contracts for the provision of medical and/or dental care, pursuant to Article 72 of the Health Insurance Act, was carried out by NHIF employees designated by order of the Governor, as well as by controlling officials within the respective Regional Health Insurance Funds. This organizational arrangement allowed for the combination of centralized management with decentralized implementation of control mechanisms at the territorial level (Health Insurance Act, 1998).

The general and specialized administrations of the Regional Health Insurance Funds supported their directors in exercising control functions through budget planning, contractual activities, reporting, legal representation, analysis of court disputes, and information services for insured people. In this way, the administrative capacity of the regional funds was established as a significant factor for the effective functioning of the control system.

The control exercised by the bodies of the NHIF is structurally and functionally integrated into the public finance system and represents a specific form of financial supervision over the expenditure of public funds. Depending on the stage of the control process, this supervision could take the form of preliminary, sudden (on-site), or subsequent control (Chilova, 2018).

Forms and Practical Implementation of Control over Medical Care

Control over the implementation of contracts with the National Health Insurance Fund is carried out through a system of inspections performed by NHIF employees and controlling officials of the Regional Health Insurance Funds. The analysis showed that the existing control framework encompassed various types of inspections differing in scope and purpose, which, according to the NHIF's approved internal instructions, could be planned

or unplanned, comprehensive or thematic, independent or joint, as well as primary and secondary (National Health Insurance Fund, 2020).

The practical implementation of control included preliminary, current (sudden/on-site), and subsequent control, carried out at different stages of the provision and financing of medical care. Preliminary control was conducted prior to the reimbursement of reported activities and included on-site inspections, documentary checks, and remote control through the NHIF Personalized Information System. Its primary objective was to verify the compliance of reported activities with regulatory requirements and contractual parameters before financing was granted.

Current or sudden control was carried out during the provision of medical care and was aimed at verifying the actual performance of medical activities. Evidence from the review suggests that this form of control assessed whether the patient was physically present at the healthcare establishment, whether approved medical algorithms were followed, and whether the reported activity met the criteria for reimbursement by the NHIF. Subsequent control was conducted after payment had been made and aimed to identify cases of unjustifiably received funds subject to recovery in accordance with the Health Insurance Act (Health Insurance Act, 1998; National Health Insurance Fund, 2020).

The study additionally identified significant limitations in the practical application of control related to the staffing of control bodies. The shortage of controllers with medical education—who were exclusively authorized to assess the quality of provided medical care—represented a serious structural problem (Health Insurance Act, 1998). The low attractiveness of these positions, driven by comparatively lower remuneration than clinical practice, high administrative workload, and the risk of professional conflicts, hindered the development of sustainable and effective control capacity. As a result of these limitations, there was a risk that control activities would focus predominantly on formal and documentary aspects of accountability rather than providing an in-depth assessment of the actual quality and medical justification of delivered care.

Financial and Budgetary Control Mechanisms at the Macro Level

The financial framework of framework contracts within the mandatory health insurance system is determined annually by the NHIF Budget Act adopted by the National Assembly, which assigns the budget a key role as an instrument for controlling public healthcare expenditures (NHIF Budget Act, 2025). Preliminary financial control was exercised already at the contracting stage, as financing was granted only to activities included in the operating license of the respective healthcare establishments. In cases of expansion of hospital medical care through the inclusion of new activities, an opinion from the NHIF regarding the feasibility of financing was required, further limiting the risk of uncontrolled expenditure growth (Health Establishments Act, 1999).

The findings demonstrated that macro-level control exercised through the NHIF budget functioned as a primary mechanism for limiting and forecasting public expenditures in the sector. Budgetary limits could be applied both at the system level and across specific subsectors, including inpatient and outpatient medical care, as well as pharmaceutical expenditures (NHIF Budget Act, 2023). Within the mandatory health insurance system, the allocation of funds for inpatient and outpatient care was carried out through specialized rules adopted by the NHIF Supervisory Board in accordance with the NHIF Budget Act for the respective year.

With regard to inpatient medical care, the rules under Article 4 of the NHIF Budget Act provided for the allocation of funds by specific activities, including clinical pathways, clinical and outpatient procedures, as well as by distinct groups of activities with indicative values, such as childbirth, hemodialysis, and oncological treatment (National Health Insurance Fund, 2025a). Exceeding the established values required additional approval, and payments were directly linked to reporting compliance and contracted financial parameters, thereby strengthening the role of the budget as a control instrument.

Amendments to the Health Insurance Act in 2025 introduced additional mechanisms aimed at limiting budget deficits, including payments to healthcare establishments only up to the contracted values and the establishment of the position of a second Deputy Governor of the NHIF to improve governance and strengthen financial control. The analysis indicated that these measures were directed toward enhancing budgetary discipline and reinforcing the sustainability of the mandatory health insurance system at the macro level.

Regulatory Restrictions as an Instrument for Cost Control

Alongside direct control mechanisms, the mandatory health insurance system also operated through indirect regulatory restrictions aimed at managing and limiting public expenditures. The analysis showed that one of the main such mechanisms was the regulation of hospital capacity through the determination of the number of hospital beds included in contracts between healthcare establishments and the National Health Insurance Fund.

After 2018, a regulatory restriction was introduced in the National Framework Contract limiting the possibility of increasing the number of beds used for activities financed by the NHIF. This restriction functioned as an instrument for controlling the volume of inpatient medical care and preventing uncontrolled growth of expenditures in the hospital sector (National Health Insurance Fund, 2023). At the same time, Article 37b of the Health Establishments Act provided for the possibility of increasing bed capacity when introducing new medical activities but only following an administrative procedure and an assessment of population needs conducted by the Ministry of Health (Ministry of Health, 2024). In this way, the regulation of hospital capacity was established as a balancing mechanism between ensuring access to medical care and maintaining the financial sustainability of the system (Chilova, 2018).

An additional regulatory mechanism concerned restrictions on physicians' participation in contracts with the NHIF. Generally, physicians were allowed to conclude no more than two contracts, with exceptions for certain medical specialties defined in the National Framework Contract for Medical Activities (National Framework Contract for Medical Activities, 2023–2025). This mechanism aimed to prevent excessive simultaneous engagement of medical professionals across multiple healthcare establishments, which could compromise the actual performance of contracted activities. In this sense, the restriction supported both more efficient allocation of human resources under conditions of workforce shortages and compliance with structural and professional standards within the system.

In response to the established shortage of medical professionals, the NHIF Supervisory Board allowed exceptions for specific specialties in which physicians could work in two inpatient healthcare establishments, typically on a part-time basis. These specialties included anesthesiology and intensive care, diagnostic imaging, clinical laboratory medicine, microbiology, clinical pathology, hematology, and nuclear medicine (National Health Insurance Fund, 2023). Compliance with these requirements was monitored at the contracting stage through verification in the NHIF information systems, including the register of medical care providers (Health Insurance Act, 2004).

Digitalization and Patient Participation as Elements of Control

The analysis showed that digitalization represents a significant factor in the development and improvement of the healthcare control system. The National Health Information System enabled the collection and processing of data on performed medical activities in both outpatient and inpatient care, while the Electronic Health Record allowed patients to monitor in near real time all medical interventions provided to them, regardless of the source of financing (Ordinance on the Functioning of the National Health Information System, 2021). In this way, conditions were created for increased transparency and more active patient participation in control processes.

The existing regulatory framework provided insured persons with the opportunity to submit complaints to the director of the respective Regional Health Insurance Fund in cases of suspected reported but not performed medical activities, low-quality care, unlawful collection of payments, or refusal of access to medical documentation (National Framework Contract for Medical Activities, 2023–2025). The findings suggest that this form of civic control remained predominantly reactive and was activated mainly after violations had already occurred, while patient participation was not sufficiently institutionalized or systematically encouraged. Despite the possibility of submitting signals in cases of discrepancies or missing data in the Electronic Health Record, the role of patients in the control system remained limited and complementary to institutional control.

As of 2025, additional electronic mechanisms for near real-time control over the prescribing and dispensing of medicinal products and medical devices had been introduced through electronic prescriptions, electronic prescribing, and integrated data exchange between healthcare establishments, pharmacies, and relevant institutions (National Health Insurance Fund, 2025; Ministry of Health, 2022). Despite the progress achieved, a fully implemented central analytical module enabling automated real-time control over all inpatient activities was still lacking. The analysis showed that such functionality was envisaged in strategic documents for the development of the National Health Information System but had not yet been fully implemented (Strategy Portal of the Republic of Bulgaria, 2023).

In view of the presented results and with the aim of systematizing the identified mechanisms, effects, and limitations, Table 1 summarizes the main forms of control over public expenditures within the system of the National Health Insurance Fund.

Table 1. Main mechanisms for controlling public expenditures in the NHIF system – summary of results

Level of control	Main mechanisms	Practical implementation	Key effects	identified	Main limitations
Institutional and organizational	Supervisory Governor, Health Insurance Funds (RHIFs), administration	Board, Adoption of budget Regional allocation rules, National Funds Framework Contract, internal contractual activities and reporting	Ensures formal governability and regulatory compliance	Complex structure, risk of administrative burden	
Financial and budgetary (macro level)	NHIF Budget Act, budget ceilings, indicative values	Expenditure limitation by subsectors and activities	Controls growth of public expenditures and budget deficit	Limited flexibility in relation to actual healthcare needs	
Contractual and operational	Planned, unplanned, preliminary, current, and subsequent inspections	Control of reported medical activities and payments	Reduces the risk of unjustified payments	Predominantly documentation-based control	
Regulatory	Restrictions on hospital bed capacity, limits on physicians' participation	Regulation of hospital volume and workforce allocation	Balances of access to care and financial sustainability	Dependence on administrative assessments and exceptions	
Human resources	Requirement for medical qualification of controllers	Assessment of the quality of medical care	Ensures professional evaluation of healthcare services	Shortage of qualified personnel	
Digital	National Health Information System, electronic health records, e-prescriptions	Real-time or near real-time monitoring and transparency	Increases accountability and traceability	Lack of a centralized analytical module	
Citizen (patient) participation	Complaints, signals, access to electronic health record	Complementary institutional control	Limits informal and non-compliant practices	Depends on patient awareness and engagement	

The summarized results indicated that the healthcare control system functioned as a multilayered mechanism combining institutional, financial, regulatory, digital, and citizen-based forms of control. Although this model contributed to limiting financial risks and increasing accountability, the analysis also identified a number of structural constraints related to the predominantly documentary nature of control, shortage of qualified control personnel, limited flexibility of budgetary mechanisms, and incomplete digital integration.

On this basis, attention should be directed toward strengthening the analytical and qualitative component of control, developing centralized digital tools for real-time analysis, improving the staffing capacity of control authorities, establishing a clearer link between regulatory restrictions and the actual healthcare needs of the population, and enhancing patient involvement in control activities. These directions provide a logical foundation for a subsequent discussion on the effectiveness of the existing mechanisms and for formulating recommendations for their improvement.

Conclusion

The control activity of the National Health Insurance Fund plays a key role in the management of public healthcare funds and in ensuring legality, accessibility, and quality of medical care. The analysis showed that Bulgaria has developed a relatively advanced regulatory and institutional framework for control, including preliminary, current, and subsequent inspections, budgetary mechanisms, regulatory restrictions, electronic traceability systems, and formally regulated opportunities for patient participation.

At the same time, the system faces a number of challenges, including a shortage of medically qualified controllers, limited capacity for real-time control over inpatient care, incomplete integration of information systems, and the

need for more effective inter-institutional coordination. The analysis also showed that, despite the existence of legally established mechanisms, patient participation in control remained limited and predominantly reactive, not sufficiently institutionally supported or systematically utilized as a source of control information. This highlights the need for modernization of the control function not only through regulatory amendments, but also through strategic development of human resources, implementation of automated analytical tools, and a targeted expansion and structuring of the patient's role in the control process.

The study contributes to the systematization of NHIF control mechanisms and outlines specific directions for their improvement in the context of the digital transformation of healthcare. Further development of control within the mandatory health insurance system represents a necessary condition for building a more transparent, sustainable, and socially legitimate healthcare system that simultaneously protects patient rights and ensures efficient management of public resources.

Recommendations

Based on the findings of the present study, several key directions for improving the control system within the mandatory health insurance framework in Bulgaria can be formulated. First, it is recommended to strengthen the analytical and qualitative dimension of control by shifting the focus from predominantly documentary verification toward outcome-oriented and clinically meaningful assessment of medical care. This requires the development of more advanced methodologies for evaluating medical necessity, treatment effectiveness, and quality of care. Second, the establishment of a centralized digital analytical platform within the National Health Information System is essential. Such a system should enable real-time data processing, cross-institutional integration, and automated detection of irregularities in the provision and reporting of medical services, thereby enhancing preventive control capabilities. Third, improving human resource capacity within control structures is necessary. This includes increasing the number of medically qualified control specialists, introducing targeted incentives to attract healthcare professionals to control functions, and ensuring continuous professional training in both clinical and regulatory aspects of healthcare oversight. Fourth, regulatory mechanisms should be more closely aligned with population health needs. In particular, restrictions related to hospital capacity, resource allocation, and contractual limits should be periodically reassessed based on epidemiological data, regional needs, and healthcare demand indicators in order to ensure a better balance between financial sustainability and access to care. Fifth, patient participation in the control process should be strengthened and systematically institutionalized. This may be achieved through improved accessibility and usability of electronic health records, structured feedback mechanisms, and the integration of patient-reported data into formal control procedures. Finally, inter-institutional coordination between all bodies involved in healthcare oversight should be enhanced. A more integrated approach involving the National Health Insurance Fund, Ministry of Health, National Revenue Agency, and other control institutions would reduce fragmentation, improve information exchange, and increase the overall effectiveness of the control system. These recommendations aim to support the transition toward a more efficient, transparent, and technologically advanced control system that ensures both financial sustainability and high-quality healthcare delivery.

Scientific Ethics Declaration

* The authors declare that the scientific ethical and legal responsibility of this article published in EPHELS journal belongs to the authors.

Conflict of Interest

* The authors declare that they have no conflicts of interest.

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Author(s) Information

Violeta Chuchulska

Medical University of Plovdiv

15a Vasil Aprilov blvd.

Plovdiv, Bulgaria

ORCID iD: <https://orcid.org/0009-0002-1330-3775>

Rumyana Stoyanova

Medical University of Plovdiv

15a Vasil Aprilov blvd., Plovdiv, Bulgaria

ORCID iD: <https://orcid.org/0000-0002-5160-6323>

*Contact e-mail: rumi_stoqnova@abv.bg

*Corresponding author(s) contact email

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The Impact of Lifestyle Factors and Biomarkers on Patients with Autoimmune Disorders

Salome Abuladze

Avicenna – Batumi Medical University

Leila Akhvlediani

Batumi Shota Rustaveli State University

Neriman Tsintsadze

Batumi Shota Rustaveli State University

Marina Nagervadze

Batumi Shota Rustaveli State University

Abstract: Rheumatoid arthritis (RA) and ankylosing spondylitis (AS) are chronic autoimmune diseases shaped by genetic predisposition and modifiable lifestyle factors. Anti-cyclic citrullinated peptide (anti-CCP) antibodies are central to RA diagnosis, but their relevance in AS remains unclear. This study investigates the impact of BMI, stress, and other lifestyle variables on anti-CCP levels in a Georgian cohort, highlighting potential mechanisms of stress-induced citrullination in AS. A cross-sectional study was conducted involving 219 Georgian participants diagnosed with RA or AS. Anti-CCP levels were analyzed against BMI, smoking status, physical activity, perceived stress, age, and sex. Statistical significance was assessed using correlation and regression analyses to evaluate lifestyle modulators of systemic inflammation and autoantibody expression. Overweight or obesity (BMI ≥ 25 kg/m²) was prevalent in 71.5% of RA patients ($p = 0.0001$) and 66.2% of AS patients ($p = 0.0497$). Most participants were non-smokers (85%, $p = 0.0001$). Physical activity showed no correlation with anti-CCP levels ($p = 0.6415$). RA patients were predominantly female (96.7%), with anti-CCP levels increasing with age ($p = 0.0001$). In AS, elevated anti-CCP levels were rare and primarily observed in younger females aged 35–44 reporting high stress ($p = 0.0075$). Perceived stress was significantly associated with increased anti-CCP levels in both RA ($p = 0.0001$) and AS ($p = 0.0034$). Anti-CCP antibodies remain diagnostically specific for RA but may be elevated in AS under stress. These findings underscore the interplay between metabolic and psychosocial factors in autoimmune disease and support lifestyle assessment in personalized care.

Keywords: Autoimmune diseases, Rheumatoid arthritis, Ankylosing spondylitis, Lifestyle

Introduction

Autoimmune diseases affect an estimated 7–9% of the global population and represent a growing public health concern due to their chronic nature, diagnostic complexity, and long-term impact on morbidity and disability (Miller, 2023). Among these, rheumatoid arthritis (RA) and ankylosing spondylitis (AS) are prototypical autoimmune disorders where genetic predisposition interacts with lifestyle and environmental factors to shape disease onset and progression. The rising prevalence of these conditions, coupled with diagnostic delays and treatment challenges, underscores the urgent need for improved biomarkers and personalized management strategies (Rosenbaum et al., 2019; Tański et al., 2022). RA affects approximately 0.5–1% of the global population, with increasing prevalence projected through 2050 (Black et al., 2023), while AS affects an estimated 0.1–1.4%, depending on genetic background and HLA-B27 distribution (Dean et al., 2014). Early and accurate

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diagnosis remains particularly challenging in AS due to limited serological markers, necessitating investigation of potential contributors such as stress-mediated autoantibody production.

The pathogenesis of RA and AS involves a complex interplay of immunological mechanisms and environmental factors. Central and peripheral tolerance mechanisms, including thymic deletion and regulatory T cell function, normally eliminate autoreactive lymphocytes. However, genetic risk alleles, environmental triggers, and modifiable lifestyle factors, including infections or smoking-induced activation of peptidyl arginine deiminase (PAD) enzymes, can disrupt these safeguards, allowing autoreactive clones to persist and initiate inflammation (Curran et al., 2020; Chauhan, et al., 2023). Molecular mimicry further contributes to disease onset, as microbial epitopes resembling joint or enthesal proteins can cross-activate autoreactive lymphocytes, amplifying immune responses through bystander activation and epitope spreading (He et al., 2024; Klareskog et al., 2013).

Under inflammatory conditions, Peptidyl arginine deiminase type 2 (PAD2) and Peptidyl arginine deiminase type 4 (PAD4), which are most strongly implicated in RA at both genetic and cellular levels (Curran et al., 2020), catalyze citrullination of proteins such as vimentin and fibrinogen, generating neoepitopes that provoke B cell production of autoantibodies including rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) (del Val del Amo et al., 2006; Erdő-Bonyár et al., 2024). These autoantibodies contribute directly to joint pathology via immune complex formation, complement activation, and synovial tissue inflammation. Emerging evidence suggests that stress-induced PAD activation may transiently elevate anti-CCP even in AS, indicating a broader role for citrullination beyond classical RA (Autoantibodies in Autoimmune Disorders, n.d.).

In addition to immunological mechanisms, modifiable lifestyle factors play a critical role in disease expression. Smoking, elevated body mass index (BMI), low physical activity, and psychological stress have all been linked to increased risk and severity of RA and AS (Conrad et al., 2023; Schäfer & Keyßer, 2022). Stress, in particular, may act through psychoneuroimmunological pathways to enhance PAD activity and autoantibody generation, representing a novel modifiable factor influencing systemic inflammation. Poor dietary quality, early-life malnutrition, and occupational strain may exacerbate inflammation and bone remodeling in AS, while smoking and socio-economic disadvantage can compound disease burden. Recent studies suggest that certain occupations, such as agricultural labor, construction work, mining, and manufacturing may increase the risk of RA and AS due to prolonged physical strain, repetitive joint stress, and exposure to environmental toxins (Work Limitations and Associated Factors in Rheumatoid Arthritis, Axial Spondyloarthritis, Osteoarthritis and Fibromyalgia - PubMed, n.d.), (Occupational Inhalable Agents Constitute Major Risk Factors for Rheumatoid Arthritis, Particularly in the Context of Genetic Predisposition and Smoking | Annals of the Rheumatic Diseases, n.d.) However, the influence of these lifestyle factors on serological markers such as anti-CCP antibodies remains unexplored, particularly in AS, where they are often treated as confounders rather than contributors.

Demographic disparities also shape disease prevalence and outcomes. RA predominantly affects older adults, with higher rates observed in women (87.8 per 100,000) compared to men (22.5 per 100,000), and regional variation ranging from 0.46% in Australasia to approximately 0.16% in East and Southeast Asia (Corrado et al., 2025; Versini et al., 2014). AS typically begins before age 45 and disproportionately affects working-age populations, with prevalence estimates ranging from 0.9–1.4% in the U.S. and 1.3–4.98 million cases across Europe and Asia (Mathkhor et al., 2022; Voigt et al., 1994).

These lifestyle and demographic factors may also influence serological markers such as anti-CCP antibodies. Anti-CCP arises from PAD-mediated citrullination and is highly specific for RA, correlating with disease severity and prognosis (Yasmeen et al., 2024). However, low-level anti-CCP positivity has been occasionally observed in AS (2–4%), particularly in women or patients reporting high psychosocial stress, suggesting potential stress-mediated PAD activation or subclinical immune overlap (Ediz et al., 2011; Mease et al., 2022; Singh Sangha et al., 2018). Citrullinated neoepitopes and anti-CCP reactivity have been detected in sacroiliac and enthesal tissues, indicating local PAD activity and the potential for neoantigen formation within AS-affected joints. Anti-CCP testing may therefore help distinguish atypical AS presentations from early or seronegative RA, refine diagnostic accuracy, and guide treatment decisions. This highlights the dual role of anti-CCP as both a diagnostic biomarker and a mechanistic readout of systemic inflammatory processes. (Basic Science Department, Dentistry College, Mustansiriyah University, Baghdad -Iraq. et al., 2025; Pisetsky, 2023). Despite these insights, the significance of anti-CCP antibodies in AS remains poorly defined, particularly within Caucasian populations. While conventionally considered RA-specific, occasional detection of anti-CCP in AS underscores the potential influence of modifiable lifestyle factors, such as BMI and psychological stress, on citrullination pathways. To date, no studies have systematically examined anti-CCP levels in RA and AS patients from the Republic of Georgia, adding to the novelty and regional relevance of this research.

The aim of this study is to evaluate the relationship between anti-CCP antibody levels and life-style factors-including BMI, smoking, physical activity, stress, age, and sex-in RA and AS patients from a Georgian cohort. By characterizing these patterns, we aim to provide mechanistic and clinically relevant insights into the interplay between modifiable factors and autoimmune activity, informing personalized management strategies.

Method

This cross-sectional observational study evaluated the relationship between anti-cyclic citrullinated peptide (anti-CCP) antibody levels and demographic and modifiable lifestyle factors-including BMI, smoking status, physical activity, stress level, age, and sex-among patients with RA and AS in the Republic of Georgia. The study design aimed to capture real-world associations between lifestyle factors and serological markers at a single time point, providing mechanistic insights into autoimmune regulation.

Participants were assessed once between February 2023 and May 2024. A total of 219 participants were enrolled: 93 patients with rheumatoid arthritis (RA), 62 patients with ankylosing spondylitis (AS), and 64 healthy controls. Healthy controls were age- and sex-matched where feasible to minimize confounding. Participants were recruited via convenience sampling from two urban outpatient clinics-JSC Seamen's Medical Center 2010 and SoloMed LLC - selected based on patient volume and access to rheumatology services. Eligible patients were approached consecutively during routine visits. All participants were ethnically Georgian and aged 16–65+ years. RA and AS diagnoses were confirmed using the 2010 ACR/EULAR criteria for RA and ASAS criteria for spondyloarthritis. Exclusion criteria included pregnancy, current immunosuppressive therapy, recent infection (within 4 weeks), and other autoimmune or inflammatory conditions (e.g., SLE, psoriasis, psoriatic arthritis, PCOS) that could confound inflammatory markers.

All participants provided written informed consent, and the study was approved by the Institutional Ethics Committee of BAU International University Batumi (reference N-MED006). Participant confidentiality was maintained using unique study codes, and all data were stored in secure databases. Blood samples (2 mL) were collected into K₃-EDTA tubes, transported within one hour, centrifuged at 3000 rpm for 15 minutes, and stored at –20°C until analysis. Anti-CCP levels were measured using the Anti-CCP hs ELISA Kit (ORGENTEC Diagnostika GmbH, Germany) according to the manufacturer's protocol.

Demographic and lifestyle data-age, sex, BMI, smoking, physical activity, and perceived stress-were collected using standardized questionnaires adapted from validated tools. Physical activity was assessed via a four-point ordinal scale: no activity, rarely active, irregularly active, or regularly active. Stress was assessed using a four-point Likert item (high, average, low, unnoticed). While feasible for outpatient settings, these measures may be subject to recall bias.

The primary outcome variable was anti-CCP antibody level (U/mL); exposure variables included age, sex, BMI, smoking, physical activity, and stress. Descriptive statistics were expressed as means $\pm$ standard deviation (SD) or percentages. The one-way ANOVA test assessed group differences (RA, AS, controls). When significant ($p < 0.05$), Tukey's post hoc test was applied for pairwise comparisons. Normality and homogeneity were evaluated using Shapiro-Wilk and Levene's tests, respectively. All variables met assumptions for parametric testing (Shapiro-Wilk $p > 0.05$; Levene's $p > 0.05$).

Missing data (<5%) were handled via pair-wise deletion without imputation. Regression analysis was not performed due to sample size and exploratory scope. Potential biases included selection bias from convenience sampling and recall bias in self-reported lifestyle data. While findings may not generalize beyond the Georgian population, they provide insight into autoimmune disease expression in a unique regional context. Ethical considerations, standardized laboratory protocols, and structured lifestyle assessments ensured methodological rigor, supporting the validity of associations between anti-CCP levels and modifiable risk factors.

Results and Discussion

A total of 219 participants were included: 93 with rheumatoid arthritis (RA), 62 with ankylosing spondylitis (AS), and 64 healthy controls (HC). No participants were excluded or lost to follow-up. Key demographic and lifestyle characteristics are summarized in Table 1 and Figures 1–3.

Table 1. Demographic and lifestyle characteristics of study participants across diagnostic

Variable	RA (n = 93)	AS (n = 62)	Control (n = 64)	p-value*
Female (%)	96.7	48.4	61.0	<0.0001
Male (%)	3.3	51.6	39.0	
Age group (%)				
16–34	10.0	11.0	5.0	<0.0001
35–44	12.0	23.0	14.0	
45–54	24.0	31.0	25.0	
55–64	37.0	15.0	37.0	
≥65	17.0	15.0	19.0	
BMI category (%)				
Underweight	2.0	2.0	6.0	0.0003
Normal weight	29.0	25.0	42.0	
Overweight	32.0	36.0	27.0	
Obesity class I	22.0	27.0	17.0	
Obesity class II	11.0	7.0	5.0	
Obesity class III	4.0	3.0	3.0	
Smoking status (%)				
Smoker	17.0	24.0	30.0	<0.0001
Non-smoker	83.0	76.0	70.0	
Stress level (%)				
High	39	34	23	0.0025
Average as all	24	32	36	
Doesn't bother	16	20	14	
Unnoticed	21	14	27	
Physical activity (%)				
regularly	16	14	21	0.015
irregularly	59	46	34	
Rarely	19	21	37	
None	6	19	8	

Sex distribution differed significantly across groups ($p < 0.0001$), with RA patients predominantly female (96.7%), controls predominantly male (73.4%), and AS patients showing near-equal gen-der representation (Figure 1). BMI classification also varied significantly ($p = 0.0003$), with overweight and obesity more prevalent in RA and AS patients compared to controls (Figure 2). Other lifestyle variables such as smoking status ($p < 0.0001$), stress level ($p = 0.0025$), and physical activity ($p = 0.015$) showed group differences and were analyzed in relation to anti-CCP levels.

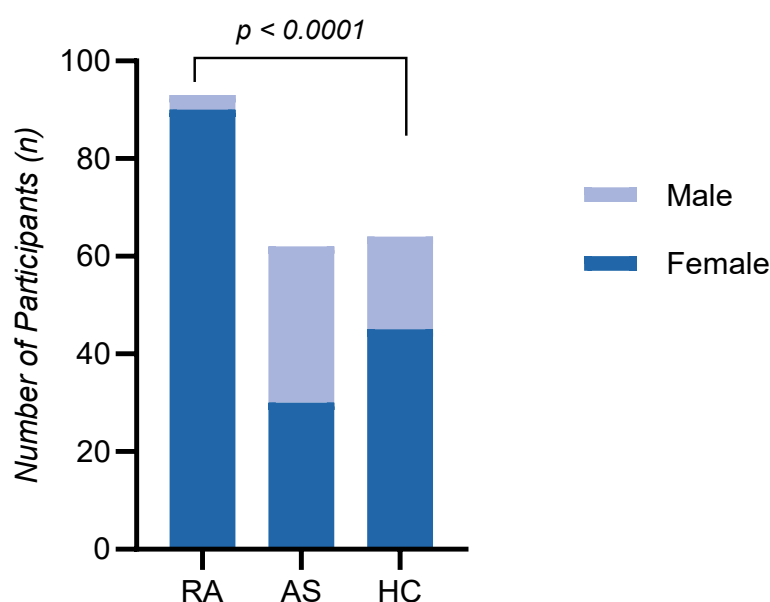


Figure 1. Distribution of RA, AS, and control groups based on sex

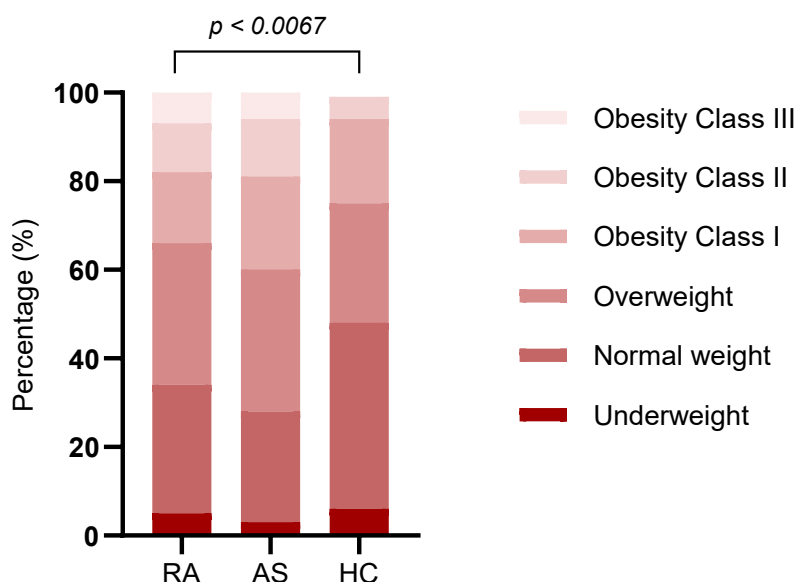


Figure 2. Distribution of RA, AS, and control groups based on BMI

Anti-CCP antibody levels were analyzed by age group and diagnosis to assess associations with demographic factors. In RA patients, anti-CCP levels increased with age, peaking in the 55–64 and ≥ 65 categories (ANOVA, $F = 9.34$, $p < 0.0001$), supporting the hypothesis that older age is associated with elevated autoantibody expression. In AS patients, elevated anti-CCP levels were observed primarily in females aged 35–44 (ANOVA, $F = 7.12$, $p = 0.0075$), suggesting a potential age- and sex-specific pattern despite anti-CCP not being a standard AS biomarker. These results are illustrated in Figure 3.

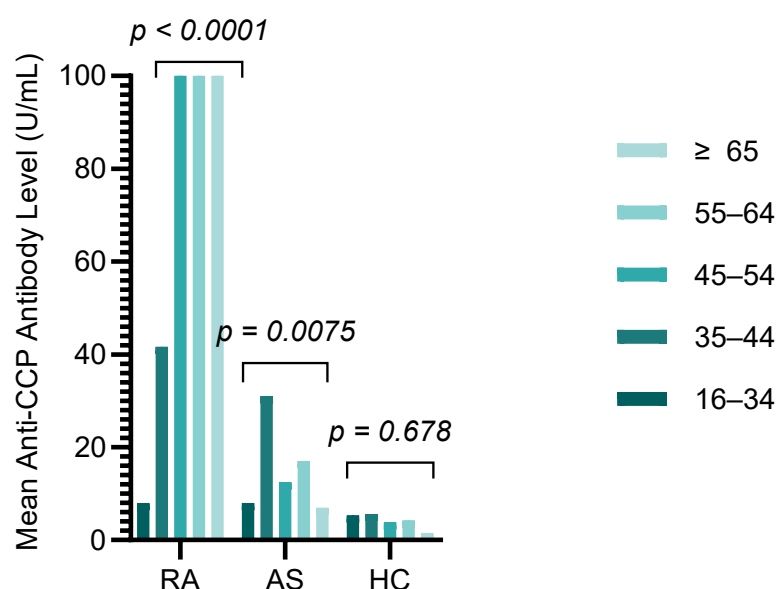


Figure 3. Anti-CCP antibody levels (U/mL) by age group across rheumatoid arthritis (RA), ankylosing spondylitis (AS), and healthy control (HC) cohorts.

Perceived stress was examined in relation to anti-CCP elevation. Among RA patients with elevated anti-CCP levels, 41% reported high stress, despite 81.7% of all RA patients having low CCP levels ($\chi^2 = 19.67$, $p < 0.0001$). In AS patients, 12% had elevated CCP levels, of whom 62.5% re-reported high stress ($\chi^2 = 8.52$, $p = 0.0034$). These findings indicate that psychological stress may act as a modifiable enhancer of citrullination in both RA and AS. Other lifestyle factors showed limited associations. Physical activity did not correlate with anti-CCP levels in either group ($p = 0.6415$), and smoking prevalence was low across cohorts as 85% were reported non-smokers. Overall, the results identify key demographic and modifiable factors-particularly age, sex, BMI, and perceived stress-that influence anti-CCP antibody levels. These associations provide a foundation for exploring behavioral and immunological interactions in autoimmune disease expression.

Conclusion

This study demonstrates that anti-cyclic citrullinated peptide (anti-CCP) antibodies remain a robust serological marker for rheumatoid arthritis (RA), with levels increasing particularly in older women and in patients with elevated BMI and high perceived stress. These findings highlight the significant interplay between metabolic and psychosocial factors in shaping systemic inflammation and autoantibody production. In ankylosing spondylitis (AS), anti-CCP elevation was rare and primarily observed in younger females reporting high stress, suggesting that psychological strain may act as a nonspecific enhancer of citrullination even outside classical RA pathology. This observation challenges the traditional view of anti-CCP as an RA-specific marker and underscores the potential role of stress-induced activation of peptidylarginine deiminase (PAD) enzymes in transient antibody production. Although smoking prevalence was low and physical activity did not directly correlate with anti-CCP levels in this cohort, these lifestyle factors remain clinically relevant as modulators of systemic inflammation and overall disease activity. The results emphasize the importance of assessing and addressing modifiable lifestyle determinants, particularly obesity and psychological stress, in personalized rheumatologic care. Future longitudinal and mechanistic studies are warranted to elucidate PAD regulation under stress, characterize tissue-specific citrullinated proteomes in AS, and evaluate interventions targeting obesity, psychosocial strain, and lifestyle factors to mitigate autoimmune disease progression. Collectively, these findings support integrating metabolic and psychosocial assessment into clinical management, enhancing both diagnostic precision and individualized therapeutic strategies for RA and AS.

Scientific Ethics Declaration

* The authors declare that the scientific ethical and legal responsibility of this article published in EPHELS journal belongs to the authors.

*All participants provided written informed consent, and the study was approved by the Institutional Ethics Committee of BAU International University Batumi (reference N-MED006). The authors declare that all procedures performed in this study were in accordance with the ethical standards.

Conflict of Interest

* The authors declare that they have no conflicts of interest

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Author(s) Information

Salome Abuladze

Avicenna – Batumi Medical University
Batumi, Tbeti st.4, Georgia
ORCID iD: <https://orcid.org/0009-0008-4869-4714>
*Contact e-mail: s.abuladze@abmu.edu.ge

Leila Akhvlediani

Batumi Shota Rustaveli State University
35 Ninoshvili Street / 32 Rustaveli Street, Georgia
ORCID iD: <https://orcid.org/0000-0002-7091-0187>

Neriman Tsintsadze

Batumi Shota Rustaveli State University
35 Ninoshvili Street / 32 Rustaveli Street, Georgia
ORCID iD: <https://orcid.org/0009-0000-8406-0446>

Marina Nagervadze

Batumi Shota Rustaveli State University
35 Ninoshvili Street / 32 Rustaveli Street, Georgia
ORCID iD: <https://orcid.org/0000-0002-5422-3192>

*Corresponding author(s) contact email

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Valorization of Selected Plant Raw Materials and Processing By-Products Commonly Found in Georgia Using Circular Economy Principles

Eteri Margalitadze

Avicenna Batumi Medical University
Batumi Shota Rustaveli State University

Khatuna Diasamidze

BAU International University Batumi
Batumi Shota Rustaveli State University

Iamze Kezheradze

Batumi Shota Rustaveli State University

Salome Gogitidze

Batumi Shota Rustaveli State University

Miranda Paksadze

Batumi Shota Rustaveli State University

Jeiran Putkaradze

Batumi Shota Rustaveli State University

Inga Kartsivadze

Batumi Shota Rustaveli State University

Ruslan Davitadze

Batumi Shota Rustaveli state university

Nona Surmanidze

Batumi Shota Rustaveli State University

Indira Jafaridze

Batumi Shota Rustaveli State University

Maia Vanidze

Batumi Shota Rustaveli State University

Aleko Kalandia

Batumi Shota Rustaveli State University

Abstract: The aim of the study was to investigate the chemical composition of several endemic plant species of Georgia, including *Prunus laurocerasus*, *Senecio platyphyllus*, *Rhododendron* L., *Juglans regia*, as well as residues generated during wine production from different grape varieties, using high-performance liquid chromatography coupled with various detection systems (UPLC-PDA-MS, Waters UPLC Acquity QDa). For each raw material, environmentally friendly (“green”) technologies were developed for the production of biologically

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active compound preparations using supercritical water extraction (SWE) with different cosolvents. The bioactive compound profiles of each raw material were investigated, and protocols for their identification and standardization based on active constituents were developed. The proposed technologies ensure not only the production of valuable preparations from the studied raw materials but also the almost complete valorization of production residues generated during processing. The antioxidant activities of the obtained preparations were evaluated, and correlations between antioxidant potential and the content of biologically active compounds were established.

Keywords: Plant raw materials; Production of bioactive preparations; UPLC-PDA-MS analysis

Introduction

Natural compounds have been widely used as biologically active components in the pharmaceutical and food industries. They have antimicrobial, antibacterial, antifungal, antiviral, and antitumor effects. Numerous studies have confirmed a proportional correlation between diet and disease. The issue of the use of artificial additives is especially acute. The medicinal and pharmaceutical properties of plant raw materials are mainly associated with secondary plant metabolites (Kashani et al., 2012; Ramawat & Mérillon, 2009). Naturally, plants produce these compounds because they are necessary for survival, although in many cases their physiological role remains unknown (Heinrich et al., 2012; Sarker & Nahar, 2006). The healing properties of secondary metabolites are frequently associated with waxes, fatty acids, alkaloids, terpenes, phenols, glycosides, phytosterols, and related compounds (Kashani et al., 2012; Sarker & Nahar, 2006).

The activity of phenolic compounds is of particular interest. Rosmarinic acid, carnosic acid, carnosol, rosmanol, epirosmanol, and methyl carnosate isolated from *Rosmarinus officinalis* exhibit antitumor activity (Sánchez-Camargo et al., 2014). Pharmacological studies of *Cordia verbenacea* have demonstrated anti-inflammatory activity due to α -caryophyllene and trans-caryophyllene (Parisotto et al., 2012). The biological activity of *Thymus vulgaris*, *Thymus hyemalis*, and *Thymus zygis* has been associated with thymol, carvacrol, and borneol (Santoyo et al., 2014). Likewise, *Salvia officinalis* possesses anti-inflammatory properties attributed to camphor, borneol, and 1,8-cineole (Arranz et al., 2014). Perillyl alcohol, a hydroxylated monoterpene identified in *Prunus avium*, has demonstrated activity against several progressive cancers (Serra et al., 2010). To obtain bioactive compounds, efficient extraction and recovery are required. This process generally consists of desorption and solubilization, internal diffusion through the solid matrix, and external diffusion through the boundary layer. Optimization of extraction depends on careful control of analytical conditions and sample preparation (Camel, 2001; Martínez, 2008; Barbosa-Cánovas et al., 2014).

Recent literature demonstrates increasing emphasis on green extraction technologies, including ultrasound-assisted extraction, subcritical water extraction, and supercritical fluid extraction (Herrero et al., 2006; Barbosa-Cánovas et al., 2014). Supercritical fluid extraction (SFE) offers several advantages over conventional extraction techniques, including improved transport properties, enhanced diffusivity, environmentally friendly solvents, and simplified coupling with chromatographic systems (Herrero et al., 2006). Carbon dioxide remains the most widely used supercritical solvent because it is inexpensive, non-toxic, and leaves no solvent residue after depressurization (Herrero et al., 2006; Zougagh et al., 2004; Solana et al., 2014). The addition of polar co-solvents can further improve extraction efficiency (Herrero et al., 2006; Barbosa-Cánovas et al., 2014). Bioactive compounds, also known as nutraceuticals, are naturally occurring substances with demonstrated biological activity and therapeutic potential (Lindy, 2014; Biesalski et al., 2009). Many of these metabolites function as defense compounds in plants while exhibiting pharmacological activity in humans (Colegate & Molyneux, 2011). Supercritical fluid technology has become increasingly important for obtaining compounds used in pharmaceuticals, foods, and cosmetics, as well as for developing novel treatments for diseases such as cancer, stroke, and Alzheimer's disease (Lindy, 2014; Sovilj et al., 2011).

Materials and Methods

Prior to chromatographic analysis, all extracts were concentrated under reduced pressure using a vacuum evaporator, followed by centrifugation and filtration through *Waters Acrodisc LC PVDF syringe filters* (13 mm, 0.45 μ m). Qualitative identification and quantitative determination of the target compounds were carried out using a *Waters ACQUITY UPLC* system equipped with a photodiode array detector (PDA) and a single quadrupole mass spectrometer (QDa) operating with an electrospray ionization (ESI) source. Chromatographic separation was performed on an *ACQUITY BEH C18* column (2.1 $\times$ 100 mm, 1.7 μ m). The mobile phase consisted of 0.1%

formic acid in water (solvent A) and acetonitrile (solvent B). Elution was achieved using the following gradient program: 0–2.0 min, 5% B; 2.0–8.0 min, 20% B; 8.0–10.0 min, 35% B; 10.0–11.0 min, 95% B; 12.0 min, 5% B; and maintained at 5% B until 15.0 min. The flow rate was set at 0.3 mL min⁻¹, the injection volume was 2 µL, and the column temperature was maintained at 40°C. Mass spectrometric detection was performed in the negative electrospray ionization mode (ESI⁻). The operating conditions were as follows: capillary voltage, 0.8 kV; cone voltage, 15 V; source temperature, 120°C; and desolvation temperature, 500°C. Data acquisition was conducted in selected ion recording (SIR) mode over an *m/z* range of 100–1000.

Different extraction techniques and solvent systems were applied to evaluate the content of biologically active compounds. Frozen green walnut husks (*Juglans regia* L.) were extracted using 30%, 40%, and 50% aqueous ethanol by ultrasonic bath-assisted extraction, ultrasonic probe-assisted extraction, and hot reflux extraction. For *Rhododendron ponticum* L. and *Rhododendron luteum* Sweet, 20% aqueous ethanol was used as the extraction solvent, while ultrasonic bath and ultrasonic probe extraction were employed. Each sample was extracted in triplicate. The resulting extracts were analyzed for total phenolic content, total flavonoid content, total catechin content, and antioxidant activity. Quantitative measurements were performed using spectrophotometric methods.

Determination of Total Phenolic Content

The total phenolic content (TPC) was determined using the Folin–Ciocalteu colorimetric assay. Briefly, 1 mL of the ethanolic extract was mixed with 5 mL of distilled water and 1 mL of Folin–Ciocalteu reagent. After incubation for 5 min, 10 mL of sodium carbonate (Na₂CO₃) solution was added. The reaction mixture was diluted to a final volume of 25 mL with distilled water and incubated for 2 h in the dark. A blank solution containing all reagents except the sample extract was prepared under identical conditions. Following incubation, the absorbance was measured at 750 nm using a spectrophotometer. The total phenolic content was quantified using a gallic acid calibration curve and calculated according to the following equation:

$$X = (Y \times V \times F \times 1000) / m$$

Determination of Total Flavonoid Content

The total flavonoid content (TFC) was determined using the aluminum chloride colorimetric method. Briefly, 1 mL of the ethanolic extract was transferred into a 10 mL volumetric flask containing 5 mL of distilled water and 0.3 mL of 5% sodium nitrite (NaNO₂). After 5 min, 0.3 mL of 10% aluminum chloride (AlCl₃) solution was added. Following an additional 6 min of incubation, 2 mL of 1 N sodium hydroxide (NaOH) was introduced into the reaction mixture. The absorbance was measured at 510 nm. A blank prepared with the corresponding ethanol solution instead of the sample extract was analyzed under identical conditions. The total flavonoid content was quantified using a rutin calibration curve.

Determination of Total Catechin Content

The total catechin content was determined using the vanillin assay. For the analysis, 1 mL of the sample extract was mixed with 3 mL of freshly prepared vanillin reagent, obtained by dissolving 1 g of vanillin in 100 mL of concentrated hydrochloric acid. The blank solution consisted of the vanillin reagent and the corresponding extraction solvent. After 3 min of incubation, the absorbance was recorded at 500 nm.

Determination of Antioxidant Activity

The antioxidant activity of the extracts was evaluated using the DPPH (2,2-diphenyl-1-picrylhydrazyl) free radical scavenging assay, one of the most widely applied spectrophotometric methods for assessing the antioxidant capacity of natural products. For the assay, 1 mL of the ethanolic extract was mixed with 3 mL of DPPH ethanolic solution and incubated in the dark for 30 min at room temperature. The absorbance was subsequently measured at 515 nm. A control solution containing DPPH and the corresponding extraction solvent was prepared under identical conditions. The free radical scavenging activity was expressed as the percentage inhibition of DPPH radicals.

Results and Discussion

The analysis of *walnut green husk* extracts demonstrated that the highest levels of biologically active compounds were obtained by conventional extraction using 50% ethanol as the extraction solvent. Under these conditions, the total phenolic content reached 18.47 and 20.21 mg/g, while the total flavonoid content was 12.78 mg/g. The highest catechin content was also observed in the same extract, reaching 0.66 mg/g. Ultrasonic probe-assisted extraction produced comparable results; however, the obtained values were slightly lower than those achieved by the conventional extraction method.

The antioxidant activity assay also confirmed the effectiveness of conventional extraction with 50% ethanol. Extracts obtained from both walnut forms exhibited the highest antioxidant activity, with 50% inhibition of DPPH radicals achieved by 12.92 and 14.28 mg of sample, respectively. A comparative evaluation of the two walnut forms revealed no substantial differences in the content of the investigated bioactive compounds or their antioxidant capacity. In addition, a positive correlation was observed between total phenolic content and antioxidant activity, suggesting that phenolic compounds are the major contributors to the antioxidant potential of walnut green husk extracts. The extracts of *Rhododendron ponticum* L. and *Rhododendron luteum* Sweet were evaluated for their total phenolic, flavonoid, and catechin contents, as well as their antioxidant activity using the DPPH radical scavenging assay.

The results demonstrated that the highest concentrations of bioactive compounds were consistently obtained in the first extract (Extract I), whereas their contents gradually decreased in the subsequent extraction cycles. A similar trend was observed for antioxidant activity, as progressively larger amounts of extract were required to achieve 50% DPPH radical inhibition, indicating a reduction in antioxidant capacity. Among the *R. ponticum* samples, the ultrasonic probe-assisted extract from the Machakhela population exhibited the highest total phenolic content (120.98 mg/g). This extract also showed the highest catechin content (19.68 mg/g), while only 2.67 mg of sample was required to achieve 50% DPPH inhibition, demonstrating its strong antioxidant potential.

Comparison of the extraction techniques revealed that ultrasonic probe-assisted extraction was more effective than ultrasonic bath extraction for the Machakhela samples. The total phenolic content reached 120.98 mg/g in the probe-assisted extract, compared with 100.58 mg/g in the ultrasonic bath extract. Accordingly, the probe-assisted extracts also exhibited superior antioxidant activity. In contrast, *R. luteum* extracts contained lower amounts of total phenolics, flavonoids, and catechins than *R. ponticum*. Nevertheless, the first extract showed the highest antioxidant activity, requiring only 0.54 mg of sample to achieve 50% DPPH radical inhibition. This finding suggests that antioxidant activity depends not only on the overall concentration of phenolic compounds but also on their qualitative composition. Furthermore, a positive correlation was observed between the contents of phenolic compounds, flavonoids, and catechins and the antioxidant activity of the extracts. Extracts enriched with these bioactive constituents exhibited greater free radical scavenging capacity, highlighting the important contribution of phenolic compounds to the antioxidant potential of *Rhododendron* extracts.

For the quantitative assessment of biologically active compounds, various extraction methods and solvents were applied. In the case of frozen green walnut husk (*Juglans regia*), extraction was performed using 30%, 40%, and 50% ethanol through three different approaches: ultrasonic bath-assisted extraction, ultrasonic probe-assisted extraction, and conventional hot extraction using a reflux condenser. For *Rhododendron ponticum* L. and *Rhododendron luteum* Sweet samples, 20% ethanol was used as the extraction solvent, and extraction was carried out using an ultrasonic bath and an ultrasonic probe. All samples underwent three consecutive extraction cycles. The obtained extracts were analyzed for the content of total phenolic compounds, flavonoids, and catechins, and their antioxidant activity was evaluated. Quantitative determination of these parameters was performed using spectroscopic methods.

The analysis of walnut green husk extracts demonstrated that the highest content of biologically active compounds was achieved using conventional extraction with 50% ethanol. In extracts obtained by this method, the total phenolic content reached 18.47 and 20.21 mg/g, while the total flavonoid content was 12.78 mg/g. The maximum catechin concentration was also observed under the same extraction conditions and amounted to 0.66 mg/g. High values were also obtained using ultrasonic probe-assisted extraction; however, these results were slightly lower compared with conventional extraction. The evaluation of antioxidant activity further confirmed the superiority of conventional extraction with 50% ethanol. Both studied forms of walnut extracts exhibited high free radical scavenging capacity, while the amount of extract required to achieve 50% inhibition of DPPH radicals was 12.92 and 14.28 mg, respectively.

Within the framework of the study, two different morphological forms of walnut were compared. According to the obtained results, no significant differences were observed between them in terms of biologically active compound content and antioxidant activity. Furthermore, a positive correlation was established between total

phenolic content and antioxidant activity, indicating the important role of phenolic compounds in determining the antioxidant properties of walnut extracts. The study also evaluated the content of total phenolic compounds, flavonoids, and catechins in extracts of *Rhododendron ponticum* L. and *Rhododendron luteum* Sweet, as well as their antioxidant activity using the DPPH assay.

The results demonstrated that in both species, the highest levels of biologically active compounds were detected in the first extract (Extract I), while their concentrations gradually decreased with each subsequent extraction cycle. A similar trend was observed in the assessment of antioxidant activity. As the content of biologically active compounds decreased, the amount of sample required to achieve 50% inhibition of DPPH radicals increased, indicating a reduction in antioxidant efficiency. Among the *Rhododendron ponticum* samples, the highest total phenolic content was detected in the ultrasonic probe-assisted extract obtained from the Machakhela population, reaching 120.98 mg/g. The same extract contained 19.68 mg/g catechins, and 50% inhibition of DPPH radicals was achieved using only 2.67 mg of extract, indicating its high antioxidant activity.

Comparison of Machakhela samples showed that ultrasonic probe-assisted extraction was more efficient than ultrasonic bath extraction. Specifically, the total phenolic content in the probe-assisted extract was 120.98 mg/g, whereas in the ultrasonic bath extract it was 100.58 mg/g. Accordingly, probe-assisted extracts also demonstrated higher antioxidant activity. The content of total phenolics, flavonoids, and catechins in *Rhododendron luteum* extracts was lower compared with *R. ponticum*. Nevertheless, the first extract exhibited the highest antioxidant activity, as only 0.54 mg of sample was required to achieve 50% DPPH inhibition. This result indicates that antioxidant activity is determined not only by the total amount of phenolic compounds but also by their qualitative composition. Analysis of the results also revealed positive correlations between the contents of total phenolic compounds, flavonoids, and catechins and antioxidant activity. Extracts rich in biologically active compounds demonstrated stronger free radical scavenging capacity, confirming the significant role of phenolic compounds in the formation of the antioxidant potential of *Rhododendron* extracts.

The distribution of bioactive compounds among different fractions of *Prunus laurocerasus* demonstrates the significant potential of processing residues as a valuable source of phytochemicals. The total phenolic content, flavonoids, catechins, leucoanthocyanins, and anthocyanins were evaluated in pulp, juice, and pomace fractions. Although the juice contained considerable amounts of soluble phenolic compounds, the pomace exhibited a remarkable accumulation of several biologically important metabolites, highlighting its potential for valorization. The most pronounced difference was observed for *anthocyanins*, which are among the most valuable secondary metabolites due to their antioxidant, anti-inflammatory, and cytoprotective properties. The pomace contained 11.39 mg/g dry weight of total anthocyanins, compared with only 1.35 mg/g in juice, demonstrating an approximately 8-fold enrichment of anthocyanins in the processing residue [Figure 1.].

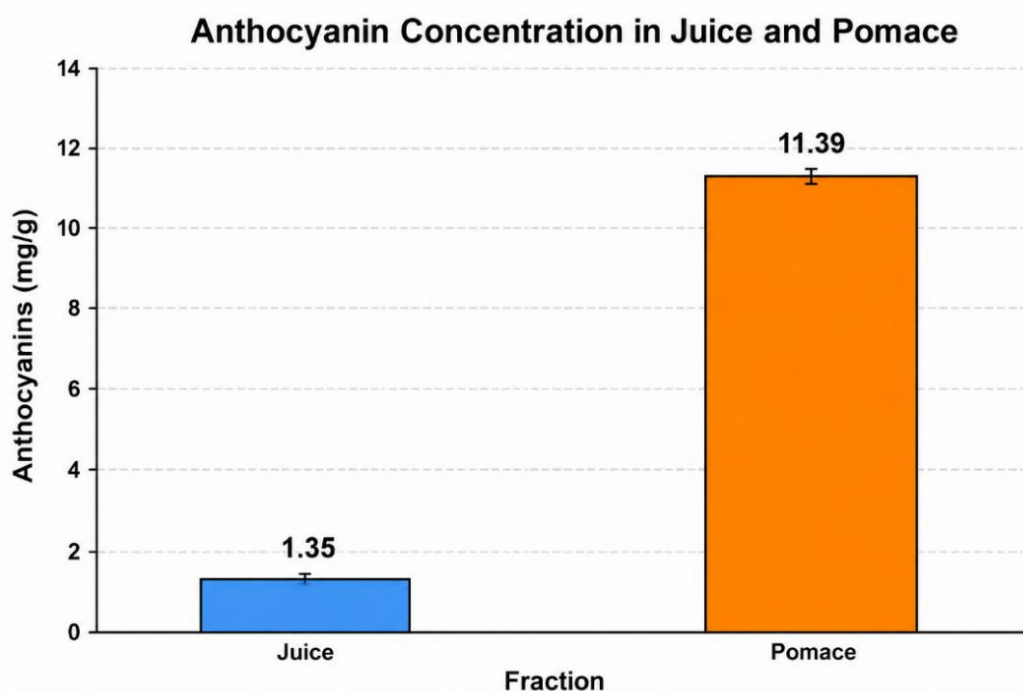


Figure 1. Comparison of anthocyanin concentration in juice and pomace of *P. laurocerasus*

Moreover, mass balance analysis revealed that approximately 90% of total anthocyanins generated during processing remained concentrated in the pomace, while only 10% was recovered in the juice fraction. This confirms that *P. laurocerasus* pomace represents the primary reservoir of anthocyanin compounds. A similar tendency was observed for *leucoanthocyanins*, with pomace containing the highest concentration (15.693 mg/g) and retaining approximately 66% of the total *leucoanthocyanin* content after juice extraction. Catechins were also preferentially accumulated in the pomace, where their content exceeded that of the juice fraction. These findings indicate that mechanical processing does not eliminate the biological value of *P. laurocerasus* residues; instead, it results in the concentration of specific bioactive constituents within the solid fraction.

Antioxidant activity, determined by the DPPH radical scavenging assay (expressed as the amount of sample required to achieve 50% inhibition; lower values indicate stronger antioxidant activity), was highest in the pomace fraction (2.796 mg), followed by the pulp (3.315 mg), whereas the juice exhibited the lowest antioxidant activity (10.666 mg). This pattern is consistent with the higher concentrations of anthocyanins and proanthocyanidins retained in the pomace, both of which are recognized as potent free radical scavengers [Figure 2].

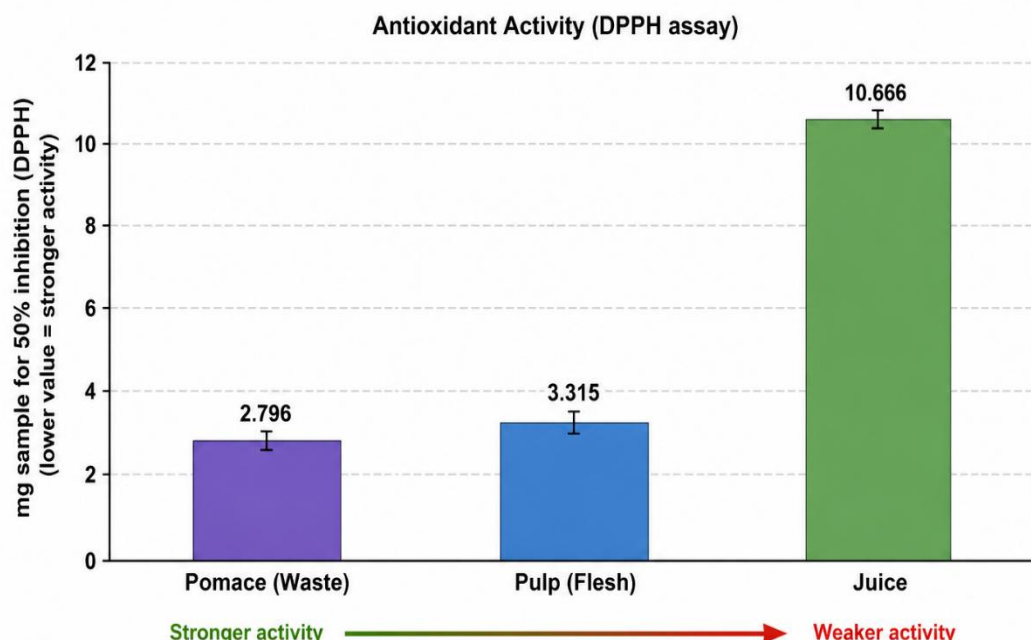


Figure 2. Antioxidant activity of *Prunus laurocerasus* fractions determined by the DPPH assay.

Considering that *Prunus laurocerasus* pomace is traditionally regarded as an agricultural by-product, the demonstrated enrichment of phenolic compounds, particularly anthocyanins, provides strong evidence for its transformation into a high-value raw material.

Conclusion

Our study demonstrated that the extraction efficiency of biologically active compounds is strongly influenced by both the extraction technique and the physicochemical characteristics of the plant material. A particularly important outcome of this study is the substantial phytochemical value retained in agro-industrial processing residues. The analysis of *Prunus laurocerasus* fractions demonstrated that pomace is not merely a waste stream but a highly enriched source of valuable secondary metabolites. Approximately 90% of the total anthocyanins remained concentrated in the pomace after juice production, while elevated levels of leucoanthocyanins and catechins were also retained in the solid residue. These findings clearly show that processing by-products can preserve, and in some cases concentrate, compounds of high functional and commercial value rather than representing a loss of useful biomass.

Collectively, these results support the valorization of agro-industrial by-products such as pomace, fruit peels, skins, green husks, seeds, and other residual plant materials as sustainable sources of high-value phytochemicals. Instead of being discarded as waste, these materials can be redirected into the production of natural antioxidants, functional food ingredients, nutraceuticals, cosmetic formulations, and pharmaceutical preparations. Such an approach is fully aligned with circular economy principles, as it promotes resource efficiency, waste minimization,

and the creation of added value from materials that are already generated within existing agricultural and food-processing chains in Georgia.

Overall, this work demonstrates that the optimization of extraction technologies, combined with the comprehensive utilization of plant raw materials and processing residues, represents a promising strategy for maximizing the recovery of bioactive compounds and advancing the sustainable exploitation of Georgia's botanical resources. Future studies should focus on process scale-up, bioavailability, biological efficacy, and industrial implementation of these valorization strategies in order to support their translation into commercially viable and environmentally responsible products.

Scientific Ethics Declaration

* The authors declare that the scientific ethical and legal responsibility of this article published in EPHELS journal belongs to the authors.

Conflict of Interest

* The authors declare that they have no conflicts of interest

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Author(s) Information	
Eteri Margalitadze Avicenna Batumi Medical University, Batumi, Georgia Batumi Shota Rustaveli State University, Batumi, Georgia ORCID iD: https://orcid.org/0009-0007-3546-2482 *Contact e-mail: eter.margalitadze@bsu.edu.ge	Khatuna Diasamidze BAU International University Batumi, Batumi, Georgia Batumi Shota Rustaveli State University, Batumi, Georgia ORCID iD: https://orcid.org/0009-0009-6085-1695
Iamze Khezheradze Batumi Shota Rustaveli State University, Batumi, Georgia ORCID iD: https://orcid.org/0009-0005-7365-4501	Salome Gogitidze Batumi Shota Rustaveli State University, Batumi, Georgia ORCID iD: https://orcid.org/0009-0006-3690-8485
Miranda Paksadze Batumi Shota Rustaveli State University, Batumi, Georgia ORCID iD: https://orcid.org/0009-0000-4395-0362	Jeiran Putkaradze Batumi Shota Rustaveli State University, Batumi, Georgia ORCID iD: https://orcid.org/0009-0006-2566-6038
Inga Kartsivadze Batumi Shota Rustaveli State University, Batumi, Georgia ORCID iD: https://orcid.org/0009-0007-4254-0717	Ruslan Davitadze Batumi Shota Rustaveli State University, Batumi, Georgia ORCID iD: https://orcid.org/0000-0002-2873-5186
Nona Surmanidze Batumi Shota Rustaveli State University, Batumi, Georgia ORCID iD: https://orcid.org/0000-0002-9044-9121	Indira Jafaridze Batumi Shota Rustaveli State University, Batumi, Georgia ORCID iD: https://orcid.org/0000-0003-2088-212X
Maia Vanidze Batumi Shota Rustaveli State University, Batumi, Georgia ORCID iD: https://orcid.org/0000-0003-0807-0735	Aleko Kalandia Batumi Shota Rustaveli State University, Batumi, Georgia ORCID iD: https://orcid.org/0000-0001-9570-9263

*Corresponding author(s) contact email

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The Impact of Modern Dietary Patterns on Structural and Functional Changes in the Digestive System

Rusudan Vadachkoria

Batumi Shota Rustaveli State University

Parvathy Narayan

Batumi Shota Rustaveli State University

Abstract: For millions of years, the human gut evolved with fiber-rich, plant-based, and natural diets. This close relationship with unprocessed food sources helped build a strong and diverse gut microbiome that supported efficient digestion, stable metabolism, and a balanced immune system. The fibrous and complex carbohydrates present in ancestral diets made the gastrointestinal system resilient and adaptable to environmental challenges (Tannock, 2024). However, in the modern era, this evolutionary relationship has been hampered by the dominance of ultra-processed foods—high in refined sugars, saturated fats, and chemical additives, yet low in fiber and nutritional diversity. These foods have altered the internal ecosystem of the human gut, speeding up digestion and disturbing metabolic stability (Fu et al., 2022). As a result, the normal function of the gastrointestinal system is increasingly compromised, leading to a decline in microbial diversity (Moles & Otaegui, 2020). Modern dietary habits are now believed to be pushing the human gut toward a new evolutionary direction—one marked more by disease than resilience. This disruption has contributed to anatomical and physiological changes within the gut, which are closely linked to the rise of chronic disorders such as inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), obesity, type 2 diabetes, and autoimmune conditions (Oliver et al., 2021). This paper explores how the transition from traditional, fiber-rich diets to highly processed Western diets has influenced the evolution of the human gastrointestinal system. It also examines how modern food processing and nutrient composition have reshaped the gut microbiota, immune responses, and digestive health. By understanding this evolutionary and nutritional shift, the study sheds light on the importance of restoring dietary diversity and fiber intake to rebuild microbial balance, enhance gut function, and reduce the risk of modern gastrointestinal and metabolic diseases.

Keywords: Gut microbiota, Ultra processed food, Dietary evolution, Gastrointestinal health

Introduction

The human gastrointestinal system has undergone extensive evolutionary adaptation, shaped largely by long-standing dietary patterns rich in diverse plant-based foods and dietary fiber. For millennia, ancestral human diets consisted predominantly of minimally processed, fiber-dense plant matter, which played a fundamental role in establishing and maintaining a resilient and diverse gut microbiota. These microbial communities, particularly those residing in the colon, co-evolved with the host and became optimized for the fermentation of complex carbohydrates and polysaccharides (Fu et al., 2022). This symbiotic relationship enabled the efficient production of short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, which are critical for maintaining intestinal integrity, modulating immune responses, and supporting overall metabolic health (Lachmansingh et al., 2024). In contrast, contemporary dietary patterns—often characterized as Westernized diets—have diverged significantly from these ancestral norms. Modern diets are typically high in refined sugars, saturated fats, and ultra-processed foods, while being markedly deficient in dietary fiber. This nutritional transition has contributed to a measurable decline in gut microbiome diversity, a condition frequently associated with dysbiosis, defined as

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the disruption or imbalance of the normal microbial community (Hrncir, 2022). The reduced intake of fermentable substrates limits microbial fermentation processes in the colon, thereby diminishing SCFA production and impairing key physiological functions linked to gut health (Vinelli et al., 2022).

Dietary fiber plays a pivotal role in sustaining gastrointestinal function and microbial ecology. Fermentable fibers resist digestion in the upper gastrointestinal tract and reach the colon intact, where they serve as essential substrates for beneficial bacteria. Through fermentation, these fibers promote the growth of commensal microbial species and enhance metabolic activity within the gut ecosystem. Additionally, non-fermentable fibers contribute to gastrointestinal motility by increasing fecal bulk and facilitating peristalsis, thereby supporting efficient digestion and preventing metabolic disturbances such as rapid glycemic fluctuations (Slavin, 2013).

The absence or insufficiency of dietary fiber has significant implications for host health. A fiber-deficient diet deprives gut microbiota of necessary nutrients, leading to reduced microbial diversity, compromised gut barrier function, and altered immune regulation (Fu et al., 2022). These changes have been linked to an increased risk of metabolic disorders, inflammatory conditions, and other chronic diseases. Furthermore, the disruption of microbial fermentation processes may reduce the bioavailability of essential nutrients and impair host–microbe interactions that are critical for maintaining physiological homeostasis.

Given these considerations, the primary objective of dietary management in modern populations is to restore and sustain optimal gut health by promoting a diverse and resilient microbiome (Hrncir, 2022). Reintegrating fiber-rich, plant-based foods into daily dietary practices represents a key strategy in mitigating dysbiosis and enhancing gastrointestinal and systemic health. This study aims to examine the impact of dietary fiber on gut microbiota composition and function, with particular emphasis on its role in maintaining microbial diversity, supporting SCFA production, and preventing diet-related health complications.

Main Body

Evolutionary Mismatch: The Decline of Fiber and Its Impact on Gut Function and Microbial Ecology

From an evolutionary perspective, the human gastrointestinal system is fundamentally adapted to a diet abundant in complex plant fibers and indigestible polysaccharides. For the majority of human history, dietary intake consisted of high-residue, fiber-rich foods that were not fully digested in the upper gastrointestinal tract. Instead, these fermentable fibers reached the large intestine intact, where they served as the primary substrate for gut microbiota (Slavin, 2013). This long-standing dietary pattern fostered a mutually beneficial relationship between host and microbes, enabling efficient fermentation processes and the sustained production of short-chain fatty acids (SCFAs), particularly butyrate, which are essential for maintaining intestinal health and metabolic homeostasis (Vinelli et al., 2022).

In contrast, the modern shift toward low-residue, fiber-deficient diets represents a significant evolutionary mismatch. Unlike ancestral diets, contemporary food patterns are characterized by highly refined and rapidly digestible carbohydrates that are absorbed early in the digestive process. This results in accelerated gastric emptying and rapid glucose absorption, leading to pronounced fluctuations in blood sugar levels and increased risk of insulin resistance. Furthermore, the absence of indigestible plant components—such as seeds, skins, and structural fibers—reduces the bulk of intestinal contents. This diminishes mechanical stimulation of the gut wall, weakens peristaltic activity, and contributes to gastrointestinal disturbances such as constipation, bloating, and increased intraluminal pressure within the colon (Liang et al., 2023).

The evolutionary consequences extend beyond mechanical digestion to the ecological stability of the gut microbiome (Gomez et al., 2019). Fiber-rich diets historically provided a continuous supply of fermentable substrates necessary for sustaining diverse microbial populations. In the absence of dietary fiber, beneficial gut bacteria are deprived of their primary energy source, leading to reduced microbial diversity and functional capacity. This decline disrupts the fermentation of complex carbohydrates and significantly lowers the production of SCFAs. As a result, colonocytes—cells lining the colon that depend on SCFAs for energy—experience nutritional deprivation, compromising the integrity of the gut barrier (Fu et al., 2022).

The reduction in SCFA availability has profound physiological implications. A weakened gut barrier increases intestinal permeability, often referred to as “leaky gut,” allowing toxins and microbial components to translocate into the bloodstream. This process can trigger systemic inflammation and has been associated with the development of metabolic and inflammatory disorders, including obesity, type 2 diabetes, and colorectal diseases.

Additionally, the diminished fermentation activity reduces the microbiota's ability to enhance nutrient bioavailability and regulate immune function, further exacerbating health risks (Desai et al., 2016).

Thus, the transition from an ancestral, fiber-rich diet to a modern low-residue dietary pattern not only impairs digestive efficiency but also destabilizes the intricate host–microbe ecosystem that has evolved over millennia. The loss of dietary fiber effectively initiates a cascade of mechanical, biochemical, and microbial dysfunctions, highlighting the critical role of fiber in maintaining both gut integrity and overall health (Desai et al., 2016).

Due to the reduction in dietary fiber, there is a significant overgrowth of harmful and opportunistic bacteria within the gut. As beneficial bacteria decline from lack of fermentable substrates, opportunistic species—often inflammatory in nature—begin to expand and dominate the microbial environment. These microbes adapt by feeding on readily available energy sources such as simple sugars, dietary fats, and even the mucus lining of the gut wall. In the process, some of these bacteria produce harmful compounds, including endotoxins such as lipopolysaccharides, which can trigger inflammatory responses (Fu et al., 2022). This microbial imbalance is referred to as dysbiosis, characterized by a disrupted and unhealthy gut ecosystem. Furthermore, in the absence of dietary fiber, bacteria increasingly turn to the gut's protective mucus layer as an alternative nutrient source, leading to its gradual erosion. As this mucus barrier thins, the integrity of the gut lining is compromised, resulting in increased intestinal permeability, commonly known as leaky gut. Consequently, harmful substances, toxins, and microbial components are able to cross into the bloodstream, promoting systemic inflammation and contributing to the development of various chronic diseases (Martinez et al., 2017).

Impact of Westernized Diets on Gut Microbiome and Intestinal Integrity

The Westernized diet, characterized by low dietary fiber and high consumption of refined carbohydrates, saturated fats, and processed foods, has led to a marked regression in gut microbiome diversity and function. The shift from fiber-rich to fiber-depleted diets has significantly altered microbial metabolism, reducing the production of short-chain fatty acids (SCFAs) and favoring the generation of long-chain fatty acids. SCFAs, such as butyrate, serve as a vital energy source for colonocytes and help maintain the structural integrity of the intestinal epithelium. Their depletion results in reduced energy availability to gut lining cells, leading to thinning of the epithelial barrier and increased intestinal permeability, commonly known as “leaky gut.” (Kang et al., 2022). This compromised barrier permits translocation of microbial components such as lipopolysaccharides (LPS) and other toxins into the bloodstream, triggering systemic inflammation. Chronic low-grade inflammation resulting from this process is strongly associated with the development of metabolic and inflammatory diseases, including obesity, insulin resistance, type 2 diabetes, and colorectal cancer (Martinez et al., 2017).

Furthermore, low-residue diets—those deficient in indigestible plant materials such as seeds, skins, and structural fibers—reduce the mechanical stimulation necessary for normal gut motility. As a consequence, gastrointestinal transit becomes sluggish, leading to constipation, bloating, and increased intraluminal pressure. Fiber normally slows glucose absorption and moderates postprandial glycemic responses. However, in the absence of sufficient fiber, food is absorbed rapidly, resulting in sharp glucose spikes and increased insulin secretion. Chronic exposure to these metabolic fluctuations contributes to insulin resistance and, over time, the onset of obesity and type 2 diabetes (Oliver et al., 2021).

Mechanically, a low-residue diet weakens intestinal muscle tone; biologically, it decreases microbial diversity and metabolic activity; and chemically, it limits the synthesis of beneficial SCFAs. The absence of fermentable fibers effectively starves beneficial gut bacteria, which depend on complex plant polysaccharides as their primary energy source. When deprived of these substrates, beneficial bacteria die off within days or weeks, leading to a significant reduction in microbial diversity. This imbalance facilitates the overgrowth of opportunistic or pathogenic species that thrive on simple sugars, fats, and even host-derived mucus. These harmful microbes can release inflammatory compounds, including endotoxins and LPS, which further exacerbate gut inflammation and promote dysbiosis—a state of microbial imbalance within the intestinal ecosystem (Oliver et al., 2021).

In the absence of adequate dietary fiber, gut microbes seek alternative nutrient sources, often degrading the protective mucus layer that lines the intestinal wall. This erosion of the mucus barrier exacerbates gut permeability and increases exposure of epithelial cells to harmful substances. The resulting condition, commonly termed “leaky gut syndrome,” allows antigens, toxins, and bacteria to cross into systemic circulation, intensifying immune activation (Usuda et al., 2021).

The gut microbiome also plays a critical role in training and modulating the host immune system. A reduction in microbial diversity and the dominance of pathogenic species can lead to immune dysregulation, where immune cells become hyperreactive and prone to misidentifying self-tissues as threats (Sun et al., 2021). This dysregulated immune response contributes to chronic low-grade inflammation and has been linked to a range of disorders, including irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), obesity, type 2 diabetes, and various autoimmune and allergic conditions (Liang et al., 2023).

In summary, the Westernized, low-fiber diet profoundly disrupts gut microbial ecology and intestinal physiology. The resulting loss of beneficial microbes, depletion of SCFAs, and erosion of the mucosal barrier collectively contribute to metabolic, inflammatory, and immune-mediated diseases. Preservation of gut health thus requires restoring dietary fiber intake to support microbial diversity, maintain epithelial integrity, and promote systemic metabolic balance (Vinelli et al., 2022).

From Foraging to Processing: How Food Diversity Reshaped the Human Gut

In recent years, modern nutritional science has increasingly emphasized not only the quantity of food intake but also the diversity and quality of foods consumed as critical determinants of gastrointestinal health. From an evolutionary standpoint, the human digestive system developed in response to a wide variety of natural, minimally processed foods. This diversity required the gastrointestinal tract to function as a highly adaptable system, capable of handling different physical structures, chemical compositions, and nutrient profiles. Consequently, both the physiological processes and anatomical features of the gut were shaped by the need to efficiently digest and extract nutrients from a broad spectrum of dietary sources (Carmody et al., 2021).

However, with the advent of modern food processing techniques—such as cooking, juicing, refining, and preservation—the physical and chemical properties of food have been significantly altered. These processes often reduce structural complexity, modify nutrient composition, and, in some cases, decrease fiber content. As a result, the digestive demands placed on the gastrointestinal system have changed. Processed foods are generally easier and faster to digest, requiring less mechanical breakdown and enzymatic activity compared to whole, unprocessed foods. Over time, such dietary shifts may influence gut motility, enzyme secretion, and even the structural and functional dynamics of the gastrointestinal tract (Vadatchkoria & Narayan, 2025).

Moreover, the variety of foods consumed plays a crucial role in shaping digestive mechanisms and microbial diversity. Different types of food substrates interact uniquely with the gastrointestinal system, influencing not only digestion and absorption but also the composition and metabolic activity of the gut microbiota. A diverse diet supports a wider range of microbial species, enhancing the overall functional capacity of the gut ecosystem. In contrast, limited dietary variation may reduce microbial diversity and restrict the adaptive potential of the gastrointestinal system (Vadatchkoria & Narayan, 2025).

To better understand how different dietary patterns influence gut function and microbial composition, modern research utilizes experimental approaches such as fecal inoculum models. These methods allow scientists to study the interactions between diet, microbiota, and host physiology under controlled conditions. Through such approaches, it becomes possible to investigate how variations in food type, processing, and diversity can modulate digestive processes and contribute to both the evolution and the ongoing adaptation of the human gastrointestinal system (McBurney & Thompson, 1987).

Diversity Lost: The Dietary Roots of Gut Disorders

Dietary diversity has long been recognized as a key factor in shaping the structural and anatomical integrity of the gastrointestinal system. A varied, fiber-rich diet supports optimal gut function by maintaining stool bulk, promoting efficient motility, and sustaining a balanced microbial ecosystem. However, a significant regression in dietary diversity—largely driven by the increased consumption of low-residue, fiber-deficient foods—has been associated with a wide spectrum of gastrointestinal disorders (Fu et al., 2022).

At the functional level, reduced fiber intake leads to decreased stool bulk and impaired intestinal motility, resulting in harder stools and increased straining during defecation (Oliver et al., 2021). This contributes to the development of common conditions such as constipation and hemorrhoids. Over time, chronic mechanical stress and elevated intraluminal pressure within the colon may lead to structural abnormalities, including diverticulosis, characterized

by the formation of outpouchings or herniations in the colonic wall. These conditions reflect not only functional impairment but also long-term anatomical consequences of inadequate dietary patterns (Martinez et al., 2017).

Beyond mechanical effects, the decline in dietary diversity significantly impacts the gut microbiome and its interaction with the host immune system. The gut microbiota plays a crucial role in training and regulating immune responses. When dietary diversity decreases and fiber intake is insufficient, beneficial microbial populations decline, allowing harmful or opportunistic bacteria to dominate. This imbalance can lead to immune dysregulation, where immune cells become overactive or improperly regulated (Desai et al., 2016).

Such immune disturbances often manifest as chronic low-grade inflammation, a key underlying factor in a range of diseases. These include gastrointestinal conditions such as irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD), as well as systemic disorders like obesity, type 2 diabetes, and various autoimmune and allergic conditions. Thus, the shift away from diverse, fiber-rich diets not only compromises gastrointestinal structure and function but also disrupts immune homeostasis, highlighting the far-reaching health consequences of modern dietary patterns (Heiman & Greenway, 2016). A low-fiber diet is strongly linked to a range of gastrointestinal disorders because fiber plays a central role in stool formation, bowel movement, and overall gut health.

When dietary fiber is low, the body produces smaller, harder stools. This leads to slower transit through the colon and increased pressure inside the intestinal walls. Over time, this repeated strain becomes a key factor in conditions like constipation and hemorrhoids. Hard stools require more force to pass, which can cause swollen veins around the rectum (hemorrhoids) and difficulty in regular bowel emptying (Heiman & Greenway, 2016). One of the most important conditions connected to low fiber intake is **Diverticulosis**. In a fiber-deficient diet, stools become compact and difficult to pass, increasing internal pressure within the colon. This pressure can cause weak points in the colon wall to bulge outward, forming small pouches called diverticula. These outpouchings are essentially structural changes caused by long-term strain and pressure from hard, low-volume stools. When these pouches become inflamed or infected, the condition can progress to **Diverticulitis**, which is more serious. In addition, low fiber intake disrupts normal bowel motility, which can contribute to disorders like **Irritable Bowel Syndrome** and worsen symptoms in other gastrointestinal conditions. A lack of fiber also reduces stool bulk, which slows intestinal movement and increases toxin exposure time within the colon (Liang et al., 2023).

Decoding Your Gut: How Science Tailors the Perfect Diet

An in vitro human gut microbiota fermentation model is a powerful laboratory system used to study how the human gut microbiome breaks down and ferments dietary components—especially fiber—outside the human body. These models replicate the conditions of the human colon, including an anaerobic (oxygen-free) environment, controlled temperature, regulated pH, and the use of a microbial inoculum (often derived from human fecal samples). Through these controlled settings, researchers can observe how gut microbes metabolize food, how microbial populations grow, and what metabolic products are formed (Oliver et al., 2021) (Rodriguez et al., 2024).

In practice, the model works by introducing a dietary substrate—commonly different types of fiber—into the system and monitoring microbial activity over time. The microbes ferment these fibers, producing important metabolites such as short-chain fatty acids (SCFAs), which play key roles in maintaining gut health, supporting the intestinal barrier, and regulating immune function. This process closely reflects what happens in the large intestine, where undigested fibers are broken down by gut bacteria (Vinelli et al., 2022).

What makes this model especially valuable is its potential application in personalized nutrition. Every individual has a unique gut microbiome, shaped by genetics, diet, lifestyle, environment, and health status. As a result, the way each person responds to the same type of fiber can vary significantly. Some individuals may produce higher levels of beneficial metabolites like butyrate, while others may experience different microbial shifts or lower fermentation efficiency (Rodriguez et al., 2024).

Using the in vitro fermentation model, scientists can test how an individual's gut microbiota responds to various types of fiber before recommending a diet. For example, by analyzing a person's microbial composition and simulating fermentation in the lab, it becomes possible to identify which fibers are most beneficial for that individual. This allows for the development of customized dietary plans that optimize gut health, improve digestion, and support overall well-being (Thomson et al., 2021) (Isenring et al., 2023).

This approach highlights a key principle: every body is different. There is no single “ideal” diet that works for everyone because each person’s gut microbiome functions uniquely. Some individuals may benefit more from certain fibers, while others may require different dietary adjustments to achieve balance. Therefore, personalized nutrition based on microbiome analysis represents a shift from a one-size-fits-all diet to a more precise, individualized approach.

In this way, the in vitro gut fermentation model serves as a bridge between scientific research and real-world dietary planning. It helps translate microbiome behavior into actionable insights, enabling healthcare professionals and researchers to design personalized, fiber-rich diets that are tailored to an individual’s unique biological needs—ultimately promoting better digestion, reduced disease risk, and improved long-term health (Isenring et al., 2023)

Conclusion

This paper highlights the intricate evolutionary relationship between dietary diversity and the structural, functional, and microbial adaptations of the human gastrointestinal system. Throughout human history, a fiber-rich and varied diet played a central role in shaping a resilient gut ecosystem, characterized by high microbial diversity, efficient digestion, and stable immune regulation. In contrast, the modern shift toward low-residue, fiber-deficient dietary patterns represents a significant departure from this evolutionary framework, leading to notable alterations in gut function and microbiome composition (Vadatchkoria & Narayan, 2025).

The reduction in dietary fiber has been shown to disrupt microbial balance, impair gut motility, weaken the intestinal barrier, and contribute to a range of gastrointestinal and systemic disorders. These changes underscore how deeply interconnected diet, microbiota, and host physiology are, and how deviations from ancestral dietary patterns can have far-reaching health consequences. From common conditions such as constipation and hemorrhoids to more complex disorders like diverticulosis, inflammatory bowel disease, and metabolic syndromes, the impact of dietary regression is evident across multiple levels of human health (Desai et al., 2016).

Importantly, this study emphasizes the critical role of dietary fiber as a foundational component in maintaining gut health and microbial diversity. Fiber not only supports the structural integrity of the gastrointestinal system but also sustains the metabolic and immunological functions of the gut microbiome. The comparison between ancestral and modern diets further reinforces the necessity of adopting balanced, fiber-rich dietary practices to preserve gut ecosystem stability and overall health (Fu et al., 2022).

In conclusion, understanding the evolutionary context of human nutrition provides valuable insight into the importance of maintaining dietary diversity. Promoting fiber-rich, minimally processed foods is essential not only for optimal digestion but also for supporting the complex and adaptive ecosystem within the human gut, ultimately safeguarding long-term health and preventing disease (Carmody et al., 2021).

Recommendations

This article is recommended for the teachers of Medical Basic Sciences, Biologist, Nutritionists, Physicians and for the students of Medical and Biological specialties, as well as for a wide range of readers in related fields.

Scientific Ethics Declaration

* This article was presented as a poster presentation at the International Conference on Medical, Health and Life Sciences (www.icmehels.net) held in Batumi/Georgia on July 09-12, 2026.

Conflict of Interest

* The authors declare that they have no conflicts of interest.

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Author(s) Information

Rusudan Vadatchkoria

Associate Professor

Batumi Shota Rustaveli State University (BSU), Natural Sciences and Health Care University, 6000, 2/35, Rustaveli/Ninoshvili Avenue Georgia.

Invited Professor

Avicenna – Batumi Medical University
4, Tbeti Str., Georgia,

ORCID iD: <https://orcid.org/0000-0001-9070-6020>

Parvathy Narayan

Student of “Medical Doctor” Program

Batumi Shota Rustaveli State University (BSU), Natural Sciences and Health Care University, 32/35, Rustaveli/Ninoshvili Avenue, 6000, Georgia

ORCID iD: <https://orcid.org/0000-0001-9070-6020>

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Tumor-Induced Osteomalacia in a Patient with Metastatic Prostate Cancer Presenting with Refractory Hypophosphatemia

Aparajita Roy

Barking, Havering and Redbridge University Hospitals NHS Trust

Kieran Mullins

Barking, Havering and Redbridge University Hospitals NHS Trust

Argyris Kyriakou

Barking, Havering and Redbridge University Hospitals NHS Trust

Emily Williams

Barking, Havering and Redbridge University Hospitals NHS Trust

Abstract: Tumor-induced osteomalacia (TIO) is a rare paraneoplastic syndrome caused by fibroblast growth factor 23 (FGF23) overproduction, which leads to renal phosphate wasting and hypophosphatemia. Herein, we present the case of an 81-year-old man with metastatic prostate adenocarcinoma who presented with fatigue, diffuse bone pain, paresthesia, carpopedal spasms, and muscle cramps. Laboratory tests revealed severe hypophosphatemia, 0.28 mmol/L (0.87 mg/dL; reference, 0.80–1.50 mmol/L [2.5–4.5 mg/dL]) and markedly elevated serum levels of alkaline phosphatase (786 U/L) and FGF23 (>1,525 RU/mL; reference, <100 RU/mL). Despite intensive oral and intravenous phosphate supplementation and cholecalciferol therapy, serum phosphate levels remained persistently low. Phosphate wasting was confirmed with a 24-hour urine phosphate excretion test. The patient had mildly elevated parathyroid hormone level with normal 25-hydroxyvitamin D level and preserved renal function, excluding common secondary causes. Therefore, TIO secondary to metastatic prostate cancer was established as the final diagnosis. This case underscores that TIO should be considered in patients with refractory hypophosphatemia and musculoskeletal symptoms. Urine phosphate excretion and serum FGF23 level measurement is essential for timely diagnosis. Burosumab, an anti-FGF23 monoclonal antibody, can be considered for treatment, although its use in malignancy-associated cases is often limited to off-label use.

Keywords: TIO, Hypophosphatemia, FGF23, Oncogenic osteomalacia, Tumor-induced osteomalacia

Introduction

In hospitalized patients, hypophosphatemia is a common biochemical abnormality often overlooked in the absence of symptoms. Persistent and severe hypophosphatemia can indicate underlying phosphate wasting syndromes, including tumor-induced osteomalacia (TIO), a rare but critical paraneoplastic syndrome resulting from excessive fibroblast growth factor 23 (FGF23) secretion that promotes renal phosphate loss and impairs vitamin D metabolism (Chong et al., 2011). Timely recognition of TIO is essential because targeted therapy can reverse symptoms (Insogna KL, Briot K, Imel EA, et al., 2020). Herein, we describe a patient with metastatic prostate adenocarcinoma and refractory hypophosphatemia who was eventually diagnosed with TIO.

Case Presentation

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- Selection and peer-review under responsibility of the Organizing Committee of the Conference

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An 81-year-old man with metastatic prostate adenocarcinoma presented with progressive fatigue, diffuse musculoskeletal pain, paresthesia, and carpopedal spasms. He reported worsening lower limb weakness and frequent muscle cramps. His medical history included prostate adenocarcinoma with osseous metastases initially diagnosed 4 years ago. He had previously received cytotoxic chemotherapy and was currently treated with zoledronic acid, 4 mg every 3 months, dexamethasone 2 mg, omeprazole 20 mg, leuporelin and bicalutamide as hormonal therapy.

Diagnostic Assessment

On examination, he appeared well, with an Eastern Cooperative Oncology Group performance status score of 1. Vital signs were within normal limits. No focal neurologic or musculoskeletal findings were noted. See Table 1 for initial laboratory investigations.

Table 1. Laboratory findings at admission

Parameter	Result (SI units)	Result (Conventional units)	Reference range (SI units)	Reference range (Conventional units)
Serum phosphate	0.28 mmol/L	0.87 mg/dL	0.80–1.50 mmol/L	2.5–4.5 mg/dL
Adjusted serum calcium	2.11 mmol/L	8.44 mg/dL	2.20–2.60 mmol/L	8.8–10.4 mg/dL
Parathyroid hormone	8.4 pmol/L	79 pg/mL	1.6–6.9 pmol/L	15–65 pg/mL
Alkaline phosphatase	786 U/L	786 U/L	30–130 U/L	30–130 U/L
Serum creatinine	88 µmol/L	1.0 mg/dL	60–110 µmol/L	0.68–1.24 mg/dL
Estimated glomerular filtration rate	71 mL/min/1.73 m ²	71 mL/min/1.73 m ²	>60 mL/min/1.73 m ²	>60 mL/min/1.73 m ²
Serum magnesium	0.89 mmol/L	2.16 mg/dL	0.70–1.00 mmol/L	1.7–2.4 mg/dL
25-Hydroxyvitamin D	71 nmol/L	28.4 ng/mL	>50 nmol/L	>20 ng/mL

Based on these findings, the initial diagnosis was drug-induced hypocalcemia with secondary reactive hyperparathyroidism and hypophosphatemia. The patient was initiated on intravenous (50 mmol) and oral phosphate supplementation (32 mmol twice daily) in addition to cholecalciferol (800 IU once daily). However, despite aggressive replacement, phosphate levels remained persistently low. Etiology of hypophosphatemia can be classified into three principal mechanisms: decreased gastrointestinal absorption, intracellular redistribution, and increased urinary phosphate excretion. In the present case, gastrointestinal malabsorption was unlikely as the patient did not have a history of chronic diarrhea or steatorrhea and did not use phosphate-binding agents such as aluminum- or magnesium-containing antacids. Intracellular redistribution was ruled out based on the absence of a history of recent insulin, glucagon or β -adrenergic agonist use and the lack of evidence of respiratory alkalosis. Increased urinary phosphate excretion was suspected and confirmed based on a 24-hour urine phosphate excretion of 62 mmol/day (1.92 g/day; reference range, 15–20 mmol/day [0.46–0.62 g/day]). Common causes of renal phosphate wasting were investigated. Vitamin D deficiency was ruled out based on a normal 25-hydroxyvitamin D level. Regarding primary and secondary hyperparathyroidism, parathyroid hormone level was mildly elevated but not consistent with a primary cause. Fanconi syndrome was ruled out based on urinalysis, which was negative for glycosuria and aminoaciduria. X-linked hypophosphatemic rickets was not applicable in our adult patient. The final diagnosis was TIO based on an elevated serum FGF23 level of >1,525 RU/mL (reference <100 RU/mL).

Treatment

The patient continued to receive aggressive oral (32 mmol twice daily) and intravenous (50 mmol) phosphate supplementation and cholecalciferol (800 IU once daily). However, serum phosphate persisted at critically low levels, limited by the gastrointestinal side effects of treatment, such as diarrhea, and the risk of nephrocalcinosis. Surgical localization of an FGF23-secreting lesion was not feasible, given widespread metastases. Off-label use

of burosumab, an anti-FGF23 monoclonal antibody approved for TIO, was considered a promising targeted therapy.

Outcome and Follow-Up

Serum phosphate levels remained refractory despite supplementation. Discussion regarding burosumab therapy included the consideration of access limitations in malignancy-associated TIO and the need for compassionate- or trial-based access. At the last follow-up evaluation, the treatment plan included monitoring of symptoms, serum phosphate levels, and bone markers while exploring access to burosumab. See Figure 1 showing the clinical timeline of our patient with TIO.

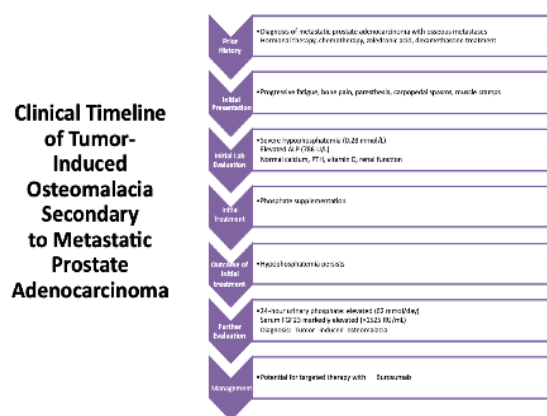


Figure 1. Clinical timeline of tumor-induced osteomalacia secondary to metastatic prostate adenocarcinoma. Abbreviations: ALP, alkaline phosphatase, FGF23, fibroblast growth factor 23; TIO, tumor-induced osteomalacia.

Discussion

TIO, also known as oncogenic osteomalacia, is caused by ectopic FGF23 secretion, commonly from mesenchymal tumors, but may occasionally originate from other malignancies, such as prostate cancer (Chong WH, Molinolo AA, Chen CC, Collins MT.,2011). Excess FGF23 can lead to the downregulation of renal NaPi-IIa/IIc cotransporters, causing phosphate wasting and the suppression of renal 1- α -hydroxylase, which reduces 1,25-dihydroxyvitamin D synthesis (Jonsson KB, Zahradnik R, Larsson T, et al.,2003). TIO diagnosis relies on the presence of renal phosphate wasting and elevated FGF23 levels (Jan de Beur SM.,2005). In patients with TIO, treatment options include surgical resection of the tumor, which is often curative, and conventional supplementation of phosphate and active vitamin D, which is limited by adverse effects. Burosumab has emerged as a targeted, effective therapeutic option for TIO in refractory cases, although its use in malignancy-associated disease remains off-label and may require special access (Insogna KL, Briot K, Imel EA, et al.,2020). The present case underscores the need for awareness of TIO in patients with refractory hypophosphatemia, especially in the setting of cancer and the potential of novel therapies to improve outcomes.

Learning Points

- Tumor-induced osteomalacia (TIO) should be included in the differential diagnosis of persistent hypophosphatemia, especially when accompanied by musculoskeletal symptoms and poor response to replacement therapy.
- Key diagnostic tests include the measurement of urine phosphate excretion and serum fibroblast growth factor 23 levels.
- TIO may occur in association with metastatic malignancies, including prostate adenocarcinoma.
- Burosumab, an anti-FGF23 monoclonal antibody, offers a targeted therapeutic approach for TIO, although its use may be off-label in patients with cancer.

Scientific Ethics Declaration

* The authors declare that the scientific ethical and legal responsibility of this article published in EPHELS journal belongs to the authors.

Conflict of Interest

* The authors declare that they have no conflicts of interest.

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Author(s) Information

Aparajita Roy

Barking, Havering and Redbridge University,
Hospitals NHS Trust, King George Hospital, Barley
Lane, Ilford, Essex, United Kingdom, IG3 8YB
ORCID iD: <https://orcid.org/0009-0001-7401-5913>
Contact e-mail: aparajita.roy1@nhs.net

Kieran Mullins

Barking, Havering and Redbridge University
Hospitals NHS Trust, King George Hospital, Barley
Lane, Ilford, Essex, United Kingdom, IG3 8YB
ORCID iD: <https://orcid.org/0000-0001-8793-9093>

Argyris Kyriakou

Barking, Havering and Redbridge University,
Hospitals NHS Trust, King George Hospital, Barley
Lane, Ilford, Essex, United Kingdom, IG3 8YB
ORCID iD: <https://orcid.org/0009-0001-7531-9580>

Emily Williams

Barking, Havering and Redbridge University
Hospitals NHS Trust, King George Hospital, Barley
Lane, Ilford, Essex, United Kingdom, IG3 8YB
<https://orcid.org/0009-0007-7500-7089>

Corresponding author(s) contact email

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Targeted Geriatric Assessment for Fast-Paced Healthcare Settings (TaGA): Validity and Reliability Study of the Turkish Version

Elif Kocaman

Kastamonu University

Neslihan Fırat

Lokman Hekim University

Ozge Tas

Kastamonu University

Aynur Ayse Karaduman

Lokman Hekim University

Abstract: This study aimed to describe the cross-cultural adaptation of the Turkish version of the Targeted Geriatric Assessment (TaGA) and to evaluate its test–retest reliability, concurrent validity, known-groups validity, and ability to discriminate frailty. This methodological study was conducted in two phases. In the first phase, the TaGA was cross-culturally adapted into Turkish according to internationally accepted guidelines. In the second phase, test–retest reliability was evaluated in 29 community-dwelling older adults, while validity analyses were performed in 98 older adults. Reliability was assessed using the intraclass correlation coefficient (ICC), Pearson and Spearman correlation coefficients, the standard error of measurement (SEM), and the minimal detectable change (MDC). Validity was examined through concurrent validity, known-groups validity, and receiver operating characteristic (ROC) curve analyses. The total TaGA score demonstrated excellent test–retest reliability, with an ICC (2,1) of 0.908 (95% CI: 0.817–0.959). Pearson and Spearman correlation coefficients were 0.912 and 0.929, respectively. The SEM and MDC were calculated as 0.038 and 0.105, respectively. Concurrent validity analyses showed that the total TaGA score was significantly associated, in the expected direction, with the Clinical Frailty Scale, FRAIL Scale, Geriatric Depression Scale, Barthel Index, Mini-Mental State Examination, Mini Nutritional Assessment, and the number of medications. In the known-groups validity analysis, frail participants had significantly higher TaGA scores than non-frail participants. ROC analysis demonstrated good discriminative ability for frailty, with an area under the curve (AUC) of 0.857, an optimal cutoff score of 0.350, a sensitivity of 85.7%, and a specificity of 75.3%. These findings indicate that the Turkish version of the TaGA is a reliable and valid instrument for the rapid screening of geriatric risks and frailty among older adults.

Keywords: Targeted geriatric assessment (TaGA), Geriatric frailty screening, Validity and reliability study, Comprehensive geriatric assessment, Frailty

Introduction

The rapid growth of the older adult population has highlighted the need for healthcare systems to adopt multidimensional approaches that address not only diseases but also functional status, frailty, cognitive function, nutritional status, depressive symptoms, social support, and medication use. Comprehensive Geriatric Assessment (CGA) represents the gold standard for such multidimensional evaluation. However, the time and resources

required to perform a full CGA may limit its routine use in busy outpatient clinics, emergency departments, and other fast-paced healthcare settings (Parker et al., 2018).

Clinical decision-making in these settings often requires the rapid identification of geriatric risks to facilitate timely prioritization of care. Therefore, there is a growing need for brief, practical, and multidimensional screening instruments capable of identifying older adults at increased risk. The Targeted Geriatric Assessment (TaGA) was developed to address this need by providing a targeted assessment of geriatric risks that can be completed in approximately 10 minutes. The TaGA evaluates ten domains, including social support, hospital admissions, falls, medication use, functional status, cognitive performance, self-rated health, depressive symptoms, nutritional status, and gait speed. Each domain is converted into a deficit score ranging from 0 to 1, and the overall TaGA score is calculated as the mean of these domain scores. This scoring system provides clinicians with an overall estimate of geriatric risk while simultaneously identifying specific domains that may require priority intervention (Aliberti et al., 2018).

The adaptation of a measurement instrument into another language involves more than a literal translation. It requires the establishment of conceptual equivalence, cultural relevance, feasibility, and the confirmation of the instrument's psychometric properties within the target population (Wild et al., 2005). Accordingly, the Turkish version of the TaGA underwent a rigorous cross-cultural adaptation process, including forward translation, back translation, expert review, and subsequent psychometric evaluation.

Older adults in Türkiye represent a heterogeneous population with respect to healthcare utilization, family support, educational level, living environment, and burden of comorbidities, reflecting substantial sociodemographic and regional diversity (TÜİK, 2024; WHO, 2020). These differences highlight the importance of validating geriatric screening instruments within the target population before their implementation in clinical practice. Establishing the psychometric properties of the Turkish version of the TaGA may facilitate standardized geriatric assessment in both clinical practice and research settings. Therefore, the aim of this study was to describe the cross-cultural adaptation of the Turkish version of the Targeted Geriatric Assessment (TaGA) and to evaluate its test–retest reliability, concurrent validity, known-groups validity, and ability to discriminate frailty.

Method

Research Design

This methodological study was conducted in two phases to evaluate the psychometric properties of the Turkish version of the Targeted Geriatric Assessment (TaGA). In the first phase, the cross-cultural adaptation of the instrument was completed, followed by an assessment of test–retest reliability by administering the Turkish version of the TaGA to the same participants on two separate occasions. In the second phase, the validity of the instrument was evaluated in a larger sample by examining the relationships between TaGA scores and established measures of frailty, functional status, cognition, nutritional status, depressive symptoms, and medication use, as well as by assessing known-groups validity. This study design enabled the comprehensive evaluation of both the temporal stability and the construct validity of the Turkish version of the TaGA. The psychometric evaluation included test–retest reliability, domain-level reliability, concurrent validity, known-groups validity, and receiver operating characteristic (ROC) analysis.

Translation and Cultural Adaptation

The Turkish adaptation of the Targeted Geriatric Assessment (TaGA) was conducted in accordance with internationally accepted guidelines for the cross-cultural adaptation of health measurement instruments (Beaton et al., 2000). Permission to translate and adapt the original instrument was obtained from the developer before the adaptation process began. The original English version was independently translated into Turkish by two bilingual translators whose native language was Turkish and who were familiar with medical terminology. The two forward translations were compared and synthesized into a single preliminary Turkish version. This version was then independently back-translated into English to verify conceptual equivalence with the original instrument. An expert committee reviewed all translated versions and resolved any discrepancies to ensure semantic, idiomatic, experiential, and conceptual equivalence, as recommended by Beaton et al. The pre-final Turkish version was subsequently pilot-tested in older adults to evaluate the clarity, comprehensibility, and cultural appropriateness of the items. Based on participant feedback, minor modifications were made where necessary, and the final Turkish version of the TaGA was established.

Participants and Data Collection

Community-dwelling older adults aged 60 years and above were recruited for this study. Individuals were eligible if they were able to communicate in Turkish and had a Mini-Mental State Examination (MMSE) score of 18 or higher. Individuals receiving palliative care, requiring hospitalization, unable to communicate in Turkish, or unwilling to participate were excluded. Test–retest reliability was evaluated using data obtained from 29 participants who completed the Turkish version of the TaGA on two separate occasions. Validity analyses were conducted in a sample of 98 participants by comparing the total TaGA score with the Clinical Frailty Scale (CFS), FRAIL Scale, Barthel Index, MMSE, Geriatric Depression Scale (GDS), Mini Nutritional Assessment (MNA), and the number of medications. A standardized demographic data collection form was used to record participants' age, sex, educational level, marital status, living arrangement, comorbidities, medication use, history of falls, and previous hospitalizations. These variables were collected to describe the characteristics of the study population.

Measures

Targeted Geriatric Assessment (TaGA); The TaGA is a multidimensional screening instrument designed to rapidly assess geriatric risk in older adults. It consists of ten domains: social support, hospital admissions, falls, medication use, functional status, cognitive performance, self-rated health, depressive symptoms, nutritional status, and gait speed. Each domain is scored as a deficit ranging from 0 to 1, and the total TaGA score is calculated as the mean of the domain scores. Higher scores indicate greater geriatric risk (Aliberti et al., 2018).

FRAIL Scale; The FRAIL Scale is a brief screening instrument that assesses frailty across five domains: fatigue, resistance, ambulation, illnesses, and weight loss (Morley et al., 2012). It was used as a comparator measure to evaluate the concurrent validity of the Turkish version of the TaGA. The Turkish version of the FRAIL Scale has previously demonstrated acceptable validity and reliability for assessing frailty in older adults (Hymabaccus et al., 2023).

Clinical Frailty Scale (CFS); The Clinical Frailty Scale (CFS) is a clinician-rated instrument that classifies older adults according to their overall level of fitness and frailty based on clinical judgment, considering functional status, comorbidities, cognition, and dependence in activities of daily living (Rockwood et al., 2005). Higher scores indicate greater levels of frailty. In the present study, the CFS was used as a comparator measure to evaluate the concurrent validity and discriminative ability of the Turkish version of the TaGA (Aşık et al., 2022).

Barthel Index (BI); The Barthel Index (BI) is a widely used instrument that assesses independence in activities of daily living (ADL), with higher scores indicating greater functional independence (Fi, 1965). In the present study, the BI was used as a comparator measure to evaluate the concurrent validity of the Turkish version of the TaGA. The Turkish version of the BI has demonstrated acceptable validity and reliability in older adults and was therefore selected as a comparator measure for concurrent validity.

Mini-Mental State Examination (MMSE), Geriatric Depression Scale (GDS), and Mini Nutritional Assessment (MNA); The Mini-Mental State Examination (MMSE) was used to assess global cognitive function (Güngen et al., 2002), the Geriatric Depression Scale (GDS) was used to evaluate depressive symptoms (Yesavage et al., 1982), and the Mini Nutritional Assessment (MNA) used and validated for the assessment of geriatric syndromes in older adults (Garry & Vellas, 1999). In the present study, these instruments were included as comparator measures to evaluate the concurrent validity of the Turkish version of the TaGA.

Statistical Analysis

Descriptive statistics were calculated for all variables. Test–retest reliability was evaluated using the intraclass correlation coefficient (ICC [2,1]), Pearson and Spearman correlation coefficients, paired-samples *t* test, Wilcoxon signed-rank test, Bland–Altman analysis, the standard error of measurement (SEM), and the minimal detectable change at the 95% confidence level (MDC₉₅). The ICC (2,1) model was based on a two-way random-effects model with absolute agreement, as recommended for reliability studies (Koo & Li, 2016). Bland–Altman analysis was used to examine agreement and identify potential systematic bias between repeated measurements (Bland & Altman, 1986). Domain-level reliability was assessed using ICC, Pearson correlation coefficients, linearly weighted kappa coefficients, and percentage agreement. For the nutrition domain, the limited variability observed at the second assessment was taken into account when interpreting the reliability estimates. Concurrent validity was examined by assessing the associations between the total TaGA score and established comparator measures.

using Pearson and Spearman correlation analyses. Known-groups validity was evaluated by comparing TaGA scores between frail and non-frail participants. The discriminative ability of the TaGA for identifying frailty was assessed using receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC), optimal cutoff score, sensitivity, and specificity were reported. Statistical significance was set at $p < 0.05$.

Results and Discussion

Reliability Sample and Score Distribution

Data from 29 participants who completed the Turkish version of the TaGA at two time points were included in the test–retest reliability analysis. The mean total TaGA score was 0.246 ± 0.131 at the first assessment (T1) and 0.234 ± 0.120 at the second assessment (T2). The median scores were 0.250 and 0.200, respectively. The minimum and maximum total scores ranged from 0.000 to 0.500 at both assessments.

Table 1. Descriptive statistics for the total TaGA score

Measures	n	Mean	SS	Median	Min	Maks
Measure 1	29	0,246	0,131	0,250	0,000	0,500
Measure 2	29	0,234	0,120	0,200	0,000	0,500

The prevalence of deficits and descriptive statistics for each TaGA domain at the first and second assessments are presented in Table 2. At the first assessment, the highest deficit prevalence was observed for self-rated health and gait speed (82.8%), whereas social support and nutritional status showed the lowest prevalence (13.8%).

Table 2. Prevalence of deficits and descriptive statistics of TaGA domains in the test–retest reliability sample (n = 29)

TaGA domain	TaGA domain	TaGA domain	TaGA domain
Social support	13,8	0,069	0,103
Hospital admission	62,1	0,362	0,362
Falls	27,6	0,207	0,224
Medication use	27,6	0,138	0,155
Functional status	24,1	0,138	0,103
Cognitive performance	41,4	0,276	0,241
Self-rated health	82,8	0,569	0,500
Depressive symptoms	20,7	0,138	0,172
Nutritional status	13,8	0,069	0,000
Gait speed	82,8	0,552	0,466

Abbreviations: TaGA, Targeted Geriatric Assessment; T1, first assessment; T2, second assessment.

Test-Retest Reliability of the Total Score

Table 3. Test–retest reliability of the total TaGA score (n = 29)

Indicator	Value
ICC (2,1)	0,908
95% CI	0,817-0,959
Pearson correlation coefficient	0,912; $p < 0,001$
Spearman correlation coefficient	0,929; $p < 0,001$
Mean difference (T2 – T1)	-0,011
SD of the differences	0,054
Paired-samples <i>t</i> test	0,278
Wilcoxon signed-rank test	0,289
Standard error of measurement (SEM)	0,038
Minimal detectable change (MDC95)	0,105
Limits of agreement	-0,116-0,094

The test–retest reliability results for the total TaGA score are presented in Table 3. The ICC (2,1) was 0.908 (95% CI: 0.817–0.959). Pearson and Spearman correlation coefficients were 0.912 and 0.929, respectively (both $p < 0.001$). The mean difference between the two assessments was -0.011 ± 0.054 . No significant differences were observed between the first and second assessments according to the paired-samples *t* test ($p = 0.278$) or the

Wilcoxon signed-rank test ($p = 0.289$). The SEM was 0.038, the MDC₉₅ was 0.105, and the limits of agreement ranged from -0.116 to 0.094.

Figure 1. Bland–Altman plot illustrating the agreement between the first (T1) and second (T2) assessments of the total Targeted Geriatric Assessment (TaGA) score. The solid blue line represents the mean difference (bias = -0.011), while the dashed red lines indicate the 95% limits of agreement (-0.116 to 0.094). Most observations were distributed within the limits of agreement, indicating good agreement between repeated measurements.

Domain-Level Reliability

The domain-level reliability results are presented in Table 4. The highest ICC was observed for the medication use domain (ICC = 0.920), followed by falls (ICC = 0.897), functional status (ICC = 0.868), hospital admission (ICC = 0.835), and depressive symptoms (ICC = 0.810). Moderate ICC values were observed for the social support (ICC = 0.529), cognitive performance (ICC = 0.632), self-rated health (ICC = 0.592), and gait speed (ICC = 0.721) domains. ICC and Pearson correlation coefficients could not be calculated for the nutritional status domain because no variability was observed at the second assessment.

Table 4. Domain-level test–retest reliability of the Turkish version of the TaGA (n = 29)

Domain	ICC (2,1)	95% CI	Pearson r	Weighted κ	Agreement (%)
Social support	0.529	-0.057–0.891	0.536	0.521	86.2
Hospital admission	0.835	0.592–0.966	0.830	0.790	86.2
Falls	0.897	0.714–1.000	0.897	0.839	89.7
Medication use	0.920	0.714–1.000	0.920	0.917	96.6
Functional status	0.868	0.481–1.000	0.874	0.826	93.1
Cognitive performance	0.632	0.263–0.821	0.634	0.488	65.5
Self-rated health	0.592	0.205–0.865	0.604	0.583	75.9
Depressive symptoms	0.810	0.333–0.968	0.811	0.722	86.2
Nutritional status	—	—	—	0.000	86.2
Gait speed	0.721	0.506–0.870	0.744	0.611	69.0

Concurrent Validity

The concurrent validity results are presented in Table 5. The total TaGA score showed significant correlations with all comparator measures in the expected directions (all $p < 0.001$). Positive correlations were observed with the Clinical Frailty Scale, FRAIL Scale, Geriatric Depression Scale, frailty status, and the number of medications, whereas negative correlations were found with the Barthel Index, Mini-Mental State Examination, and Mini Nutritional Assessment. The strongest correlations were observed with the Clinical Frailty Scale ($r = 0.649$, $p = 0.604$) and the Mini Nutritional Assessment ($r = -0.549$, $p = -0.489$).

Table 5. Concurrent validity of the Turkish version of the TaGA

Comparator measure	Expected direction	Pearson r	Spearman ρ	p-value
Clinical Frailty Scale	+	0.649	0.604	<0.001
FRAIL Scale	+	0.525	0.532	<0.001
Barthel Index	–	-0.503	-0.411	<0.001
Mini-Mental State Examination	–	-0.344	-0.342	<0.001
Geriatric Depression Scale	+	0.492	0.556	<0.001
Mini Nutritional Assessment	–	-0.549	-0.489	<0.001
Frailty status	+	0.554	0.511	<0.001
Number of medications	+	0.360	0.401	<0.001

Known-Groups Validity and Discriminative Ability

The results of the known-groups validity analysis are presented in *Table 6*. Frail participants had significantly higher total TaGA scores than non-frail participants (0.440 ± 0.130 vs. 0.254 ± 0.112 , $p < 0.001$). The ROC curve analysis demonstrated an area under the curve (AUC) of 0.857 for identifying frailty. The optimal cutoff score was 0.350 , with a sensitivity of 85.7% and a specificity of 75.3% . The ROC curve is presented in *Figure 2*.

Table 6. Known-groups validity of the Turkish version of the TaGA

Group	n	Mean $\pm$ SD	Median	p-value
Non-frail	77	0.254 ± 0.112	0.250	
Frail	21	0.440 ± 0.130	0.440	<0.001

Table 7. Receiver operating characteristic (ROC) analysis for frailty

Parameter	Value
Reference standard	Frailty status
Sample size	98
Area under the curve (AUC)	0.857
Optimal cutoff score	0.350
Sensitivity	85.7%
Specificity	75.3%

Discussion

The findings of the present study indicate that the Turkish version of the Targeted Geriatric Assessment (TaGA) demonstrates excellent test-retest reliability, good concurrent validity, satisfactory known-groups validity, and good discriminative ability for identifying frailty among community-dwelling older adults. The total TaGA score showed an ICC of 0.908 , indicating excellent reliability according to the recommendations of (Koo & Li, 2016). Furthermore, the SEM and MDC_{95} values provide clinically meaningful information beyond reliability coefficients by quantifying measurement error and identifying the minimum amount of change required to represent true change over repeated assessments (Beckerman et al., 2001). These measurement properties support the use of the Turkish version of the TaGA for both cross-sectional assessment and longitudinal follow-up.

As a multidimensional assessment instrument, the TaGA is designed to evaluate multiple domains of geriatric health rather than a single clinical construct. Therefore, moderate to strong correlations with established measures of frailty, functional status, cognition, nutrition, depression, and medication use were expected. The significant positive correlations observed with the Clinical Frailty Scale, FRAIL Scale, Geriatric Depression Scale, frailty status, and the number of medications, together with the negative correlations with the Barthel Index, Mini-Mental State Examination, and Mini Nutritional Assessment, support the concurrent validity of the Turkish version. These findings indicate that the Turkish version preserves the multidimensional conceptual framework of the original instrument while demonstrating appropriate associations with established geriatric assessment measures.

The known-groups validity analysis further demonstrated that frail participants had significantly higher TaGA scores than non-frail participants. In addition, the ROC analysis showed good discriminative performance for identifying frailty, with an AUC of 0.857 . The optimal cutoff score of 0.350 yielded a sensitivity of 85.7% and a specificity of 75.3% , suggesting that the Turkish version of the TaGA can successfully distinguish between frail and non-frail older adults. These findings support the use of the Turkish version of the TaGA as a screening instrument for identifying individuals who may benefit from a more comprehensive geriatric assessment. However, the proposed cutoff score should be interpreted as a screening threshold rather than a diagnostic criterion and should be externally validated in independent populations before routine clinical implementation.

The TaGA was originally developed as a brief multidimensional assessment tool for rapidly identifying geriatric risk in busy healthcare settings where comprehensive geriatric assessment may not always be feasible. The original validation study reported excellent inter-rater reliability (ICC = 0.92), a strong correlation with the Frailty Index (Spearman coefficient = 0.79), superior discrimination of frailty compared with the Identification of Seniors at Risk (ISAR), and a mean administration time of approximately 9.5 minutes (Aliberti et al., 2018). Similarly, the Turkish version demonstrated excellent reliability and good discriminative ability, indicating that the cross-cultural adaptation process preserved the psychometric characteristics of the original instrument. Although the cutoff score identified in the present study differs from that reported in the original validation study, this difference is expected because cutoff values are influenced by population characteristics, frailty prevalence, and the reference

standard used for classification. Overall, the present findings indicate that the Turkish version retains the multidimensional measurement properties and clinical applicability of the original TaGA.

Comprehensive geriatric assessment is considered the reference approach for evaluating older adults because it simultaneously addresses functional, cognitive, nutritional, psychological, and social domains rather than focusing on a single clinical outcome (Ellis et al., 2011; Veronese et al., 2022). However, the implementation of CGA may be limited in routine clinical practice because of the time, expertise, and multidisciplinary resources required. Consequently, several brief geriatric screening instruments have been developed to facilitate the early identification of older adults who require comprehensive assessment (Parker et al., 2018). Consistent with this multidimensional perspective, the Turkish version of the TaGA demonstrated significant associations with established measures representing these domains. Although several brief geriatric screening instruments, including the Rapid Geriatric Assessment (RGA), have recently been adapted for use in Türkiye (Çavdar et al., 2025), each instrument targets different clinical constructs and uses different scoring systems. Unlike most existing screening tools, the TaGA integrates ten geriatric domains into a cumulative deficit-based score, providing both an overall estimate of geriatric risk and domain-specific information to guide clinical decision-making. Therefore, the present study provides psychometric evidence supporting the use of the Turkish version of the TaGA as a brief multidimensional screening instrument for Turkish-speaking older adults.

At the domain level, medication use, falls, hospital admission, functional status, and depressive symptoms demonstrated higher reliability than social support, cognitive performance, self-rated health, and gait speed. Higher reliability observed in objectively assessed domains is expected because these variables are generally less susceptible to short-term fluctuations than self-reported measures. In contrast, self-rated health and perceived social support may vary according to temporary physical, emotional, and environmental factors. No ICC could be estimated for the nutritional status domain because no variability was observed at the second assessment. This finding should be interpreted cautiously, as it is more likely to reflect the limited variability of the study sample than inadequate measurement performance of the nutritional domain. Future studies including more heterogeneous populations with a broader range of nutritional risk are warranted to further evaluate the reliability of this domain.

Strengths and Limitations

The present study has several strengths. To our knowledge, this is the first study to evaluate the cross-cultural adaptation and psychometric properties of the Turkish version of the Targeted Geriatric Assessment (TaGA). A major strength of the study is the comprehensive evaluation of multiple psychometric properties, including test–retest reliability, measurement error, concurrent validity, known-groups validity, domain-level reliability, and discriminative ability for frailty. Furthermore, the inclusion of several well-established geriatric assessment instruments as comparator measures strengthened the evaluation of construct validity and provided a comprehensive assessment of the multidimensional performance of the Turkish version of the TaGA.

Nevertheless, several limitations should be acknowledged. First, the test–retest reliability analysis was conducted in a relatively small reliability sample, which may have contributed to the wide confidence intervals observed for some domain-specific ICC estimates. Second, the absence of variability in the nutritional status domain at the second assessment prevented the estimation of ICC and Pearson correlation coefficients for this domain. Third, frailty status was used as the reference standard for the ROC analysis; therefore, the proposed cutoff score may differ when evaluated against other clinically relevant outcomes. Finally, because this study evaluated the cross-sectional psychometric properties of the Turkish version of the TaGA, its predictive validity for clinically important outcomes, including hospitalization, falls, functional decline, institutionalization, and mortality, could not be determined.

Clinical Implications and Future Directions

The findings of this study suggest that the Turkish version of the TaGA may serve as a practical multidimensional screening instrument for identifying older adults who may benefit from comprehensive geriatric assessment. In addition to providing an overall estimate of geriatric risk, domain-specific scores may assist healthcare professionals in identifying priority areas for further assessment and individualized care planning. The MDC₉₅ value may facilitate the interpretation of longitudinal changes by distinguishing true clinical change from measurement error. However, the proposed cutoff score should be interpreted as a screening threshold rather than a diagnostic criterion and should always be considered in conjunction with comprehensive clinical assessment.

Future multicenter studies should evaluate the predictive validity, responsiveness, and external validity of the Turkish version of the TaGA in larger and more heterogeneous populations. Additional research should also investigate its ability to predict clinically relevant outcomes, including hospitalization, falls, functional decline, institutionalization, and mortality, as well as its applicability across different healthcare settings.

Conclusion

The Turkish version of the Targeted Geriatric Assessment demonstrated excellent test–retest reliability, good concurrent validity, satisfactory known-groups validity, and good discriminative ability for identifying frailty among community-dwelling older adults. These findings support the reliability and validity of the Turkish version of the TaGA as a brief multidimensional geriatric screening instrument for Turkish-speaking older adults. The instrument may facilitate the identification of individuals who could benefit from comprehensive geriatric assessment, particularly in settings where rapid multidimensional screening is needed. Further multicenter and longitudinal studies are warranted to confirm these findings, evaluate predictive validity and responsiveness, and examine the performance of the proposed cutoff score in different clinical populations.

Scientific Ethics Declaration

* Ethical approval for this study was obtained from the appropriate Institutional Ethics Committee, and permission to translate and use the Targeted Geriatric Assessment (TaGA) was obtained from the original developer. Written informed consent was obtained from all participants prior to enrollment in the study.

* The authors declare that the scientific ethical and legal responsibility of this article published in EPHELS journal belongs to the authors.

Data Availability Statement

* The anonymized datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request, subject to ethical and institutional regulations. The English and Turkish versions of the scale in which the study was conducted are attached.

Conflict of Interest

* The authors declare that they have no competing interests.

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Authors' Contributions

Elif Kocaman: Conceptualization, methodology, investigation, data collection, formal analysis, interpretation of the data, and drafting of the manuscript.

Neslihan Fırat: Methodology, data curation, formal analysis, interpretation of the data, manuscript writing, and critical revision of the manuscript.

Özge Taş: Formal analysis and interpretation of the data.

Aynur Ayşe Karaduman: Supervision, methodology, interpretation of the findings, critical revision of the manuscript, and final approval of the version to be published.

All authors read and approved the final manuscript.

AI Disclosure Statement

* During the preparation of this manuscript, the authors used an artificial intelligence–assisted writing tool for language editing, academic formatting, and improving clarity and consistency of expression. No artificial intelligence tool was used to generate, analyze, or interpret the study data. The authors take full responsibility for the scientific content, analyses, interpretations, and the final version of the manuscript.

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Author(s) Information

Elif Kocaman

Kastamonu University, Catalzeytin Vocational School,
Department of Therapy and Rehabilitation, Kastamonu,
Türkiye

ORCID iD: <https://orcid.org/0000-0002-9783-7637>

*Contact e-mail: elifyurdakul@kastamonu.edu.tr

Neslihan Fırat

Lokman Hekim University, Institute of Health Sciences,
Ankara, Türkiye

ORCID iD: <https://orcid.org/0009-0003-8445-763X>

Ozge Tas

Kastamonu University, Catalzeytin Vocational School,
Department of Computer Technologies, Kastamonu,
Türkiye

ORCID iD: <https://orcid.org/0000-0001-7220-5054>

Aynur Ayşe Karaduman

Lokman Hekim University, Faculty of Health Sciences,
Department of Physiotherapy and Rehabilitation, Ankara,
Türkiye

ORCID iD: <https://orcid.org/0000-0001-6252-1934>

*Corresponding author(s) contact email

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Appendix 1. TaGA-Targeted Geriatric Assessment for rapid healthcare settings Turkish version

SOSYAL DESTEK	Kiminle yaşıyorsun?	Yalnız [sonraki soru]	Aile veya bakıcı [0.0]	Kurumda Yaşıyor [0.5]	Puan
Sadece yalnız yaşayanlar için: Bir yatağa bağımlı olsaydınız, size yardım edebilecek kişilere ulaşılır mı?					
Her zaman veya neredeyse her zaman [0.5]		Bazen, nadiren veya asla [1.0]			
HASTANE BAŞVURULARI Son 6 Ayda	Hiç [0.0]	Acil Servis Ziyareti [0.5]	Hastaneye Yatış [1.0]		
DÜŞMELER Son 12 Ayda	Hiç [0.0]	1 Düşme [0.5]	≥2 Düşme [1.0]		
İLAÇLAR Sürekli Kullanımdaki Sayı	<5 [0.0]	5-9 [0.5]	>10 [1.0]		
FONKSİYONELLİK	Günlük Yaşam Aktivitelerinde Katz Bağımsızlık İndeksi (Katz ve diğerleri, 1976)				
Banyo Yapma: Tamamen kendi kendine yıkanır veya vücudunun yalnızca tek bir bölümünü yıkamak için yardıma ihtiyaç duyar.					Hayır 1
Giyinme: dolaplardan kıyafet alır ve düğmeli elbise ve dış giysileri giyer.					Evet 0
Tuvalet: Yardımsız tuvalete gider, Kıyafetini çıkarır, tuvaletini yapar ve kıyafetlerini tekrar giyer.					1
Transfer: Yataktan sandalyeye ve ya tersi etkinliği tek başına ve ya baston ya da cihaz yardımıyla yapar.					0
Kontinans: İdrara çıkma ve dışkılama üzerinde tam bir öz kontrol sağlar.					1
Beslenme: Yiyecekleri tabaktan yardım almadan ağzına götürür.					0
[0.0] 0 Puan		[0.5] 1-2 Puan		[1.0] ≥ 3 Puan	
KOGNİTİF DURUM	Eğitim Düzeyi İle Düzeltilmiş 10 Puanlı Bilişsel Tarama Aracı (Apolinario ve diğerleri, 2016):				
Zaman Oryantasyonu: Bugünün tarihi ☐ Ay ☐ Yıl ☐					
Şu kelimeleri tekrarlayın: Araba-Vazo-Tuğla (Gerekirse 3 denemeye kadar; _____)					
Kategorik Akıcılık: 1 Dakikada Hayvanlar ☐ 0-5=0 ☐ 6-8=1 ☐ 9-11=2 ☐ 12-14=3 ☐ ≥15 =4					
1. _____ 2. _____ 3. _____ 4. _____ 5. _____ 6. _____ 7. _____ 8. _____					
9. _____ 10. _____ 11. _____ 12. _____ 13. _____ 14. _____ 15. _____ 16. _____					
Kelime hatırlama: Araba ☐ Vazo ☐ Tuğla ☐					
Ham Skor(10 CS): ____/10 Eğitim göre düzeltilmiş puan (10-CS-Eğİ.): ____/10					
(örgün eğitim yok: 2 puan ekleyin: 1-3 yıllık eğitim: 1 puan ekleyin; maksimum puan-10)					
[0.0] ≥8 Puan		[0.5] 6-7 Puan		[1.0] 0-5 Puan	
ÖZ SAĞLIK BİLDİRİMİ	"Genel olarak sağlığınızın mükemmel, çok iyi, iyi, orta veya kötü olduğunu söyleyebilir misiniz?"				
Cevap verilemiyor (eğer 10-CS skoru=0 ise)	Mükemmel/Çok iyi [0.0]	İyi [0.5]	Orta / kötü [1.0]		
DEPRESYON SEMPTOMLARI	4 Maddelik Geriatrik Depresyon Ölçeği (van Marwijk ve ark. 1995)				
Cevap verilemiyor (eğer 10-CS skoru=0 ise)	-Genel olarak hayatınızdan memnun musunuz?				Hayır 1
	-Aktivitelerinizin ve ilgi alanlarınızın birçoğunu bıraktınız mı?				Evet 0
	-Çoğu zaman kendinizi mutlu hissediyor musunuz?				1
	- Evde kalmayı dışarı çıkmaya tercih eder misiniz?				0
[0.0] 0-1 Puan		[0.5] 2 Puan		[1.0] 3-4 Puan	
BESLENME DURUMU	Kilo kaybı: ≥ 4.5 kg önceki yıl içerisinde Hayır ☐ Evet ☐				
	Beden Kitle İndeksi (BKİ) _____ (kilo-kg) / (boy-m) ²				
Not: BMI mevcut değilse baldır çevresi (CC) ile değiştirin: CC <31 cm (veya 12,2 inç) bozulma anlamına gelir.					
[0.0] kilo kaybı yok ve BKİ≥22		[0.5] kilo kaybı veya BKİ<22		[1.0] kilo kaybı ve BKİ <22	
YÜRÜME HIZI	Her zamanki tempoda iki kez 4,5 metre yürütün; en iyi performansı dikkate alın.				
Zaman 1: _____ sn		Zaman 2: _____ sn			
[0.0] ≤4.4 s		[0.5] 4.5-7.5s		[1.0] ≥ 7.6 s veya yürüyemiyor	
TaGA puanı (0'dan 1'e: puanların toplamının değerlendirilen alan sayısına bölümü)					

Appendix 2. TaGA-Targeted Geriatric Assessment for rapid healthcare settings original version

SOCIAL SUPPORT		Who do you live with?	Alone [next question]	Family or caregiver [0.0]	Institutionalized [0.5]	POINTS
Only for those who live alone: How often would someone be available to help you if you were confined to bed?			Always or almost always [0.5]	Sometimes, rarely or never [1.0]		_____
PREVIOUS ADMISSIONS		None [0.0]	Emergency department visit [0.5]	Hospitalization [1.0]		_____
In the prior six months:						
FALLS		None [0.0]	1 fall [0.5]	≥ 2 falls [1.0]		_____
In the last 12 months:						
MEDICATIONS		< 5 [0.0]	5 – 9 [0.5]	≥ 10 [1.0]		_____
Number in continuous use:						
FUNCTIONALITY		Katz Index of Independence in Activities of Daily Living (Katz et al., 1976):				
		No Yes				
Bathing: bathes self completely or needs help in bathing only a single part of the body.		1 0				
Dressing: gets clothes from closets and puts on clothes and outer garments complete with fasteners.		1 0				
Toileting: goes to toilet, gets on and off, arranges clothes, cleans genital area without help.		1 0				
Transferring: moves in and out of bed or chair unassisted. Mechanical transferring aides are acceptable.		1 0				
Continence: exercises complete self control over urination and defecation.		1 0				
Eating: gets food from a plate into the mouth without help.		1 0				
		[0.0] 0 points	[0.5] 1 – 2 points	[1.0] ≥ 3 points		_____
COGNITIVE STATUS		Education-corrected 10-Point Cognitive Screener (Apolinario et al., 2016):				
Temporal orientation: ☐ today's date ☐ month ☐ year						
Repeat these words: CAR – VASE – BRICK (up to 3 attempts if necessary; does not score)						
Categorical fluency: animals in 1 min ☐ 0-5 = 0 ☐ 6-8 = 1 ☐ 9-11 = 2 ☐ 12-14 = 3 ☐ ≥ 15 = 4						
1. _____ 2. _____ 3. _____ 4. _____ 5. _____ 6. _____ 7. _____ 8. _____						
9. _____ 10. _____ 11. _____ 12. _____ 13. _____ 14. _____ 15. _____ 16. _____						
Word recall: ☐ CAR ☐ VASE ☐ BRICK						
Crude score (10-CS): _____ /10		Education-corrected score (10-CS-Edu): _____ /10				
		(no formal education: add 2 points; 1–3 years of education: add 1 point; max score=10)				
		[0.0] ≥ 8 points	[0.5] 6 – 7 points	[1.0] 0 – 5 points		_____
SELF-RATED HEALTH		"In general, would you say that your health is excellent, very good, good, fair, or poor?"				
☐ Unable to answer (if 10-CS crude score=0)		Excellent or very good [0.0]	Good [0.5]	Fair or poor [1.0]		_____
DEPRESSIVE SYMPTOMS		4-item Geriatric Depression Scale (van Marwijk et al., 1995):				
		No Yes				
☐ Unable to answer (if 10-CS crude score=0)		Are you basically satisfied with your life?				
		1 0				
		Have you dropped many of your activities and interests?				
		0 1				
		Do you feel happy most of the time?				
		1 0				
		Do you prefer to stay at home, rather than going out and doing new things?				
		0 1				
		[0.0] 0 – 1 point	[0.5] 2 points	[1.0] 3 – 4 points		_____
NUTRITIONAL STATUS		Weight loss: ≥ 10 pounds in the prior year ☐ No ☐ Yes				
		Body mass index (BMI): _____ (weight in kg) / (height in m) ²				
		Note: if BMI is not available, replace it with calf circumference (CC); CC < 310 mm (or 12.2 inches) means impairment.				
		[0.0] no weight loss and BMI ≥ 22	[0.5] weight loss or BMI < 22	[1.0] weight loss and BMI < 22		_____
GAIT SPEED		Walking two times 4.5 meters at a usual pace; consider the best performance.				
		Time 1: _____ seconds Time 2: _____ seconds				
		[0.0] ≤ 4.4 seconds	[0.5] 4.5 – 7.5 seconds	[1.0] ≥ 7.6 seconds or unable to walk		_____
		TaGA score (from 0 to 1: sum of the points divided by the number of evaluated domains)				_____

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Breastfeeding Status and Response to Growth Hormone Therapy in Children with Isolated Growth Hormone Deficiency

Ayca Altuntepe
Selçuk UniversityTolga Unuvar
Aydın Adnan Menderes University

Abstract: This study aimed to evaluate the association of breastfeeding status and duration with growth parameters, biochemical markers, and response to growth hormone (GH) therapy in children with isolated growth hormone deficiency (IGHD). In this retrospective study, the medical records of 162 children aged 3–17 years diagnosed with IGHD between January 1, 2019, and December 31, 2024, were reviewed. Overall, 67.9% of the children were breastfed, with a mean duration of 16.4 ± 8.6 months. No significant differences were found between breastfed and non-breastfed children regarding baseline growth and biochemical parameters or treatment response ($p > 0.05$). Overall, 62.96% of the patients achieved a favorable treatment response, which showed no significant association with breastfeeding duration. In multivariable analysis, GH treatment duration emerged as the sole independent predictor of treatment response (OR = 1.355, 95% CI: 1.026–1.791, $p = 0.032$). In conclusion, neither breastfeeding status nor duration was significantly associated with growth trajectories or GH therapy response in children with IGHD, whereas GH treatment duration was a key determinant of therapeutic success.

Keywords: Breastfeeding, Growth hormone therapy, Isolated growth hormone deficiency

Introduction

Isolated Growth Hormone Deficiency and Growth

Isolated growth hormone deficiency (IGHD) represents one of the primary endocrine etiologies of pediatric growth failure. Growth hormone therapy is the cornerstone treatment aimed at accelerating growth velocity in children with IGHD; however, therapeutic responsiveness is modulated by various patient-specific clinical characteristics and treatment-related factors (Dattani & Preece, 2004; Witkowska-Sędek et al., 2018).

The Role of Breast Milk and Bioactive Components in Pediatric Growth

Early life nutrition represents one of the crucial determinants of postnatal growth and development. Breast milk contains essential macronutrients and micronutrients, as well as a multitude of bioactive components—including growth factors (e.g., IGF-1), hormones, and cytokines—that support childhood growth and maturation (Yi & Kim, 2021; Szyller et al., 2024). Beyond basic nutritional support, human milk functions as a dynamic biological system that modulates metabolic programming and long-term endocrine regulation during early development (Table 1).

Among the extensive array of bioactive molecules in human milk, the principal components exerting decisive effects on neonatal development, tissue repair and immunological response are categorized and detailed in Table 1 (Ballard & Morrow, 2013). However, evidence regarding the association between breastfeeding status, breastfeeding duration, and subsequent growth outcomes or response to GH therapy in children with IGHD is

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limited. Although the effects of breastfeeding on overall childhood growth have been widely investigated, studies specifically examining whether early-life breastfeeding parameters are associated with long-term growth parameters and therapeutic response to GH therapy in children with IGHD remain scarce. Therefore, this study aimed to evaluate the potential effects of breastfeeding status and duration on growth parameters and response to GH therapy in children diagnosed with IGHD. In addition, clinical and biochemical variables that may influence treatment response were evaluated using multivariable analysis. Through this approach, the study aimed to contribute to a better understanding of the relationship between early-life nutritional history and treatment response in children with IGHD.

Table 1. Human milk bioactives and functions

Component Category	Key Bioactive Factors	Biological Function and Effect on Growth
Cellular Components	Macrophages, Stem cell	Protection against infection, T-cell activation, tissue regeneration and structural repair
Growth Factors	IGF-1, IGFBP-3, EGF, VEGF	Stimulation of somatic growth and tissue maturation; upregulation of red blood cell mass and hemoglobin synthesis.
Immunoglobulins	IgA/sIgA, IgG, IgM	Antimicrobial activity and activation of phagocytosis; anti-inflammatory effects and regulation of allergic responses.
Cytokines	IL-6, IL-7, IL-8, IL-10, IFN- γ , TGF- β , TNF- α	Regulation of inflammatory responses, enhancement of thymic output and neutrophil recruitment, induction of antibody synthesis, and promotion of immune tolerance.
Antimicrobial	Lactoferrin, Lactadherin	Acute-phase immune response, iron-chelating capacity, antibacterial, antiviral, and antioxidant activities.

Method

Study Design and Participants

This retrospective study reviewed the medical records of children diagnosed with IGHD between January 1, 2019, and December 31, 2024, at the Pediatric Endocrinology Clinic of Aydın Adnan Menderes University Hospital. A total of 162 children aged 3–17 years were included in the study.

Data Collection

Demographic characteristics, birth characteristics, anthropometric measurements, breastfeeding status and duration, vitamin D prophylaxis, IGF-1, IGFBP-3, and data related to GH therapy were obtained from the medical records. Information on breastfeeding status and duration was collected through telephone interviews with parents and based on parental self-report.

Assessment of Treatment Response

Response to GH therapy was evaluated based on the change in height SDS (Δ height SDS), calculated as the difference between height SDS at the last follow-up and at diagnosis. As illustrated in Figure 1, patients were categorized into two distinct response groups: those with a Δ height SDS ≥ 0.5 were classified as favorable responders, whereas those with a Δ height SDS < 0.5 were categorized as inadequate responders.

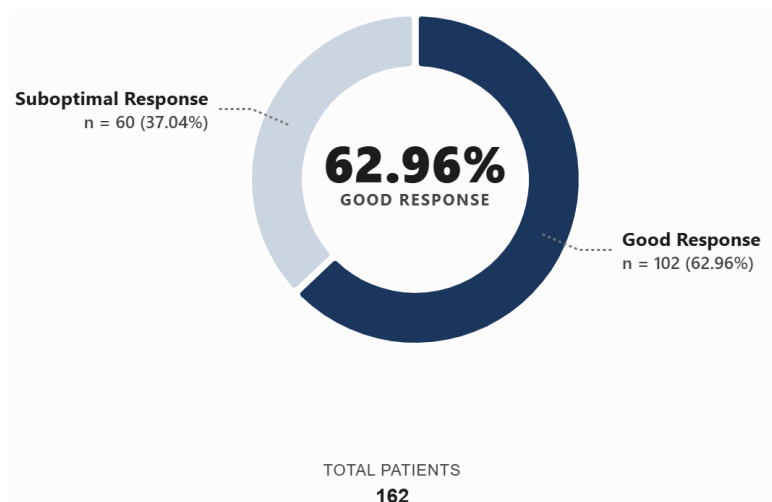


Figure 1. Distribution of treatment response status based on delta (Δ height SDS ≥ 0.5) height SDS

Statistical Analysis

Statistical analyses were performed using SPSS version 26.0. The chi-square test was used to compare categorical variables, the Mann–Whitney U test for comparisons between two groups of continuous variables, and the Kruskal–Wallis test was used for comparisons among more than two groups. Associations between continuous variables were assessed using Spearman’s correlation analysis, and multivariable logistic regression analysis was performed to identify independent factors associated with treatment response. A p-value < 0.05 was considered statistically significant.

Results and Discussion

A total of 162 children aged 3–17 years diagnosed with IGHD were included in the study.

Table 2. Baseline demographic and clinical characteristics of participants

Variable	Total (n=162)
Age, years	10.2 $\pm$ 2.7
Male, n (%)	88 (54.3)
Female, n (%)	74 (45.7)
Breastfed, n (%)	110 (67.9)
Breastfeeding duration, months	16.4 $\pm$ 8.6

As summarized in *Table 2*, the study cohort demonstrated a balanced gender distribution with a predominant history of infant breastfeeding. Among the breastfed participants, the duration of breastfeeding was sustained for an average of over 16 months. Comparative analysis of baseline anthropometric and biochemical parameters revealed no statistically significant differences between breastfed and non-breastfed children regarding age at diagnosis, height SDS, weight SDS, vitamin D levels, IGF-1 SDS, or IGFBP-3 SDS ($p > 0.05$). These findings indicate that the baseline anthropometric and biochemical characteristics of the two groups were overall comparable at the time of diagnosis.

In a study by Clayton et al. (2024), participants were categorized into three groups based on early-life feeding patterns: exclusively breastfed, partially breastfed/mixed-fed, and exclusively formula-fed. In their study, exclusively breastfed children demonstrated lower weight SDS compared to formula-fed peers. Such discrepant findings in the literature suggest that the impact of breastfeeding on early growth parameters may vary according to the target population, age at clinical evaluation, breastfeeding duration, and confounding socioeconomic factors including maternal education, economic status, and environmental conditions during early development. This finding indicates that the distinctive impact of breast milk on growth parameters may vary depending on time and developmental stages. Anthropometric differences driven by bioactive components in human milk during infancy and early childhood tend to gradually attenuate as children grow and environmental dietary factors diversify. Particularly in evaluations conducted at older ages, such as at the time of diagnosis, individual genetic potential,

lifestyle, socioeconomic conditions, and underlying chronic or endocrine conditions become the primary determinants of the growth trajectory, rather than the mode of infant feeding.

When comparing breastfed and non-breastfed children, no statistically significant differences were found regarding GH treatment duration, GH dose, baseline growth parameters, or treatment response ($p > 0.05$). A favorable treatment response was observed in 61.5% of the non-breastfed group and 63.6% of the breastfed group ($p = 0.796$). Adverse drug effects were observed only in the non-breastfed group, and the difference between the groups was statistically significant.

In this study, no adverse drug effects were observed in the breastfed group, whereas adverse effects were reported in 3.8% of patients in the non-breastfed group, and this difference was statistically significant. This finding may suggest a potential role of breastfeeding in treatment tolerability. According to large-scale data from the KIGS cohort, pediatric GH therapy is generally well tolerated, with the majority of adverse events being mild and transient. Treatment-related adverse effects have been reported at low rates, while events requiring discontinuation of therapy have rarely been reported (Maghnie et al., 2022). However, the paucity of prior research evaluating breastfeeding patterns in this context precludes a direct comparative analysis with existing literature. Moreover, due to the retrospective nature of our study and the scarce evidence exploring the interaction between infant feeding history and GH therapy-related adverse events, these observations do not establish definitive causality.

The observed outcomes must therefore be interpreted with discretion, acknowledging that unmeasured confounders—such as age at diagnosis, medication adherence, and socioeconomic background—could have partially skewed these observational findings. Evaluation of breastfeeding duration revealed no statistically significant correlation with height SDS gain, weight SDS gain, first-year growth velocity, or final height SDS ($p > 0.05$). This finding is consistent with previous literature reporting that although breastfed infants may exhibit different weight gain trajectories compared to formula-fed counterparts, linear growth (height) remains unaffected (Akova et al., 2012).

In the multivariable logistic regression analysis, age at diagnosis and baseline vitamin D levels were not identified as independent predictors of favorable treatment response ($p > 0.05$). In contrast, duration of GH therapy emerged as an independent and significant predictor (OR=1,355; %95 GA: 1,026–1,791; $p=0,032$). Specifically, each additional year of GH treatment was associated with an approximately 1.36-fold increase in the odds of achieving a favorable response, independent of potential confounders. This finding highlights that therapeutic success is closely tied to treatment continuity and sustained GH exposure. As emphasized by Darendeliler (2009), long-term compliance and continuous therapy remain critical determinants for maintaining an optimal cumulative growth response in pediatric patients.

Conclusion

In conclusion, neither breastfeeding status nor its duration showed a significant association with clinical parameters or response to growth hormone therapy in pediatric IGHD patients. Notably, although adverse events were observed solely in non-breastfed patients, suggesting a potential protective effect of breastfeeding on treatment tolerability, this finding warrants cautious interpretation due to the retrospective nature of the study. Additionally, the duration of growth hormone therapy emerged as a critical independent predictor of treatment success.

Recommendations

Larger-scale, multicenter, and prospective studies are required to fully elucidate the impact of breastfeeding status and duration on growth trajectories and therapeutic responsiveness in pediatric patients with IGHD. Future research should also evaluate the potential influence of seasonal variations, vitamin D status, and the specific bioactive composition of breast milk on growth and treatment outcomes. Furthermore, since the duration of GH therapy emerged as a key determinant of treatment response, long-term and regular monitoring of growth parameters throughout therapy remains essential.

Scientific Ethics Declaration

* Ethics committee approval for this study was obtained from the Non-Interventional Clinical Research Ethics Committee of Aydın Adnan Menderes University, Institute of Health Sciences (Date: [25.03.2026], Approval No: [2026/27]). Institutional permission was also granted by Aydın Adnan Menderes University Hospital. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

* The authors declare that the scientific ethical and legal responsibility of this article published in EPHELS journal belongs to the authors.

Conflict of Interest

* The authors declare that they have no conflicts of interest.

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Author(s) Information

Ayca Altuntepe

Selçuk University, Institute of Health Sciences
Konya, Türkiye
ORCID iD: <https://orcid.org/0009-0005-0290-0779>

*Contact e-mail: aycaaltuntepe4@gmail.com

Tolga Unuvar

Aydın Adnan Menderes University,
Aydın, Türkiye
ORCID iD: <https://orcid.org/0000-0002-5517-5030>

*Corresponding author(s) contact email

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