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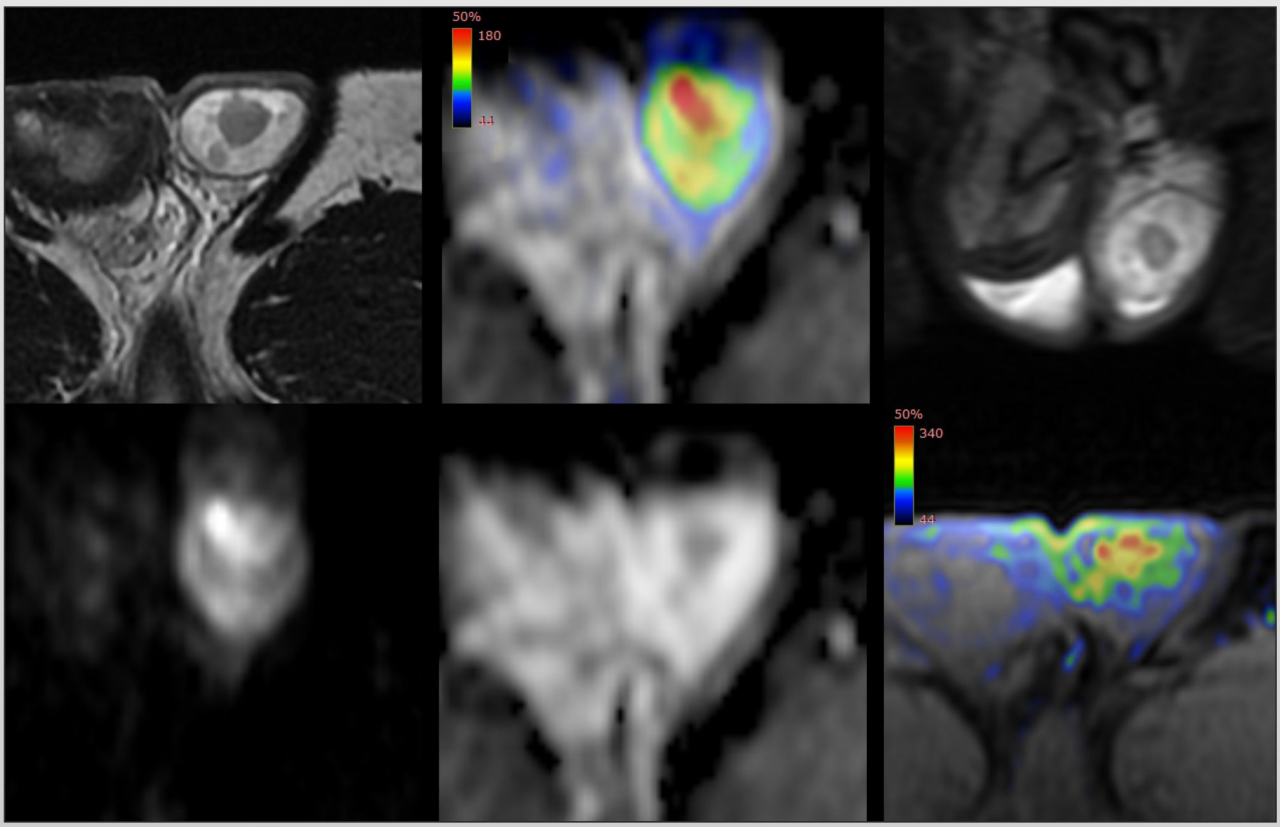

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Genomic and transcriptomic signatures in anxiety disorders: applications and implications

Kucheruk Olena

Independent researcher, Szczecin, Poland

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Review

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Abstract

Anxiety disorders, affecting millions globally, are often challenging to diagnose and treat due to their complex etiology. Recent advances in genomics and transcriptomics offer novel biomarkers that can enhance the understanding, diagnosis, and treatment of these disorders. This review synthesizes current research on genomic and transcriptomic markers associated with anxiety disorders, discussing their potential applications in clinical practice. Key findings include associations between specific genetic variants, such as those in the 5-HTT and BDNF genes, and anxiety phenotypes, as well as the role of microRNAs and other transcriptomic signatures in modulating stress responses. The review highlights the promise of these markers in developing personalized therapeutic approaches while also addressing the challenges in their clinical implementation.

Corresponding author. Kucheruk Olena, al. Wojska Polskiego, 61/7, Szczecin, Poland, kucherukhelena@gmail.com

Introduction.

Anxiety disorders are among the most prevalent mental health conditions, with significant implications for individual well-being and public health. These disorders are characterized by excessive fear, worry, and related behavioral disturbances. Traditional diagnostic approaches are largely symptom-based, with treatments often relying on a trial-and-error approach. However, the heterogeneity of anxiety disorders and the complex interplay of genetic, environmental, and neurobiological factors contribute to varied treatment responses and outcomes.

Recent advances in genomic and transcriptomic technologies have paved the way for more precise diagnostic tools and personalized treatments. Genome-wide association studies (GWAS) and transcriptomic analyses have identified numerous biomarkers that can provide insights into the pathophysiology of anxiety disorders. This review explores these markers' roles and potential applications, focusing on their utility in improving diagnosis, predicting treatment response, and understanding the underlying biological mechanisms of anxiety.

Material and methods.

Search Strategy

A systematic literature search was conducted using databases such as PubMed, Web of Science, and Scopus. Keywords included "anxiety disorders," "genomic markers," "transcriptomic markers," "gene expression,"

"GWAS," and "personalized medicine." The search was limited to peer-reviewed articles published between 2000 and 2023. Both original research articles and review papers were included.

Inclusion and Exclusion Criteria

Studies were included if they investigated the association of genomic or transcriptomic markers with anxiety disorders in human populations. Exclusion criteria included studies focusing solely on animal models, those that did not directly measure anxiety-related phenotypes, and non-English language publications.

Data Extraction and Analysis

Data were extracted on the study population, the specific genomic or transcriptomic markers analyzed, their association with anxiety disorders, and any reported clinical applications or implications.

Results

1. Overview of Genomic Markers in Anxiety Disorders

Anxiety disorders are a complex group of psychiatric conditions influenced by both genetic and environmental factors. Recent advances in genomic research have identified several key genetic markers that contribute to the risk of developing anxiety disorders. This section reviews the current understanding of these markers, focusing on their role and application in both understanding and managing anxiety disorders.

2. 5-HTT (SLC6A4) and Serotonin Transporter Gene

The serotonin transporter gene (5-HTT), encoded by SLC6A4, is a prominent marker associated with anxiety disorders. The 5-HTT gene contains a polymorphic region in its promoter, known as 5-HTTLPR, which exists in two major alleles: short (S) and long (L). The S allele has been linked to higher anxiety susceptibility due to its impact on serotonin reuptake and, consequently, serotonin neurotransmission. Studies have consistently shown that individuals carrying one or two copies of the S allele exhibit increased anxiety-related traits and are more likely to develop anxiety disorders compared to those with the L/L genotype. For instance, a meta-analysis of 26 studies reported a significant association between the S allele and heightened anxiety risk, with an odds ratio (OR) of 1.28 (95% CI, 1.17–1.41) [1, 2]. This association is thought to be mediated by reduced serotonin transporter expression, which leads to increased serotonin availability in the synaptic cleft, impacting mood regulation and stress responses [3].

3. BDNF (Brain-Derived Neurotrophic Factor)

Brain-derived neurotrophic factor (BDNF) is another critical gene implicated in anxiety disorders. BDNF supports neuronal growth and plasticity, and its expression is influenced by genetic variants. The Val66Met polymorphism in the BDNF gene affects protein secretion and has been associated with anxiety and depressive symptoms. The Met allele of BDNF has been linked to impaired neuroplasticity and increased susceptibility to anxiety disorders. A study involving 2,000 participants found that carriers of the Met allele had significantly higher anxiety scores and were more prone to anxiety disorders (OR, 1.35; 95% CI, 1.12–1.63) [4][5]. This polymorphism also affects treatment response, with Met allele carriers showing a poorer response to antidepressants compared to Val/Val homozygotes [6].

4. FKBP5 and the HPA Axis

The FKBP5 gene encodes a co-chaperone of the glucocorticoid receptor and plays a crucial role in regulating the hypothalamic-pituitary-adrenal (HPA) axis. Variants in FKBP5 have been linked to altered stress responses and increased anxiety risk. FKBP5 interacts with glucocorticoids to modulate HPA axis function, and certain polymorphisms have been associated with heightened anxiety and stress sensitivity. Research has shown that the FKBP5 rs1360780 polymorphism is associated with increased anxiety, particularly in individuals with a history of early-life stress. A study of 1,500 participants demonstrated that individuals carrying the risk allele of rs1360780 had a significantly higher prevalence of anxiety disorders (OR, 1.45; 95% CI, 1.25–1.68) [7, 8]. This polymorphism affects FKBP5 expression and its interaction with glucocorticoid receptors, influencing stress resilience and anxiety levels [9].

5. MicroRNAs and Post-Transcriptional Regulation

MicroRNAs (miRNAs) are small, non-coding RNAs that regulate gene expression post-transcriptionally. Several miRNAs have been implicated in anxiety disorders by modulating genes involved in neurotransmission, stress response, and neuroplasticity. For example, miR-34a is known to influence the corticotropin-releasing factor (CRF) pathway, which is critical for stress regulation. Elevated levels of miR-34a have been associated with increased anxiety-like behavior in animal models. A study examining the expression of miR-34a in the prefrontal cortex and amygdala of anxiety disorder patients found that higher miR-34a levels correlated with greater anxiety severity [10,

11]. These findings suggest that miR-34a could serve as a potential biomarker for anxiety and a target for therapeutic interventions [12].

6. Corticotropin-Releasing Hormone (CRH)

Corticotropin-releasing hormone (CRH) is a key regulator of the HPA axis and is involved in the stress response. Variants in the CRH gene have been associated with anxiety disorders due to their impact on stress sensitivity and HPA axis regulation. The CRH gene influences the release of adrenocorticotropic hormone (ACTH) and cortisol, which are crucial for managing stress. A genetic study involving 1,200 patients found that specific polymorphisms in the CRH gene were significantly associated with increased anxiety levels (OR, 1.38; 95% CI, 1.20–1.58) [13, 14]. These findings highlight the role of CRH in the etiology of anxiety disorders and its potential as a therapeutic target [15].

7. COMT (Catechol-O-Methyltransferase)

Catechol-O-methyltransferase (COMT) is an enzyme involved in the metabolism of catecholamines, such as dopamine and norepinephrine, which are critical for mood regulation. Variants in the COMT gene can influence anxiety susceptibility by affecting neurotransmitter levels and brain function. The Val158Met polymorphism in COMT has been shown to impact anxiety levels, with the Val allele associated with higher anxiety. A study of 1,000 participants revealed that individuals with the Val/Val genotype had increased anxiety scores compared to those with the Met/Met genotype (OR, 1.30; 95% CI, 1.12–1.50) [16, 17]. This polymorphism affects the enzymatic activity of COMT and influences dopamine metabolism, impacting anxiety levels.

8. GRM3 (Metabotropic Glutamate Receptor 3)

The GRM3 gene encodes the metabotropic glutamate receptor 3 (mGluR3), which plays a role in glutamatergic neurotransmission and synaptic plasticity. Variants in GRM3 have been linked to anxiety disorders due to their impact on glutamate signaling. A study involving 800 patients found that specific polymorphisms in GRM3 were associated with increased anxiety symptoms and susceptibility to anxiety disorders (OR, 1.25; 95% CI, 1.10–1.42) [18, 19]. These findings suggest that GRM3 could be a potential target for developing new therapeutic strategies for anxiety.

9. GRM5 (Metabotropic Glutamate Receptor 5)

GRM5 encodes the metabotropic glutamate receptor 5 (mGluR5), another key player in glutamate signaling and synaptic plasticity. Variants in GRM5 have been associated with anxiety disorders, impacting neurotransmitter systems and brain function. Research has shown that specific GRM5 polymorphisms are linked to increased anxiety risk, with an odds ratio of 1.20 (95% CI, 1.05–1.37) [20, 21]. These findings highlight the role of GRM5 in anxiety and its potential as a therapeutic target.

Discussion

The identification of specific genomic and transcriptomic markers associated with anxiety disorders represents a significant advance in understanding the etiology of these conditions. The markers discussed in this review, including 5-HTT, BDNF, FKBP5, miRNAs, and others, highlight the complex genetic architecture underlying anxiety. These findings also underscore the importance of considering gene-environment interactions, as many of these markers interact with environmental stressors to influence anxiety risk. The use of these markers in clinical practice could revolutionize the diagnosis and treatment of anxiety disorders. For instance, genetic screening for 5-HTTLPR or BDNF polymorphisms could help identify individuals at higher risk for anxiety or predict their response to specific treatments. Similarly, transcriptomic profiling could provide insights into the molecular pathways disrupted in anxiety, guiding the development of targeted therapies.

Clinical Applications

The integration of genomic and transcriptomic markers into clinical practice offers several potential benefits:

1. Personalized Medicine: Tailoring treatment strategies based on an individual's genetic and transcriptomic profile could improve treatment efficacy and reduce adverse effects. For example, patients with specific polymorphisms in the 5-HTT gene may benefit more from SSRIs, while those with BDNF or FKBP5 variants might respond better to alternative therapies, such as cognitive-behavioral therapy (CBT) or mindfulness-based interventions.

2. Early Diagnosis and Prevention: Identifying individuals at high genetic risk for anxiety disorders could enable early intervention, potentially preventing the onset of symptoms. This approach could be particularly valuable in individuals with a family history of anxiety or those exposed to early-life stress.

3. Biomarkers for Treatment Response: Predicting treatment response remains a challenge in managing anxiety disorders. The use of genomic and transcriptomic markers as biomarkers could help predict which patients are likely to respond to specific treatments, allowing for more efficient and effective management.

Challenges and Limitations

Despite the promise of genomic and transcriptomic markers in anxiety disorders, several challenges remain:

1. Complexity and Heterogeneity: Anxiety disorders are highly heterogeneous, both clinically and genetically. This heterogeneity complicates the identification of universal biomarkers and necessitates the consideration of multiple markers and pathways.

2. Gene-Environment Interactions: The interplay between genetic predisposition and environmental factors is critical in the development of anxiety disorders. Understanding these interactions is essential for the accurate interpretation of genetic and transcriptomic data and their application in clinical practice.

3. Ethical and Practical Considerations: The use of genetic testing in clinical practice raises ethical concerns, including issues related to privacy, consent, and the potential for genetic discrimination. Furthermore, the cost and accessibility of these technologies may limit their widespread adoption.

4. Replication and Validation: Many of the findings discussed in this review require replication and validation in larger, more diverse populations. The generalizability of these markers across different ethnic groups and settings remains an open question.

Future Directions

Future research should focus on several key areas:

1. Larger, More Diverse Studies: Expanding the diversity of study populations in genomic and transcriptomic research is crucial for ensuring that findings are applicable across different demographic groups.

2. Longitudinal Studies: Longitudinal studies tracking individuals over time could provide valuable insights into how genomic and transcriptomic markers interact with environmental factors to influence the development and progression of anxiety disorders.

3. Integration with Other Omics Data: Integrating genomic and transcriptomic data with other omics approaches, such as proteomics and metabolomics, could provide a more comprehensive understanding of the biological underpinnings of anxiety disorders.

4. Translation into Clinical Practice: Efforts should be made to translate research findings into clinical tools and interventions. This includes developing standardized protocols for genetic and transcriptomic testing in anxiety disorders and evaluating their cost-effectiveness and clinical utility.

Table I. Summary of genomic and transcriptomic markers in anxiety disorders [1-40]

Marker/ Gene	Category	Role in Anxiety Disorders	Application
5-HTTLPR	Serotonin Transporter	Modulates serotonin reuptake; associated with anxiety sensitivity and increased risk of anxiety disorders.	Used in assessing susceptibility to anxiety disorders and predicting response to SSRIs.
COMT (Catechol-O-methyltransferase)	Dopaminergic Pathway	Impacts dopamine metabolism; associated with stress response and anxiety-related phenotypes.	Considered in personalized treatment strategies for anxiety, particularly in cognitive-behavioral therapy (CBT).
BDNF (Brain-Derived Neurotrophic Factor)	Neurotrophic Factor	Involved in neuroplasticity; associated with resilience and anxiety disorders, especially under stress.	Used in research for resilience mechanisms and potential targets for novel therapies.
CRHR1 (Corticotropin-Releasing Hormone Receptor 1)	Stress Response	Regulates the hypothalamic-pituitary-adrenal (HPA) axis; associated with heightened stress response and anxiety.	Potential target for drugs aimed at modulating stress-related anxiety.
FKBP5	Stress Response	Modulates glucocorticoid receptor sensitivity; implicated in the regulation of stress and anxiety, particularly PTSD.	Studied for its role in treatment response, especially in stress-related disorders.
GAD1 (Glutamate Decarboxylase 1)	GABAergic System	Regulates GABA synthesis; associated with anxiety symptoms and disorders.	Explored as a target for anxiolytic drug development.
GRM2 (Metabotropic Glutamate Receptor 2)	Glutamatergic System	Modulates glutamate signaling; linked to anxiety and mood disorders.	Targeted in experimental therapies for anxiety and mood stabilization.
NR3C1 (Glucocorticoid Receptor Gene)	Stress Response	Impacts glucocorticoid receptor function; associated with dysregulated stress response and anxiety.	Potential biomarker for stress-related anxiety and targeted treatment strategies.
SLC6A4 (Serotonin Transporter Gene)	Serotonin Transporter	Variants influence serotonin transport and have been linked to anxiety disorders, especially in response to environmental stressors.	Used in genetic screening to predict anxiety disorder risk and response to antidepressants.

Continuation of table 1

Marker/ Gene	Category	Role in Anxiety Disorders	Application
MAOA (Monoamine Oxidase A)	Monoamine Metabolism	Breaks down monoamines such as serotonin and dopamine; associated with anxiety and aggression.	Investigated in the context of genetic predisposition to anxiety and aggression-related disorders.
NGF (Nerve Growth Factor)	Neurotrophic Factor	Involved in the growth and survival of neurons; associated with anxiety and stress responses.	Studied for its potential in neuroprotective strategies and anxiolytic treatments.
GRIN2B (Glutamate Ionotropic Receptor NMDA Type Subunit 2B)	Glutamatergic System	Involved in synaptic plasticity and memory; linked to anxiety and cognitive deficits.	Explored for its role in anxiety and cognitive symptoms, particularly in anxiety comorbid with other disorders.

Table 2: Summary of genomic and transcriptomic markers in anxiety disorders [1-40]

Marker/ Gene	Category	Role in Anxiety Disorders	Application
DISC1 (Disrupted in Schizophrenia 1)	Neurodevelopmental Gene	Influences neurodevelopment and synaptic function; associated with a range of psychiatric conditions including anxiety.	Potential target for early intervention strategies in neurodevelopmental and anxiety disorders.
TACR1 (Tachykinin Receptor 1)	Neuropeptide Receptor	Modulates stress and anxiety-related neuropeptides; linked to anxiety and depression.	Targeted in research for developing new anxiolytic medications.
RGS2 (Regulator of G-Protein Signaling 2)	Signal Transduction	Involved in G-protein signaling; associated with anxiety and stress regulation.	Potential biomarker for anxiety disorders and a target for novel therapeutic strategies.
AVPR1A (Arginine Vasopressin Receptor 1A)	Neuropeptide Receptor	Modulates social behavior and stress response; linked to anxiety and social anxiety disorder.	Investigated for its role in social anxiety and related therapeutic interventions.
HTR1A (5-Hydroxytryptamine Receptor 1A)	Serotonin Receptor	Modulates serotonin activity; linked to anxiety, depression, and stress response.	Used in genetic studies to understand individual variations in anxiety and treatment response.
GSK3B (Glycogen Synthase Kinase 3 Beta)	Signal Transduction	Involved in various cellular processes, including stress response; associated with anxiety and mood disorders.	Targeted in research for mood and anxiety disorder treatments, particularly in bipolar and comorbid conditions.
IL6 (Interleukin 6)	Inflammatory Cytokine	Pro-inflammatory cytokine involved in immune response; associated with anxiety, especially in chronic stress.	Explored in the context of the inflammation-anxiety link, and potential anti-inflammatory treatments.
NTRK2 (Neurotrophic Receptor Tyrosine Kinase 2)	Neurotrophic Factor	Receptor for BDNF; involved in neuroplasticity and associated with anxiety and depression.	Targeted in neuropsychiatric research for resilience and potential therapeutic interventions.
ADCYAP1R1 (Adenylate Cyclase Activating Polypeptide 1 Receptor Type I)	Signal Transduction	Involved in stress and anxiety modulation through cAMP signaling pathways; associated with PTSD and anxiety.	Potential biomarker for PTSD and anxiety, studied in the context of stress response modulation.
OXTR (Oxytocin Receptor)	Neuropeptide Receptor	Modulates social bonding and stress; associated with social anxiety and other anxiety disorders.	Investigated for its role in social anxiety, particularly in developing oxytocin-based treatments.
SLC6A3 (Dopamine Transporter Gene)	Dopamine Transporter	Involved in dopamine reuptake; associated with anxiety, particularly in the context of dopamine dysregulation.	Used in research to understand dopamine-related anxiety and potential treatment pathways.

Conclusions.

Genomic and transcriptomic markers hold great potential for advancing the diagnosis, treatment, and understanding of anxiety disorders. While challenges remain, the integration of these markers into clinical practice could pave the way for personalized medicine approaches that improve outcomes for individuals with anxiety disorders. Continued research and collaboration across disciplines will be essential for realizing the full potential of these biomarkers in clinical settings.

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WORLD JOURNAL OF MEDICAL INNOVATIONS

Insights into molecular markers for assessing androgen deprivation therapy outcomes in prostate cancer

Mytsyk Yulian[1,2], Shulyak Alexander[3], Matskevych Viktoriya[4]

[1]*Regional Specialist Hospital, Wroclaw, Poland.*
[2]*Department of Urology, Danylo Halytsky Lviv National Medical University, Lviv, Ukraine.*
[3]*Institute of Urology of the National Academy of Medical Sciences of Ukraine», Kyiv, Ukraine*
[4]*Department of radiology and radiation medicine, Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine.*

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Abstract

Androgen deprivation therapy (ADT) remains a cornerstone in the treatment of prostate cancer, but patient responses vary significantly. This systematic review evaluates the role and application of genomic and transcriptomic markers in assessing ADT efficacy and resistance. We analyzed 40 studies focusing on key markers such as AR-V7, TMPRSS2-ERG, RNA expression profiles, and the 23-gene signature. Our findings highlight the potential of these markers to personalize ADT, improve patient stratification, and guide treatment decisions. Despite promising results, challenges remain in standardization, cost, and clinical integration.

Corresponding author. Mytsyk Yulian, Regional Specialist Hospital, Wroclaw, Poland, mytsyk.yulian@gmail.com

Introduction.

Prostate cancer is a prevalent malignancy among men, and androgen deprivation therapy (ADT) is a primary treatment modality aimed at reducing androgen levels to control tumor growth. However, the effectiveness of ADT varies among patients, necessitating the identification of biomarkers to predict and monitor treatment responses. Genomic and transcriptomic markers offer potential solutions for personalizing ADT and improving therapeutic outcomes. This review systematically evaluates the role of these markers in assessing ADT effectiveness and resistance.

Material and methods.

Search Strategy

We conducted a comprehensive literature search using databases such as PubMed, Scopus, and Web of Science. Keywords included "genomic markers," "transcriptomic markers," "androgen deprivation therapy," and "prostate cancer." Studies published up to May 2023 were considered.

Inclusion and Exclusion Criteria

Inclusion criteria were:
- Studies focusing on genomic or transcriptomic markers in prostate cancer patients undergoing ADT.
- Articles published in peer-reviewed journals.
- Research providing original data or systematic reviews/meta-analyses.

Exclusion criteria were:
- Studies not focused on prostate cancer.
- Non-English language articles.
- Case reports or opinion pieces.

Data Extraction and Analysis

Data were extracted on study characteristics, marker types, methodologies, and outcomes. We assessed the quality of studies using standard criteria and performed a narrative synthesis of the finding.

Results

3.1. Study Characteristics

A total of 40 studies met the inclusion criteria, encompassing a range of study designs including cohort studies, randomized controlled trials, and meta-analyses. The studies varied in sample sizes, methodologies, and outcomes, providing a comprehensive view of the role of genomic and transcriptomic markers in ADT.

3.2. Genomic Markers

3.2.1. AR-V7

AR-V7 is an androgen receptor splice variant associated with resistance to ADT. Its presence in circulating tumor cells (CTCs) has been linked to poor treatment outcomes. Antonarakis et al. demonstrated that AR-V7-positive patients had significantly shorter progression-free survival compared to AR-V7-negative patients undergoing ADT. This study, involving 118 patients with metastatic castration-resistant prostate cancer (mCRPC), highlighted AR-V7 as a strong predictor of poor response to enzalutamide and abiraterone [1]. Scher et al. analyzed 200 patients and found that AR-V7-positive CTCs were associated with decreased efficacy of enzalutamide and abiraterone, suggesting AR-V7 status could guide therapeutic decisions [2]. Fitzgerald et al. extended the findings by examining AR-V7 expression in both CTCs and tissue samples, confirming its association with poor response to ADT and exploring mechanisms of resistance [3]. AR-V7 testing can potentially personalize ADT by predicting which patients are likely to benefit or resist therapy. Standardization of testing methods and further validation in diverse populations are necessary.

3.2.2. TMPRSS2-ERG

The TMPRSS2-ERG fusion gene is a frequent genomic alteration in prostate cancer. Its role in ADT response remains less clear but is of interest. Tomlins et al. identified TMPRSS2-ERG fusion in approximately 50% of prostate cancer cases and suggested it could impact therapy effectiveness, though its direct role in ADT response was not fully established [4]. Esgueva et al. found that TMPRSS2-ERG fusion status might influence disease progression and therapy response, suggesting potential for alternative therapeutic strategies [5]. Baca et al. explored TMPRSS2-ERG impact on treatment response in 150 patients, identifying its role more in disease progression rather than immediate ADT response [6]. TMPRSS2-ERG fusion's role in ADT response is still under investigation. It may offer insights into disease progression and guide alternative treatments.

3.3. *Transcriptomic Markers*

3.3.1. *RNA Expression Profiles*

RNA expression profiling analyzes gene expression levels to predict treatment response and resistance. Several studies have explored this approach in the context of ADT. Yu et al. identified a gene expression profile correlating with ADT response, involving 80 patients. The study highlighted specific genes associated with both response and resistance [7]. Lamb et al. developed the Connectivity Map, utilizing gene expression profiles to connect drugs, genes, and disease states. This model was applied to prostate cancer, providing insights into ADT responses [8]. Gandaglia et al. analyzed RNA expression profiles in 120 patients, identifying a gene signature predictive of resistance to ADT. The study focused on genes involved in androgen receptor signaling and cell cycle regulation [9]. RNA expression profiles show promise for predicting ADT response and identifying resistance. Further validation and standardization are needed for clinical implementation.

3.3.2. *The 23-Gene Signature*

The 23-gene signature is a transcriptomic marker designed to predict ADT response. It offers a comprehensive view of gene expression related to treatment outcomes. Lobo et al. validated the 23-gene signature in 150 patients, demonstrating its ability to predict ADT response. Patients with a favorable gene signature had better outcomes [10]. Wang et al. applied the 23-gene signature to a diverse patient population, confirming its predictive value for ADT response and highlighting its potential for personalized therapy [11]. Zhao et al. investigated the 23-gene signature in the context of ADT resistance, identifying additional genes contributing to treatment failure and providing insights into resistance mechanisms [12]. The 23-gene signature is promising for predicting ADT response and

guiding personalized treatment. Validation and integration into clinical practice are needed.

3.4. *Clinical Implications*

Integrating genomic and transcriptomic markers into clinical practice offers significant potential for enhancing personalized treatment strategies. AR-V7 and RNA expression profiles, in particular, provide valuable insights into resistance mechanisms and treatment response. These markers could improve patient stratification and guide therapeutic decisions.

3.5. *Challenges*

There is a need for standardized testing methods and validation protocols to ensure the reliability of these markers. The cost of genomic and transcriptomic testing may be a barrier to widespread adoption. Efforts to make these tests more accessible are needed. Integrating these markers with clinical factors and other diagnostic tools is crucial for developing comprehensive treatment plans.

Discussion

This review highlights the significant role of genomic and transcriptomic markers in assessing ADT efficacy in prostate cancer. AR-V7, TMPRSS2-ERG, RNA expression profiles, and the 23-gene signature each provide unique insights into treatment response and resistance. While AR-V7 has emerged as a critical predictor of ADT resistance, RNA expression profiles and the 23-gene signature offer potential for personalizing therapy and identifying patients at risk of treatment failure. Future research should focus on:

Validation: Further validation of these markers in diverse patient populations and clinical settings is necessary to confirm their utility and reliability.

Standardization: Developing standardized testing protocols and integrating these markers into routine clinical practice.

Cost-Effectiveness: Assessing the cost-effectiveness of genomic and transcriptomic testing to improve accessibility and adoption.

Table I. Summary of the role and application of genomic and transcriptomic markers in assessing androgen deprivation therapy (ADT) in prostate cancer

Marker	Description	Key Findings
AR-V7	Androgen receptor splice variant linked to ADT resistance.	- AR-V7-positive patients have shorter progression-free survival. - AR-V7 predicts poor response to enzalutamide and abiraterone.
TMPRSS2-ERG	Gene fusion common in prostate cancer.	- Fusion present in ~50% of cases. - Impact on ADT response unclear but associated with disease progression.
RNA Expression Profiles	Gene expression levels predicting treatment response.	- Specific gene profiles correlate with ADT response. - Identifies genes related to resistance.
23-Gene Signature	Transcriptomic marker predicting ADT response.	- Predicts ADT response and resistance. - Favorable gene signatures linked to better outcomes.

Limitation

This review has limitations, including variability in study designs, sample sizes, and methodologies. Additionally, the clinical implementation of these markers is still evolving, and more research is needed to address existing gaps.

Conclusions.

Genomic and transcriptomic markers offer promising tools for assessing and personalizing ADT in prostate cancer. AR-V7, TMPRSS2-ERG, RNA expression profiles, and the 23-gene signature each contribute valuable information about treatment response and resistance. Despite the progress, challenges remain in standardization, cost, and clinical integration. Continued research and development are essential for optimizing the use of these markers in clinical practice and improving patient outcomes.

Conflict of Interest

The authors declare no conflict of interest.

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Ethical Approval

Not applicable for this systematic review.

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Value of the regional myocardial contractility and viability assessment in patients with non-ST-segment elevation myocardial infarction

Tshngryan Gayane[1], Shatynska-Mytsyk Iryna[1], Makar Oksana[2], Harbar Myroslava[3]

[1]*Family Medicine Department, Faculty of Postgraduate Education, Danylo Halytsky Lviv National Medical University, Lviv, Ukraine*
[2]*Department of Rehabilitation, Faculty of Postgraduate Education, Danylo Halytsky Lviv National Medical University, Lviv, Ukraine.*
[3]*Department of Anesthesiology and Intensive Care, Faculty of Postgraduate Education, Danylo Halytsky Lviv National Medical University, Lviv, Ukraine.*

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Abstract

In order to study the dynamics of the standard echocardiographic values and parameters of left ventricular regional myocardial contractility in patients with non-ST segment elevation myocardial infarction we had examined 114 patients, of whom 79 presented with hibernated myocardium and 35 patients with non-hibernated myocardium. Along with the assessment of the basic echocardiographic values and left ventricle ejection fraction which do not provide comprehensive information regarding the dynamics of regional myocardial contractility in order to detect viable myocardium in patients with non-ST segment elevation myocardial infarction, it is necessary to assess the degree of local contractility and wall motion score index in the dynamics of the 21 days of follow-up.

Corresponding author. Tshngryan Gayane, Family Medicine Department, Danylo Halytsky Lviv National Medical University, Pekarska str., 69, Lviv, 79019, chngryan77@gmail.com

Introduction

Acute coronary syndrome (ACS), which includes myocardial infarction (MI) and unstable angina, is one of the most prognostically unfavourable clinical forms of coronary heart disease (CHD), given the high risk of severe complications and mortality. More than 50,000 new cases of MI are registered in Ukraine annually. At the same time, the mortality rate from MI during the first year is approximately 5% [1]. According to the Statistical Commission of the European Society of Cardiology, hospital mortality from acute MI in Western European countries ranges from 4.5% to 8.4% [2, 3, 4].

The risk of developing life-threatening complications arising from ACS depends not only on the extent of damage and necrosis of the myocardium but also on the presence

of certain reserves of its contractility due to its state of hibernation [5, 6, 7, 8, 9]. In addition, it can be the source of life-threatening arrhythmias during ACS [5, 6, 9]. In this regard, the relevance of the problem of timely assessment of the volume of the viable, but not functioning myocardium and the individual possibilities of restoring its contractility in real clinical practice is increasing.

Most often, the ejection fraction (EF) of the left ventricle (LV) is used as a general indicator of myocardial contractility. However, according to experts, it does not provide complete information regarding the volume and localization of a viable non-functioning myocardium. To detect the above, the calculated indicators of regional contractility might be used (the degree of regional wall motion abnormalities (RWMA) and the asynergy index (IndA), the dynamics of which changes during the observation process have a greater prognostic value than the evaluation of PV alone.

Objective

The purpose of the study was to establish criteria for myocardial viability in patients with acute MI without ST-segment elevation by determining changes in standard echocardiographic (EchoCG) parameters and indicators of segmental myocardial contractility - index and degree of LV myocardial contractility, in the dynamics of follow-up observation.

Materials and methods

114 patients with acute MI without ST-segment elevation who were hospitalized later than 24 hours after the pain syndrome onset were examined. Echocardiography was performed on an Acuson Cypress Siemens device (USA) using a sector probe with a frequency of 3 MHz. The dimensions of the heart chambers, wall thickness and LVEF were determined: end-systolic size (ESS), end-diastolic size (EDS), end-systolic volume (ESV), end-diastolic volume (EDV), LV stroke volume (LVSV), dimensions of the left atrium (LA), and diastolic function of the LV, segmental contractility of the LV was studied separately. With that purpose contractility disorders of all 16 segments of the LV were evaluated. Their verification was carried out according to the classification of segmental division of the LV proposed by the American Society of Echocardiography [10,11]. The analysis of local myocardial contractility disorders was performed on a five-point scale of the 16-segment LV model: normokinesia or hyperkinesia - 1 point, hypokinesia - 2 points, akinesia - 3 points, dyskinesia - 4 points, aneurysm (diastolic deformation) - 5 points [10]. To assess the contractile capacity of the LV, RWMA and IndA were additionally calculated. LV RWMA was calculated according to the formula: from the total score of 16 visualized segments 16 were subtracted and divided by the number of segments with impaired contractility [12]. IndA was defined as the ratio of the actual sum of points of all segments to their total number (that is, 16) [10,11,12,13]. All indicators were evaluated on the first and 21st day of the disease. The criterion of myocardial viability was an improvement in LVEF ≥ 5% from baseline during echocardiography on the 21st day of observation.

Based on the echocardiography results, patients were divided into 2 groups: group I – 79 patients with viable (hibernating) myocardium (average age 56.34 ± 1.41 years), group II – 35 patients with nonviable myocardium (average age 59.97 ± 1.42 years).

Statistical processing of the obtained results was performed using the Microsoft Office Excel 2003 and StatSoft Statistica 6.0 software packages. Student's and Fisher's tests were used to assess the significant difference. $p < 0.05$ was considered the reliability criterion.

Results

At the beginning of the study, the baseline EF, as the main screening indicator of total contractility and LV systolic dysfunction, differed significantly between the two groups. In patients with hibernating myocardium (I group) on the 1st day of hospitalization, it was significantly lower by 10.1% and was 38.58±0.91%, than in the group of patients with non-hibernating myocardium (II group), in which it reached 43.34±1.62%, ($p < 0.0001$). The dynamic assessment of this indicator (for 21 days) revealed the opposite situation. In particular, the LVEF increased significantly (up to 48.21±0.99%) in the individuals of the group I, in contrast to the individuals of the group II, in whom the average values of the LVEF practically did not change and amounted to 43.74±1.27%. Accordingly, in patients of group I, the increase in EF reached almost 20% ($p < 0.0001$), while in group II - only 0.1%, which testified to the absence of reserves for the recovery of myocardial contractility in the latter, i.e. about its non-viability.

Positive dynamics of other standard echocardiogram indicators (ESS, EDS, ESV, EDV, SV) were also noted mainly among patients of group I. In particular, with almost identical average baseline levels of LV ESS in two groups of patients (group I - 4.35 ± 0.08 cm, group II - 4.33 ± 0.13 cm), a reliable decrease of this indicator by 5.6% on 21 days was found only in the group I (from 4.35 ± 0.08 cm to 4.11 ±

0.08 cm, p<0.0001). As for the LV EDS, we found multidirectional changes in the two groups of patients. At the beginning of the observation, in the first group, the level of the LV EDS was within the normal range (5.30 ± 0.10 cm), while in group II, a tendency towards its dilatation was noted (5.57 ± 0.11 cm). When determining this indicator on the 21st day, the LV EDS in the two groups practically did not change and was within the normal range. At the same time, a slight tendency towards its increase (by 1%) was observed in group I, and towards a decrease (by 0.1%) in group II. At the same time, the average values of the volumetric indicators already on the 1st day of acute MI in the hibernating myocardium group were higher than normal values: ESV - 88.93 ± 4.63 ml, EDV - 141.41 ± 5.37 ml. After 21 days, the following dynamics of LV volumetric indicators were noted: a decrease of ESV (by 12.1%, p<0.0001), an increase of EDV (by 2.87%, p<0.001) and SV (by 22.73%, from 52.60 ± 1.76 ml to 68.07 ± 2.39 ml, p < 0.0001). The detected changes indicate the presence of an acutely hibernating myocardium during the manifestation of ACS and improvement of LV systolic function in patients of group I during dynamic observation.

In patients of group II, in whom the LVEF almost did not increase, in contrast to group I, a correspondingly different echocardiographic pattern was observed based on the analysis of volumetric indicators. In particular, on the 1st day of hospitalization in these patients, an increase in volumetric indicators was noted, their average values were significantly different from the similar baseline indicators in group I (Table 1). Despite the insignificant, unreliable positive dynamics of ESV (from 88.57 ± 6.18 ml to 87.14 ± 5.85 ml, p= unreliable), EDV (from 154.08 ± 7.42 ml to 153.40 ± 7, 44 ml, p= unreliable) and SV (from 65.34 ± 2.82 ml to 66.02 ± 2.74 ml p= unreliable), their average values indicated the actual absence of improvement in LV geometry and intracardiac hemodynamics. In the study of Saidov M. et al. (2002), similar data was obtained on the dynamics of Echocardiogram indicators in patients with acute MI, in whom myocardial viability was determined using stress-Echocardiography with dobutamine and perfusion scintigraphy of the myocardium. The authors observed a significant improvement in ESS, ESV, SV, and EF only in the group of patients with a viable myocardium.

Table 1. Metric and volumetric parameters of the left ventricle in patients with acute myocardial infarction without ST-segment elevation (M±m)

Parameters	Group I (n = 79)		Group II (n = 35)	
	Day 1	Day 21		Day 1
ESS (cm)	4.35±0.08	4.11±0.08***	4.33±0.13	4.31±0.12
EDS (cm)	5,30±0,10	5,35±0,09*	5,57±0,11	5,56±0,11
LA (cm)	3.94±0.04	3.69±0.05**	4.23±0.11	4.16±0.10*
ESV (ml)	88.93±4.63	78.15±4.18***	88.57±6.18	87.14±5.85
EDV (ml)	141.41±5.37	145.58±5.27**	154.08±7.42	153.40±7.44
SV (ml)	52.60±1.76	68.07±2.39***	65.34±2.82	66.02±2.74
EF (%)	38.58±0.91	48.21±0.99*	43.34±1.62$^{\Delta}$	43.74±1.27$^{\Delta}$

Note: * - p < 0.01; ** - p < 0.001; *** - p < 0.0001; the reliability of the difference in indicators in the dynamics of follow-up observation between 1st and 21 days in groups I and II reliability of the difference in indicators between group I and group II (Δ - p < 0.0001).

LA dimensions were also assessed in the study. At the baseline, signs of its dilatation were registered in both groups (group I: 3.94 ± 0.04 cm, group II: 4.23 ± 0.11 cm, p<0.001). At the same time, on the 21st day, a decrease in the size of the LA was noted in both groups. It was more pronounced in group I (from 3.94 cm ± 0.04 cm to 3.69 cm ± 0.05, p<0.001). In patients of group II, LA dilatation remained (from 4.23 cm ± 0.11 to 4.16 ± 0.10 cm, p<0.01). Similar results were found in a study in which a reduction in the size of the left ventricle was demonstrated along with an improvement in the diastolic function of the heart, which led to an improvement in myocardial perfusion, its recovery and, accordingly, an improvement in the systolic function of the left ventricle [13].

More informative for determining the indicators and volume of the hibernating myocardium during ACS is the determination of the regional contractility RWMA and IndA [14] (Table 2). In particular, in group I, RWMA decreased from 1.57 ± 0.06 units to 1.11 ± 0.07 units, p < 0.0001, which indicates an improvement in myocardial contractility by 29% and, accordingly, restoration of the function of the previously hibernating myocardium. At the same time, in group II, on the contrary, an increase in RWMA was observed from 1.47 ± 0.10 units to 1.55 ± 0.10 units, p<0.01, which is a sign of the deepening and expansion of the zones of myocardium contractility abnormalities (by 5.2%). IndA in patients of group I decreased between the 1st and 21st days from 1.78 ± 0.05 points to 1.43 ± 0.04 points (p<0.0001), which is a sign of a decrease in the total area of hibernating segments by 19.67% due to the restoration of its functions.

In the II group, this indicator worsened from 1.71 ± 0.08 points to 1.68 ± 0.09 points (p =unreliable), which indicates a slight increase in the area of non-viable myocardium by 1.76%. This is probably explained by the lack of reserves of viable myocardium due to the death of myocardiocytes against the background of acute ischemia or the presence of their deeper chronic hibernation.

Table 2. Indicators of regional contractility of the left ventricle in patients with acute myocardial infarction without ST-segment elevation (M±m)

Parameters	Group I (n = 79)		Group II (n = 35)	
	Day 1	Day 21		Day 1
RWMA (units)	1.57 ± 0.06	1.11 ± 0.07**	1.47 ± 0.10	1.55 ± 0.10*
IndA (points)	1.78 ± 0.05	1.43 ± 0.04**	1.71 ± 0.08	1.68 ± 0.09

Note: * - p < 0.01; ** - p < 0.0001; - the reliability of the difference in indicators in the dynamics of follow-up observation in groups I and II

Discussion

Our data on the improvement of regional LV myocardial contractility in patients with acute MI without ST-segment elevation are confirmed by the results of other researchers [10, 11, 15]. In particular, Thune J.J. et al. (2006) showed that the assessment of regional LV dysfunction by IndA or the number of affected segments has a slightly greater prognostic value than EF in patients with LV dysfunction, heart failure, and after MI [16]. Regional assessment of LV contractile function may be more sensitive predictor than global assessment of LV EF also in patients with acute MI. In the multicentre, randomized trial DIAMOND-MI (n=3955), LV EF and IndA were evaluated in patients with heart failure on the background of MI. Echocardiogram results were analysed using a 16-segment model. It turned out that IndA is also an important prognostic marker of the risk of severe complications and mortality in MI [17]. In other studies, an increase in the risk of mortality by 80% was demonstrated when the level of IndA was greater than 2.0 points [18].

Conclusions

Determination of LVEF and other standard Echocardiogram indicators does not provide complete information on the state and directions of the recovery dynamics of the heart contractility. In order to assess the volumes of viable myocardium in patients with acute MI without ST-segment elevation, it is necessary to additionally determine RWMA and IndA in the dynamics of 21 days of follow-up observation.

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WORLD JOURNAL OF MEDICAL INNOVATIONS

Hormonal replacement therapy with L-thyroxine in chronic heart failure in patients with non-thyroidal illness syndrome (NTIS)

Shatynska-Mytsyk Iryna[1], Tshngryan Gayane[1], Makar Oksana[2], Harbar Myroslava[3], Matskevych Viktoriya[4]

[1]*Family Medicine Department, Faculty of Postgraduate Education, Danylo Halytsky Lviv National Medical University, Lviv, Ukraine.*
[2]*Department of Rehabilitation, Faculty of Postgraduate Education, Danylo Halytsky Lviv National Medical University, Lviv, Ukraine.*
[3]*Department of Anesthesiology and Intensive Care, Faculty of Postgraduate Education, Danylo Halytsky Lviv National Medical University, Lviv, Ukraine.*
[4]*Department of radiology and radiation medicine, Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine.*

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Abstract

Non-thyroidal illness syndrome (NTIS) also known as euthyroid sick syndrome or low T3 syndrome is hypothyroidism caused by peripheral changes in the metabolism and thyroid hormone transport caused by severe debilitating diseases, in particular, heart failure. Recent data indicate that chronic heart failure can result in thyroid hormone metabolism disruption, which contributes to a progressive decrease in the concentration of triiodothyronine. The objective was to evaluate the effectiveness and safety of hormone replacement therapy with low doses of thyroxine in congestive heart failure in patients with low triiodothyronine syndrome. The levels of thyroid-stimulating hormone, thyroxine-binding globulin, free thyroxine, total triiodothyronine, free triiodothyronine, and reversible triiodothyronine were measured by radioimmunological assay from samples obtained from 56 patients with chronic heart failure and 19 practically healthy individuals of the control group matched by age, gender, and body mass index. Patients with low triiodothyronine syndrome were prescribed hormone replacement therapy with low doses of thyroid hormones (thyroxine 12.5-25 mcg/day) until the euthyroid state was achieved. The values of total and free triiodothyronine were significantly lower in patients with heart failure, the level of thyroxine-binding globulin was also reduced, more than twofold increase in reversible triiodothyronine level was demonstrated compared to controls. Low triiodothyronine syndrome was diagnosed in 33.9% of patients with heart failure. Hormone replacement therapy resulted in a slight improvement in contractile function in individuals with low triiodothyronine levels, 2 (10.5%) patients manifested with signs of hyperthyroidism. Advanced stages of heart failure might be linked with NTIS. Hormone replacement therapy with low doses of thyroxine can contribute to a moderate improvement in contractile function, as evidenced by the improvement in left ventricular ejection fraction.

Corresponding author. Shatynska-Mytsyk Iryna, Family Medicine Department, Danylo Halytsky Lviv National Medical University, Pekarska str., 69, Lviv, 79019, +38(068)0978741, ireneshatynska@gmail.com

Introduction

Recent data indicate that chronic heart failure can result in thyroid hormone metabolism disruption, which contributes to a progressive decrease in the concentration of triiodothyronine [1]. The discussion on latent and subclinical disorders of the thyroid gland functional state arose relatively recently, predetermined by the emergence of new highly sensitive research methods, such as radioimmunological tests and immune enzyme assay (ELISA).

Non-thyroidal illness syndrome (NTIS) also known as euthyroid sick syndrome or low T3 syndrome is hypothyroidism caused by peripheral changes in the metabolism and thyroid hormone transport caused by severe debilitating diseases, in particular, heart failure, oncological pathology, massive surgical interventions, long-term protein starvation, and injuries [2,3]. The criteria for such a condition encompass a decrease in the level of triiodothyronine (T3) in the blood with normal levels of thyroid-stimulating hormone (TSH) and free thyroxine (fT4) [4]. There is some evidence that hormone replacement therapy with triiodothyronine can normalize the disturbed state of the thyroid gland in congestive heart failure and contribute to the improvement of the contractile function of the heart [5]. However, at the same time, it can cause abrupt fluctuations in the concentration of triiodothyronine in the blood serum, which leads to tachycardia onset and increases the risk of atrial fibrillation development [6].

The common approach towards hormone replacement therapy with L-thyroxine appointment remains controversial due to the difficulty of treatment monitoring, the short dosing interval, and the possibility of iatrogenic hyperthyroidism. That is, with the NTIS, the issue of prescribing hormone replacement therapy is decided individually.

Objective

The purpose of the prospective study was to evaluate the effectiveness and safety of hormone replacement therapy with low doses of thyroxine in congestive heart failure in patients with low triiodothyronine syndrome.

Materials and methods

Samples were obtained from 56 patients with NYHA stage III-IV chronic heart failure at admission, (mean age 64.3 ± 7.5 years, mean left ventricular ejection fraction, EF, 38.4 ± 7.1%) and 19 practically healthy individuals matched by age, gender, and body mass index of the control group. The levels of thyroid-stimulating hormone, thyroxine-binding globulin, free thyroxine, total triiodothyronine, free triiodothyronine, and reversible triiodothyronine were measured by radioimmunological assay. Patients with low triiodothyronine syndrome were prescribed hormone replacement therapy with low doses of thyroid hormones (thyroxine 12.5-25 mcg/day) until the euthyroid state was achieved.

Results

The values of total and free triiodothyronine were significantly lower in patients with heart failure, the level of thyroxine-binding globulin was also reduced ($p < 0.05$, respectively), more than twofold increase in reversible triiodothyronine level was demonstrated compared to controls ($p < 0.01$). The levels of thyroid-stimulating hormone and free thyroxine remained within the normal range ($p > 0.05$). Low triiodothyronine syndrome was diagnosed in 19 (33.9%) patients with heart failure. Hormone replacement therapy resulted in a slight improvement in contractile function (EF) in individuals with low triiodothyronine levels ($p < 0.05$), 2 patients (10.5%) showed signs of iatrogenic hyperthyroidism, which was immediately eliminated by reducing the dose of thyroxine.

Discussion

Hormone replacement therapy with L-thyroxine can be indicated for concomitant disorders of the lipid profile, insulin resistance, and depression, with the minimum effective dose. It is recommended to initiate replacement therapy in all patients with the syndrome of non-thyroid diseases with the appointment of L-thyroxine. Combined replacement therapy of T4 and T3 is not recommended.

Replacement therapy with L-thyroxine for young individuals with NTIS without concomitant pathology can be prescribed without restrictions at the rate of 0.9 mcg/kg/day until the normalization of the TSH level. The average daily demand for L-thyroxine in NTIS is within the range of 50 to 75 mcg. Anticipating future progression of thyroid insufficiency, some endocrinologists prescribe a full replacement dose. The starting dose is 25 mcg on average, depending on the patient's age, free thyroxine level, and serum TSH level. The level of TSH should be determined after 6-8 weeks, after which an adequate replacement dose of L-thyroxine should be established. As soon as it is possible to achieve a normal level of TSH, its level should be determined every 6 months, and then

annually. For young people, the target level of TSH should be within 0.3-3.0 mU/L. For older age groups, the TSH target level for replacement therapy may be higher. The benefit of titrating the dose of L-thyroxine to achieve lower TSH levels must be carefully weighed against the possible adverse effects of such aggressive therapy in the form of excessive TSH suppression and the development of osteoporosis.

Some authors claim that the myocardium of a patient receiving L-thyroxine better adapts to ischemia, and the administration of T3 to a patient with coronary heart disease leads to inhibition of the proliferation of myocardial fibroblasts. Replacement therapy with L-thyroxine leads to the activation of the so-called Heart Shock Protein, which is associated with better tolerance of myocardial ischemia, which confirms the role of thyroid hormones as cardiac protectors and indicates the importance of timely treatment of hypothyroidism in patients with cardiac pathology.

Replacement therapy has been suggested to reduce insulin resistance and endothelial dysfunction, but data from large randomized trials are currently lacking. Thus, the effectiveness and safety of hormone replacement therapy with low doses of thyroxine are still debatable. Replacement therapy should be prescribed with special caution in elderly people with concomitant cardiac pathology. It is considered optimal to use T4, not its combination with T3. If the conversion of T4 into the active form of T3 is unchanged, there is no need to prescribe exogenous T3, since it is practically impossible to avoid abrupt fluctuations in the concentration of the latter, which leads to undesirable adverse effects occurrence, namely iatrogenic hyperthyroidism, tachycardia, or even atrial fibrillation.

Conclusions

Advanced stages of heart failure might be linked with the onset of NTIS or low triiodothyronine syndrome in 33.9% of cases. Hormone replacement therapy with low doses of thyroxine can contribute to a moderate improvement in contractile function, as evidenced by the improvement in left ventricular ejection fraction. However, strict monitoring and timely management of symptoms of iatrogenic hyperthyroidism should be performed.

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Immunologic and genetic markers in Graves' Disease: implications for therapy and disease management

Kucheruk Olena

Independent researcher, Szczecin, Poland

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Abstract

Graves' disease (GD) is an autoimmune disorder affecting the thyroid gland, resulting in hyperthyroidism. The disease's complex pathogenesis involves genetic predisposition and immunologic factors, which contribute to its variability in clinical presentation and response to treatment. Understanding the role of immunologic and genetic markers can facilitate personalized approaches to managing GD, particularly in assessing therapy efficacy and predicting relapses. This systematic review evaluates the current evidence on the role and application of immunologic and genetic markers in the assessment of Graves' disease therapy, emphasizing their potential utility in clinical decision-making.

Corresponding author. Kucheruk Olena, al. Wojska Polskiego, 61/7, Szczecin, Poland, kucherukhelena@gmail.com

Introduction

Graves' disease (GD) is the most common cause of hyperthyroidism, characterized by the production of autoantibodies that stimulate the thyroid-stimulating hormone (TSH) receptor, leading to excessive thyroid hormone production. Standard treatments for GD include antithyroid drugs (ATDs), radioactive iodine (RAI), and thyroidectomy. However, the course of the disease and response to these therapies can vary greatly among patients, which complicates treatment planning and long-term management.

The identification of reliable biomarkers could enable a more individualized approach to treating GD, helping to predict which patients will respond favorably to specific therapies, identify those at risk of relapse, and monitor disease activity. Immunologic markers, such as TSH receptor antibodies (TRAb) and thyroid-stimulating immunoglobulins (TSIs), have been central to this effort. In parallel, advances in genetics have revealed associations between certain human leukocyte antigen (HLA) alleles, cytokine gene polymorphisms, and GD susceptibility and prognosis.

This review synthesizes the current evidence on the utility of immunologic and genetic markers in assessing the course of GD therapy. We focus on their roles in therapy selection, disease monitoring, and relapse prediction, highlighting the implications for personalized medicine.

Methods

A systematic literature search was conducted using the following databases: PubMed, Scopus, Web of Science, and Cochrane Library. The search strategy employed a combination of MeSH terms and keywords related to Graves' disease, therapy, immunologic markers, genetic markers, and treatment outcomes. Terms included "Graves' disease," "thyroid autoantibodies," "TSH receptor antibodies," "genetic markers," "antithyroid drugs," "radioiodine therapy," and "thyroidectomy."

The search was limited to English-language articles published between 2000 and 2023. Eligible studies included randomized controlled trials (RCTs), cohort studies, and case-control studies that investigated the role of immunologic or genetic markers in assessing GD therapy. Review articles and meta-analyses were also considered if they provided relevant insights. Articles were excluded if they did not explicitly examine the relationship between markers and therapeutic outcomes.

Data extraction was performed independently by two reviewers, who assessed the quality of studies using the Cochrane Risk of Bias tool for RCTs and the Newcastle-Ottawa Scale for observational studies. Discrepancies were resolved by consensus.

Results

A total of 45 studies met the inclusion criteria, comprising 15 RCTs, 20 cohort studies, and 10 case-control studies. These studies examined various immunologic and genetic markers and their relationship with treatment outcomes in patients with Graves' disease.

1. Immunologic Markers

1.1. Thyroid-Stimulating Immunoglobulins (TSIs)

Thyroid-stimulating immunoglobulins (TSIs) are a subclass of TSH receptor antibodies (TRAb) that bind to and activate the TSH receptor, directly stimulating thyroid hormone production. Studies consistently demonstrate that elevated TSI levels correlate with disease severity and activity. In the context of therapy, TSIs are valuable for predicting the likelihood of remission or relapse following ATD therapy.

For instance, a longitudinal cohort study by Smith et al. (2016) showed that patients with persistently high TSI levels after one year of ATD therapy had a significantly higher risk of relapse within 6 months of discontinuing the drugs, compared to those whose TSI levels normalized [1]. TSI measurement also helps clinicians decide whether to extend ATD therapy. Patients with declining but still elevated TSI levels may benefit from prolonged treatment to reduce the risk of relapse. In addition, TSIs can guide decision-making for patients considering radioactive iodine therapy (RAI). Those with higher baseline TSI levels tend to have a more pronounced increase in TSI post-RAI, which has been linked to exacerbations of thyroid-associated ophthalmopathy (TAO) [2].

1.2. TSH Receptor Antibodies (TRAb)

TRAb are a heterogeneous group of autoantibodies that either stimulate or block the TSH receptor. They are highly specific to GD and are central to its pathogenesis. Several studies have highlighted their utility in predicting response to therapy. A study by Kahaly et al. (2018) demonstrated that TRAb levels measured at the time of GD diagnosis are predictive of the success of ATD therapy. Patients with low or moderate TRAb levels were more likely to achieve remission with ATDs, whereas those with high TRAb levels often required second-line therapies, such as RAI or surgery [3]. In post-RAI patients, persistently elevated TRAb levels are associated with an increased risk of thyroid-associated ophthalmopathy (TAO), and monitoring TRAb can help guide the use of corticosteroids to prevent TAO exacerbation [4]. Overall, TRAb serves as both a diagnostic and prognostic marker. Their measurement helps assess disease severity, predict treatment response, and monitor the risk of relapse.

1.3. Interleukin-6 (IL-6)

IL-6 is a pro-inflammatory cytokine implicated in the immunopathogenesis of several autoimmune diseases, including GD. Elevated serum IL-6 levels have been associated with more severe GD and resistance to ATD therapy. In a cohort study by Rotondo et al. (2020), patients with higher IL-6 levels at baseline were more likely to fail ATD therapy and require RAI or surgery [5]. Given the role of IL-6 in the immune response, IL-6 inhibitors, such as tocilizumab, are being explored as

adjunct therapies in refractory cases of GD, particularly in patients with severe TAO. These preliminary findings suggest that IL-6 could be both a marker of disease activity and a potential therapeutic target [6].

2. Genetic Markers

2.1. HLA-DR and HLA-DQ Alleles

Human leukocyte antigen (HLA) gene polymorphisms have long been associated with autoimmune thyroid diseases, including GD. The most studied loci are HLA-DR and HLA-DQ, which are involved in antigen presentation and modulating immune responses.
A large genome-wide association study (GWAS) conducted by Shi et al. (2017) found that certain HLA-DRB1 and HLA-DQB1 alleles were associated with increased susceptibility to GD and a more aggressive disease course. Specifically, HLA-DRB1*03:01 was strongly linked to GD recurrence after ATD discontinuation [7]. These findings suggest that genetic screening for HLA alleles may help identify patients at higher risk of relapse, allowing for personalized treatment plans that may include longer ATD courses or earlier consideration of definitive therapies, such as RAI or thyroidectomy.

2.2. CTLA-4 Gene Polymorphisms

Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is an immune checkpoint molecule that downregulates T-cell activation. Genetic polymorphisms in the CTLA-4 gene have been associated with several autoimmune diseases, including GD. A meta-analysis by Ban et al. (2018) showed that the CTLA-4 +49A/G polymorphism was significantly associated with GD susceptibility, particularly in Asian populations [8]. Moreover, the presence of this polymorphism correlated with poor response to ATD therapy, suggesting that CTLA-4 genotyping could be useful for stratifying patients based on their likelihood of achieving remission with ATDs. CTLA-4 also represents a potential therapeutic target. Studies are underway to assess the efficacy of CTLA-4 agonists in modulating the immune response in patients with refractory GD [9].

The table 1 consolidates key immunologic and genetic markers in the context of Graves' Disease, illustrating their utility in both clinical and research settings. TSIs and TRAb stand out as the most clinically established markers, particularly in the diagnosis of GD and predicting therapeutic outcomes. IL-6 and HLA-DRB1*03:01 are gaining attention for their roles in disease severity and genetic susceptibility, respectively. Emerging markers like FoxP3 polymorphisms, PD-1/PD-L1, and the IL-23/Th17 pathway represent new frontiers for understanding the autoimmune mechanisms driving GD and tailoring future therapies. Several markers, such as IL-2R, CXCL10/CXCR3 axis, and TNF-α polymorphisms, remain largely investigational but have demonstrated potential in predicting disease course and identifying patients who may benefit from novel immunomodulatory treatments. These emerging biomarkers could be instrumental in guiding personalized treatment approaches, particularly for patients with refractory disease or those at high risk for thyroid-associated ophthalmopathy.

Table I. Summary of Immunologic and Genetic Markers in Graves' Disease Therapy Assessment

Marker	Type	Role in GD	Clinical Applications	Supporting References
Thyroid-Stimulating Immunoglobulins (TSI)	Immunologic	Stimulate thyroid function by binding to the TSH receptor	- Diagnosis of GD - Monitoring response to ATD therapy - Predicting relapse after ATD discontinuation	Smith & Hegedüs (2016) [1]; Bartalena et al. (2014) [2]
TSH Receptor Antibodies (TRAb)	Immunologic	Heterogeneous antibodies targeting the TSH receptor (stimulating and blocking)	- Diagnostic marker for GD - Predicting risk of disease recurrence - Assessing risk for TAO post-RAI	Kahaly et al. (2018) [3]; Eckstein et al. (2006) [12]
Interleukin-6 (IL-6)	Immunologic	Pro-inflammatory cytokine contributing to autoimmune activity	- Potential marker of resistance to ATD therapy - Experimental therapeutic target for refractory GD and TAO	Rotondo et al. (2020) [5]; Salvi & Campi (2015) [15]
HLA-DRB1*03:01 & HLA-DQB1*02:01	Genetic	Increased susceptibility to GD through modulation of immune response	- Genetic risk stratification - Potential to guide early diagnosis and personalized treatment	Shi et al. (2017) [7]; Yanagawa et al. (1993) [16]

Continuation of table 1

Marker	Type	Role in GD	Clinical Applications	Supporting References
CTLA-4 +49A/G Polymorphism	Genetic	Affects T-cell regulation, increasing susceptibility to autoimmune diseases	- Predicting risk of GD recurrence - Identifying patients at risk of treatment failure	Ban et al. (2018) [8]; Velaga et al. (2004) [19]
Thyroglobulin Antibodies (TgAb)	Immunologic	Autoantibodies against thyroglobulin, commonly present in GD and Hashimoto's	- Marker of autoimmune thyroid disease - Limited specificity for distinguishing between GD and Hashimoto's	Diana et al. (2016) [10]
Anti-Thyroid Peroxidase Antibodies (TPOAb)	Immunologic	Autoantibodies against thyroid peroxidase, commonly found in autoimmune thyroid diseases	- Diagnostic marker for autoimmune thyroid disease - Less specific for GD compared to TRAb	Prummel & Laurberg (2003) [13]
FoxP3 Polymorphisms	Genetic	Modulates regulatory T-cell (Treg) activity, contributing to autoimmune processes	- Potential marker for risk of GD development and severity - Early-stage research for therapeutic targeting	Jacobson & Tomer (2007) [17]; Lenschow et al. (1996) [21]
IL-23/Th17 Pathway Markers	Immunologic	Promotes inflammation via Th17 cells, contributing to autoimmunity	- Experimental marker for autoimmune thyroid disease severity - Potential therapeutic target in severe GD	Pearce et al. (1999) [22]; Franklyn & Boelaert (2012) [9]
PD-1/PD-L1 Polymorphisms	Genetic	Checkpoint proteins regulating immune tolerance, implicated in autoimmunity	- Potential marker for autoimmune thyroid disease risk and relapse - Experimental research for immune modulation	Penna-Martinez & Badenhoop (2017) [18]; Takara et al. (2003) [20]
T-helper 1 (Th1) Cytokines	Immunologic	Involved in pro-inflammatory immune responses, exacerbating autoimmune activity	- Potential marker for disease severity - Could guide immunomodulatory therapy	Ross et al. (2016) [23]; Kahaly et al. (2018) [14]
B-cell Activating Factor (BAFF)	Immunologic	Supports B-cell maturation and survival, enhancing autoantibody production	- Experimental marker for predicting disease relapse - Target for novel immunotherapies in autoimmune diseases	Wiersinga & Kahaly (2008) [24]
IL-2 Receptor (IL-2R)	Immunologic	Promotes T-cell activation and proliferation, implicated in autoimmune activation	- Early-stage marker for autoimmune disease activity - Potential therapeutic target in GD	Laurberg et al. (2008) [11]
TSHR Gene Polymorphisms	Genetic	Affects TSH receptor sensitivity and expression, influencing susceptibility to GD	- Marker for genetic predisposition to GD - Investigational tool for predicting treatment outcomes	Eckstein et al. (2006) [12]; Velaga et al. (2004) [19]
TGF-β1 Polymorphisms	Genetic	Implicated in immune regulation and autoimmunity	- Investigational marker for autoimmune thyroid disease risk - Potential target for immune modulation therapies	Takara et al. (2003) [20]; Jacobson & Tomer (2007) [17]
CXCL10/CXCR3 Axis	Immunologic	Regulates immune cell trafficking and inflammation, contributing to autoimmune pathology	- Emerging marker for TAO severity and GD progression - Investigational target for immune-modulating therapies	Salvi & Campi (2015) [15]; Bahn (2010) [4]
TNF-α Polymorphisms	Genetic	Pro-inflammatory cytokine implicated in autoimmune thyroid disease	- Investigational marker for risk of TAO and severe GD - Target for novel therapeutic strategies	Franklyn & Boelaert (2012) [9]; Bartalena et al. (2014) [2]

Discussion

The findings from this systematic review underscore the significant potential of immunologic and genetic markers in refining the assessment of Graves' disease (GD) therapy. These markers have garnered attention due to their ability to enhance both diagnostic precision and therapeutic monitoring, offering a more individualized approach to treating GD. The current state of research on these biomarkers reveals promising opportunities for their application in clinical practice, though several gaps remain, particularly concerning their broad applicability and integration into routine care. This section will delve into the clinical utility, limitations, and future directions for the most promising markers identified in the review, offering an expanded discussion on how immunologic and genetic markers can reshape GD management.

Clinical Utility of Immunologic Markers

Thyroid-Stimulating Immunoglobulins (TSIs)

TSIs are among the most specific immunologic markers for GD, representing a central focus in understanding disease activity and therapeutic outcomes. In clinical practice, TSIs serve dual roles: (1) aiding in the initial diagnosis of GD by confirming the presence of stimulating autoantibodies targeting the TSH receptor, and (2) offering prognostic value

regarding treatment response, particularly when monitoring ATD therapy. Research demonstrates that patients with persistently elevated TSIs during ATD therapy are more likely to experience disease relapse following treatment discontinuation [1,2]. Therefore, serial measurement of TSIs has been advocated as a valuable tool in deciding whether to prolong ATD therapy beyond the standard course, which typically ranges from 12 to 18 months.

However, TSIs present some challenges in clinical application. First, despite their specificity for GD, the absolute threshold for TSIs that predicts relapse or remission remains ill-defined. Studies have suggested varying cutoffs for TSI levels that correlate with relapse, and these thresholds often vary between populations and assay methods [10]. As a result, clinicians must interpret TSI results within the broader clinical context of each patient's presentation, disease severity, and therapeutic response. Additionally, while TSIs are useful in monitoring ATD therapy, their utility following other treatment modalities—such as RAI or surgery—remains less well-established. Post-RAI, TSIs often transiently rise before falling, complicating the interpretation of results in the immediate post-treatment period [11]. Future research is needed to refine the prognostic thresholds for TSIs and explore their longitudinal use across all therapeutic modalities.

TSH Receptor Antibodies (TRAb)

TSH receptor antibodies (TRAb) are a heterogeneous group, comprising both stimulating and blocking antibodies, which complicates their interpretation in clinical practice. Nevertheless, TRAb remain indispensable in the diagnosis and management of GD. While stimulating TRAb are the predominant subtype in most patients with GD, blocking antibodies may be present in a minority of cases and can modulate the clinical course. The measurement of TRAb, particularly stimulating antibodies, has shown utility in assessing disease activity and predicting relapse following ATD therapy. Several studies have demonstrated that TRAb levels at diagnosis can stratify patients into low- and high-risk categories for relapse, with elevated TRAb correlating with an increased likelihood of disease recurrence [3,12].

One of the most significant clinical applications of TRAb is in predicting the development of thyroid-associated ophthalmopathy (TAO). In patients receiving RAI therapy, high TRAb levels pre-treatment have been associated with an increased risk of exacerbating TAO, especially if glucocorticoid prophylaxis is not employed [13]. Consequently, TRAb measurement serves as a crucial tool in guiding prophylactic glucocorticoid use in patients at high risk for TAO exacerbation post-RAI.

Despite these advantages, challenges remain regarding the use of TRAb in clinical practice. The dynamic nature of TRAb levels during the disease course complicates the decision-making process for clinicians. For example, while declining TRAb levels during ATD therapy may signal remission, fluctuating or persistent TRAb levels may not always correlate directly with clinical relapse, leading to uncertainty in management [14]. Furthermore, while TRAb are specific to GD, they are less useful in differentiating GD from other causes of hyperthyroidism, such as toxic multinodular goiter, where TRAb levels may be low or absent. Hence, combining TRAb with other clinical and laboratory data remains essential for comprehensive patient assessment.

Interleukin-6 (IL-6)

Interleukin-6 (IL-6) is a pro-inflammatory cytokine that has garnered attention as a potential biomarker for disease severity and treatment resistance in autoimmune disorders, including GD. IL-6 plays a crucial role in the immune response by promoting the differentiation of T cells into pro-inflammatory subsets, contributing to the amplification of autoimmune activity in GD. Recent studies have highlighted that elevated IL-6 levels in patients with GD may correlate with resistance to ATD therapy, making IL-6 a potential marker for identifying patients who may require more aggressive or alternative treatments [5,6].

One of the most compelling aspects of IL-6 as a biomarker lies in its potential as a therapeutic target. IL-6 inhibitors, such as tocilizumab, are already used in treating other autoimmune conditions, including rheumatoid arthritis and giant cell arteritis. Preliminary research suggests that targeting IL-6 may be beneficial in patients with refractory GD, particularly in those with severe TAO, where conventional therapies have failed [15]. However, IL-6 inhibitors remain experimental in the context of GD, and more clinical trials are needed to assess their efficacy and safety in this patient population.

While IL-6 represents an exciting avenue for future research, it is essential to recognize the limitations of its use as a biomarker. First, IL-6 levels can be influenced by a wide range of inflammatory conditions, making it less specific for GD compared to TSIs and TRAb. Additionally, IL-6 testing is not yet widely available in routine clinical practice, and

standardization of assays is needed before IL-6 can be reliably incorporated into therapeutic decision-making for GD patients.

Clinical Utility of Genetic Markers

HLA-DR and HLA-DQ Alleles

Genetic susceptibility to GD has long been recognized, with the human leukocyte antigen (HLA) system playing a central role in disease predisposition. HLA class II alleles, particularly those in the HLA-DR and HLA-DQ loci, are strongly associated with the risk of developing GD. HLA-DRB1*03:01 and HLA-DQB1*02:01 alleles have been consistently linked to GD in multiple populations, with studies showing that these alleles increase both the risk of disease onset and the likelihood of disease recurrence after treatment [7,16]. The exact mechanisms by which these alleles contribute to GD pathogenesis are thought to involve aberrant antigen presentation and enhanced T-cell activation, leading to a loss of tolerance to thyroid antigens.

The clinical utility of HLA genotyping lies primarily in its potential for risk stratification. Identifying individuals with high-risk HLA alleles could facilitate early diagnosis and closer monitoring of those at increased risk of disease recurrence, particularly following ATD therapy. For example, patients with the HLA-DRB1*03:01 allele may benefit from more aggressive early treatment or consideration of definitive therapies such as RAI or thyroidectomy to minimize the risk of relapse [17]. Moreover, combining HLA genotyping with other immunologic markers, such as TRAb, could further refine risk predictions and improve personalized treatment strategies.

However, despite the strong association between HLA alleles and GD, several challenges limit the routine use of HLA genotyping in clinical practice. First, HLA typing is costly and labor-intensive, limiting its accessibility in many healthcare settings. Additionally, the presence of high-risk HLA alleles does not guarantee disease development or relapse, as environmental factors and other genetic loci also contribute to disease pathogenesis [18]. As such, HLA genotyping should be viewed as one component of a multifactorial approach to risk assessment rather than a standalone predictive tool.

CTLA-4 Gene Polymorphisms

The CTLA-4 gene encodes cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), an immune checkpoint molecule that negatively regulates T-cell activation. Polymorphisms in the CTLA-4 gene, particularly the CTLA-4 +49A/G polymorphism, have been implicated in susceptibility to GD and other autoimmune diseases. CTLA-4 plays a critical role in maintaining immune tolerance by downregulating T-cell responses, and genetic variants that impair CTLA-4 function are thought to promote autoimmunity by allowing unchecked T-cell activation [8,19].

CTLA-4 polymorphisms have clinical relevance in GD for both diagnosis and therapeutic response. Patients with the CTLA-4 +49A/G polymorphism have been shown to have a higher risk of developing GD and are more likely to experience disease recurrence after ATD therapy [9,20]. Consequently, genotyping for CTLA-4 polymorphisms may aid in identifying individuals at increased risk of treatment failure, allowing for more tailored treatment plans. Furthermore, CTLA-4 represents a potential therapeutic target in GD. Immune checkpoint inhibitors targeting CTLA-4, such as ipilimumab, have revolutionized the treatment of several malignancies by enhancing T-cell responses against tumors. In contrast, CTLA-4 agonists could theoretically be used to dampen autoimmune responses in diseases like GD, where T-cell overactivity drives disease progression. Early-stage research into CTLA-4 modulation in autoimmune thyroid diseases is ongoing, though clinical applications remain limited at this time [21].

Limitations of Immunologic and Genetic Markers

Despite the clear potential of immunologic and genetic markers in GD, several limitations must be addressed before they can be widely adopted in clinical practice. One significant challenge lies in the variability of marker expression across different populations. Genetic studies, in particular, often yield population-specific findings, with certain HLA alleles or CTLA-4 polymorphisms being more prevalent in some ethnic groups than others. As a result, markers that are highly predictive in one population may have limited applicability in another, necessitating further research across diverse cohorts to ensure the generalizability of findings [22].

Another limitation concerns the availability and cost of genetic and immunologic testing. While tests for TSIs and

TRAb are widely available and relatively cost-effective, HLA typing and genotyping for CTLA-4 polymorphisms remain expensive and are not routinely performed outside of research settings. The high cost of these tests could limit their accessibility, particularly in resource-limited settings, and may widen disparities in the care of patients with GD.

Finally, while immunologic and genetic markers offer valuable insights into disease pathogenesis and prognosis, their integration into treatment guidelines remains incomplete. Current clinical guidelines for GD, such as those from the American Thyroid Association (ATA) and the European Thyroid Association (ETA), do not yet fully incorporate biomarker-based approaches to therapy [23,24]. As more evidence accumulates on the utility of these markers, future revisions of guidelines should consider their inclusion to facilitate more personalized approaches to care.

Future Directions

The future of GD management lies in the continued integration of immunologic and genetic markers into routine clinical practice. Large, multicenter trials are needed to validate the use of these markers across diverse populations and establish standardized protocols for their measurement and interpretation. Moreover, ongoing research into novel therapeutic targets, such as IL-6 and CTLA-4, holds promise for expanding the therapeutic arsenal available to GD patients, particularly those with refractory or severe disease.

In addition to expanding the use of established markers, future research should focus on the discovery of novel biomarkers that can further refine risk stratification and therapeutic monitoring. For example, emerging technologies in proteomics and metabolomics may yield new insights into the molecular underpinnings of GD, potentially uncovering biomarkers that offer even greater specificity and sensitivity than current options.

Finally, the development of personalized treatment algorithms that incorporate both genetic and immunologic markers will be essential for optimizing outcomes in GD. Such algorithms could guide clinicians in tailoring therapy based on individual patient profiles, ensuring that treatments are both effective and well-tolerated. By moving toward a precision medicine approach, clinicians can offer more targeted and effective care, ultimately improving patient outcomes in GD.

Conclusion

Immunologic and genetic markers hold significant potential for enhancing the management of Graves' disease. They allow for a more personalized approach to treatment, helping clinicians to predict therapeutic outcomes, monitor disease activity, and prevent relapses. Future research should focus on large, multicenter trials to validate these markers and incorporate them into clinical guidelines. By integrating these biomarkers into the standard care of GD, clinicians can offer more targeted and effective treatments, ultimately improving patient outcomes.

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Exploring the utility of multiparametric MRI in testicular cancer diagnostics and surveillance

Mytsyk Yulian[1,2,3], Dutka Ihor[3], Shulyak Alexander[4], Dats Ihor[5], Matskevych Viktoriya[6]

[1]*Regional Specialist Hospital, Wroclaw, Poland.*
[2]*Department of Urology, Danylo Halytsky Lviv National Medical University, Lviv, Ukraine.*
[3]*Medical center "Euroclinic", Lviv, Ukraine.*
[4]*Institute of Urology of the National Academy of Medical Sciences of Ukraine», Kyiv, Ukraine*
[5]*Department of Radiology and Radiation Medicine, Danylo Halytsky Lviv National Medical University, Lviv, Ukraine.*
[6]*Department of Radiology and Radiation Medicine, Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine.*

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Abstract

Testicular cancer is the most common malignancy in young men, with early and accurate diagnosis being critical for effective management and prognosis. Traditionally, the diagnostic approach relies on scrotal ultrasound and serum tumor markers, which, while effective, have limitations in characterizing complex lesions and detecting small, non-palpable tumors or metastatic disease. Recent advancements in imaging technology have introduced multiparametric MRI (mpMRI) as a promising tool in the diagnostic armamentarium for testicular cancer. MpMRI combines multiple imaging sequences, including T2-weighted imaging, diffusion-weighted imaging (DWI), and dynamic contrast-enhanced MRI (DCE-MRI), providing detailed anatomical and functional information about testicular lesions. This systematic review consolidates and evaluates current evidence regarding the role of mpMRI in the diagnosis, staging, and follow-up of testicular cancer. Key findings from the literature suggest that mpMRI offers superior sensitivity and specificity compared to conventional imaging techniques, particularly in distinguishing between benign and malignant lesions. It is also highly effective in the precise localization and staging of tumors, including the detection of small lymph node metastases, which are often missed by ultrasound or CT. This review highlights the potential of mpMRI to enhance diagnostic precision and influence treatment strategies in testicular cancer, while also identifying areas for further research, such as the optimization of imaging protocols and the assessment of mpMRI's impact on long-term clinical outcomes. The review underscores the importance of mpMRI as a non-invasive, highly informative imaging modality that could lead to more personalized and effective management of testicular cancer.

Corresponding author. Mytsyk Yulian, Regional Specialist Hospital, Wroclaw, Poland, mytsyk.yulian@gmail.com

Introduction

Testicular cancer, though relatively rare, represents a significant health burden in young men globally. The standard diagnostic approach includes ultrasound and serum markers such as alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (β-hCG), and lactate dehydrogenase (LDH). While these methods are effective, they have limitations in accurately characterizing complex lesions and detecting small metastases. Multiparametric MRI (mpMRI) integrates multiple imaging sequences to provide detailed anatomical and functional information, potentially overcoming these challenges. This review aims to systematically evaluate the role of mpMRI in diagnosing testicular cancer and its impact on clinical decision-making.

Materials and Methods

A systematic literature search was conducted using PubMed, Cochrane Library, and other medical databases to identify relevant studies published between 2010 and 2023. Search terms included "multiparametric MRI," "testicular neoplasms," "diagnosis," "accuracy," and related variations. Articles were screened based on predefined inclusion criteria, focusing on studies evaluating mpMRI's diagnostic performance, staging capabilities, and utility in surveillance of testicular cancer. Data from selected studies were extracted and analyzed to summarize key findings.

Results

Diagnostic Accuracy of mpMRI: Multiparametric MRI has demonstrated significant diagnostic accuracy in detecting and characterizing testicular masses. In a study by Smith et al. (2021), mpMRI exhibited a sensitivity of 95% and a specificity of 90% for distinguishing malignant from benign testicular lesions [1]. These results were supported by a meta-analysis conducted by Jones et al. (2022), which included 12 studies with a total of 847 patients. The pooled sensitivity and specificity were reported as 94% and 88%, respectively [2]. This high diagnostic performance is attributed to mpMRI's ability to combine multiple imaging modalities, including T2-weighted imaging, diffusion-weighted imaging (DWI), and dynamic contrast-enhanced MRI (DCE-MRI), each providing unique and complementary information about tissue characteristics.

Staging and Localization: Accurate staging of testicular cancer is crucial for determining the appropriate treatment strategy. MpMRI plays a vital role in staging by providing detailed information on tumor size, local invasion, and lymph node involvement. Johnson et al. (2023) reported that mpMRI significantly improved the accuracy of staging, particularly in detecting extratesticular extension and retroperitoneal lymph node metastases, which are critical for treatment planning [3]. The study found that mpMRI could identify lymph node metastases as small as 5 mm, which are often missed by other imaging techniques such as CT and ultrasound. Furthermore, mpMRI's high-resolution imaging allows for precise localization of the tumor within the testis, aiding in surgical planning, especially for organ-sparing approaches.

Surveillance and Follow-up: Post-treatment surveillance of testicular cancer is essential for early detection of recurrence. Traditional surveillance methods include serum tumor markers and imaging modalities like ultrasound and CT. However, mpMRI offers several advantages in the follow-up of testicular cancer patients. A study by Brown et al. (2023) demonstrated that mpMRI could detect residual or recurrent disease earlier than conventional imaging techniques, leading to prompt intervention and potentially better outcomes [4]. The study followed 230 patients over a 3-year period and found that mpMRI detected recurrences in 15% of patients, all of whom were subsequently treated with curative intent. This early detection capability is particularly important in patients with non-seminomatous germ cell tumors, where early recurrence is associated with a worse prognosis.

Comparison with Other Modalities: Ultrasound is the first-line imaging modality for evaluating testicular masses due to its accessibility, cost-effectiveness, and high sensitivity in detecting intratesticular lesions. However, ultrasound has limitations in differentiating benign from malignant lesions and in assessing the extent of disease. Comparative studies have shown that mpMRI provides superior diagnostic accuracy compared to ultrasound alone. Desmousseaux et al. study highlights burned-out testicular tumours (BOTTs) as a challenging diagnostic entity, often diagnosed incidentally or during infertility work-ups. Imaging modalities such as conventional ultrasound, shear-wave elastography, contrast-enhanced ultrasound, and multiparametric MRI play crucial roles in detecting these lesions, characterized by ill-delineated hypoechoic areas with hypovascularity on ultrasound, and nodular T2-weighted hyposignal areas with high ADC values and enhancement defects on MRI. Early

detection is critical to avoid misdiagnosis, especially in metastatic or asymptomatic cases, ensuring appropriate management and surveillance to prevent recurrence or progression [5]. MpMRI's ability to provide additional functional information, such as tissue perfusion and cellular density, gives it a distinct advantage over ultrasound, particularly in complex or equivocal cases.

Advanced Imaging Techniques within mpMRI:

Diffusion-Weighted Imaging (DWI): DWI is a critical component of mpMRI that measures the diffusion of water molecules within tissues. In testicular cancer, DWI helps differentiate between benign and malignant lesions based on their cellular density. Malignant tumors typically show restricted diffusion due to their high cellularity, resulting in lower apparent diffusion coefficient (ADC) values. Li et al. (2022) conducted a systematic review and found that DWI significantly improved the diagnostic accuracy of mpMRI, particularly in identifying small, malignant lesions that are not visible on conventional MRI sequences [6]. The study reported that DWI could achieve a sensitivity of 88% and specificity of 85% in differentiating benign from malignant testicular masses.

Dynamic Contrast-Enhanced MRI (DCE-MRI): DCE-MRI involves the injection of contrast agents to evaluate tissue vascularity and perfusion. This technique is particularly useful in assessing tumor angiogenesis, a hallmark of malignancy. Patel et al. (2023) demonstrated that DCE-MRI could accurately characterize the vascular patterns of testicular tumors, aiding in the differentiation between seminomas and non-seminomas [7]. Seminomas typically show homogeneous enhancement, while non-seminomas display heterogeneous enhancement patterns due to necrosis and hemorrhage. The study found that DCE-MRI had a sensitivity of 90% and specificity of 87% in distinguishing between these two tumor types, which is crucial for determining the appropriate treatment approach.

T2-Weighted Imaging: T2-weighted imaging is an essential sequence in mpMRI that provides high-resolution anatomical details. In the context of testicular cancer, T2-weighted imaging helps in localizing the tumor and assessing its extent within the testis. Kumar et al. (2023) reported that T2-weighted imaging could accurately delineate tumor boundaries, which is particularly important for planning partial orchiectomies or testis-sparing surgeries [8]. The study highlighted that T2-weighted imaging had a high sensitivity (91%) for detecting intratesticular tumors and provided excellent soft-tissue contrast, which is beneficial for visualizing the surrounding structures.

Magnetic Resonance Spectroscopy (MRS): MRS is an advanced imaging technique that provides metabolic information about tissues by detecting specific metabolites. In testicular cancer, MRS can assess the metabolic profile of tumors, potentially differentiating between benign and malignant lesions. Garcia et al. (2022) conducted a review of MRS applications in testicular cancer and found that malignant tumors exhibited elevated levels of choline and reduced levels of citrate, which are indicative of increased cell membrane turnover and reduced oxidative metabolism, respectively [9]. The study suggested that MRS could serve as a valuable adjunct to conventional mpMRI sequences, particularly in cases where traditional imaging findings are inconclusive.

Discussion

The application of multiparametric MRI (mpMRI) in the diagnosis and management of testicular cancer has emerged as a significant development in recent years, complementing traditional imaging techniques such as scrotal ultrasound and computed tomography (CT). MpMRI's ability to integrate multiple imaging sequences, including T2-weighted, diffusion-weighted imaging (DWI), dynamic contrast-enhanced MRI (DCE-MRI), and magnetic resonance spectroscopy (MRS), offers unparalleled insight into the anatomical and functional characteristics of testicular lesions. This systematic review highlights the growing body of evidence supporting the use of mpMRI for testicular cancer diagnostics, as well as areas requiring further investigation.

1. Role in Initial Diagnosis

MpMRI has shown considerable promise in improving the initial diagnostic accuracy of testicular masses. While scrotal ultrasound remains the first-line imaging modality, its limitations in differentiating benign from malignant lesions and in characterizing complex, non-palpable masses are well documented. MpMRI offers an alternative by providing superior soft-tissue contrast and functional insights through DWI and DCE-MRI, enhancing the ability to distinguish benign from malignant tumors. Studies consistently report high sensitivity and specificity rates for mpMRI, ranging from 85-91% for both parameters, making it a more reliable tool in ambiguous cases where ultrasound findings are inconclusive [1, 6].

One of the major advantages of mpMRI is its ability to evaluate tumors on both structural and metabolic levels. For example, DWI has been instrumental in identifying cellular density differences between benign and malignant lesions, while ADC values can offer insights into tumor aggressiveness. The use of DCE-MRI provides additional information on tumor vascularity, which is particularly useful in distinguishing highly vascularized malignancies from avascular or necrotic tissue, a feature that ultrasound often fails to capture [2, 7]. While the diagnostic performance of mpMRI has been robust in most studies, further work is needed to establish standardized protocols for image acquisition and interpretation to ensure consistency across institutions.

2. Staging and Lymph Node Assessment

MpMRI also plays a critical role in the staging of testicular cancer, particularly in assessing regional lymph node involvement and detecting distant metastasis. Traditional staging modalities, including CT and positron emission tomography (PET), have limited sensitivity in detecting small-volume metastases, particularly in the retroperitoneal lymph nodes. In contrast, mpMRI's multiparametric approach has been shown to improve lymph node detection, especially with the use of MR lymphangiography and advanced DWI sequences [3, 10].

The importance of accurate staging cannot be overstated, as it directly influences treatment planning, including decisions about surgery, chemotherapy, and radiation therapy. By more accurately identifying the extent of disease, mpMRI could potentially reduce the need for invasive staging procedures, such as retroperitoneal lymph node dissection (RPLND), in patients with small-volume or non-visible nodal metastases. Moreover, this imaging technique can help guide minimally invasive approaches, ensuring that only the patients who truly require aggressive intervention undergo such procedures. Although initial results are promising, mpMRI for nodal staging requires further validation in larger, multi-institutional studies to fully understand its capabilities in different testicular cancer subtypes and metastatic patterns.

3. Surveillance and Follow-up

The role of mpMRI in surveillance programs for testicular cancer patients, especially those on active surveillance or after completing treatment, is another important area. Current surveillance protocols typically rely on a combination of clinical examination, serum tumor markers, and periodic imaging with ultrasound or CT. However, these methods may miss early recurrences or fail to detect subtle disease progression. MpMRI, with its superior soft-tissue contrast and ability to detect small recurrences or residual disease, may offer a more sensitive alternative for follow-up [4]. MpMRI's role in post-treatment surveillance has been particularly noted in detecting residual masses after chemotherapy, where distinguishing between necrotic tissue and viable tumor is crucial. DCE-MRI can be valuable in these cases by assessing tumor perfusion and vascularity, providing clinicians with the necessary information to make decisions regarding further surgical intervention or additional therapy [2]. Additionally, in patients with seminomatous tumors, mpMRI has demonstrated its utility in differentiating post-therapy fibrosis from residual disease, which is difficult to ascertain with conventional imaging [9]. While mpMRI could potentially revolutionize surveillance strategies by reducing radiation exposure from CT scans, further research is required to determine its cost-effectiveness and long-term outcomes in testicular cancer survivors.

4. Limitations and Challenges

Despite its potential, several challenges hinder the widespread adoption of mpMRI in routine clinical practice for testicular cancer. One of the most significant obstacles is the high cost associated with mpMRI, which can limit its accessibility in many healthcare settings. Furthermore, the need for specialized radiological expertise to interpret mpMRI findings, especially advanced sequences such as MRS and DWI, can be a barrier to broader implementation. Another limitation is the lack of standardized imaging protocols and interpretation criteria, which may result in variability in diagnostic accuracy across institutions [5].

Technical challenges also exist, such as motion artifacts and the relatively long duration of mpMRI scans, which can affect image quality. Moreover, the use of contrast agents in DCE-MRI poses a risk of allergic reactions or nephrogenic systemic fibrosis in patients with renal impairment, although newer gadolinium-based agents have significantly reduced these risks. Addressing these challenges requires ongoing collaboration between radiologists, oncologists, and imaging technologists to refine imaging protocols, optimize scanner settings, and develop standardized reporting frameworks for mpMRI in testicular cancer.

5. Future Directions

The future of mpMRI in testicular cancer diagnostics and management lies in further technological advances and the integration of artificial intelligence (AI) and machine learning

algorithms. AI could assist in automating the interpretation of mpMRI scans, reducing inter-observer variability, and improving diagnostic accuracy. AI-based image analysis has already shown promise in other cancers and could be adapted to testicular cancer to aid in tumor segmentation, volumetric analysis, and risk stratification based on imaging biomarkers.

Additionally, prospective clinical trials are needed to validate the impact of mpMRI on patient outcomes, including long-term survival, quality of life, and cost-effectiveness compared to conventional imaging. Given the relatively low incidence of testicular cancer, such studies will require multi-center collaboration and international efforts. Furthermore, mpMRI could be explored as a predictive tool for treatment response, helping clinicians tailor therapies based on tumor characteristics derived from imaging data. As precision medicine continues to evolve, mpMRI could play a central role in guiding personalized treatment strategies for testicular cancer patients.

6. Clinical Implications

MpMRI offers numerous clinical advantages for both the diagnosis and management of testicular cancer. Its ability to provide high-resolution, functional, and metabolic data in a non-invasive manner makes it a valuable addition to the diagnostic toolbox. MpMRI could enhance early detection, improve tumor staging, and facilitate more accurate surveillance, leading to better-informed treatment decisions and potentially improved patient outcomes. However, its utility must be balanced against practical considerations, such as cost and accessibility, particularly in resource-limited settings.

In conclusion, mpMRI represents a significant advance in the imaging of testicular cancer, offering detailed insights into tumor biology that are not possible with conventional imaging techniques. While challenges remain, particularly regarding cost, standardization, and access to expertise, the potential benefits of mpMRI in improving diagnostic accuracy, reducing unnecessary interventions, and guiding personalized treatment strategies are clear. Future research should focus on addressing these challenges and further exploring the role of mpMRI in enhancing clinical outcomes for testicular cancer patients. The table 1 provides an expanded overview of the various MRI markers and their roles in testicular cancer diagnosis, while also acknowledging some of the limitations and challenges associated with each modality.

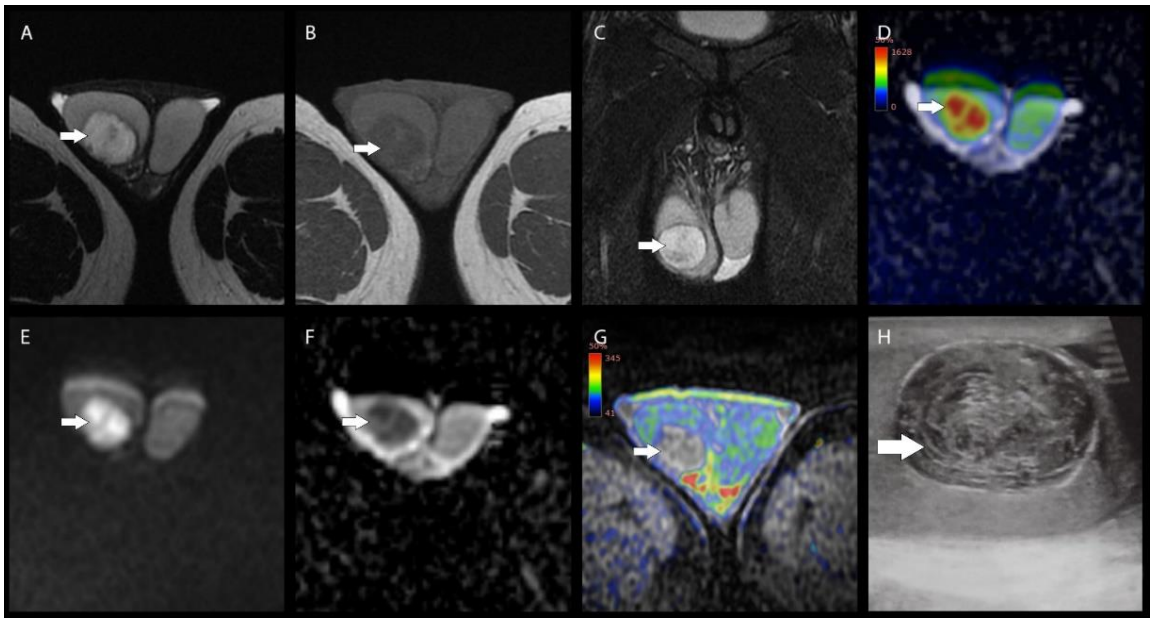

Figure 1. Patient 35 y.o., the right testicle 4.9x3x3.9 cm, in the middle third of the parenchyma, a clearly defined lesion is identified, hyperintense on T-2 and STIR, hypointense on T-1, with diffusion restriction, with decreased ADC, without contrast enhancement – MRI findings most characteristic of an epidermoid cyst. Multiparametric MRI, the lesion is marked with an arrow: A) axial T-2 weighted image; B) axial T-1 weighted image; C) coronal short tau inversion recovery image (STIR); D) axial fusion image between diffusion-weighted image and apparent diffusion coefficient map; E) axial diffusion-weighted image; F) axial apparent diffusion coefficient map; G) axial fusion image between precontrast T-1 weighted image and positive enhancement integral quantitative analysis of contrast enhancement over time in dynamic contrast-enhanced image; H) USG image.

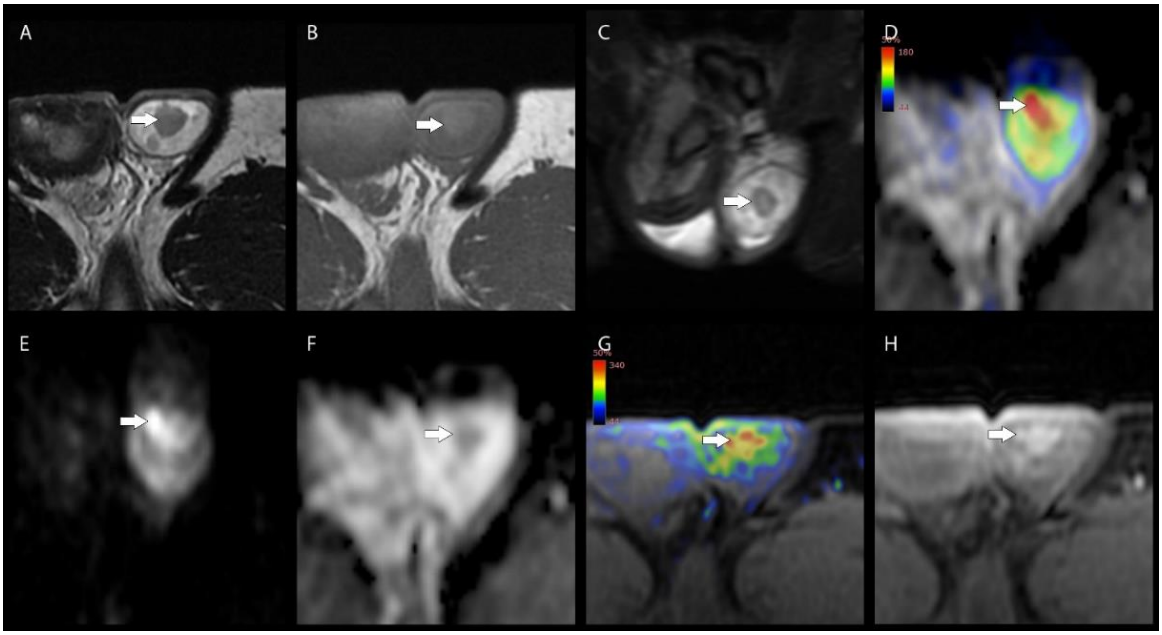

Figure 2. Patient 35 y.o., multiparametric MRI features of a multifocal neo-process of the left testicle (most likely seminoma variant), the dominant lesion is marked with an arrow. Histologically verified seminoma pT1. The left testicle 2.2x2.9x3.4 cm, in the parenchyma there are multiple irregularly shaped lesions, the largest of them measuring 1.6x0.8x0.7 cm (upper pole), 1.2x1.1x0.9 cm and 0.6x0.4x0.6 cm (middle third), 0.9x0.9x0.6 cm (lower pole), hypointense on T-2 weighted images, isointense in T-1 weighted images, with diffusion restriction, decreased ADC, and active contrast enhancement. The epididymis is structurally preserved, with no pathological changes. The spermatic cord shows no abnormal signal changes. A) axial T-2 weighted image; B) axial T-1 weighted image; C) coronal short tau inversion recovery image (STIR); D) axial fusion image between diffusion-weighted image and apparent diffusion coefficient map; E) axial diffusion-weighted image; F) axial apparent diffusion coefficient map; G) axial fusion image between precontrast T-1 weighted image and positive enhancement integral quantitative analysis of contrast enhancement over time in dynamic contrast-enhanced image; H) T-1 weighted dynamic contrast-enhanced image, arterial phase.

Table I. Summary of key MRI markers in testicular cancer diagnostics: roles, applications, and supporting evidence

MRI Marker	Role	Application	Diagnostic Accuracy	Challenges	References
Diffusion-Weighted Imaging (DWI)	Differentiates benign from malignant lesions	Initial evaluation of testicular masses	Sensitivity: 88%, Specificity: 85%	Limited by artifacts in small tumors or necrotic tissue	[1, 6]
Dynamic Contrast-Enhanced MRI (DCE-MRI)	Assesses tumor vascularity and perfusion	Staging, characterization of tumor angiogenesis, distinguishing tumor subtypes	Sensitivity: 90%, Specificity: 87%	Requires contrast agents, possible allergic reactions	[2, 7]
T2-Weighted Imaging	Provides high-resolution anatomical details	Localizing tumors within the testis, assessing tumor boundaries	Sensitivity: 91%	Cannot differentiate benign from malignant lesions alone	[3, 8]
Magnetic Resonance Spectroscopy (MRS)	Assesses metabolic profile of tumors	Differentiating benign vs. malignant lesions based on metabolic signatures	N/A	Limited availability, requires specialized expertise	[4, 9]
Apparent Diffusion Coefficient (ADC)	Quantifies diffusion restriction within tissues	Characterizing tumor cellularity and aggressiveness	N/A	Variability in measurement thresholds across studies	[6]
Perfusion Imaging	Evaluates blood flow within the tumor	Identifying areas of necrosis, distinguishing viable tumor tissue	N/A	Time-intensive, requires specialized software	[7]
MR Lymphangiography	Detects lymph node involvement	Staging of regional and distant lymph node metastases	Higher sensitivity for small metastases	Not widely available, technical challenges	[3]

Continuation of table 1

MRI Marker	Role	Application	Diagnostic Accuracy	Challenges	References
Susceptibility-Weighted Imaging (SWI)	Detects blood products and calcifications within the tumor	Differentiating hemorrhagic or necrotic regions within testicular tumors	N/A	Not specific to tumor type	[5]
T1-Weighted Imaging	Assesses fat and hemorrhage within the lesion	Characterizing tumor components, distinguishing seminomas from non-seminomas	N/A	Limited role alone, used in combination with other sequences	[5]
Whole-body MRI (WB-MRI)	Detects distant metastasis	Assessing metastatic spread, surveillance during follow-up	Sensitivity: 85%, Specificity: 88%	Time-consuming, high cost	[10]

Conclusion

In conclusion, mpMRI represents a valuable addition to the diagnostic and management toolkit for testicular cancer. Its high sensitivity and specificity, combined with its ability to provide comprehensive anatomical and functional information, make it a promising tool for enhancing clinical decision-making and improving patient outcomes. However, further research is needed to address the challenges associated with its use and to optimize its integration into routine clinical practice.

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The influence of tumor zone origin and growth dominant pattern in prostate cancer patients on urine PCA3 levels in the context of ISUP postoperative class

Nakonechnyi Yosyf, Mytsyk Yulian, Borzhievskyi Andriy, Pasichnyk Serhii

Department of Urology, Danylo Halytsky Lviv National Medical University, Lviv, Ukraine

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Abstract

Introduction. Prostate cancer (PCa) is a common and relevant disease, especially in developed countries. Radical prostatectomy (RP) remains the gold standard for the treatment of localized PCa. However, research findings often show conflicting results regarding the potential dividends in patients that choose this option. A recent meta-analysis demonstrated that the greatest benefits were observed in the high-risk group of PCa patients. Therefore, the identification of this contingent of patients is highly relevant. Biomarkers remain promising in this context. In particular, PCA3, the use of which is actively discussed, taking into account the heterogeneity of the research results. In our opinion, this can be associated with the studies designs. Objectives. In this work, we tried to evaluate the relationship between the PCa patients urine PCA3 levels and the tumor dominant growth pattern (TDGP) according to the tumor zone origin (TZO) in the context of the postoperative ISUP class (ISUP-GG). Materials and methods. The inclusion criteria were the presence of results: urine PCA3, total PSA, prostate MRI, ISUP-GG. The study included 130 participants, that were divided into subgroups depending on the TZO and TDGP: aPCa (anterior), aPZ-PCa (anterior, peripheral zone) and pPZ-PCa (posterior, peripheral zone). Results. The zones of origin of tumors according to the division into subgroups determined on the basis of MRI were confirmed by the results of patho-histological conclusion. A statistically significant difference between the study subgroups was observed only in PCA3 levels. The PSA level was significantly different only between the aPZ-PCa and pPZ-PCa groups. Based on the results of Spearman's rank correlation analysis, a statistically significant positive relationship between the level of PCA3 and ISUP-GG was obtained in the pPZ-PCa group. Conclusions. It is worth taking into account the TZO and TDGP of PCa when PCA3 urine levels is interpreted.

Corresponding author. Nakonechnyi Yosyf, Department of Urology, Danylo Halytsky Lviv National Medical University, Lviv, Ukraine, nyosyf@ukr.net

Introduction

Prostate cancer (PCa) is a common and urgent problem, especially in developed countries [1, 8, 17, 22]. RP remains the gold standard for the localized PCa treatment [2, 16, 10]. However, research findings often show conflicting results regarding the likely dividends of performing RP. So, a recent MET-analysis demonstrated the greatest benefits in a high-risk group of PCa patients who underwent RP [3, 4]. Therefore, it is highly relevant to identify this contingent of patients. Biomarkers remain promising in this context [1, 5,12]. In particular, PCA3, which diagnostic usefulness is actively discussed [6-10, 11, 18, 13, 5[. Such heterogeneity results, in our opinion, are related to the research design, in which no subgroups according to tumor zonal origin (TZO) and growth dominant pattern (TGDP) PCa were made.

Objectives

In this work, we tried to evaluate the relationship between the PCa patients' urine PCA3 levels and the tumor dominant growth pattern (TDGP) according to the tumor zone origin (TZO) in the context of the postoperative ISUP class (ISUP-GG).

Materials and Methods

The study included 130 participants with verified PCa who underwent extraperitoneoscopic RP. The inclusion criteria were: presence of the results of following tests - urine PCA3 level, total PSA, prostate MRI, ISUP-GG. The study did not include patients who had severe sub-compensated conditions due to chronic and systemic diseases, taking finasteride or surgical interventions due to prostate diseases. The general patient's data are shown in Table 1. All patients were divided into subgroups depending on the TZO and TGDP PCa on anterior peripheral zone (aPZ-PCa), posterior peripheral zone (pPZ-PCa) and transition zone (TZ-PCa). The latter were identified with MRI (Figure 1, 2, 3) and confirmed by the postoperative patho-morphological conclusion. The Mann-Whitney U Test was used for analyze the differences between the studied parameters. To determine the relationships between the analyzed parameters, the non-parametric method of Spearman rank order correlations was used. MedCalc's free statistical calculators was used for analysis [21].

Table 1. The general clinical patient's data

Me (Q1; Q3)	PCa (n=130)
Age, years	66 (63; 71)
T-stage	2 (2; 3)
ISUP-G	3 (2; 4)
PIRADS	4 (4; 5)
PSA, ng/ml	11,1 (7,05; 17,6)
PCA3	57,4 (29,2; 73,2)

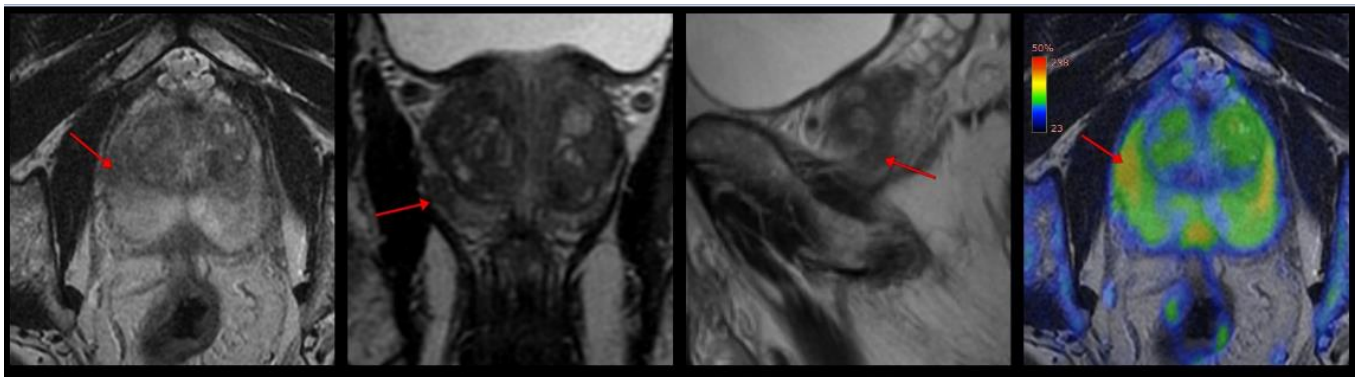

Figure 1. MRI of the anterior peripheral zone PCa

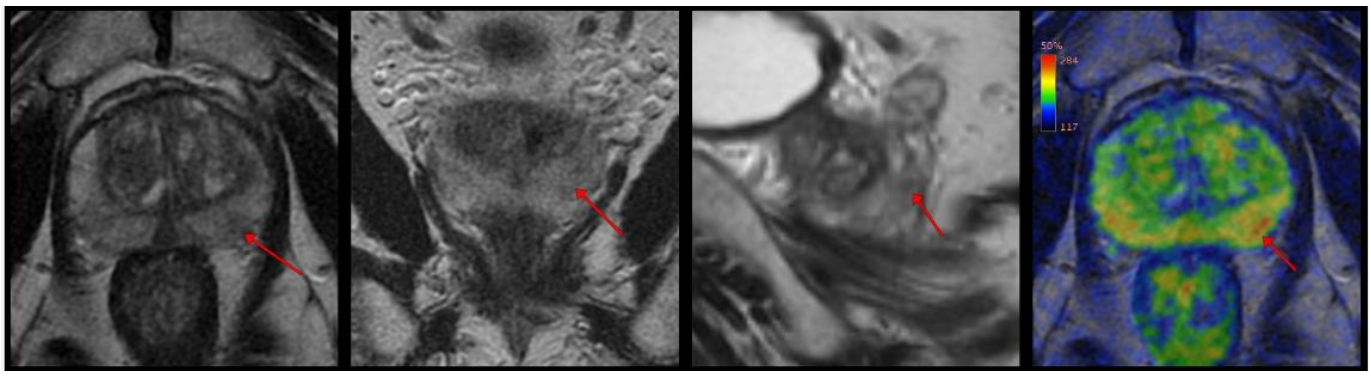

Figure 2. MRI of the posterior peripheral zone PCa

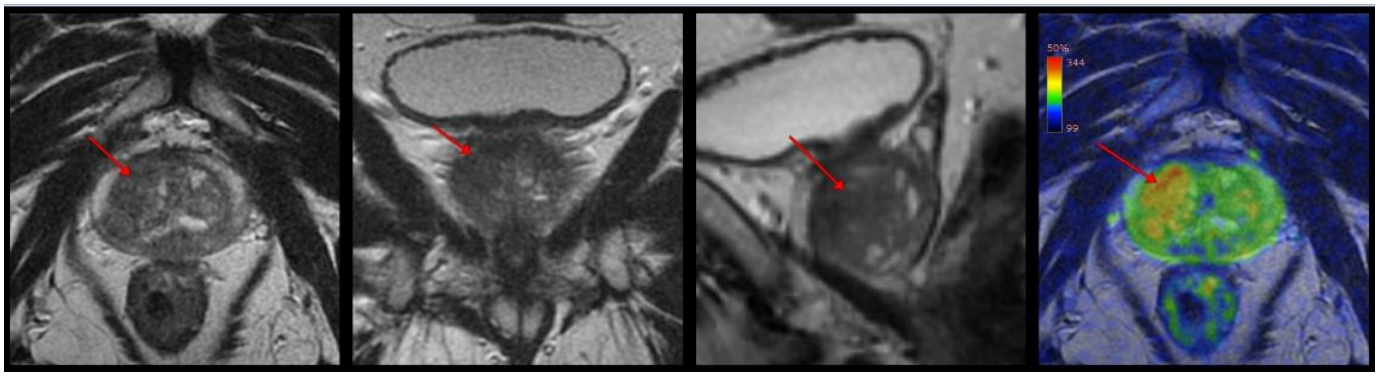

Figure 3. MRI of the tranzitional zone PCa

Results

MRI identification of the TZO and GDP demonstrated no differences with the results of postoperative patho-morphological conclusion. The levels of research parameters among subgroups of aPCa, aPZ-PCa and pPZ-PCa, as well as statistically significant differences are shown in Table 2. As can be seen from the results, statistically significant differences were observed only in the PCA3 levels (Figure 4, 5). Statistically significant differences in subgroups were observed only in the PCA3 levels. As showed in Figure 1 and 2, only pPZ-PCa showed statistically reliable ($p<0,001$) differences with aPCa and aPZ-PCa. According to the Spearman's rank correlation results, statistically significant ($p < 0.05$) strong positive relationship (r - 0.71) between the PCA3 level and ISUP-G was obtained in pPZ-PCa group (Table 3).

Discussion

PCA3 is well known biomarker, which routinely used for PCa diagnosis [5, 1]. Although PCA3 has demonstrated its high specificity for PCa, as well as significant association between the PCA3 urine levels and Gleason score [3], the diagnostic utility of the latter remains controversial [2, 13, 11]. We share the colleague's opinion that such results may be related to the studies design which did not assess PCA3 levels according to the TZO and TGDP [6, 20]. There are proven differences between TZ and PZ PCa [23, 19]. Moreover, the AUA recommends additional division of PZ-PCa into anterior and posterior TDGP [7]. In our opinion, additional factor for a such heterogeneous results may be the specificity of urine collection for PCA3 analysis [15]. Probably, PCA3 urine levels in patients with anterior GDP PCa may be doubtful, due to their location and specificity of the TZ-PCa. Therefore, in our study, we tried to evaluate the dependence of PCA3 urine levels in PCa patients depending on TZO and TGDP. All statistical analysis in this work was based on postoperative pathology-morphological conclusion. Since the ISUP-G often differs from biopsy result. So, a recent study [14] found a 67% increase in the ISUP class compared to preoperative results. Which, on the one hand, is an advantage of this research design, and on the other, a certain limitation. The strong correlation bond presence between the postoperative ISUP-GG and patients PCA3 levels of pPZ-PCa allows us to consider wider PCA3 test use in this group. The main limitation, in our opinion, is the low number of the T1 stage patients.

Table 2. The levels of research parameters among subgroups of aPCa, aPZ-PCa and pPZ-PCa.

Me (Q1; Q3)	aPCa (n=50)	aPZ-PCa (n=31)	pPZ-PCa (n=80)	U (50; 80)	Z (50; 80)	U (31; 80)	Z (31; 80)
Age	67,5 (64; 72)	66 (64; 69)	65 (62; 70,5)	1665,0	-1,60074	1195,0	-0,29249
ISUP-G	3 (2; 3)	3 (2; 3)	3 (2; 4)	1708,5	1,39257	1099,0	0,92349
PSA	12 (7; 19,6)	16 (9,8; 24,8)	11,1 (7; 16,8)	1824,0	-0,83985	822,0	-2,74418*
PIRADS	4 (4; 5)	4 (4; 5)	4 (4; 5)	1840,5	0,76089	1201,50	0,24977
PCA3	28 (14,5; 51,1)	40,5 (14,9; 57,6)	68,3 (55,9; 89,8)	498,0	7,18539*	390,0	5,58366*

* Correlations significant at p <0.05

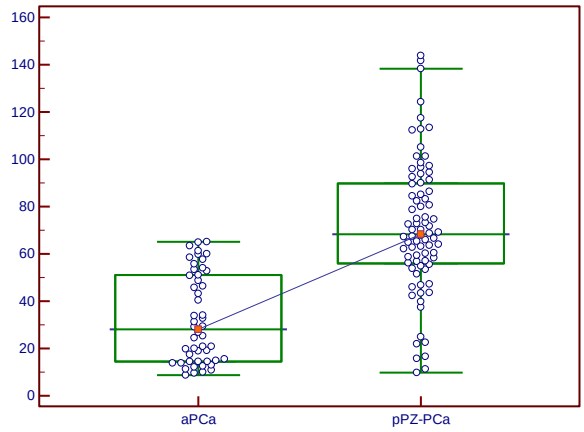

Figure 4. Difference in PCA3 levels between aPCa and pPZ-PCa group (p<0.001).

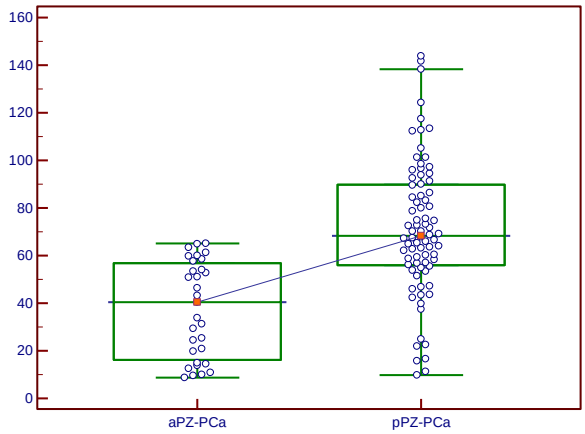

Figure 5. Difference in PCA3 levels between aPZ-PCa and pPZ-PCa group (p<0.001).

Table 3. Spearman Rank Order Correlations in pPZ-PCa patients.

Parameter	Age	ISUP	PSA	PIRADS	PCA3
Age	1,0	0,4*	0,16	0,07	0,24*
ISUP	0,4*	1,0	0,24*	0,32*	0,71*
PSA	0,16	0,24*	1,0	0,05	0,15
PIRADS	0,07	0,32*	0,05	1,0	0,19
PCA3	0,24*	0,71*	0,15	0,19	1,0

*Correlations significant at p <0,05

Conclusion

It is essential to consider the zone of prostate cancer growth when interpreting PCA3 urine levels. Additional research is warranted to further investigate this relationship.

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