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# EUROPEAN JOURNAL OF TRANSLATIONAL AND CLINICAL MEDICINE

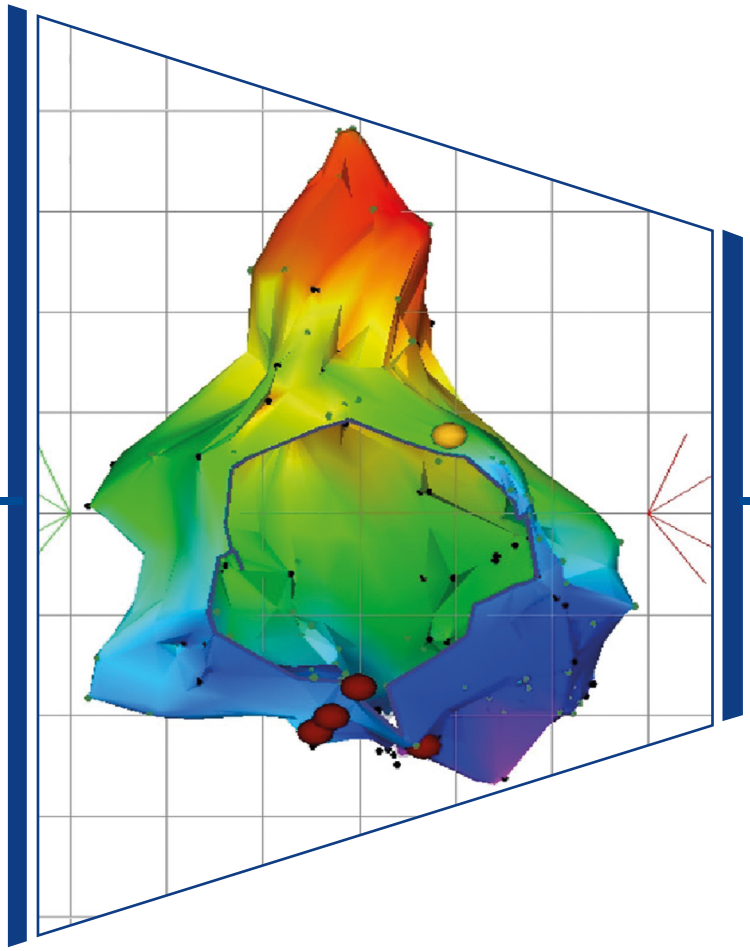

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Photo on the cover of the issue by Mikołaj Młyński et al. (page 9)


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INVITED EDITORIAL

# Precision medicine and improving the outcomes of atrial tachycardia ablation: a comprehensive review

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## Abstract

Atrial tachycardia (AT) is a prevalent cardiac arrhythmia characterized by rapid, abnormal electrical activity originating from the atria. It represents a significant clinical challenge due to its potential for recurrence, adverse cardiovascular outcomes and impact on quality of life. Catheter ablation has emerged as a primary therapeutic modality for AT, offering the potential for rhythm control and symptom alleviation. Despite advancements in techniques and technology, the success of AT ablation can vary widely among patients. Identifying prognostic factors associated with successful AT ablation and potential outcome improving techniques is imperative for optimizing patient care.

**Keywords:** atrial tachycardia · catheter ablation · prognostic factor · procedural technique · precision medicine

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## Introduction

Atrial tachycardia poses a considerable clinical challenge due to its propensity for recurrence and adverse cardiovascular outcomes. Focal AT represents up to 17% of supraventricular arrhythmias referred for catheter ablation treatment [1]. This treatment modality has revolutionized the management of AT, providing a cure for many patients. However, the efficacy of AT ablation is influenced by numerous factors, ranging from patient demographics to procedural intricacies and post-ablation monitoring strategies [2-9].

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Advancements in predictive modeling and risk stratification algorithms enable clinicians to assess the likelihood of procedural success and arrhythmia recurrence more accurately [7, 10-14]. Incorporating clinical, electrocardiographic, imaging and genetic data into comprehensive risk assessment tools allows for personalized treatment recommendations and informed decision-making [3]. Furthermore, longitudinal data collection through large-scale registries and multicenter studies facilitates ongoing refinement of prognostic models and validation of novel biomarkers.

The identification of novel outcome predictors for successful ablation of AT is an active area of research aimed at improving procedural efficacy and patient outcomes. While traditional predictors (e.g. demographic factors, concomitant diseases) remain important [4], recent advancements have led to the exploration of additional techniques and candidate selection strategies that may enhance risk stratification and treatment planning (Figure 1).

## Precision medicine approaches

The concept of precision medicine, which emphasizes individualized treatment based on patients' unique characteristics, is gaining traction in the field of AT ablation [10]. Tailoring treatment strategies to patients' genetic profiles, atrial substrate characteristics and comorbidities enables more effective targeting of arrhythmogenic mechanisms and optimization of procedural outcomes. Integrating approaches such as genetic testing, biomarker analysis, advanced imaging modalities, multi-omics (i.e. the analysis of multiple data sets regarding for example genomics, metabolomics etc.) and personalized ablation strategies, into clinical practice holds promise for further improving patient care and long-term outcomes.

Multivariable risk scores incorporate demographic factors, comorbidities, electrocardiographic parameters, imaging findings and genetic biomarkers to stratify patients into low, intermediate, and high-risk categories [11-12, 15-17]. Personalized risk assessment facilitates shared decision-making, treatment planning, and optimization of post-ablation management strategies tailored to each patient's unique profile.

### Patient characteristics

Patient-related variables play a crucial role in determining the success of AT ablation. Although age and the presence of comorbidities (e.g. coronary artery disease, cardiomyopathy, valvular heart disease) is not clearly correlated with higher arrhythmia recurrence rates in the population of patients with supraventricular tachycardias (SVT), their presence can correlate with a decreased success rate and increased occurrence of complications and major adverse cardiac events [4]. This may be attributed to age-related changes in atrial tissue characteristics and its electrical properties [18-19], however the lack of symptom improvement can be also attributed to the natural course of the primary concomitant cardiovascular diseases. Additionally, the presence of comorbidities (e.g. hypertension, diabetes, obesity) can have impact on procedural efficacy and long-term arrhythmia recurrence [5, 20].

Novel patient characteristics, including genetic variants, inflammatory profiles, autonomic modulation, comorbidity burdens and metabolic phenotypes, can play critical roles in determining the success of AT ablation [4, 6, 20-22]. Understanding the interplay between patient demographics, comorbidities and genetic factors is essential for personalized risk stratification and treatment planning in AT ablation [4-6,

| **Atrial tachycardias** |
|---|
| Sinus tachycardia |
| • Physiological sinus tachycardia<br>• Inappropriate sinus tachycardia<br>• Sinus nodal re-etrant tachycardia |
| Focal AT |
| Multifocal AT |
| MRAT |
| • Cavotricuspid isthmus-dependent MRAT<br>– Typical atrial flutter, counter-clockwise (common) or clockwise (reverse)<br>– Other cavotricuspid isthmus-dependent MRAT<br>• Non-cavotricuspid isthmus-dependent MRAT<br>– RA MRAT<br>– LA MRAT |
| AF |

| **AV junctional tachycardias** |
|---|
| Atrioventricular nodal re-entrant tachycardia (AVNRT) |
| • Typical<br>• Atypical |
| Non-re-entrant junctional tachycardia |
| • JET (junctional ectopic or focal junctional tachycardia)<br>• Other non-re-entrant variants |
| **Atrioventricular re-etrant tachycardia (AVRT)** |
| • Orthodromic (including PJRT)<br>• Antidromic (with retrograde conduction through the AVN or, rarely, over another pathway) |

AF – atrial fibrillation; AT – atrial tachycardia; AV – atrioventricular; AVN = atrioventricular node; JET – junctional ectopic tachycardia; RA – right atrial; LA – left atrial; MRAT – macro-re-entrant atrial tachycardia; PJRT – permanent junctional reciprocating tachycardia; RA – right atrial



**Figure 1. Atrial tachycardia classification according to the 2019 ESC Guidelines**

23-24]. Incorporating those into risk stratification algorithms and personalized treatment approaches can optimize procedural outcomes, minimize complication risks, and improve long-term arrhythmia-free survival in patients with AT [5-6, 10, 23, 25].

### Genetic variants and biomarkers

Advancements in genetic profiling and biomarker discovery have identified specific genetic variants associated with general susceptibility to SVT, arrhythmia mechanisms, and treatment response, most importantly for atrial fibrillation (AF) [6]. Genetic polymorphisms in ion channel genes, cardiac structural proteins and regulatory molecules may influence atrial electrophysiology and arrhythmogenic substrate (i.e. the cardiac tissue, where the arrhythmia originates from) remodeling [6].

Although the mechanisms for AT development have been studied most thoroughly in patients with specific genetic disorders (e.g. RAS/MAPK pathway) [26], it has also been investigated in animal models, such as the tafazzin mutation [27]. Moreover, it has been shown, that certain genetic mutations can be related to an increased risk of isolated atrial cardiomyopathy and atrial arrhythmias [28-30]. Genome-wide association studies (GWAS) and candidate gene analyses can identify polymorphisms in genes encoding ion channels (e.g. potassium channels), cardiac structural proteins, such as gap junction proteins, and regulatory molecules that modulate atrial electrophysiology and arrhythmogenesis [26-30].

### Inflammatory and immune profiles

Growing evidence suggests that systemic inflammation and immune activation play a crucial role in the pathogenesis and recurrence of atrial arrhythmias. Elevated levels of pro-inflammatory cytokines, chemokine and circulating immune cells correlate with atrial remodeling, fibrosis and electrical instability [21, 25]. In the past years, it has been shown that genetic polymorphisms in the structure of proteins such as interleukin-6 are related to an increased risk of postoperative atrial fibrillation [21]. It is noteworthy that in some studies this correlation has not been confirmed for AT [25]. The existence of an inflammatory-mediated AT pathway may create a possibility for the implementation of immunomodulatory therapies targeting inflammatory pathways in order to attenuate atrial fibrosis, reduce arrhythmia burden and improve ablation outcomes [31].

Markers of atrial fibrosis, inflammation and extracellular matrix remodeling, which are consistent with atrial myopathy, have emerged as potential predictors of ablation success and long-term outcomes, documented mostly in atrial fibrillation. Serum biomarkers such as galectin-3, soluble ST2 and matrix metalloproteinases (MMPs) reflect underlying atrial structural changes and myocardial injury [23-24]. Integration of biomarker data into risk prediction algorithms may enhance risk stratification and facilitate targeted therapeutic interventions.

### Autonomic modulation

Although described mostly in animal experimental models and patients with AF, the role of the autonomic nervous system (ANS) dysregulation, including heterogenic or increased autonomic innervation of the cardiac tissue, contributes to atrial arrhythmogenesis and treatment resistance [22, 32]. Assessment of stellate ganglion nerve activity and vagal nerve activity may be beneficial in the prognostic evaluation of tachyarrhythmias. Novel intervention strategies targeting sympathetic activation or vagal tone may enhance procedural success rates and reduce arrhythmia recurrence in susceptible individuals [33-35].

## Individualized arrhythmia considerations

The characteristics of the AT itself profoundly influence the success of catheter ablation. AT can arise from various mechanisms (including focal ectopy, reentrant circuits, triggered activity), each requiring distinct ablation strategies for successful termination. Focal AT originates from discrete sites within the atria, often exhibiting centrifugal activation patterns and rapid ectopic firing rates [1-2]. In contrast, reentrant AT involves the formation of macro-reentrant circuits, commonly involving areas of scar or abnormal tissue conduction [1-2]. Electrocardiographic features, such as P-wave morphology, atrial activation patterns and atrial substrate characteristics, provide valuable insights into the underlying arrhythmia mechanism and guide ablation strategies [2]. Advanced imaging modalities, such as cardiac magnetic resonance imaging (MRI) and three-dimensional electroanatomic mapping systems, offer additional tools for characterizing arrhythmogenic substrates and optimizing ablation targets [1-2, 36] (Figure 2, Figure 3).

### Substrate-focused approach

Important factors to consider are the location, origin and pathophysiology of the arrhythmogenic substrates. ATs more often emerge from foci located in the right atrium, most commonly from crista terminalis, which is associated with a good prognosis and long-term ablation success rate [1, 7, 37]. On the contrary, procedures performed in delicate regions of the atria, close to critical structures (e.g. atrioventricular node

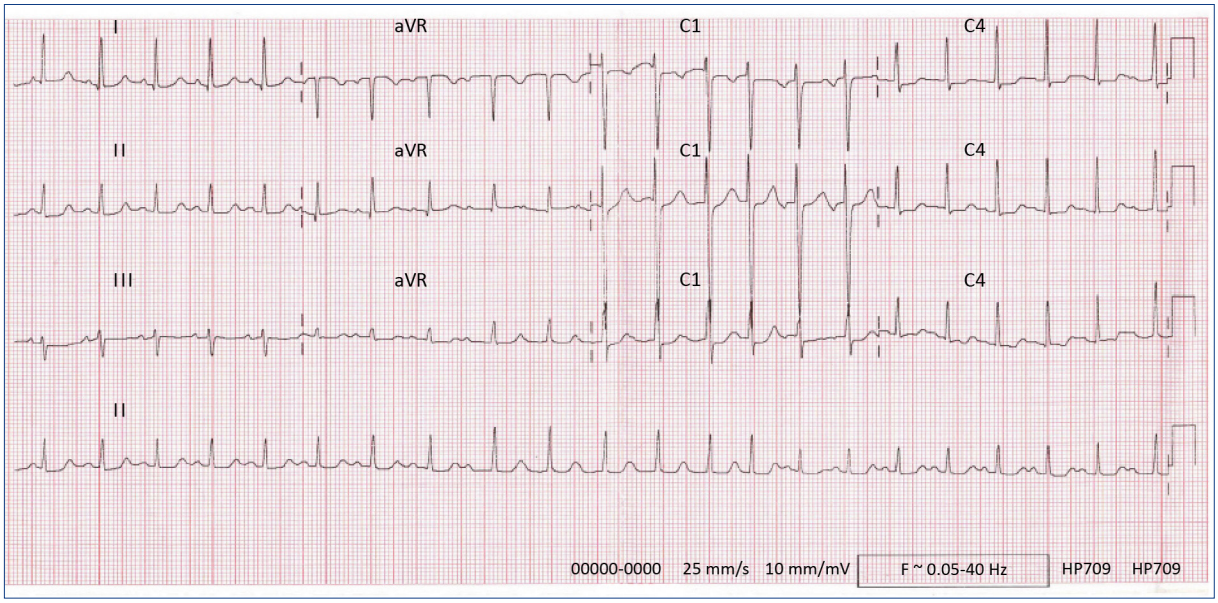


**Figure 2. Electrocardiogram of focal AT**

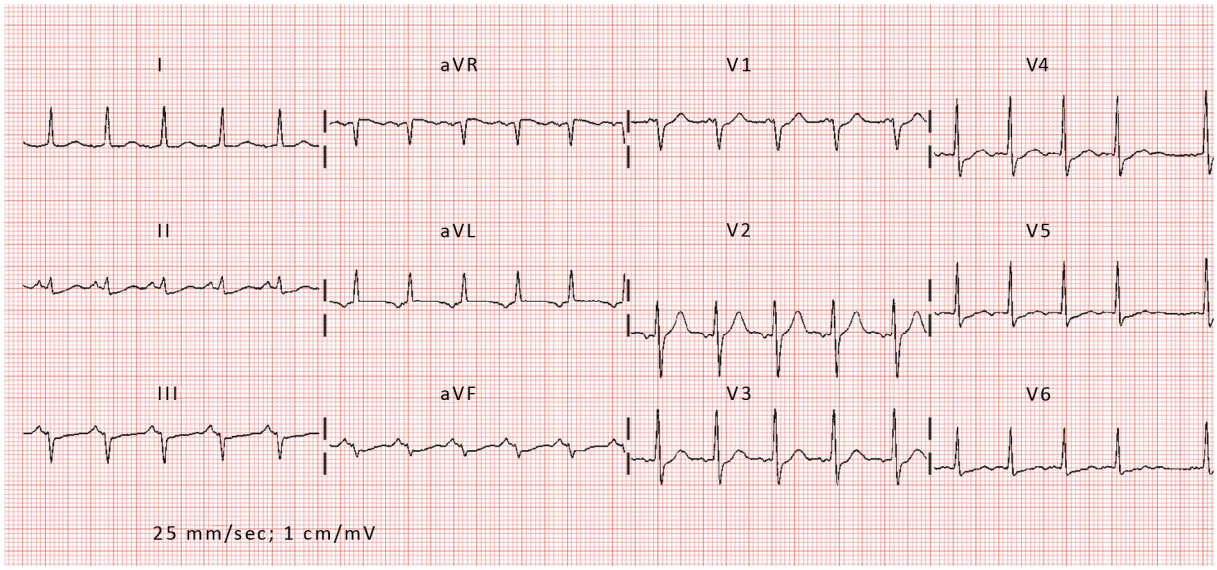


**Figure 3. Electrocardiogram of reentrant AT**

(AVN) or local nerves) require a more cautious approach and pose a greater risk of complications [1-2].

Precision medicine approaches recognize the heterogeneity of atrial substrate underlying AT and tailor ablation strategies accordingly. While procedural advancements, namely electroanatomic mapping modalities, have led to significant improvement in ablation success rate [38], the use of non-invasive imaging modalities, such as magnetic resonance is not always beneficial, when combined with standard diagnostic protocol [39]. However, in some studies, the assessment of late gadolinium enhancement (LGE) patterns in cardiac MRI – consistent with atrial fibrosis and scarring – has been shown to significantly increase procedural success rate and decrease risk in ablation of AF and AT substrates [36, 40-41]. Other imaging modalities, such as speckle-tracking echocardiography can be used to assess the risk of arrhythmia recurrence after catheter ablation [42].

Additional factors, including the origin of atrial scarring can contribute to the clinical characteristics of AT treatment. The emergence of substrates after surgical procedures involving atria is well known. However, the phenomenon of spontaneous scarring (SS), unrelated to prior surgery or significant structural heart disease can contribute to the development of atrial arrhythmia. Patients with SS have a higher prevalence of

AT, with a lower ablation success rate and an increased risk of concomitant sinus node dysfunction [43-44].

Interestingly, novel techniques of patient-specific substrate modelling are being investigated, including MRI-based myocardial fiber organization. In silico this technique has shown satisfying results in both focal and rotor-based AT, when compared to procedural data such as local activation time (LAT) tracking accuracy [8].

## Procedural factors

Technical aspects of the ablation procedure significantly contribute to its success. Operator experience, catheter technology, mapping methodologies and energy delivery modalities influence procedural efficacy and safety. Experienced operators with proficiency in catheter manipulation, electroanatomic mapping (EAM) interpretation and ablation lesion creation are essential for achieving optimal outcomes. Comprehensive procedural planning, including pre-procedural imaging, EAM, and intra-procedural monitoring, optimizes ablation outcomes and minimizes procedural complications (Figure 4).

In general, the choice of catheter type and energy source depends on the arrhythmia mechanism, atrial anatomy and operator preference. Emerging techniques, such as contact force sensing catheters, high-density mapping and robotic navigation systems, hold promise for further improving procedural success rates and reducing complication risks.

## Contact force sensing catheters

Optimal catheter-tissue contact force (CF) and lesion quality are crucial for procedural precision and efficacy, leading to better patient outcomes. Maintaining optimal CF enhances lesion transmurality, reduces impedance changes and minimizes the risk of steam pops and thrombus formation. CF-sensing catheters provide real-time, quantitative feedback during ablation procedures, that is normally derived from indirect parameters, e.g. baseline impedance, tactile feedback and electrogram (EGM) amplitude. Although some studies have promising results regarding the decreased number of energy applications and total procedure time during radiofrequency (RF) ablation, the available randomized controlled trials (RCTs) have not proved the superiority of CF-sensing catheter over standard equipment [45-47].

## Energy delivery

Radiofrequency (RF) energy remains the most commonly used ablation modality, delivering localized thermal energy

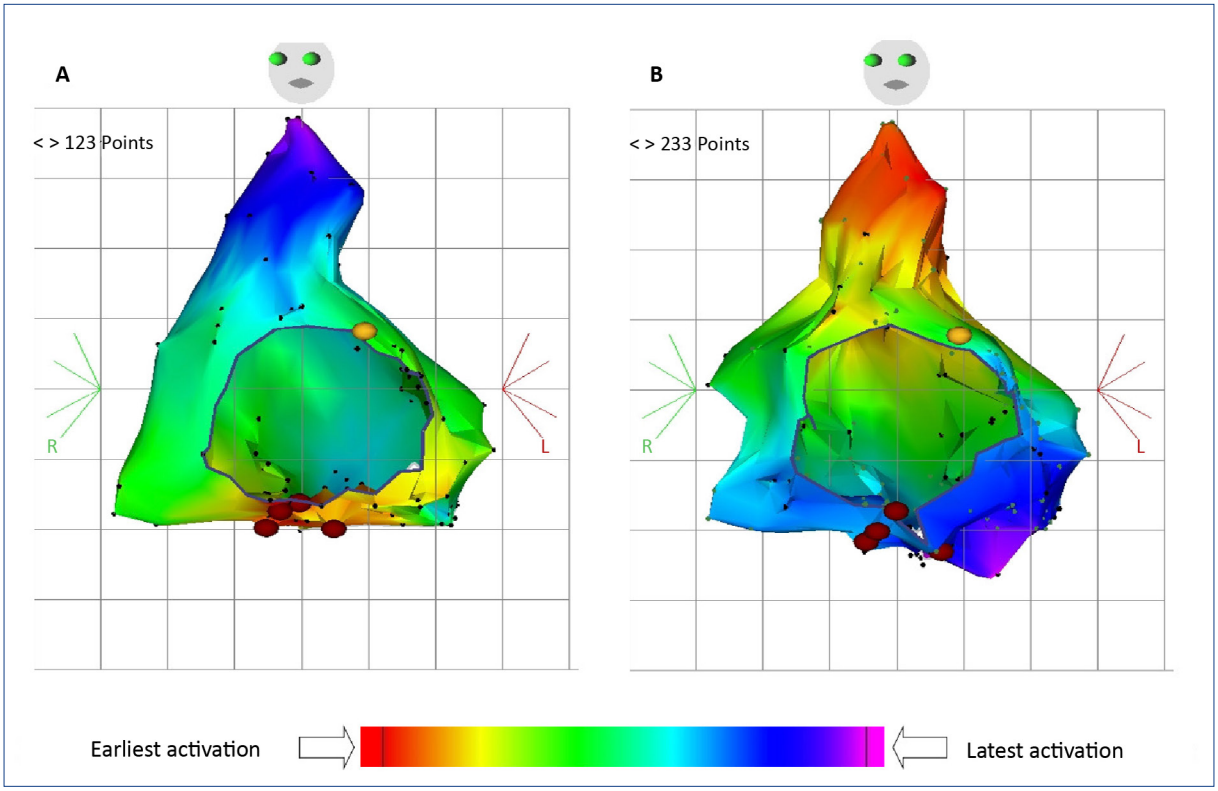


**Figure 4. Three-dimensional mapping of atrial potentials during an electrophysiological study**

to create transmural lesions. However, RF ablation may be limited by inadequate lesion depth, tissue charring and the risk of collateral damage to adjacent structures. In contrast, cryoablation, utilizing freezing temperatures to produce reversible tissue injury, provides more accurate and localized lesion application. Current data shows that RF ablation remains the most effective method, although cryoablation may be considered during procedures performed in regions of close proximity to vital structures (e.g. near the phrenic nerve or in para-Hisian arrhythmic substrates) [1-2, 48-49]

Modulation of ablation energy parameters, including power, duration and lesion depth, optimizes lesion formation and procedural efficacy. Novel energy delivery modalities, such as pulsed field ablation (PFA), offer precise and controlled lesion creation while minimizing collateral damage to surrounding tissues [50-51]. PFA utilizes non-thermal, rapid electrical pulses to induce cell death mediated by membrane electroporation [50]. Current data supports the possible efficiency and safety of this modality in the treatment of ATs, however no RCTs have been published, comparing its outcomes to standard treatment protocol [50-54].

## Mapping technologies

Standard electrophysiologic mapping, based on local activation time (LAT) assignation can be insufficient, often upon examination of low-voltage regions within atrial scarring [9, 55]. In recent years we have seen the introduction of high-resolution mapping systems, such as high-density mapping (HDM) catheters and basket catheters, which allow for more detailed characterization of atrial substrate and precise identification of arrhythmia targets [9, 55]. These technologies enable operators to create accurate electroanatomic maps of the atria, facilitating targeted ablation and reducing procedural times [1-2, 9, 55-56]. Nevertheless, HDM has also been shown to lack accuracy, displaying local pseudo-reentrant patterns in patients with AT upon encountering electric wavefront collision or annotating noise, resulting in incorrect lesion application during ablation [56]. Other advanced methods, such as ripple mapping (RM), which serves as a three-dimensional graphic representation of electrograms, have been proven to increase the success rate of AT ablation [56-58].

Innovative pacing and activation mapping techniques, including entrainment mapping, voltage mapping, and pace-mapping algorithms, aid in the identification of arrhythmia mechanisms and critical isthmuses. Entrainment mapping confirms the participation of specific sites within the reentrant circuit, guiding targeted ablation strategies [59]. Voltage mapping identifies areas of low-voltage substrate and scar tissue, delineating regions at high risk for arrhythmia recurrence [60-61].

Furthermore, introduction of functional substrate mapping (FSM) may lead to a more accurate assessment of atrial electroanatomic remodeling or heterogeneity. This method investigates activation complexity and conduction velocity, calculating conduction delay between adjacent tissue locations. Current data supports the correlation between critical isthmus (CI) location in macro-reentrant ATs, low voltage regions and findings such as deceleration zones during isochronal late activation mapping, achieved via FSM during sinus or paced rhythm. FSM may provide additional guidance for substrate mapping and lesion placement in AT ablation [62-64].

Additionally, adjunctive strategies, such as adenosine--guided effectiveness assessment may help identify areas of incomplete isolation, facilitating targeted substrate modification and reducing arrhythmia recurrence rate [54, 65].

## Imaging-guided ablation

Advanced imaging modalities can provide detailed anatomical information and substrate characterization for targeted ablation, not only in the pre-procedural planning period but also during the intervention. Intracardiac echocardiography (ICE) and rotational angiography allow real-time visualization of catheter position and can be used to assess the accuracy of catheter-tissue contact, which translates to better procedural outcomes [66]. ICE imaging has been reported to facilitate ablation of critically located substrates, as in para-Hisian ATs [66], and in cases with altered atrial anatomy, as in patients with surgically corrected congenital heart disease [67]. Intracardiac thrombus detection is another potential contribution of this imaging modality to procedural safety is attributed to [68]. Additionally, when combined with EAM techniques, ICE can serve as a substitute for fluoroscopy monitoring in transseptal puncture for ablation of left-sided arrhythmias [69].

## Data science meets medicine

### *Computational modeling and simulation*

Advanced analysis of electrogram characteristics, including signal amplitude, duration, fractionation, and voltage mapping, provides insights into atrial substrate properties and arrhythmia mechanisms. Precise delineation of atrial anatomy, scar tissue distribution and arrhythmogenic foci localization guides catheter navigation and lesion creation during ablation procedures. Novel algorithms utilizing machine learning and artificial intelligence techniques can identify subtle electrogram features associated with arrhythmogenic substrate and may eventually be able to predict ablation success [13, 70-71].

| | |
|---|---|
| **Advanced age** | • Decreased success rate and higher procedural risk |
| **Comorbidities (e.g. hypertension, DM, CAD, valvular disease, cardiomyopathy, obesity)** | • Decreased success rate and higher procedural risk<br>• Higher risk of recurrence |
| **Atrial myocardium fibrosis** | • Potentially decreased success rate and worse long-term outcomes |
| **Unfavorable genetic and immunological profile** | |
| **Prior magnetic resonance imaging** | • LGE mapping – increased success rate and decreased procedural risk<br>• Myocardial fiber organization – potentially increased success rate |
| **Atrial strain on echocardiography** | • Better recurrence prediction |
| **Intracardial echocardiography** | • Increased safety and improved outcomes |
| **Catheter contact force assessment** | • Potentially shorter procedure duration and less energy applications |
| **Radiofrequency ablation** | • More efficient<br>• Higher risk of adverse outcomes |
| **Cryoablation** | • Less efficient<br>• More precise and safe in critical locations |
| **Advanced mapping technologies** | • HDM – more precise; can lead to unnecessary applications in regions of pseudo-reentry<br>• RM – increased success rate<br>• FSM – better substrate identification; increased accuracy |

**Figure 5. Factors impacting the AT ablation success and prognosis**
CAD – coronary artery disease; DM – diabetes mellitus; FSM – functional substrate mapping; HDM – high density mapping; LGE – late gadolinium enhancement; RM – ripple mapping

### *Artificial intelligence (AI) and machine learning*

Artificial intelligence (AI) and machine learning algorithms integrated into electrophysiology workflows hold promise for improving procedural planning, navigation and outcomes. AI-driven algorithms analyze vast amounts of patient data, including electrocardiographic signals, imaging studies and procedural outcomes, to identify patterns and predict optimal treatment strategies. By assisting in substrate identification, ablation site selection and lesion assessment, AI-powered technologies have the potential to enhance procedural success rates and reduce complication risks. By analyzing diverse patient characteristics, clinical variables, imaging parameters, and electrophysiological data, machine learning algorithms identify complex relationships and patterns that inform individualized treatment decisions [14, 72-73]. Integration of real-time data streams and continuous learning frameworks enhances the adaptability and accuracy of predictive models over time [14, 72-74].

### Coordination of multidisciplinary care

Effective implementation of precision medicine in AT ablation requires close collaboration among multidisciplinary teams, including electrophysiologists, imaging specialists, genetic counselors and clinical pharmacologists [75]. Multidisciplinary care coordination can provide comprehensive evaluation, personalized treatment planning, and integrated follow-up care to optimize patient outcomes [75]. As in all fields of contemporary medicine, shared decision-making principles can be effective in empowering patients to actively participate in treatment decisions, contribute to their care plans, and engage in lifestyle modifications that support long-term rhythm control and cardiovascular health (Figure 5).

## Conclusion

Successful ablation of AT requires a multidimensional approach, incorporating patient-specific factors, arrhythmia characteristics, procedural techniques and long-term monitoring strategies. Continued research efforts aimed at elucidating novel prognostic markers, refining ablation strategies and leveraging digital health technologies are essential for advancing the field of AT ablation and improving patient care in the future. Precision medicine applications hold promise for improving the success and safety of atrial tachycardia ablation by individualizing treatment strategies based on patient-specific characteristics.

## Conflict of interest

None.

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None.

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RESEARCH ARTICLE

# Edmonton Frail Scale – caregiver is a reliable source of information about the functional status of a hospitalized elderly patient

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## Abstract

**Background:** The success of geriatric care requires cooperation with the patient's caregivers. This study aims to compare the perspectives of elderly patients and their caregivers on functional efficiency, as measured by the Edmonton Frail Scale. By examining the discrepancies in these assessments, we hope to better understand perceptions of frailty-related functional limitations and improve the personalized approaches in geriatric care. **Material and methods:** This cross-sectional study enrolled a sample of hospitalized patients, based on availability of researchers. Exclusion criteria involved: age < 65, communication barriers, manual disability, exacerbation of a chronic disease or acute condition, no contact to the caregiver, lack of consent. The McNemar-Bowker test and the Wilcoxon signed-rank test were used to compare patients' and their caregivers' responses. **Results:** Forty five patients were enrolled. The answers concerning cognitive functions, laundry, and functional performance were statistically different ($p < 0.001$). Whereas after applying the Holm-Bonferroni method for multiple testing only the judgment of cognitive functions remained statistically different. Other domains showed no statistical differences. **Conclusions:** Our results may in general confirm the credibility of caregivers' perspective in the patients' functional assessment.

**Keywords:** frailty · caregiver history · elderly · history taking

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## Abbreviations

- EFS – Edmonton Frail Scale
- AMTS – Abbreviated Mental Test Score
- CGA – Comprehensive Geriatric Assessment

## Introduction

The dynamic progress of medicine contributes to the extension of the average life expectancy, which results in a constant increase in the population of the elderly. In Poland, this trend is expected to continue until at least the middle of the 21st century [1]. One of the most important problems in the field of geriatrics is frailty. It is described as a decrease in the body's physiological reserves and is associated with a longer (or inability to) return to balance in the event of a stress factor. It is a multidimensional problem, involving a disorder of the patient's functioning in the physical, mental and social dimensions [2]. There is evidence that self-reported exponents of this syndrome (e.g. weight loss, slow gait pace, fatigue and lack of physical activity) are predictors of adverse outcomes of greater predictive power and discrimination compared to the assessment of objective exponents [3].

The aims of our study were to investigate differences in the responses of patients and their caregivers to the questions regarding functional status included in the Edmonton Frail Scale (EFS) and to compare their perspective on gait and cognitive status.

## Material and methods

The study was conducted at the Department of Rheumatology, Clinical Immunology, Geriatrics and Internal Medicine of the Medical University of Gdańsk, Poland. The research group was recruited from among the patients hospitalized from January to June 2022. Data collection process depended on the organizational accessibility of the researchers.

The exclusion criteria were: aged < 65, cognitive deficits unabling logical communication or other communication barriers (visual or hearing impairment), manual disability, exacerbation of a chronic disease or acute condition at the time of the examination, isolation due to infectious disease, absence or lack of opportunity to contact the caregiver, and lack of consent of the patient or the caregiver/family member to participate in the study. Presence of cognitive deficits were assessed on the basis of the Abbreviated Mental Test Score (AMTS) [4], which was performed by each participant before qualifying for the study. Participants who scored < 7 points on the AMTS were excluded.

The study consisted of two parts. First, we used the EFS to assess the severity of frailty syndrome among patients. The EFS assesses 10 domains of life in a mixed way: subjectively and objectively. The survey questions concern the subjective assessment of general health, functional independence, social support, medication intake, nutrition, mood and urinary continence. In addition, the EFS includes two performance tests assessing cognitive abilities and the risk of fall. The overall score can range from 0 to 17 points. Higher score represents a greater severity of the frailty syndrome [5-6]. The EFS was chosen because of its feasibility of use at the bedside and short examination time compared to a full comprehensive geriatric assessment (CGA). Moreover, EFS was validated to be used by non-specialists without background and experience in geriatric care [5].

In the second part of our study we contacted (by phone or in person) the caregiver or family member, who was previously authorized by the patient, and used the questionnaire part of the EFS in order to evaluate their perspective on the presence of frailty syndrome features in the examined patient.

Furthermore, we asked about the type of relationship with the senior (child, spouse, sibling, other relative, friend or social worker), whether they live together with the patient, their acquaintance with the senior's everyday life, the frequency of mutual contacts, and the senior's cognitive and gait abilities from the caregivers' point of view. For these last two examined items we suggested two original questions, possibly accurate for an average caregiver's assessment of a patient's health.

"Do you think your relative needs help while walking?"

Three possible answers were given to the responder, in relation to the values that could be obtained from the functional performance test:

1) "No", considered as a value of '0';

2) "Yes, they need slight support from time to time", considered as '1';

3) "Yes, they are unable to walk without assistance of another person or supportive devices such as cane or walking frame", considered as '2'.

"Do you think your relative suffers from dementia?"

Three possible answers were given as well:

1) "No" considered as a value of '0';

2) "Yes, mild stage", considered as '1';

3) "Yes, advanced stage", considered as '2'.

## Results

During the 6-month study period 233 patients were screened to participate in the study. The final number of eligible patients was 45 (Figure 1). The characteristics of seniors and their caregivers are presented in Table 1.

EFS results were normally distributed, 71% (n = 32) of patients met the frailty criteria. The EFS score did not correlate with age. People living with a caregiver showed, on average, a higher severity of frailty syndrome (mean EFS score 8.28 compared to 6.75).

To compare the answers of patients and their caregivers, the Bowker-McNemar test was used for questions in which the answers were on a nominal scale. For variables in which there was an ordinal scale, the Wilcoxon signed-rank test was used. The answers of the senior and his caregiver turned out to be statistically different in the question addressing the ability to do laundry on their own and in two domains outside the questionnaire part – cognitive abilities, and functional performance. However, after applying the Holm method for multiple testing, only the results of the cognitive assessment were statistically different. The answers regarding other domains did not show statistically significant differences. Comparison of the cognitive ability assessment measured by objective test and opinion of a carer turned out to be the least convergent.

Some caregivers declared insufficient knowledge to answer several questions, specifically about taking medications (question 1 n = 4; question 2 (n = 4), preparing meals (n = 1), mood (n = 4), incontinence (n = 2). The results of statistical tests are presented in Table 2.

## Discussion

Despite the well-established importance of taking a collateral history in geriatrics [7], literature exploring this field is scarce, usually focusing on assessing the presence of cognitive disorders [8]. Nevertheless, even in the presence of dementia symptoms, physicians rarely take collateral history or the obtained history is incomplete [9]. Physicians also report a lack of training and tools facilitating the collection of anamnesis from the patient's family [10].

Statistical analysis of the obtained data showed that there were no significant differences between the responses of patients and caregivers to questions included in the questionnaire part of EFS. While there was no statistical difference in the results regarding functional performance, there was a difference between the cognitive performance of seniors and the assessment of seniors' cognitive abilities by their caregivers.

Our study has several limitations. First of them is the small study group (n = 45), limited to a single center. Secondly, many patients who met the clinical and organizational inclusion criteria declined to participate in the study (n = 17). We hypothesize that patients who agreed to participate in the study had

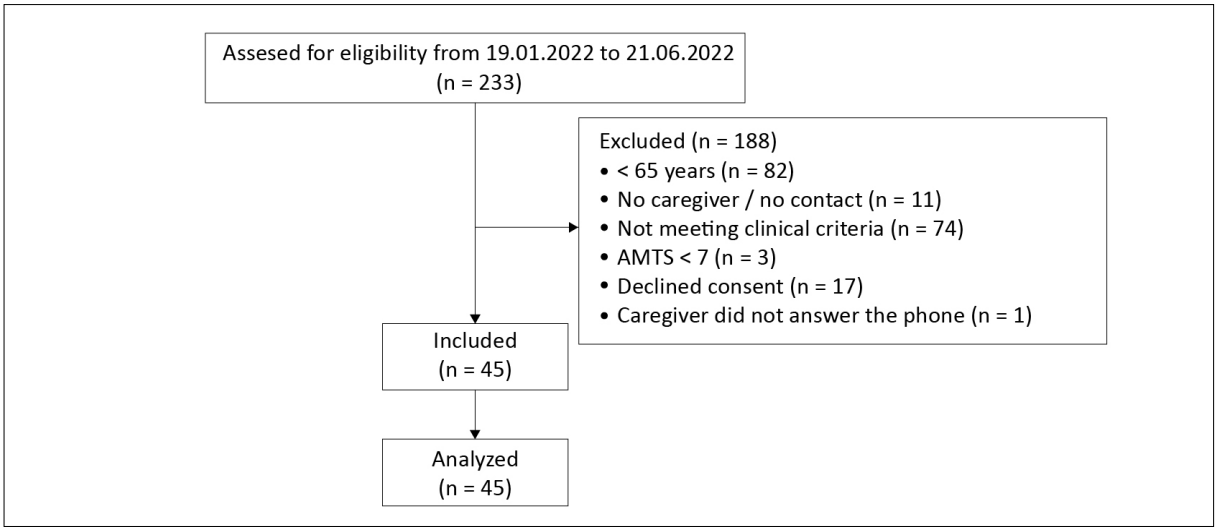


**Figure 1. Study flow diagram**

**Table 1. Characteristics of the study group**

| Variable | Population (n = 45) |
|---|---|
| **Elderly patient** | |
| Age | 72 years old |
| Male | 15 (33.3%) |
| Frailty | 32 |
| Mild | 8 |
| Moderate | 11 |
| Severe | 13 |
| Vulnerable | 10 |
| Fit | 3 |
| **Caregiver** | |
| Child | 21 |
| Spouse | 16 |
| Siblings | 4 |
| Other family member | 3 |
| Friend | 1 |
| Live with the elderly patient | 25 |
| See the elderly patient at least once a week | 39 |
| Claim to be familiar with the elderly patient's daily life | 42 |

better relationships with their caregivers, and therefore the results may be biased.

In the EFS the cognitive domain is assessed using the clock-drawing test. It is worth mentioning that despite its recognized value, the clock-drawing test is a screening test and should not be applied as the sole diagnostic tool for dementia [11]. Moreover, the clock-drawing test allows objective assessment of the patients' cognition, not subjectively. Hence, the obtained results are difficult to compare to the caregivers' responses.

We would also like to point out that for organizational reasons our study included a group of patients that did not have severe cognitive impairment, which was excluded using the AMTS. Therefore our results may not be applicable to seniors with advanced cognitive deficits.

**Table 2. Comparison of patient and caregiver responses**

| Frailty domain | P-value | |
|---|---|---|
| | Before Holm method | After Holm method |
| Cognition | 2.552E - 8 † | 4.338914E - 7 |
| Admission to hospital | 0.5135† | 1 |
| Health | 0.7177† | 1 |
| Meal preparation | 0.2888‡ | 1 |
| Shopping | 0.0771‡ | 1 |
| Taking medications | 0.505‡ | 1 |
| Housekeeping | 0.7518‡ | 1 |
| Telephone | X** | X** |
| Transportation | 0.1824‡ | 1 |
| Money management | 0.0771‡ | 1 |
| Laundry | 2.993E - 6‡ | 0.3911831 |
| Social support | 0.7019† | 1 |
| Medication use | 1‡ | 1 |
| Forgetting medication | 0.6276‡ | 1 |
| Nutrition | 0.5465‡ | 1 |
| Mood | 0.2113‡ | 1 |
| Continence | 1‡ | 1 |
| Functional performance | 0.02149† | 0.5555709 |

*** P-value indicates statistical significance of differences between the patients' performance/answers and caregivers' answers.**
****Assumptions for the test not met – the test could not be performed.**
**† Wilcoxon's signed rank test**
**‡ McNemar-Bowker test**

## Conclusions

The results of our study suggest that the caregiver is a reliable source of information about the patient's functional status. This is valuable when patients for various reasons (e.g. acute illness or dementia) are unable to answer questions about their previous functioning [9, 12]. Due to the limitations mentioned above, larger studies are needed to confirm our results.

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The authors used the Edmonton Frail Scale (bedside version), copyright 2000. All rights reserved. Created by Dr. Darryl Rolfson et al. and used under license from the University of Alberta: https://edmontonfrailscale.org

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None to report.

## Conflicts of interest

None to report.

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RESEARCH ARTICLE

# Subtrochanteric fracture location effect on surgical management using intermedullary nail (IMN) versus extramedullary plate (EMP): a finite element method analysis

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## Abstract

**Background:** Finite element method (FEM) analysis of the subtrochanteric fracture (STF) location effect in the subtrochanteric region (STR) fixated with the intermedullary nail (IMN) versus extramedullary plate (EMP) implant. **Material and methods:** A femur computed tomography (CT) scan was used to create a femur FE-model with a straight-line fracture located at the STR. During the analysis, the fracture was stepwise lowered from 0.5 to 4.5 cm below the lesser trochanter (LT) with a total of 9 steps of 0.5 cm. The IMN (using proximal femoral nail antirotation) and EMP (using dynamic hip screw) implants were modelled and implemented for fracture management. **Results:** EMP illustrated lower Von-Mises stress for the proximal fractures (until 3.5 cm below LT); whereas IMN showed lower stress for distal fractures (from 4 cm below LT). The mean Von-Mises stress ratio for IMN versus EMP also decreased from proximal (1.93) to distal (0.47) of STR, with an intersection cross-point at 3.8 cm below LT. **Conclusions:** the simulation shows that for the straight-line STF, EMP seems more favourable for proximal and IMN is more likely favourable for distal fractures. However, more FEM studies need to be conducted (e.g., with different fractures or implant types) on this topic.

**Keywords:** finite element method (FEM) · subtrochanteric fracture (STF) location · subtrochanteric region (STR) · intermedullary nail (IMN) · extramedullary plate (EMP)

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## Introduction

Subtrochanteric fractures (STF) are defined as fractures of the proximal femur that occur within 5 cm of the lesser trochanter [1]. Approximately 5-10% of proximal femoral fractures occur in the subtrochanteric region (STR), with an estimated overall incidence of about 15-20 per 100,000 for STF [2-4]. In the Netherlands, it makes up 3-4 of annual hip fracture admissions [5-6]. STF occurs mainly in older osteopenic patients after a low-energy fall or younger patients involved in high-energy trauma [1, 4, 7-8]. Roughly two-thirds of all STFs occur in patients over 50 years of age, with another 25% occurring in patients younger than 40 years old [1-2, 8-10]. Females suffer 2-3 times higher incidence compared to males [1, 11]. Risk factors such as low total hip bone mineral density, diabetes mellitus, and the use of bisphosphonate medications increase the probability of STF [1, 12-13].

Non-surgical treatments are associated with significant complications such as shortening and malrotation as well as an increase in prolonged immobilization, decubitus, and mortality [1, 14-15]. Surgical internal fixation leads to better bone healing and mobility recovery as well as reducing morbidity and preventing mortality [16]. The intermedullary nail (IMN) and the extramedullary plate (EMP) are one of the most common surgical methods used for STF management [17-24]. The effect of both implants has been studied in previous biomechanical studies (e.g., using simulation analysis) [25-28].

In the literature, there are uncertainties regarding STF management. Firstly, what is the effect of fracture location in the STR on fracture management? Secondly, does the fracture location in the STR justify the choice between IMN versus EMP implant? Therefore, this study aims to evaluate the impact of simple straight-line STF location in STR fixated by IMN versus EMP using the Finite Element Method (FEM) simulation analysis.

## Material and methods

### Femur model

A Computed Tomography (CT) scan (Siemens, SOMATOM Force model, Munich, Germany) of a normal cadaveric femur was used to generate a Digital Imaging and Communication in Medicine file (DICOM). The CT scan was made using the bone setting with a tube voltage of 90 kV, a tube current of 2.5 mA, and a matrix size 512x512. The 3D Slicer software (version 4, www.slicer.org) was used to create a three-dimensional (3D) femur model from the DICOM file and converted it to a Standard Triangle Language (STL) file. The femur STL-file was imported into Solidworks software (version 2014, 3D Modelling and Simulation, Waltham, Massachusetts, USA).

A straight-line fracture was created in the STR (the area from LT to 5 cm distal) (Figure 1). The fracture was then lowered from 0.5 to 4.5 cm below the LT, from proximal to distal, by steps of 5 mm with a total of 9 fracture locations (Figure 1). E.g., fracture 1 is located at the proximal section of STR and 0.5 cm below LT; fracture 9 is located at the distal section of STR and 4.5 cm below LT. The simple straight-line fracture was chosen for two reasons: (1) to optimally observe the effect of the two different implant systems used for the STF management, and (2) for an easier simulation of the fracture location effect in the STR concerning fracture management and fixation stability.

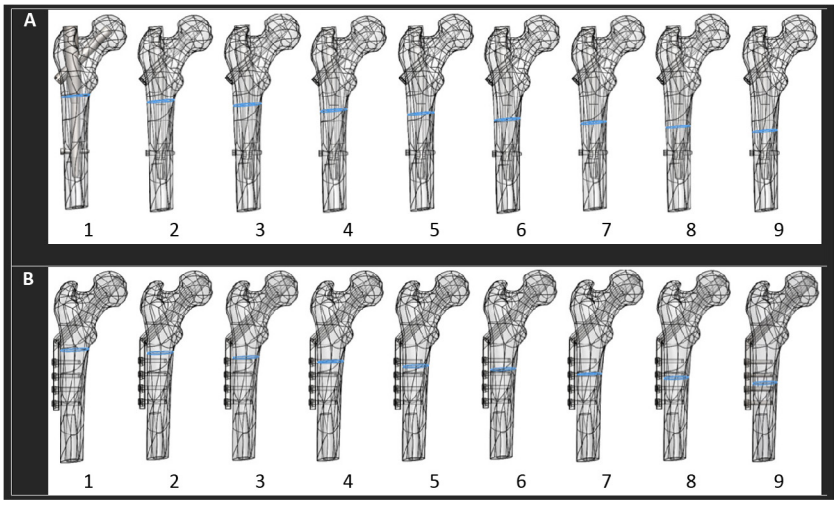


**Figure 1. (A and B, 1-9) Simple straight-line fracture located in the STR, lowered from proximal to distal region in 9 steps with a 5 mm distance between each step, starting from 0.5 cm to 4.5 cm below the LT; (A) STF fixated using the IMN (PFNA) and (B) the EMP (DHS) fixation.**
DHS – dynamic hip screw, EMP – Extramedullary plate, LT – lesser trochanter, IMN – intermedullary Nail, PFNA – proximal femoral nail antirotation, STR – subtrochanteric region

### IMN and EMP model

Standard commercially available implants (DePuy Synthes, Raynham, MA, United State) were selected for the study. For the IMN, the proximal femoral nail antirotation (PFNA) was selected; and for the EMP, the dynamic hip screw (DHS). The implant fixation systems were 3D modelled in the Solidworks with identical mechanical material properties (Figure 1).

The PFNA implant (IMN) consisted of a short intramedullary nail, a lag screw, and a distal locking screw. The nail was 180 cm in length, with a target angle range of 135 degrees. The nail had a proximal diameter of 17.5 mm, where the lag screw was inserted for fixation inside the femoral head. The nail had a distal diameter of 11 mm, where the locking screw was inserted for fixation with femoral shaft. The lag screw was 90 mm in length and 12 mm in diameter. The distal locking screw had a diameter of 5 mm and a total length of 34 mm.

The DHS implant (EMP) consisted of a plate, a lag screw, and four screws. The plate had a thickness of 7 mm with a standard 38 mm barrel length in 135 degrees angle. The lag screw was 90 mm in length with a diameter of 12 mm. The four distal plate screws had a diameter of 5 mm and a total length of 34 mm.

## FEM assembly

In the IMN (PFNA system) assembly: the nail was inserted inside the femur, with the lag screw positioned inside the femoral head, and the distal screw in the femoral shaft (Figure 1A). For the EMP (DHS system) assembly: the plate was positioned as close as possible to the femoral shaft, with the lag screw in the centre of the femoral head, and the four distal screws in the femoral shaft (Figure 1B). In both methods, the lag screw was positioned in the centre of the femoral head, and the distal screw(s) in the femoral shaft accordingly.

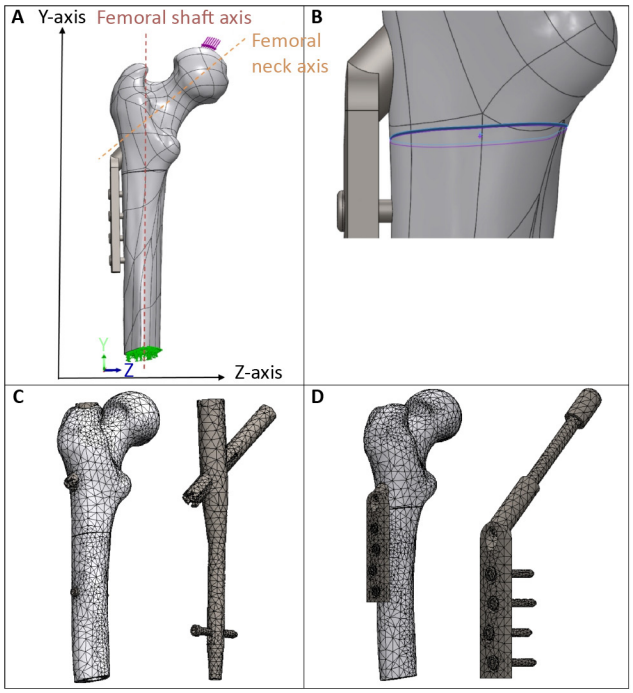


**Figure 2. (A) Applied force on the femoral head (downward in the Y-axis or the gravitational force direction, 8 degrees from to the femoral neck axis); and applied fixture at the formal shaft. (B) Contact-Set of 0.05 mm distance with no penetration between the fracture surfaces. (C-D) Impression of the applied converged mesh for resp. the IMN (PFNA) and the EMP (DHS) assemblies.**
DHS – dynamic hip screw, EMP – Extramedullary plate, LT – lesser trochanter, IMN – intermedullary Nail, PFNA – proximal femoral nail antirotation, STF – subtrochanteric fracture

## FEM simulation setup

Using Solidworks, a total of 18 assemblies were simulated, 9 assemblies used IMN (PFNA) (Figure 1A) and 9 EMP (DHS) (Figure 1B) fixation method.

In each assembly, a force was applied at the femoral head downward in relation to the y-axis, representing the gravitational direction, at an angle of 8 degrees from the femoral neck axis (Figure 2A: illustration of applied force) [29-30]. During each analysis, the force was increased from 125 to 500 newton (N), replicating various body weights [31]. The femur was fixed at the femoral shaft using the Fixed Geometry option in the Solidworks (Figure 2A: illustration of the fixation).

The connection-option in the Solidworks provided the definition of the boundary conditions for the assemblies. Firstly, the fracture surfaces were defined by using the Contact-Sets option with 0.05 mm fixed distance with no penetration between the fracture surfaces, representing optimal fracture reduction (Figure 2B). When the fracture surfaces touch under application of load, there was no friction and only forces normal to the surfaces could be exchanged. Secondly, the Contact-Sets and the Component-Contacts option, was applied to define the interactions between the femur and the implants.

For the IMN fixation method, the proximal lag screw was set as fixed inside the femoral head, and the distal screw was set as fixed inside the formal shaft. Meaning that the intermedullary nail was held in a fixed position by the lag screw and the distal screw. The interaction between the nail and femur was set as contact. Furthermore, the nail, the lag screw, and the distal screw were set as fixed. Meaning, that the implant components (nail, lag screw, and distal screw) were modelled as one single piece.

For the EMP, the plate was placed as close as possible to the femoral shaft, and the plate barrel was set as contact inside the femur. The lag screw was set as fixed inside the femoral head, and the four distal plate screws were set as fixed inside the femoral shaft. Meaning, that the plate was held in a fixed position by the lag screw and the four distal screws. The interactions between the plate, the lag screw, and the four screws were set as fixed. This means that the whole implant (plate, lags crew, and distal screws) was set as one single piece.

The material properties of the femur were set at an elastic modulus of 14500 megapascal (MPa), shear modulus of 3280 MPa, mass density of 1180 kg/m3, tensile strength of 150 MPa, yield strength of 160 MPa, and Poisson's ratio of 0.3 [32-33].

For the fixation implants, the material properties were set at an elastic modulus of 210000 MPa, shear modulus of 79000 MPa, mass density of 7700 kg/m³, tensile strength of 723.83 MPa, yield strength of 620.42 MPa, and Poisson's ratio of 0.28 [34].

A curvature-based mesh was created with a maximum element size of 11.8 to 12 mm, a minimum element size of 2.3 to 2.4 and, an element size ratio of 1.6 (Figure 2C and 2D). Mesh dimensions were checked using the Mesh Quality Check option in Solidworks. Furthermore, the mesh size was decreased until the results were independent of the mesh size.

## Results

The FEM outcomes are represented in the form of the Von-Mises stress in the megapascal [MPa] unit (table 1), determining whether the assembly will yield or distort during the complex loading condition. The increase in force from 125 to 500 N resulted in a rise in the Von-Mises stress for both IMN (PFNA) and EMP (DHS) implants (Figure 3A and 3B). The analysis showed a linear relationship between the amount of force and the Von-Mises stress (Supplementary Figure 1).

### IMN (PFNA) and STF location

The IMN (using PFNA implant) analysis shows a decrease in the Von-Mises stress, when the fracture is lowered from proximal to distal of STR (Table 1). The location of the maximum Von-Mises stress remains similar for the fracture locations 1 to 8 (from 3.5 to 4.0 cm below LT), but changes for the fracture location 9. For the fracture locations 1 to 8: the maximum Von-Mises stress is at the upper border of the distal locking screw, where it touches the top side of the distal intramedullary nail hole (Figure 4A). For the fracture location 9: the maximum stress is located at the lag screw, mainly between the lower part of the lag screw and the proximal intramedullary nail hole (Figure 4B).

### EMP (DHS) and STF location

The EMP (using a DHS implant) analysis generates an opposite result compared to the IMN (using a PFNA implant) outcomes. For the EMP analysis, the Von-Mises stress increases when the fracture is lowered in the STR from proximal to distal region (Table 1). The location of the maximum Von-Mises stress remains the same for all the fracture locations. The maximum stress is located on the distal plate screw, located at the upper contact point with the extramedullary plate (Figure 5A and 5B).

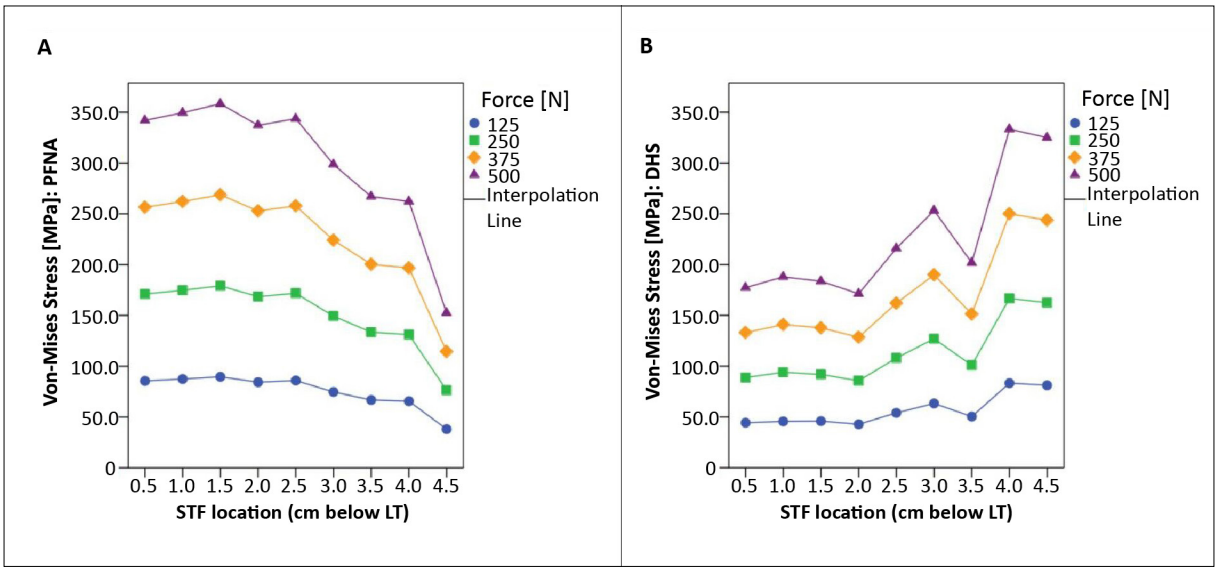


**Figure 3. Scatter plots representing the relationship between Von-Mises stress in MPa and STF location for (A) the IMN (using PFNA) and (B) the EMP (using DHS) implant. Hence: The STF location is based on the fracture distance below the LT in steps of 5 mm (e.g., location 1 is 0.5 cm and location 9 is 4.5 cm below LT).**

DHS – dynamic hip screw, EMP – extramedullary plate, IMN – intermedullary nail, LT – lesser trochanter, MPa – megapascal, N – newton, PFNA – proximal femoral nail antirotation, STF – subtrochanteric fracture

**Table 1. FEM von-Mises stress simulation results in MPa between PFNA versus DHS implants for 9 different fracture locations in STR**

| STF Location* (cm) | FEM Simulation Result: Von-Mises Stress in MPa | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 125 N | | 250 N | | 375 N | | 500 N | |
| | PFNA | DHS | PFNA | DHS | PFNA | DHS | PFNA | DHS |
| **1 (0.5)** | 85.5 | 44.3 | 171 | 88.7 | 256.5 | 133 | 342 | 177.3 |
| **2 (1.0)** | 87.4 | 45.6 | 174.8 | 94 | 262.1 | 140.9 | 349.5 | 187.9 |
| **3 (1.5)** | 89.6 | 45.9 | 179.1 | 91.8 | 268.7 | 137.7 | 358.3 | 183.6 |
| **4 (2.0)** | 84.3 | 42.8 | 168.5 | 85.6 | 252.8 | 128.5 | 337.1 | 171.3 |
| **5 (2.5)** | 85.9 | 54 | 171.8 | 108 | 257.8 | 162 | 343.7 | 216 |
| **6 (3.0)** | 74.7 | 63.3 | 149.3 | 126.9 | 224 | 189.9 | 298.6 | 253.2 |
| **7 (3.5)** | 66.8 | 50.4 | 133.5 | 100.9 | 200.3 | 151.3 | 267 | 201.8 |
| **8 (4.0)** | 65.6 | 83.3 | 131.1 | 166.7 | 196.7 | 250 | 262.2 | 333.3 |
| **9 (4.5)** | 38.1 | 81.2 | 76.3 | 162.5 | 114.4 | 243.7 | 152.5 | 325 |

* Fracture locations in STR measured from the LT, lowered from proximal to distal region (from 0.5 to 4.5 cm below LT) in steps of 5 mm.
DHS – dynamic hip screw, FEM – finite element method, LT – lesser trochanter, MPa – megapascal, N – newton, PFNA – proximal femoral nail antirotation, STF – subtrochanteric fracture, STR – subtrochanteric region

### Von-Mises stress ratio between IMN versus EMP

The mean Von-Mises stress ratio (for 125 to 500 N force) between the IMN (using a PFNA implant) versus the EMP (using a DHS implant) is shown in figure 6A. The ratio tends to gradually decrease when the fracture is lowered inside the STR from proximal to distal (resp. 1.93 at STF location 1 to 0.49 at location 9). The observation of the ratio shows that IMN (PFNA) stress is higher until STF location 7 (3.5 cm below LT). From fracture location 8 (from 4 cm below the LT), EMP (DHS) stress is higher compared to IMN (PFNA). The calculated inter-

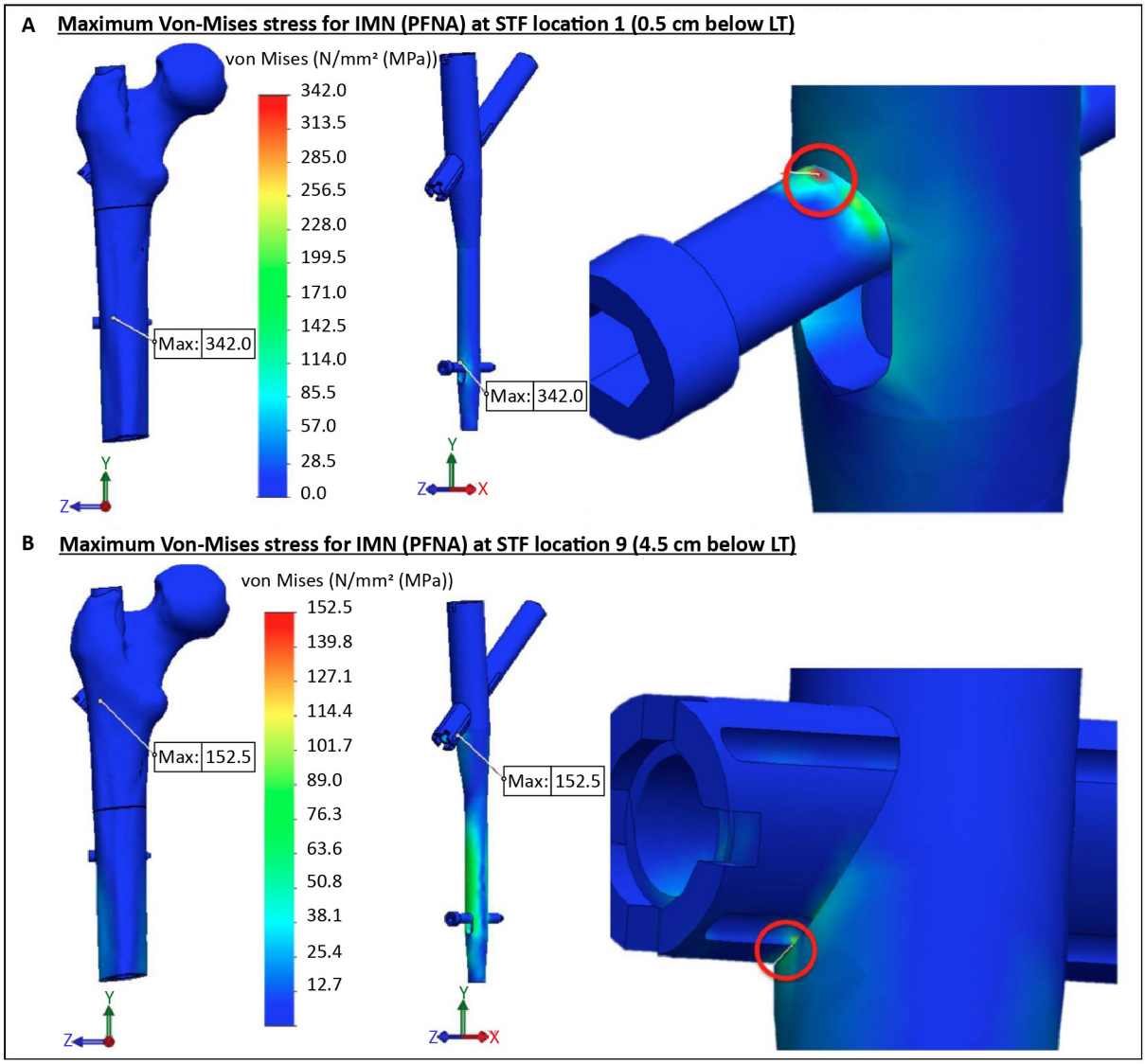


**Figure 4. The Von-Mises stress distribution and the maximum stress position for the IMN (using PFNA) at the maximum force of 500 N: (A) the maximum stress at the STF location 1 (0.5 cm below LT), and (B) the maximum stress at the STF location 9 (4.5 cm below the LT).**
IMN – intermedullary nail, LT – lesser trochanter, MPa – megapascal, N – newton, PFNA – proximal femoral nail antirotation, STF – subtrochanteric fracture

section cross-point between the IMN versus the EMP (PFNA versus DHS) is 3.8 cm below LT (Figure 6B).

## Discussion

The FEM study aimed to determine the effect of fracture location in STR for fracture management using the IMN (PFNA) versus the EMP (DHS) implants. The study illustrates that the IMN versus the EMP technique leads to different Von-Mises stress effects depending on the fracture location in STR.

The Von-Mises stress determines whether a material will yield when subjected to loading. It defines the threshold state of material between elastic and plastic or brittle failure deformations [36]. It combines the three principal stresses (in x-, y- and z-axis) into an equivalent stress. The stress is then compared to the yield stress property to judge the failure condition of the material. Therefore, the ratio between materials yield strength versus Von-Mises stress should remain greater or equal to one (ratio ≥ 1) to reduce the failure threshold and prevent assembly collapse [36, 37]. Based on the Von-Mises stress outcomes in this simulation study, the EMP (DHS) implant gives a more stable fracture management with a lower stress for the proximal STF's (Figure 3B). For fractures located at the distal STR, the IMN (PFNA) implant tends to be the more suitable implant due to the lower Von-Mises stress (Figure 3A). The intersection cross-point for the mean Von-Mises stress (for 125 to 50 N) between the IMN and the EMP is 3.8 cm

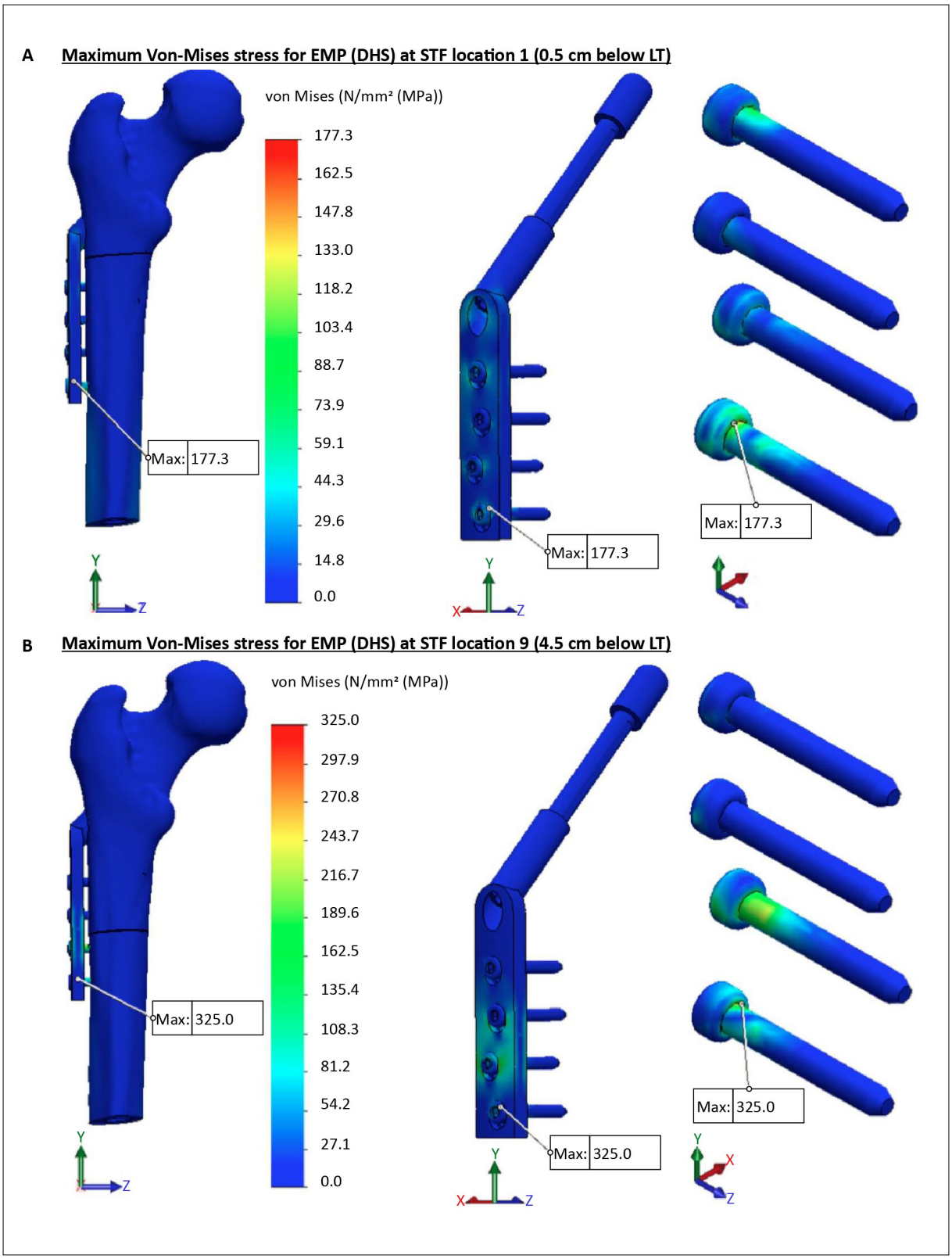


**Figure 5. The Von-Mises stress distribution and maximum stress position for the EMP (using DHS) at the maximum force of 500 N: (A) the maximum stress at the STF location 1 (0.5 cm below LT), and (B) the maximum stress at the STF location 9 (4.5 cm below the LT).**
DHS – dynamic hip screw, EMP – extramedullary plate, LT – lesser trochanter, MPa – megapascal, N – newton, STF - subtrochanteric fracture

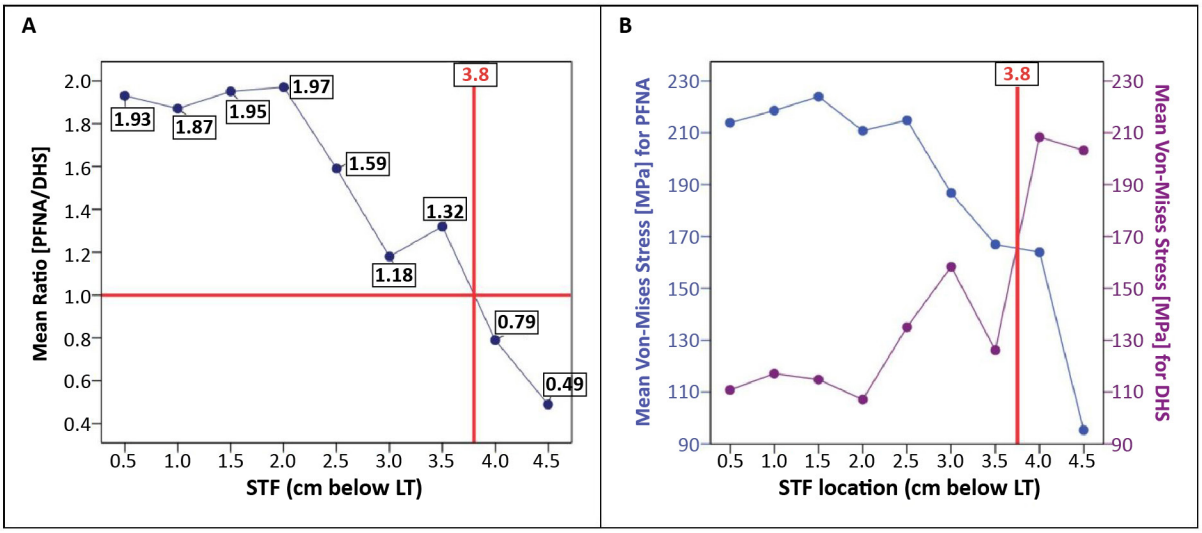


**Figure 6. (A) The mean Von-Mises stress ratio (average stress ratio for 125 to 500 N forces) between the IMN versus the EMP (PFNA versus DHS) for the different STF locations. The equilibrium between the IMN and the EMP is reached at ratio 1 (at 3.8 cm below LT). (B) Illustrating mean Von-Mises stress (average stress between 125 to 500 N forces) intersection cross point between the IMN versus the EMP (PFNA versus DHS [3.8 cm below the LT]. Hence: The STF location is based on the fracture distance below the LT in steps of 5 mm (e.g., location 1 is 0.5 cm and location 9 is 4.5 cm below LT).**
DHS – dynamic hip screw, EMP – extramedullary plate, IMN – intermedullary nail, LT – lesser trochanter, MPa – megapascal, N – newton, PFNA – proximal femoral nail antirotation, STF – subtrochanteric fracture

below the LT (Figure 6B). At this point, the effect of stress for the straight-line fracture in the STR changes, where above this level is the EMP implant suitable due to less stress, and the IMN implant seems more favourable below the point. Hence, in the analysis, the material properties, including the yield strength for the PFNA (IMN) and the DHS (EMP), are identical. The yield strength of implants is higher compared to the femur (resp. 620.42 to 160 MPa). In the study, the maximum stress remains on the implant parts and not the femur (Figures 4 and 5).

An important point to notice is that the applied force in the assembly has a linear relationship with the amount of stress for both IMN (PFNA) and EMP (DHS) (Supplementary Figure 1). Firstly, it is logical that a change in the load will have a linear effect on the amount of stress. Therefore, this linear relationship verifies that the simulation analysis is correctly executed. Secondly, an increase in load will eventually result in material failure. It seems that the proximal fractures can withstand more loading when using the EMP compared to the IMN; whereas for the distal fractures, the IMN can withstand more loading than the EMP before the failure threshold is reached (Figure 6B).

Furthermore, the maximum stress location differed between the IMN and the EMP implants. The EMP (DHS) implant gives the same maximum Von-Mises stress position for all the STF locations (Figure 5A and 5B). For the IMN (PFNA), the maximum stress position remains similar for the STF locations 1 to 8 (Figure 4A), but changes for the STR location 9 (Figure 4B). The changes in the maximum stress location for the IMN implant analysis can be explained by the biomechanical changes caused by different STF locations that result in changes in the magnitude and direction of forces and moments within the assembly. This effect is eliminated for the EMP (DHS plate) analysis because the DHS plate uses four distal screws in the femoral shaft instead of only one distal screw used in the PFNA nail system.

The study has a few limitations. First, implant configuration and placement must be done according to the fracture type; as well as weight-bearing should be adapted accordingly to the fracture type, implant type, and bone quality [37]. In the current study, the analysis is done based on a straight-line fracture; therefore, other fracture types or configurations would generate different outcomes. The study uses a simple straight-line fracture which does not resemble a true traumatic fracture type in the STR. However, this fracture configuration was chosen for two reasons: (1) for an easier simulation of the fracture location effect in the STR concerning fracture management and fixation stability, and (2) to optimally observe the effect of the two different implant systems used for the STF management. In future studies, we recommend using different fracture types and configurations. Second, only PFNA and DHS (respectively as the IMN and the EMP fixation methods) were analysed since they are the most common implant of choice; however, other implant types or configurations (e.g., DCS) may produce different results. Third, the unphysiological applied force in the study does not resemble

a true double leg stance, and different force congratulations will lead to different outcomes. Therefore, it would be wise to study the effect of different force configurations on this topic. Finally, the study makes use of the FEM computer simulation analysis where from one side it simplifies the clinical setting and gives a proper visual explanation regarding STF management based on various fracture locations in the STR. However, it only gives a suggestion regarding STF management. Therefore, future studies need to be conducted to analyse other fracture types, configurations, and implants. Furthermore, retro- or prospective clinical studies or laboratory (e.g., cadaveric, or polymeric mechanical testing) can be considered for clinical validation.

## Conclusion

The subtrochanteric fracture location in the subtrochanteric region seems to have a major effect on the fracture stability. Furthermore, the required implant for the optimal subtrochanteric fracture stability (nail versus plate) can vary based on the different fracture configurations. However, this requires a substantial analysis to determine what type of an implant should be applied for what type of a subtrochanteric fracture location or configuration. Finally, the application of the finite element method seems to be a promising tool for the proximal femoral fractures management analysis.

## Acknowledgment

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## Conflict of interest

None.

## Funding

None.

## Supplementary material

The linear relationship between force and stress is represented in supplementary figure 1. Furthermore, the FEM setup and all the simulation outcomes are available online at https://ejtcm.gumed.edu.pl/articles/187180.

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RESEARCH ARTICLE

# Association of hand grip strength with psychological stress, exercise habits and body composition amongst medical students: a cross-sectional study

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## Abstract

**Background:** The aim of this study was to assess the effectiveness of hand grip strength (HGS) test in identifying highly stressed individuals and to examine the effect of exercise and lifestyle on HGS and stress measures. **Material and method:** It is cross-sectional study. Students of the Medical University of Gdańsk, Poland were asked to fill out a questionnaire, undergo body composition analysis, perform HGS test and provide a saliva sample for cortisol measurement. **Results:** Self-rated stress (SRS) was significantly higher in pre-clinical years (PCY) compared to clinical years (CY). HGS was significantly lower in PCY males than CY males. Participants who performed some form of exercise had significantly higher HGS compared with those who did not exercise. A positive correlation between HGS and BMI was noted. Students with low HGS were found to have lower levels of salivary cortisol (SC). However, there was no significant difference in SC levels between PCY and CY students. **Conclusions:** HGS may be a reliable method of identifying stressed individuals and promoting healthy lifestyle behaviors. HGS testing is a safe, cheap and easy to perform method for a large number of participants while being time economical.

**Keywords:** exercise · psychological stress · medical students · hand grip strength

## Citation

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## Abbreviations

- BMI – body mass index
- CY – clinical years
- ELISA – enzyme-linked immunosorbent assay
- HGS – hand grip strength
- HPAA – hypothalamic-pituitary-adrenal axis
- MUG – Medical University of Gdańsk
- PCY – pre-clinical years
- SC – salivary cortisol
- SRS – self-rated stress

## Introduction

It is a widely accepted that medical studies are challenging and can put medical students under high stress. Several factors contribute to the psychological stress amongst medical students, such as their competitive environment, hierarchical student-teacher/consultant relationships, personal and social expectations, reduced leisure time, facing death and suffering [1-3]. According to the literature, nearly a 1/3 of medical students are suffering from psychological distress, depression and/or anxiety [4-6]. Exposure to chronic levels of stress may have detrimental effects on the individual's physical, mental and immunological functioning and predispose them to chronic illnesses, e.g. cardiovascular diseases, diabetes, depression, metabolic syndrome and autoimmune diseases [7-8].

Hand grip strength (HGS) has become an increasingly popular measurement to assess the physical fitness and well-being, particularly in the elderly population [9]. It is defined as the force generated by squeezing one's hand. HGS indicates strength, muscle mass and protein levels, thereby may be used clinically as a proxy for overall health profile [10]. A hand-held dynamometer is a simple, inexpensive and reliable tool for HGS measurement [11]. In the elderly population, HGS was found to predict the risk of all-cause mortality as well as disease-specific causes such as cardiovascular diseases, cancer, strokes and others [10-12]. HGS is also associated with injury from falls, cognitive function, depression, age-related disability, severity of several diseases, comorbidities and hospitalization rates [9, 12-15]. The associations of HGS seen in the elderly are primarily derived from the effect of sarcopenia (low muscle mass), which is a major issue in this population. Musculoskeletal aging is a public health concern, which results in sarcopenia and is also associated with the factors mentioned above [16]. Recently, the assessment of HGS was extended into younger populations, including children, with the goal of finding normative reference values in different regions of world [17]. According to Doods et al., HGS increased during 4-30 years of age and slowly decreased starting from 40 years of age, independently of sex and country. The impact of HGS on the general health of young people is not fully known. Most recently, an analysis of the correlations between muscle mass, HGS and cardiovascular markers in young adults indicated that gaining body muscle is an important factor for avoiding heart disease [18].

Chronic levels of psychological stress are known to cause dysregulation in the functioning of the hypothalamic-pituitary-adrenal axis (HPAA) [19-20]. Repeated or prolonged exposure to a similar stressor, over a period of time, may result in changes of baseline HPAA activity as well as the body's responsiveness to the stressor, resulting in cumulative glucocorticoid burden. Although the exact mechanisms of HPAA dysregulation in chronic stress remains unclear, a new model developed by Karin et al. suggests that prolonged activation of the adrenal glands results in their hypertrophy and leads to overproduction of cortisol [21]. Stress response is also mediated by the sympathetic nervous system and its continuous stimulation may result in high systemic levels of catabolic stress hormones such as cortisol, epinephrine and glucagon [19]. The catabolic effects of cortisol, particularly when in excess, are well-known. Persistent stress may induce chronic elevation of cortisol levels, which via its catabolic effect may result in decreased muscle mass, increased fat mass, insulin resistance and other metabolic changes [22]. Moreover, hypercortisolism-induced abdominal obesity may increase the oxidative stress and inflammatory cytokine levels resulting in the development of processes such as sarcopenia [23].

Considering all of the above, we raised the question of whether HGS test may be a reliable indicator of stress levels amongst medical students. We hypothesized that low HGS may be associated with increased levels of stress in medical students with the aim of assessing the effectiveness of HGS test in identifying highly stressed individuals. Specifically we aimed to measure the HGS and stress levels subjectively, via self-reported stress (SRS) and objectively (via salivary cortisol, SC) as well as body composition of medical students in order to find any potential associations with their lifestyle factors. The secondary aim of the study was to examine the effect of exercise habits of medical students on HGS and stress measures.

## Materials and methods

We implemented a cross-sectional study design and recruited medical students at the Medical University of Gdańsk (MUG) in Poland. During normal working days, the students were invited to our laboratory on campus, where they were explained the purpose and objectives of our study. All students volunteered and signed written informed consent forms. Data were collected while maintaining the students' anonymity by

providing each participant a unique code, used to label their information and samples. The students were asked to fill out an online questionnaire, undergo body composition analysis, perform HGS test and provide their saliva samples. The data was collected during the months of October-December, between 12:00-18:00 hours. The study was approved by the Independent Bioethics Committee for Scientific Research at MUG (NKBBN/120/2018).

### Study group

A total of 161 students were initially recruited for the study. Three participants were excluded from the study because they did not perform HGS test, thus 158 students were included: 80 females (50.6%) and 78 males (49.4%). There were 27 1st year students, 20 2nd year students and 42 3rd year students (together included in the pre-clinical years (PCY) group of 89 students) and 38 4th year, 9 5th year and 22 6th year students (included in the clinical years (CY) group of 69 students). This grouping was based on the curriculum and workload of medical studies at the MUG. The PCY tend to involve longer class schedules per day with higher number of exams during a semester as compared to the CY of studies. Additionally, during the PCY the international students are also getting used to life on their own and in a new country, while also managing their workflow and approach towards medical studies, all of which are an additional stressor. The intention of such grouping was to establish two groups with contrasting amount of stressful environment.

### Self-reported stress and lifestyle habits

We created an 18-item questionnaire, consisted of open-ended and multiple-choice questions, which included questions about demographic data of the participants (age, sex, year of study), lifestyle factors (diet, water intake, smoking, alcohol use, type and intensity of exercise, vitamin D supplementation and sleep (duration and pattern), relationship status, the number of upcoming exams in the ongoing semester and self-rated stress (SRS). The participants' SRS was measured on a 10-point scale (1 = least stressed, 10 = extremely stressed).

### Body composition

The TANITA SC-240 medical bioimpedance analyzer (Tanita Corporation, Tokyo, Japan), was used for the body composition examination (weight, fat%, fat-free% and muscle mass%). Body mass index (BMI) was calculated from the participants' self-reported height. For each scan, the participants were asked to remove their shoes, excess clothing as well as remove all material which could affect the bioelectrical impedance analysis of the scale.

### Hand grip strength test

HGS was measured using a Saehan Squeeze Dynamometer (#SH5008, Saehan Corporation, Incheon-City, South Korea). While sitting down, the participants were instructed to place their forearm parallel to the table, and to form a 90º angle with their arm, then asked to squeeze the bulb of the dynamometer as hard as possible with each hand twice. The participants also indicated their dominant hand during the data collection process. The maximum HGS measurement (kilogram force), obtained with the dominant hand was used for statistical analysis.

### Salivary cortisol measurement

The participants were asked to provide their saliva samples at least 2 hours after their last meal. Before collecting the samples, all participants were asked to rinse their oral cavity with water to remove any residual food. The saliva samples were collected using Salivette Cortisol tubes (Sarstedt, Nümbrecht, Germany). They were then processed according to the instructions provided by the manufacturer [22]. SC levels were analyzed using Salimetrics Salivary Cortisol ELISA kit (Salimetrics, Carlsbad, CA, USA) in accordance with the manufacturer's instructions. The level of SC was used as an objective measure of stress of each participant in this study.

### Statistical analysis

Normality distribution was analyzed using Shapiro-Wilk Test. This analysis did not confirm normal distribution for most of the data. Therefore, Mann-Whitney U test and Chi-square test were used to analyze these data, for continuous and categorical variables, respectively. Interestingly, when data concerning saliva cortisol, HGS, SRS and BMI were grouped based on different exercise habits of participants (Table 2) they displayed normal distribution (Shapiro-Wilk test) which allowed for use of the ANOVA test. Type of test used for each parameter is provided in the legend of each table. Significance of the analysis was assumed if two-tailed P-value was less than 0.05. Additionally, correlation analysis between stress measures, body composition and HGS were performed using Spearman's rank correlation test. Microsoft Excel (version 16.0.1, Microsoft Corporation, Redmond, WA, USA) and GraphPad Prism (version 8.0.1, GraphPad Software Inc., Boston, MA, USA) software were used for data computation and statistical analysis.

**Table 1. Demographic characteristics, hand grip strength (HGS), stress measures and body composition parameters dichotomized according to the year of study and sex**

| | Males (n = 78) | | | Females (n = 80) | | |
|---|---|---|---|---|---|---|
| | PCY (n = 46) | CY (n = 32) | | PCY (n = 43) | CY (n = 37) | |
| | Mean (SD) | Mean (SD) | p-value[A] | Mean (SD) | Mean (SD) | p-value[A] |
| **Age** | 22.35 (3.23) | 24.78 (3.45) | **0.0006** | 21.93 (2.04) | 23.86 (1.69) | **< 0.0001** |
| **HGS (kgf)** | 23.04 (6.63) | 28.25 (10.1) | **0.0207** | 17.23 (5.92) | 18.3 (4.78) | 0.1104 |
| **Stress parameters** | | | | | | |
| Cortisol (µg/dl) | 0.21 (0.17) | 0.22 (0.16) | 0.3549 | 0.19 (0.17) | 0.23 (0.18) | 0.5281 |
| SRS | 5.35 (2.48) | 4.28 (2.81) | 0.0432 | 5.83 (1.77) | 4.41 (2.3) | **0.004** |
| **Body composition** | | | | | | |
| BMI (kg/m$^2$) | 22.78 (2.99) | 25.56 (3.16) | **0.0002** | 22.93 (3.40) | 21.84 (2.68) | 0.1259 |
| Fat Free Mass (kg) | 61.48 (6.04) | 64.74 (7.02) | 0.0707 | 45.31 (4.75) | 44.78 (3.09) | 0.9713 |
| Fat Mass (kg) | 10.96 (5.46) | 16.13 (6.85) | **0.0003** | 17.79 (8.18) | 16.09 (5.95) | 0.6432 |
| Muscle Mass (kg) | 58.4 (5.74) | 59.56 (11.6) | 0.1776 | 43.01 (4.52) | 42.5 (2.93) | 0.9675 |
| | | | | | | |
| | n (%) | n (%) | p-value[B] | n (%) | n (%) | p-value[B] |
| **Status** | | | | | | |
| In a relationship | 17 (36.96) | 13 (40.63) | 0.8149 | 10 (23.26) | 18 (48.65) | **0.0207** |
| Single | 29 (63.04) | 19 (59.38) | | 33 (76.74) | 19 (51.35) | |
| **Place of living** | | | | | | |
| City | 43 (93.48) | 28 (87.5) | 0.4363 | 32 (74.42) | 27 (72.97) | > 0.999 |
| Countryside | 3 (6.52) | 4 (12.5) | | 11 (26.58) | 10 (27.03) | |

**Results are shown as mean (SD) or number (%). Statistical tests used are Mann-Whitney U test ([A]), Chi-square test ([B]).**
BMI – body mass index; CY – clinical years; HGS – hand grip strength; kgf – kilogram-force; PCY – preclinical years; SRS – self-rated stress

**Table 1. Demographic characteristics, hand grip strength (HGS), stress measures and body composition parameters dichotomized according to the year of study and sex (continued)**

| | Males (n = 78) | | | Females (n = 80) | | |
|---|---|---|---|---|---|---|
| | PCY (n = 46) | CY (n = 32) | | PCY (n = 43) | CY (n = 37) | |
| | Mean (SD) | Mean (SD) | p-value[A] | Mean (SD) | Mean (SD) | p-value[A] |
| **Diet** | | | | | | |
| Vegetarian | 4 (8.7) | 3 (9.38) | > 0.999 | 12 (27.91) | 8 (21.62) | 0.6087 |
| Non-vegetarian | 42 (91.3) | 29 (90.63) | | 31 (72.09) | 29 (78.38) | |
| **Water/day** | | | | | | |
| < 1 Litre | 10 (21.74) | 3 (9.38) | 0.3402 | 14 (32.56) | 10 (27.03) | 0.7512 |
| 1-3 Litres | 33 (71.74) | 26 (81.25) | | 27 (62.79) | 26 (70.27) | |
| > 3 Litres | 3 (6.52) | 3 (9.38) | | 2 (4.65) | 1 (2.7) | |
| **Smoking** | | | | | | |
| Yes | 10 (21.74) | 7 (21.88) | > 0.999 | 11 (25.58) | 2 (5.41) | **0.0168** |
| No | 36 (78.26) | 25 (78.13) | | 32 (74.42) | 35 (94.59) | |
| **Alcohol** | | | | | | |
| Yes | 32 (69.57) | 25 (78.13) | 0.4474 | 32 (74.42) | 32 (86.49) | 0.2629 |
| No | 14 (30.43) | 7 (21.88) | | 11 (25.58) | 5 (13.51) | |
| **Caffeine** | | | | | | |
| Yes | 37 (80.43) | 28 (87.5) | 0.5417 | 34 (79.07) | 29 (78.38) | > 0.999 |
| No | 9 (19.57) | 4 (12.5) | | 9 (20.93) | 8 (21.62) | |
| **Exercise** | | | | | | |
| Yes | 25 (54.35) | 26 (81.25) | 0.0166 | 21 (48.84) | 25 (67.57) | 0.1146 |
| No | 21 (45.65) | 6 (18.75) | | 22 (51.16) | 12 (32.43) | |
| **Exercise (days/week)** | | | | | | |
| 1-4 Days | 20 (80) | 14 (53.85) | 0.0746 | 16 (76.19) | 21 (84) | 0.7114 |
| 5-7 Days | 5 (20) | 12 (46.15) | | 5 (23.81) | 4 (16) | |

**Table 1. Demographic characteristics, hand grip strength (HGS), stress measures and body composition parameters dichotomized according to the year of study and sex (continued)**

| | Males (n = 78) | | | Females (n = 80) | | |
|---|---|---|---|---|---|---|
| | PCY (n = 46) | CY (n = 32) | | PCY (n = 43) | CY (n = 37) | |
| | Mean (SD) | Mean (SD) | p-value[A] | Mean (SD) | Mean (SD) | p-value[A] |
| **Exercise (type)** | | | | | | |
| Aerobic | 8 (32) | 5 (20) | 0.6166 | 9 (42.86) | 9 (36) | 0.3734 |
| Strength | 9 (36) | 10 (40) | | 4 (19.05) | 2 (8) | |
| Mixed | 8 (32) | 10 (40) | | 8 (38.1) | 14 (56) | |
| **Sleep (pattern)** | | | | | | |
| During the night | 45 (97.83) | 32 (100) | > 0.999 | 40 (93.02) | 35 (94.59) | > 0.999 |
| During the day | 1 (2.17) | 0 | | 3 (6.98) | 2 (5.41) | |
| **Sleep (duration)** | | | | | | |
| < 5 hours | 11 (23.91) | 1 (3.13) | **0.0339** | 10 (23.26) | 6 (16.22) | 0.7342 |
| 6-9 hours | 34 (73.91) | 29 (90.63) | | 32 (74.42) | 30 (81.08) | |
| > 9 hours | 1 (2.17) | 2 (6.25) | | 1 (2.33) | 1 (2.7) | |
| **Number of exams** | | | | | | |
| 0-1 | 3 (6.52) | 15 (46.88) | **< 0.0001** | 5 (11.63) | 13 (35.14) | **0.0003** |
| 2-4 | 23 (50) | 15 (46.88) | | 18 (41.86) | 21 (56.76) | |
| 5+ | 20 (43.48) | 2 (6.25) | | 20 (46.51) | 3 (8.11) | |
| **Vitamin D supplementation** | | | | | | |
| Yes | 17 (51.52) | 16 (48.48) | 0.3516 | 12 (27.91) | 24 (64.86) | **0.0015** |
| No | 29 (64.44) | 16 (35.56) | | 31 (72.09) | 13 (35.14) | |

## Results

### Pre-clinical year (PCY) vs clinical year (CY) participants

A total of 158 medical university students (mean age 23.07 years) were included in this study. The demographic characteristics along with questionnaire responses, HGS, SC and body composition values dichotomized according to the groups based on the year of study (PCY vs CY) and sex are presented in Table 1.

Among the male participants, the HGS was significantly lower, while the SRS was significantly higher in the PCY as compared to the CY. The questionnaire responses indicated that during the PCY males were significantly less likely to exercises, significantly fewer of them slept 6-9 hours per night and they had significantly higher number of exams in the ongoing semester compared to the CY male participants. There was no significant difference between the two groups in terms of SC levels. In contrast, the BMI and fat mass of PCY male participants was significantly lower than that of CY male participants.

Similar to males, the female participants in their PCY of studies had significantly higher SRS than the females in their CY. However, there was no significant difference seen in the HGS and SC levels between females in PCY and CY. Based on the lifestyle questionnaire, it appeared that females in the PCY were significantly more likely to smoke, supplement vitamin D and had more exams in the ongoing semester in comparison to females in CY. Additionally, the questionnaire revealed that females in PCY were significantly more likely to be single as compared to those in CY of studies.

### Effect of exercise on HGS, stress measures and body composition

Data related to exercise habits and their effect on HGS, stress measures and BMI are presented in Table 2. Regardless of gender, participants who performed some form of exercise had significantly higher HGS when compared with those who did not exercise. Additionally, male participants who exercised had significantly higher BMI than those who did not exercise. No significant difference was seen in either stress measure (SRS and SC levels) between participants who exercised and those who did not. These four parameters were also compared based on the number of days the participants exercise in a week. In this analysis, the only significant difference was seen in the HGS of males, with those who exercise 5-7 days/week having higher HGS than those who did it 1-4 days/week.

In addition, we analyzed the effect of exercise type (strength, aerobic or mixed (strength + aerobic)) on these parameters. The BMI of males who did primarily strength training was significantly higher in comparison to those who did aerobic or mixed training. Moreover, the HGS of both male and female participants was found to be stronger in those doing mixed training than only aerobic or strength training.

### Correlation analyses

The univariate analyses revealed no significant correlation between the subjective stress measure (SRS) and objective stress measure (SC) in the entire study group. There was no significant correlation between SC levels and HGS SRS or BMI when the entire study group was taken into consideration (Table 3). Additionally, no significant correlation was noticed between HGS and SRS. However, it was found that HGS had a positive correlation with BMI and age of the participants, seen as the entire study group (Table 3).

The HGS of our study group was dichotomized according to sex and year of study (PCY vs CY) and compared with SC, SRS and body composition parameters (Table 4). Regardless of the group, we noticed that the HGS had a significant positive correlation with fat-free mass. Similarly, a significant correlation between HGS and muscle mass was seen in all groups except for males in the CY group. Additionally, an isolated significant correlation was noticed between HGS and BMI of males in the PCY group ($R = 0.517$, $p = 0.0003$). Finally, we analyzed the results obtained for students with high SC/low HGS in comparison to those with low SC/high HGS. These groups were identifies by analyzing students with outlying SC and HGS results. The results of this analysis are presented in Table 5.

## Discussion

It is well-recognized that medical school is a stressful environment [2, 24-25]. In our study, we found that the SRS was significantly higher in the PCY participants, regardless of the sex. We expected such result based on our initial assumption that PCY tend to be more stressful for MUG students, based on reasons stated in the Methods section. These assumptions were further verified by the findings of PCY participants being less likely to get adequate sleep, exercise and having more exams. Almojali et al. have previously highlighted the importance of adequate sleep and its effect on increasing stress levels in medical students [5]. Furthermore, Heinen et al. corroborated the fact that perceived stress is quite high, particularly among 1$^{st}$ year medical students. [24]. We found lower HGS in the “more stressed” PCY males than in the “less stressed” CY suggesting a potential relationship between HGS and the SRS. However, such associations were not observed in female

**Table 2. HGS, stress and BMI in terms of exercise habits of the male and female participants**

| | Males (n = 78) | | | Females (n = 80) | | |
|---|---|---|---|---|---|---|
| | Exercise (n = 51) | No exercise (n = 27) | | Exercise (n = 46) | No exercise (n = 34) | |
| | Mean (SD) | Mean (SD) | p-value[A] | Mean (SD) | Mean (SD) | p-value[A] |
| **HGS (kgf)** | 26.25 (8.55) | 23.15 (8.38) | **0.0278** | 18.96 (6.37) | 16.06 (16.06) | **0.0046** |
| **Stress parameters** | | | | | | |
| Cortisol (µg/dl) | 0.22 (0.18) | 0.2 (0.13) | 0.8469 | 0.18 (0.13) | 0.25 (0.23) | 0.1927 |
| SRS | 4.52 (2.38) | 5.7 (2.97) | 0.0855 | 4.89 (2.26) | 5.4 (2.05) | **0.3359** |
| **Body composition** | | | | | | |
| BMI (kg/m$^2$) | 24.6 (3.23) | 22.82 (3.42) | **0.0272** | 22.37 (2.99) | 22.56 (3.24) | 0.4709 |
| **Exercise (days per week)** | | | | | | |
| | 1-4 days (n = 34) | 5-7 days (n = 17) | | 1-4 days (n = 37) | 5-7 days (n = 9) | |
| HGS (kgf) | 24.32 (6.96) | 30.12 (10.23) | 0.0242 | 19.03 (7.02) | 18.67 (2.5) | 0.5985 |
| **Stress parameters** | | | | | | |
| Cortisol (µg/dl) | 0.20 (0.16) | 0.25 (0.21) | 0.5087 | 0.18 (0.13) | 0.21 (0.10) | 0.2142 |
| SRS | 4.65 (2.36) | 4.18 (2.51) | 0.5138 | 4.92 (2.18) | 5.22 (2.44) | 0.8224 |
| **Body composition** | | | | | | |
| BMI (kg/m$^2$) | 24.09 (3.36) | 25.32 (2.69) | 0.1936 | 22.46 (3.25) | 21.93 (1.97) | 0.644 |

**Results are reported as means (SD). Statistical tests used are Mann-Whitney U test (A) and ANOVA test (B).**
BMI – body mass index; HGS – hand grip strength; kgf – kilogram force; SRS – self- rated stress

**Table 2. HGS, stress and BMI in terms of exercise habits of the male and female**

| | Males (n = 78) | | | | Females (n = 80) | | | |
|---|---|---|---|---|---|---|---|---|
| **Exercise type** | | | | | | | | |
| | **Aerobic (n =1 3)** | **Strength (n = 19)** | **Mixed (n = 18)** | **p-value[A]** | **Aerobic (n =1 8)** | **Strength (n = 6)** | **Mixed (n = 22)** | **p-value[A]** |
| HGS (kgf) | 22.69 (7.66) | 25.94 (6.38) | 29.47 (10.03) | 0.1387 | 17.18 (3.89) | 18.5 (2.81) | 20.39 (8.09) | 0.3099 |
| **Stress parameters** | | | | | | | | |
| Cortisol (µg/dl) | 0.22 (0.23) | 0.26 (0.19) | 0.19 (0.13) | 0.4876 | 0.20 (0.12) | 0.15 (0.13) | 0.18 (0.13) | 0.6263 |
| SRS | 3.69 (1.55) | 4.28 (2.49) | 5.16 (2.71) | 0.2787 | 5.24 (2.39) | 6.33 (1.97) | 4.44 (2.02) | 0.1045 |
| **Body composition** | | | | | | | | |
| BMI ($kg/m^2$) | 22.85 (2.91) | 25.89 (2.47) | 24.57 (3.37) | 0.0251 | 22.07 (3.75) | 23.52 (3.94) | 22.27 (2.14) | 0.6022 |

**Table 3. Correlation analyses of cortisol and HGS with parameters such as SRS, BMI and age**

| | | R | p-value |
|---|---|---|---|
| **Cortisol versus** | **HGS** | 0.106 | 0.2324 |
| | **SRS** | -0.057 | 0.5068 |
| | **BMI** | 0.134 | 0.1226 |
| **Hgs versus** | **SRS** | -0.145 | 0.0732 |
| | **BMI** | 0.332 | **< 0.0001** |
| | **Age** | 0.181 | **0.0259** |

**The data shown are results from the entire study group regardless of year of study and gender. Statistical analyses were performed using Spearman's rank correlation test.**

BMI – body mass index; HGS – hand grip strength; SRS – self-rated stress

**Table 4. Correlation analyses comparing HGS with stress measures and body composition parameters and comparing fat-free mass with BMI and muscle mass**

| | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| **Hgs versus** | **PCY (N = 46)** | | **CY (N = 32)** | | **PCY (N = 43)** | | **CY (N = 37)** | |
| | **R** | **p-value** | **R** | **p-value** | **R** | **p-value** | **R** | **p-value** |
| **Cortisol** | 0.067 | 0.67 | 0.262 | 0.169 | -0.295 | 0.089 | 0.173 | 0.345 |
| **SRS** | 0.105 | 0.493 | -0.114 | 0.536 | -0.218 | 0.165 | 0.121 | 0.477 |
| **Fat-free mass** | 0.341 | **0.022** | 0.409 | **0.019** | 0.384 | **0.012** | 0.445 | **0.006** |
| **Fat mass** | 0.424 | **0.004** | 0.209 | 0.250 | 0.238 | 0.129 | 0.055 | 0.748 |
| **Muscle mass** | 0.341 | **0.022** | **0.392** | **0.0292** | 0.384 | **0.012** | 0.443 | **0.006** |
| **BMI** | 0.518 | **0.0003** | 0.271 | 0.134 | 0.234 | 0.135 | 0.063 | 0.717 |

**Statistical analyses were performed using Spearman's rank correlation test.**
BMI – body mass index; CY – clinical years; HGS – hand grip strength; PCY – preclinical years; SRS – self-rated stress

participants. It is worth noting that male students in CY were older and exercised more often.

Based on the HPAA dysregulation caused by chronic stress, we expected to find higher SC levels in the PCY than in the CY group. However, our results did not show any such correlations. Additionally, we did not notice any correlation between our subjective stress measure (SRS) and objective stress measure (SC). This may bring into question the effectiveness of SC in estimating chronic stress levels. Cortisol in the saliva, as in other biological fluid (e.g. serum, plasma or urine) is modulated by several different factors such as time of testing, fluctuations due to acute stressors and recent use of stimulants such as caffeine or nicotine [26-29].

The beneficial effects of regular exercise are well-established [30-31]. It has been consistently proven that physical activity has a positive effect on psychological well-being, while also reducing the risk of cardiovascular disease, obesity, hypertension, diabetes, mental health problems as well as mortality and morbidity [30-33]. In our study, the higher HGS seen in participants who exercise may suggest lower stress levels. However, we did not see any associations between SRS, SC and exercise type and habits (e.g. diet, smoking, water intake, alcohol use, caffeine intake). Contrary to our findings, but as expected, Nakandala et al. demonstrated that physical activity in young undergraduate students was associated with higher HGS [34]. A potential explanation for higher HGS with exercise may simply be the effect of strength training and increased muscle mass. This seems to be more likely in our case given that of male participants who exercised, 37% primarily did strength training compared to only 13% female participants. Looking at the entire sample, the majority of participants with low SC levels also had low HGS. It is worth noting the outliers in this group: those who had low SC and high HGS were mostly males (92.31%), who performed exercise (77%) and rated their stress an average of 5.23. We also observed that the majority of these participants supplemented vitamin D s (69.23%).

**Table 5. Comparison of students with high cortisol-low HGS and low cortisol-high HGS**

| | High cortisol – low hgs (n = 11) | Low cortisol – high hgs (n = 13) | |
|---|---|---|---|
| | Mean (SD) | Mean (SD) | p-value[A] |
| **HGS (kgf)** | **17.55 (4.34)** | **42.08 (6.71)** | **< 0.0001** |
| **Stress parameters** | | | |
| Cortisol (µg/dl) | 0.69 (0.14) | 0.28 (0.13) | **< 0.0001** |
| SRS | 4.91 (2.63) | 5.23 (3.03) | 0.9885 |
| **Body composition** | | | **p-value[B]** |
| BMI (kg/m2) | 23.09 (3.07) | 26.25 (2.35) | **0.0024** |
| Fat free mass (kg) | 49.11 (9.316) | 65.65 (6.98) | **0.0002** |
| Fat mass (kg) | 15.84 (7.223) | 17.51 (5.57) | 0.3098 |
| Muscle mass (kg) | 46.64 (8.861) | 57.55 (16.46) | **0.0037** |
| **Sex** | **n (%)** | **n (%)** | |
| Male | 4 (36.36) | 12 (92.31) | **0.0078** |
| Female | 7 (63.64) | 1 (7.69) | |
| **Place of living** | | | |
| City | 11 (100) | 8 (61.54) | **0.0411** |
| Countryside | 0 (0) | 5 (38.46) | |
| **Vitamin D supplementation** | | | |
| Yes | 1 (9.09) | 9 (69.23) | **0.0045** |
| No | 9 (90.91) | 4 (30.77) | |

**Results are reported in mean (SD) and number (%). Statistical tests used are Mann-Whitney U test ([A]), Chi-square test ([B]).**

On the contrary, those with high SC and low HGS were mostly females (63.64%), less than half of them exercised (45%), who reported lower SRS (4.91) and few of them supplemented vitamin D (9%). It is worth noting that a proportion of participants (mainly females) had very low HGS (< 19), similar to the measurements seen in frail elderly [35].

### Limitations

There are several limitations to our study. First, our study group was small and quite heterogenous, because it included primarily international students of different ethnicities. Regarding this element, a recent meta-analysis showed that there are significant differences in HGS of people from developed countries and underdeveloped countries [17]. Differences could be also related to differences in body size and composition including muscle mass. In our study, the majority of students had rather low muscle mass and size, which can partially explain the differences. It is noteworthy that medical students at the beginning of their studies were weaker and had lower knowledge regarding healthy lifestyle. Stress and long hours spent on studying could be responsible for not exercising enough. The CY group of participants seemed to have more knowledge regarding healthy lifestyle and more time to exercise. It is also worth to notice that this phenomenon regarding exercises occurs mostly in male students.

Second, saliva samples were collected in the afternoon (12:00-18:00), which may have potentially influenced our findings. This time period was chosen due to the time constraints of the medical students' schedules. For these reasons, our analysis might have resulted in less significant findings regarding cortisol. Lastly, we applied only univariate analyses which prevents taking into consideration the potential confounders. Regardless of these limitations, this appears to be the first study to examine the association between HGS and stress amongst medical students and their lifestyle.

## Conclusions

Our findings suggest that HGS has some association with the perceived stress of medical students as seen by the significantly lower values in the "more stressed" group (PCY) as compared to the "less stressed" group (CY), particularly in male students. Future studies are required to consolidate the association of HGS and stress in young, healthy individuals with a more focused assessment of objective stress measures, potentially hair cortisol. In conclusion, HGS may be a reliable method of identifying stressed individuals and promoting healthy lifestyle behaviors such as mixed-type (aerobic + strength) exercise and adequate sleep among others.

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## Conflict of interest

None.

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RESEARCH ARTICLE

# Post-development sentiment and statistical analysis of different groups of psychiatric medications

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## Abstract

**Background:** medications are complex and influence the body in multiple ways. Post-development analysis of medications remains highly advantageous, as it allows for comprehensive understanding of the safety profile over extended periods and can direct future improvements to enhance the therapeutic benefits while minimizing risks. Our primary goal was to examine whether a substantial relationship exists between such patient experiences and the statistical analysis of data about the same medications from clinical trials. **Methods:** Patient feedback regarding medication commonly prescribed for psychiatric conditions was obtained from a publicly available website webmd.com. We searched clinicaltrials.gov for statistical analysis regarding the same medications. Data from webmd.com was subjected to sentiment analysis, while clinicaltrails.gov data underwent statistical analysis. **Results:** the findings suggest a general connection between the two data sources. Medications with a greater amount of patient feedback generally attract more research attention, although with some exceptions. Additionally, medications approved for children receive less feedback online compared to those for adults and seniors. Medications for seniors receive more positive and neutral feedback in contrast to those for children and adults. **Conclusions:** online platforms offer a space for patients to share their experiences with using specific medications, potentially contributing to the enhancement of patient care and aiding researchers in further studies.

**Keywords:** anxiety · clinical trials · SSRIs · sentiment analysis · psychiatric medication

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## Introduction

The process of developing a new medication is complex and involves multiple steps e.g. pharmacology research, preclinical studies on animals, clinical studies on small groups of human volunteers, regulatory agency approval, marketing and more [1]. Medications may have various long-term adverse effects and drug interactions, which may require significant observation time to reveal. Post-development analysis of medications, including a series of analytical techniques, may be employed to reveal more details on different aspects of long-term adverse effects.

In general, there are two different approaches to examining the long-term effects of medications. The first approach involves collecting patient feedback. Online platforms allow patients to express their opinions about the medications they use. Since this feedback is provided by non-experts, it often lacks technical terms but instead conveys different feelings and sentiments. Patients might express dissatisfaction or satisfaction with a specific medication. Consequently, computer science techniques such as natural language processing (NLP), particularly sentiment analysis, can be employed to analyze these feedback data and provide a collective overview for a given medication [2]. The second approach involves conducting independent research trials related to the particular medication.

Healthcare-related websites, such as webmd.com, frequently showcase patient feedback, which can be valuable resources for individuals seeking information and support concerning medications [3]. Patient reviews/feedback, particularly for psychiatric medications, offer significant insights into the effects of these medications, revealing aspects that might not have been evident during the initial stages of drug development. These reviews provide information on a medication's effectiveness, adverse effects, dosage, onset and duration of action, tolerability and comparisons to other medications.

The clinicaltrials.gov website serves as a repository encompassing both privately and publicly funded clinical studies conducted in various countries around the world. The details of these studies (e.g. conditions, number of participants and their demographic characteristics, intervention, outcomes) are inputted into the database manually. Users can search this repository for trials associated with specific medical conditions or medications. For instance, in our previous study analyzed the adverse effects of oxycodone by extracting data from all the clinical trials registered at clinicaltrials.gov [4].

Sentiment analysis [5], also known as opinion mining, is a natural language processing (NLP) technique that involves using machine learning models to determine the sentiment or emotional tone expressed in a piece of text, typically written or spoken language. Its primary goal is to classify text as positive, negative, or neutral based on the underlying emotions or opinions expressed.

Our primary aim was to examine whether there is a correlation between the patient experiences (assessed via sentimental analysis) with using medication commonly prescribed for psychiatric conditions and the statistical analysis of data about the same medications from clinical trials [6-12].

## Material and methods

A variety of chemical and natural medications can be used to treat depression and anxiety [13]. We used a list of medications categorised by Constable et al. into seven groups based on their chemical structure and mode of action (see Table 1) [14].

We collected from webmd.com all reviews and feedback for each medication listed in Table 1 and conducted a sentiment analysis on each specific review/piece of feedback. Specifically, we wrote a script in the Python programming language (version 3.10, Python Software Foundation, Delaware, USA) to extract information from web pages and organize it in a structured format. Then, we used the valence aware dictionary and sentiment reasoner (VADER), a rule-based sentiment analysis tool developed by Hutto et al. [9]. It assessed the medication review/feedback text and assigned polarity labels (ranging from -1 (most negative) to +1 (most positive)) and calculated a compound score that represents th overall sentiment (see Figure 1).

In addition to webmd.com, we also searched the clinicaltrials.gov repository for studies involving the same medication and extracted the following details: the number of studies, the number of participants in each study, age and gender of participants (categorized as child, adult, senior). This data was collected manually in a .csv file that was generated by the clinicaltrials.gov. After extracting the data for each chosen medication from both sources, we wrote the following research questions:

- Question 1. Which medications generally receive more positive and negative feedback from patients, and is there a discernible pattern among them in relation to their medication groups?
- Question 2. Which medications generally receive more attention from researchers, and is there a pattern related to their medication groups?
- Question 3. Is there a meaningful relationship between patients' feedback on a given medication and the number of clinical trials for the same medication?

We explored the pairwise relations between the features of the webmd.com dataset and the features of the clinicaltrials.gov dataset. The p-value and Pearson correlation coefficient (PCC) were utilized to evaluate these interdependencies.

**Table 1. List of a number of psychiatric medications categorized in their groups**

| Medication group | Medication |
|---|---|
| Tricyclic antidepressants | Amitriptyline |
| | Clomipramine |
| | Doxepin |
| | Nortriptyline |
| | Imipramine Dosulepin dothiepin |
| Monoamine oxidase inhibitors | Tranylcypromine |
| | Moclobemide |
| | Phenelzine |
| SSRIs | Citalopram |
| | Fluoxetine |
| | Fluvoxamine |
| | Paroxetine |
| | Sertraline |
| | Escitalopram |
| SNRIs | Venlafaxine |
| | Desvenlafaxine |
| | Duloxetine |
| Benzodiazepines | Temazepam |
| | Nitrazepam |
| | Diazepam |
| | Oxazepam |
| | Alprazolam |
| | Lorazepam |
| Typical antipsychotics | Risperidone |
| | Aripiprazole |
| | Clozapine |
| | Olanzapine |
| | Quetiapine |
| | Ziprasidone |
| Gammaaminobutyric acid analogues | Pregabalin |
| | Gabapentin |

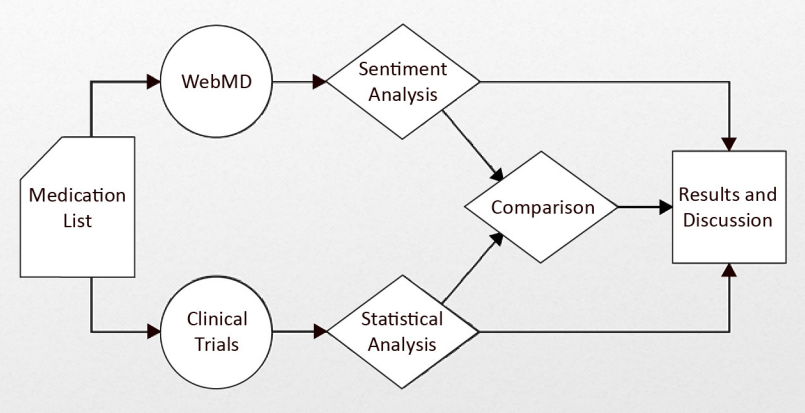


**Figure 1. The entire process of this study**

Schober et al. detailed the correlation coefficient in their work which is regarded as a conventional method for interpreting the PCC [15]. We quoted the information their work in our Table 3 and used it as a reference for interpretation. In this study, we used the Pearsonr from the Scipy module (a Python application programming interface). In addition to the PCC (r), the Pearsonr function also calculates the p-value. The p-value is employed to assess the rejection of the null hypothesis (H0), which states that there is no relationship between two distributions of values. A p-value < 0.05 is commonly accepted as evidence to reject the null hypothesis, indicating the possibility of a linear relationship between the two distributions. All the analyses, including the sentiment analysis via VADER, were performed using Python code developed by the Authors. All the employed data and code can be found at github.com/farshad1982/Clinical-WebMD.

## Results

Our analysis indicates that citalopram, escitalopram, risperidone, gabapentin, pregabalin, olanzapine, quetiapine, aripiprazole, duloxetine, sertraline and fluoxetine, were each included in > 300 clinical trials. However, the list of medications with the highest number of clinical trial participants is different: clozapine, duloxetine, venlafaxine, citalopram, escitalopram, fluoxetine, sertraline, paroxetine, desvenlafaxine, quetiapine and fluvoxamine, each having more than 4 million participants in total.

Medications with the highest number of female participants are: gabapentin, duloxetine, pregabalin, citalopram, escitalopram, fluoxetine, diazepam and sertraline. Medications with the highest focus on male participants are: citalopram, escitalopram, pregabalin, gabapentin, olanzapine, paroxetine, fluoxetine and aripiprazole.

We also identified medications with the highest focus on children, e.g. risperidone, aripiprazole, fluoxetine, gabapentin, olanzapine and sertraline. Medications with the highest focus on seniors are citalopram, escitalopram, pregabalin and gabapentin.

Additionally, we noted 4 medications that have not received a single review on webmd.com but were included in a few clinical trials: dosulepin and dothiepin (2 clinical trials each) and moclobemide, nitrazepam (14 and 17 trials respectively).

After analyzing our results, we answered our previously-mentioned 3 research questions.

Question 1. Table 2 displays various medications, each color-coded to indicate the overall sentiment associated with them. Red signifies high negativity (i.e. large gap between negative and positive), orange represents medium negativity (i.e. medium gap between negative and positive), yellow indicates low negativity (i.e. low gap between negative and positive), gray illustrates an equal sentiment between positive and negative (i.e., no gap between negative and positive), blue denotes low positivity (i.e. low gap between positive and positive) and green reflects high positivity (i.e. large gap between positive and positive). Within the SSRI group, there are no medications with an overall positive sentiment. However, the Benzodiazepine group appears to have three medications with an overall positive sentiment and two with low negativity. GABA analogues generally display high or medium levels of negativity. Benzodiazepines in general, show the highest positive feedback, while MAO inhibitors, GABA analogues and SSRIs received the highest overall negative feedback. Other medication groups received a mix of positive and negative feedback

Question 2. Table 4 presents the targeted medications categorized by their respective groups, with each medication color-coded based on the number of trials conducted. For instance, dark-green signifies a high number of trials, yellow represents a medium count, while light-red and dark-red indicate low number and very low attention, respectively. In general, GABA analogues were included in the highest number of trials, followed by the typical antipsychotics. SSRI medications were also relatively often included in trials. Conversely, TCA antidepressants and MAO inhibitors were not as extensively researched in clinical trials compared to other groups. Hence, the answer to this research question is “yes,” indicating a meaningful relationship between the medication groups and the number of clinical trials.

**Table 2. The details of sentiment analysis from the data collected from webmd.com**

| Group | Name | Neg Count | Neu Count | Pos Count | Total | Neg % | Neu % | Pos % |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |
| 1 | Amitriptyline | 529 | 101 | 431 | 1061 | 0.5 | 0.095 | 0.405 |
| | Clomipramine | 27 | 8 | 27 | 62 | 0.435 | 0.13 | 0.435 |
| | Doxepin | 91 | 30 | 112 | 233 | 0.39 | 0.13 | 0.48 |
| | Nortriptyline | 246 | 42 | 146 | 434 | 0.565 | 0.1 | 0.335 |
| | Imipramine | 56 | 9 | 25 | 90 | 0.62 | 0.1 | 0.28 |
| | Dothiepin | - | - | - | - | - | - | - |
| | | | | | | | | |
| 2 | Tranylcypromine | 3 | 1 | 1 | 5 | 0.6 | 0.2 | 0.2 |
| | Moclobemide | - | - | - | - | - | 0.0 | - |
| | Phenelzine | 7 | 0 | 1 | 8 | 0.88 | | 0.12 |
| | | | | | | | | |
| 3 | Citalopram | 683 | 141 | 568 | 1392 | 0.49 | 0.1 | 0.41 |
| | Fluoxetine | 176 | 27 | 164 | 367 | 0.48 | 0.07 | 0.45 |
| | Fluvoxamine | 27 | 3 | 27 | 57 | 0.475 | 0.05 | 0.475 |
| | Paroxetine | 160 | 26 | 98 | 284 | 0.56 | 0.09 | 0.35 |
| | Sertraline | 308 | 51 | 230 | 589 | 0.52 | 0.09 | 0.39 |
| | Escitalopram | 118 | 20 | 84 | 222 | 0.53 | 0.09 | 0.38 |
| | | | | | | | | |
| 4 | Venlafaxine | 328 | 37 | 169 | 534 | 0.61 | 0.07 | 0.32 |
| | Desvenlafaxine | 1 | 0 | 2 | 3 | 0.33 | 0.0 | 0.67 |
| | Duloxetine | 162 | 38 | 81 | 281 | 0.58 | 0.13 | 0.29 |
| | | | | | | | | |
| 5 | Temazepam | 138 | 61 | 161 | 360 | 0.38 | 0.17 | 0.45 |
| | Nitrazepam | - | - | - | - | - | - | - |
| | Diazepam | 108 | 30 | 116 | 254 | 0.42 | 0.12 | 0.46 |
| | Oxazepam | 17 | 7 | 22 | 46 | 0.37 | 0.15 | 0.48 |
| | Alprazolam | 272 | 72 | 220 | 564 | 0.48 | 0.13 | 0.39 |
| | Lorazepam | 230 | 61 | 208 | 499 | 0.46 | 0.12 | 0.42 |

**Table 2. The details of sentiment analysis from the data collected from webmd.com (continued)**

| Group | Name | Neg Count | Neu Count | Pos Count | Total | Neg % | Neu % | Pos % |
|---|---|---|---|---|---|---|---|---|
| 6 | Risperidone | 97 | 21 | 74 | 192 | 0.50 | 0.11 | 0.39 |
| | Aripiprazole | 21 | 9 | 31 | 61 | 0.34 | 0.15 | 0.51 |
| | Clozapine | 24 | 7 | 19 | 50 | 0.48 | 0.14 | 0.38 |
| | Olanzapine | 54 | 23 | 41 | 118 | 0.46 | 0.19 | 0.35 |
| | Quetiapine | 71 | 29 | 85 | 185 | 0.38 | 0.16 | 0.46 |
| | Ziprasidone | 71 | 9 | 40 | 120 | 0.59 | 0.075 | 0.335 |
| | | | | | | | | |
| 7 | Pregabalin | 64 | 17 | 41 | 122 | 0.52 | 0.14 | 0.34 |
| | Gabapentin | 1009 | 166 | 450 | 1625 | 0.62 | 0.1 | 0.28 |

**Group 1: Tricyclic antidepressants, Group 2: Monoamine oxidase inhibitors, Group 3 represents SSRIs, Group 4: SNRIs, Group 5: Benzodiazepines, Group 6: Typical antipsychotics, Group 7: Gammaaminobutyric acid analogues**

**Table 3. Interpretation of PCC**

| Absolute value of PCC | Interpretation |
|---|---|
| 0.00-0.10 | Negligible correlation |
| 0.10-0.39 | Weak correlation |
| 0.40-0.69 | Moderate correlation |
| 0.70-0.89 | Strong correlation |
| 0.90-1.00 | Very strong correlation |

Question 3. Table 5 displays the existing correlations between the features from clinicaltrials.gov and the features from webmd.com. The following presents the notable correlations among these two datasets:

(a) clinicaltrials.gov focused on females exhibit the highest PCC (moderate correlation) and the lowest p-values with various types of feedback, including total feedback, from webmd.com. This implies that an increase in the number of negative feedback correlates with a rise in the number of trials focusing on female participants, and vice versa. Particularly negative feedback, as indicated by the highest PCC and the lowest p-value.

(b) clinicaltrials.gov centered around on seniors also reveal moderate correlations with higher volume of feedback from webmd.com. Specifically, negative feedback increases with the rise in clinical trials involving seniors.

(c) clinicaltrials.gov focused on males tend to exhibit only weak correlations with various types of feedback from webmd.com,

(d) clinicaltrials.gov focused on adults also display a weak correlation, only with the negative feedback. This observation may suggest that adults contribute more to providing negative feedback exclusively. This pattern contrasts with the seniors, who contribute to positive and neutral feedback as well.

(e) There is no correlation between the trials involving children and the feedback posted on webmd.com.

## Discussion

Conducting two sets of analyses on the same set of medications provides insight into how patient feedback might influence research studies. Two notable medications are cit-

**Table 4. The details of statistical analysis from the data collected from clinicaltrials.gov**

| Group | Name | Size | Enrollment | All | Male | Female | Child | Adult | Older Adults |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | |
| 1 | Amitriptyline | 161 | 102238 | 142 | 7 | 12 | 15 | 149 | 114 |
| | Clomipramine | 36 | 78631 | 30 | 6 | 0 | 3 | 32 | 27 |
| | Doxepin | 22 | 1044686 | 20 | 1 | 1 | 2 | 20 | 18 |
| | Nortriptyline | 70 | 97065 | 68 | 1 | 1 | 3 | 68 | 60 |
| | Imipramine | 48 | 78269 | 43 | 1 | 4 | 2 | 45 | 33 |
| | Dosulepin | 2 | 73441 | 2 | 0 | 0 | 0 | 2 | 2 |
| | Dothiepin | 2 | 73441 | 2 | 0 | 0 | 0 | 2 | 2 |
| | | | | | | | | | |
| 2 | Tranylcypromine | 32 | 12302 | 32 | 0 | 0 | 2 | 31 | 28 |
| | Moclobemide | 14 | 7884686 | 12 | 1 | 1 | 5 | 12 | 9 |
| | Phenelzine | 13 | 565 | 10 | 2 | 1 | 0 | 13 | 8 |
| | | | | | | | | | |
| 3 | Citalopram | 691 | 4922739 | 631 | 25 | 35 | 54 | 665 | 474 |
| | Fluoxetine | 395 | 4921063 | 352 | 11 | 32 | 93 | 357 | 242 |
| | Fluvoxamine | 100 | 4339066 | 92 | 7 | 1 | 19 | 92 | 56 |
| | Paroxetine | 323 | 4877887 | 290 | 15 | 18 | 27 | 314 | 225 |
| | Sertraline | 421 | 4881349 | 393 | 7 | 20 | 59 | 395 | 287 |
| | Escitalopram | 691 | 4922739 | 631 | 25 | 35 | 54 | 665 | 474 |
| | | | | | | | | | |
| 4 | Venlafaxine | 263 | 5126956 | 244 | 7 | 11 | 20 | 255 | 216 |
| | Desvenlafaxine | 101 | 4728355 | 87 | 1 | 13 | 10 | 95 | 64 |
| | Duloxetine | 421 | 5186847 | 364 | 7 | 50 | 23 | 402 | 349 |
| | | | | | | | | | |
| 5 | Temazepam | 23 | 2556 | 23 | 0 | 0 | 3 | 20 | 16 |
| | Nitrazepam | 17 | 3084 | 17 | 0 | 0 | 7 | 12 | 12 |
| | Diazepam | 198 | 73675 | 170 | 7 | 21 | 42 | 171 | 141 |
| | Oxazepam | 19 | 1313 | 19 | 0 | 0 | 2 | 18 | 14 |
| | Alprazolam | 108 | 10461 | 100 | 4 | 4 | 8 | 101 | 48 |
| | Lorazepam | 201 | 250521 | 182 | 9 | 10 | 37 | 185 | 138 |

**Table 4. The details of statistical analysis from the data collected from clinicaltrials.gov**

| Group | Name | Size | Enrollment | All | Male | Female | Child | Adult | Older Adults |
|---|---|---|---|---|---|---|---|---|---|
| 6 | Risperidone | 613 | 3296686 | 591 | 9 | 12 | 128 | 564 | 330 |
| | Aripiprazole | 448 | 2015280 | 433 | 11 | 4 | 114 | 393 | 247 |
| | Clozapine | 192 | 31035882 | 188 | 1 | 1 | 24 | 187 | 125 |
| | Olanzapine | 542 | 3352926 | 508 | 16 | 17 | 75 | 521 | 350 |
| | Quetiapine | 502 | 4415341 | 483 | 9 | 10 | 55 | 479 | 347 |
| | Ziprasidone | 167 | 3055204 | 163 | 3 | 1 | 32 | 150 | 96 |
| | | | | | | | | | |
| 7 | Pregabalin | 578 | 137986 | 507 | 23 | 48 | 35 | 568 | 472 |
| | Gabapentin | 580 | 2516941 | 488 | 16 | 76 | 78 | 553 | 457 |

**Group 1: Tricyclic antidepressants, Group 2: Monoamine oxidase inhibitors, Group 3: SSRIs, Group 4: SNRIs, Group 5: Benzodiazepines, Group 6: Typical antipsychotics, Group 7: Gammaaminobutyric acid analogues**

**Table 5. Statistical analysis of data about medication collected from webmd.com and clinicaltrials.gov**

| | webmd.com | clinicaltrials.gov | p value | PCC |
|---|---|---|---|---|
| 1 | Negative | Female | 0.0 | 0.618 |
| 2 | Total | Female | 0.001 | 0.57 |
| 3 | Neutral | Female | 0.002 | 0.557 |
| 4 | Positive | Female | 0.011 | 0.468 |
| 5 | Negative | Older-Adult | 0.019 | 0.434 |
| 6 | Total | Older-Adult | 0.024 | 0.418 |
| 7 | Neutral | Older-Adult | 0.03 | 0.402 |
| 8 | Total | Male | 0.033 | 0.398 |
| 9 | Positive | Male | 0.034 | 0.396 |
| 10 | Negative | Male | 0.037 | 0.39 |
| 11 | Total | Total | 0.039 | 0.385 |
| 12 | Negative | Adult | 0.041 | 0.382 |
| 13 | Neutral | Male | 0.043 | 0.378 |
| 14 | Negative | Size | 0.044 | 0.377 |
| 15 | Positive | Older-Adult | 0.045 | 0.375 |
| 16 | Total | Size | 0.048 | 0.37 |

**The upper part of Table 5 displays pairs of features (one from webmd.com and the second from clinicaltrials.gov) with p-values < 0.05 and a PCC > 40% (indicating moderate correlation), while the lower part shows pairs with p-values < 0.05 and a PCC between 30%-40% (indicating weak correlation).**

alopram and gabapentin. Citalopram is a primary focus for researchers due to the number of trials and one of the most reviewed medications on webmd.com. One of the main reasons for prescribing Citalopram is its perceived safety [16]. Gabapentin, having the highest number of reviews on webmd.com, also has a relatively high number of clinical trials. This could be due to the multi-functionality of gabapentin in the treatment of seizures, neuropathic and chronic pain, restless leg syndrome, migraines, anxiety disorder, hot flashes and certain mood disorders [17-18].

Additionally, medications aimed at children receive less online feedback compared to those for adults. Medications targeting older adults receive more positive and neutral feedback in contrast to those targeting children and adults. This trend may be attributed to the higher prevalence of chronic conditions among older adults, leading to more sustained use and thus more opportunities for feedback. Conversely, medications for children might have fewer feedback instances due to lower usage frequency or parental concerns about sharing information online. Furthermore, the higher positive and neutral feedback for medications targeting older adults could be influenced by their effectiveness in managing chronic conditions that significantly impact quality of life. These medications might also benefit from more robust clinical trials and post-market surveillance, contributing to better patient outcomes and satisfaction. It is also possible that older adults, or their caregivers, are more diligent in reporting their experiences with medications due to a more consistent interaction with healthcare providers. Additionally, the marketing strategies for medications targeting different age groups could play a role, influencing both the perception and feedback frequency. Finally, social and cultural factors, such as stigma or acceptance of medication use in various age groups, could also affect the nature and volume of feedback received.

Our data also suggests a correlation between the number of negative feedback instances and the increase in clinical trials focusing on female participants. This trend highlights the importance of addressing adverse reactions reported by females and underscores the need for gender-specific research in clinical trials.

There are other several tools other than VADER designed for sentiment analysis, e.g. the DistilBertForSequenceClassification, a pre-trained transformed-based model which is a variant of the original BERT (Bidirectional Encoder Representations from Transformers) [19-20]. However, we decided not to use the DistilBert model due to its limitations, e.g. insufficient data to train the model, complex fine-tuning requirements and a dependency on specific task types, leading to reduced generalization. Given the absence of training data in our work, machine learning tools such as DistilBert were not likely to be useful. In contrast, VADER functions based on a set of pre-defined rules (a lexicon) to interpret a text's sentiment (emotional content, also termed as „valence"), considering word intensity, punctuation, capitalization and other linguistic features. For instance, VADER is accurate enough to recognize the negative sentiment in phrases such as "I am not happy," despite the presence of the word 'happy.' Additionally, VADER can identify emoticons often used in informal language that is often found in user-provided reviews or feedback comments.

### Limitations of our study

Our work utilized data available from an openly accessible forum created by patients. Although this platform allows patients from any location, ethnicity, and condition to report their experiences, there is still a risk of biased feedback for various reasons, which can potentially impact the final results. Detecting biased feedback is fundamentally challenging as this platform does not reveal the identity of the patient or confirm whether the patient has used the medication (non-biased) or not (biased). Our work employed an automated sentiment analysis technique (Vader), which is a rule-based method. Similar to AI-based techniques, there is a possibility for feedback to be sentimentally misinterpreted, often due to the grammatical structure of the feedback, such as the use of slang, colloquialisms or even non-English terms.

## Conclusions

To the best of our knowledge, there is very little literature investigating the link between clinical trials and patient feedback about medications. Our findings suggest a general connection between the registered clinical trials and the feedback posted on webmd.com about the same medication. Clinical trials focusing on females and trials focusing on seniors were correlated with one or more type of feedback posted on webmd.com. Medications with a higher number of feedback generally attract more attention of researchers, although there are some exceptions. By integrating feedback from platforms like webmd.com with data from clinicaltrials.gov, researchers can better understand and respond to the unique medical needs of female patients, ultimately leading to more effective and inclusive healthcare solutions.

## Conflict of interest

None.

## Funding

None.

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REVIEW ARTICLE

# Diabulimia – a diagnostic and therapeutic challenge in the Emergency Department

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## Abstract

Diabulimia is the intentional omission or reduction of insulin administration in a patient with insulin-dependent diabetes mellitus (IDDM) and a coexisting eating disorder in the attempt to reduce or avoid weight gain. Although the true incidence of diabulimia is unknown, it is estimated that between 20-30% of girls and up to 40% young women with IDDM have experienced diabulimia since their diagnosis of IDDM was made. Patients with diabulimia frequently present to the emergency department, therefore early recognition of the eating disorder and prompt psychiatric consultation are essential. The aim of this review article is to summarize the existing literature about diabulimia and to raise awareness amongst emergency physicians about how to identify and treat these patients.

**Keywords:** diabulimia · eating disorders · ketoacidosis · emergency department

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## Introduction

Diabulimia is not a new disorder. The coexistence of eating disorders with insulin-dependent diabetes mellitus (IDDM) was first described in the 1980s [1] and the term "diabulimia" first appeared in the literature in 2007 [2]. Nevertheless, the clinicians' awareness of diabulimia is still lagging in 2024. The current edition of the Statistical Manual of Mental Disorders (DSM V published in 2013) does include the intentional omission or reduction of insulin with the intention to reduce or prevent weight gain, although this is not described as diabulimia [3]. Whereas the International Classification of Diseases 11$^{th}$ edition (ICD-11) released in 2019, does not mention diabulimia or any equivalent [4].

Although the term "bulimia" is part of the name, patients with diabulimia may also meet criteria for anorexia nervosa (AN). Bulimia nervosa (BN) is the psychotic overeating, characterized by lack of control during the eating binge, followed by feelings of guilt, shame and compensation with self-induced vomiting, use of laxatives, diuretics, food deprivation and vigorous exercise [5]. AN overlaps many of the symptoms of BN, with the difference that these patients with AN typically do not binge-eat [6]. In both eating disorders, the psychological long-term effects can lead to low self-esteem, feelings of incompetence, anxiety, depression and even suicidality (defined as the risk of suicide, indicated by suicidal ideation or intent) [7]. The main objective of patients with diabulimia is to avoid the anabolic effects of insulin with regards to weight gain. Their body image is so distorted, they are willing to suffer the consequences and present to the ED with all the clinical features of poorly controlled diabetes plus the complications of the underlying eating disorder. The aim of this article is to review the unique challenges that exist in the identification and treatment of patients with diabulimia at the Emergency Department (ED) and to raise awareness amongst emergency physicians (EPs).

## Material and methods

We used PubMed and Google Scholar to search for literature using keywords such as "diabulimia" and "eating disorders in diabetes." The criteria of inclusion were: article type (clinical trial, randomized control trial or systematic review), language (English or Polish) and description of patient management. This is a narrative review, therefore meta-analysis was not performed.

## Results

The initial literature search retrieved 966 records (44 about diabulimia and 922 about eating disorders in diabetes). After applying the exclusion criteria, 866 abstracts were excluded. Full texts of the remaining 144 records were read and 111 of them were excluded due to lack of description of patient management at the ED. Finally, 29 full text articles (including 3 guidelines) were included in the analysis. Full text articles were searched for relevant references regarding the epidemiology and pathophysiology of diabulimia.

## Discussion

Currently, there is little data on the etiopathogenesis of diabulimia. However, based on the literature review, two relationships can be distinguished:

– due to the need to strictly follow the diet and numerous dietary restrictions that require the elimination of particular types of food, as well as focusing on the caloric value of food, diabetes may predispose to the development of eating disorders;

– eating disorders and irregular food intake, frequent binge eating resulting in excessive load on the endocrine system may contribute to the development of diabetes [5, 8].

The above hypotheses are reflected in the research. An experiment conducted on a group of adults suffering from insulin-dependent diabetes, with a median age of 51 years, determined the frequency of probable eating disorders among the research group at 21.7% (20.6% in men and 24.2% in women). However, incorrect use of insulin occurred in 39% of respondents [9]. Other studies conducted on a group of adolescents suggest that 23.9% of patients with type I diabetes present symptoms characteristic of diabetes-related eating disorders, while 32.6% of the respondents had symptoms of at least one mental disorder [10].

The true incidence of diabulimia is unknown and currently it is estimated that between 20-30% of girls and up to 40% young women with IDDM have experienced diabulimia since the diagnosis of IDDM was made [11]. Although the most common eating disorders in the population are AN and BN, data from the Polish literature suggest that diabulimia may occur in 20-30% of girls and young women diagnosed with type I diabetes [7], that men are less likely to present symptoms of this disorder and it often coexists with other mental disorders (mainly anxiety and depression). Interestingly, a population study from Germany revealed that although eating disorders among adolescents with IDDM are more common in females than males (31.2% versus 11.7%), there was little difference in their use of insulin restriction (20.5% of the females versus 18.5% of the males with IDDM) [12].

The mortality rate of IDDM for young girls is estimated at 2.2 per 1000-person years, whereas for girls with an eating disorder the mortality rate is 7.3 (the highest of all psychiatric disorders) and when combining both IDDM and eating disorders the mortality is as high as 34.6 per 1000-person years [13]. It should not be surprising that in psychiatry and endocrinology community, diabulimia is considered the most dangerous eating disorder.

The majority of patients with diabulimia are young women with a low body mass index (BMI), often educated, highly functional and very rational in other aspects of their lives, who have been admitted several times to the hospital due to an IDDM-related complication [14]. These patients are well-aware of the consequences of lowering insulin doses, but their fear of gaining weight is so strong and stressful, that it leads them ignore all that rational thinking.

## Management in the Emergency Department

EPs are trained and experienced in the management the metabolic complications of poorly controlled IDDM, e.g. hyperglycemia, DKA, dehydration and electrolyte abnormalities. However, identifying an eating disorder in an ED patient still remains a challenge [15]. The role of the EP is particularly important in the diagnosis of this disorder because the ED is often where these patients have contact with the healthcare system. The frequent episodes of diabetes-associated complaints are an important feature of diabulimia. These presentations should raise the suspicion and prompt the clinician to ask more questions to unveil the possibility of eating disorder. It is worth mentioning that the diagnosis of diabulimia does not need to be made in the ED, however it is the responsibility of EPs to identify the patients with risk factors for an eating disorder and refer them to mental health professionals for evaluation and treatment.

If the EP suspects that a patient with IDDM has an eating disorder, it is important to collect a more detailed history and to dive deeper into the patient's medical record. Eating disorders are often either well-hidden or denied. In a non-judgmental approach, asking questions to uncover insulin availability, food insecurity and body image dissatisfaction can be extremely helpful. We suggest asking the following 5 questions:

- Do you have access to insulin and the supplies needed to administer your insulin doses?
- Do you have enough food at home for you and your family?
- Have you ever been overweight?
- How often do you reduce or omit your insulin doses?
- Have you ever made yourself vomit or taken laxatives, diuretics or weight loss supplements?

- **History of depression, anxiety or an eating disorder**
- **Significant weight loss**
- **Excessive focus on calorie intake, body shape, body weight and appearance**
- **Missing follow-up appointments**
- **Recurrent hospital admissions with diabetic ketoacidosis (DKA)**
- **Persistent hyperglycemia**
- **High HgA1c**
- **Complications of poorly controlled IDDM**
- **Amenorrhea (females) or poor virilization (males)**
- **Refusing to be weighed**

**Figure 1. Details in the history and physical exam of a patient with IDDM that should raise the clinician's suspicion of diabulimia.**

The first 2 questions are to screen for access to insulin and food insecurity, and the following 3 questions are more specific to having an eating disorder. If the patient has no problems with access to medications and is not food insecure; but screens positive for body image, reducing insulin dosage or using alternative weight loss medications, then it is likely this patient suffers a concomitant eating disorder, and a psychiatric referral is warranted.

This assessment can be done while in the ED (as long as it doesn't interfere with the ongoing treatment) or at the ward the patient is admitted. A problem may arise if the patient refuses mental health assessment. In such case, it is important to proceed in accordance with the mental health law/s applicable in your country of practice. For example, in Poland psychiatric examination can be conducted without the patient's consent in accordance with Article 21 of the amended Mental Health Protection Act of August 19, 1994:

"1. A person whose behavior indicates that, due to mental disorders, he or she may directly threaten his or her own life or the life or health of other people, or is unable to meet basic life needs, may also be subjected to a psychiatric examination without his or her consent, and a minor or incapacitated person completely – also without the consent of its legal representative" [16]. Having said that, it is important to acknowledge that different laws may apply in different jurisdictions. In case of doubt, seek advice from the legal department of your hospital or the institution that issued your license to practice medicine.

### Special considerations

Patients with diabulimia arrive at the ED with the same complications as any patient with poorly-controlled IDDM: microangiopathy, retinopathy, diabetic nephropathy, peripheral neuropathy, electrolyte abnormalities, diabetic ketoacidosis (DKA) and potentially fatal coma [7]. When adding the eating disorder, the complication rate increases exponentially, adding negative energy balance, low BMI, increased catabolism, hypokalemia, hypomagnesemia, hypophosphatemia, prolonged QT interval, orthostatic disorders, endocrine abnormalities and decreased bone density causing pathological bone fractures [17]. However, the underlying psychiatric disorder (diabulimia) adds unique diagnostic and treatment challenges for clinicians in the ED. These include hypoglycemia, DKA and refeeding syndrome (RS).

### Hypoglycemia

Hypoglycemia is the most common life-threatening acute complication of diabetes treatment [18]. Diabulimic patients are at risk for hypoglycemia for several reasons: decreased insulin clearance due to nephropathy (therefore even small doses of insulin can have prolonged effect) and reduced calorie intake which leads to low glycogen storage [19].

### Diabetic ketoacidosis

The basic management of DKA in a patient with diabulimia is the same as in any patient with IDDM and has been described in detail in several guidelines [20-22]. However, in addition to the metabolic derangements of DKA, the nutritional deficiencies caused by the restrictive diet some of these patients follow can lead to severe electrolyte deficiencies, e.g. hypocalcemia, hypokalemia, hypomagnesemia and hypophosphatemia [23]. Patients with these abnormalities can present with severe muscle weakness (including the respiratory muscles), tetany, ataxia, paresthesias, nystagmus, diplopia, confusion, seizures, irritability, arrhythmias and even cardiac arrest. Therefore, the initial laboratory analysis should include these electrolytes and the correction of their abnormalities is of paramount importance.

### Refeeding syndrome

As implied by its name, RS occurs when the malnourished body receives nutrients again [24]. Besides the serious electrolyte deficiencies (hypokalemia, hypomagnesemia and hypophosphatemia), patients with RS often have sodium and water shifts that can cause fluid overload with pulmonary edema and hypotension [20, 24]. Prolonged hypokalemia can lead to hypokalemic nephropathy and chronic kidney injury [23]. The other important deficiency that becomes evident during RS is thiamine. This B-vitamin is crucial in the glucose metabolism, thus when deficient, patients can develop severe neurological complications. Thiamine supplementation should be routine in these patients with diabulimia prior to alimentation [25]. RS is not a health problem we typically address in the ED. However, the lack of ICU beds is not an uncommon situation in many hospitals, thus we manage patients in the ED longer and longer [26-27]. Having a basic understanding of the possible complications during feeding of patients with diabulimia is important for the EP.

### Further management

IDDM complicated with an eating disorder requires a multidisciplinary approach because of the complex social, medical, nutritional and psychological needs of the patients [25]. Cognitive behavioral therapy and SSRIs (mainly fluoxetine) seem to have some effect in reducing complications and promoting weight gain in patients with diabulimia [28-30]. Patient and family education play an important role in reducing maladaptive coping mechanisms and improving the self-image, nutrition and insulin therapy [31]. The use of diabetes-related software (e.g. mobile apps) can also help in patient education and provide ongoing support for decisions regarding insulin therapy and nutrition [32-33].

## Conclusions

As the society continues to promote an unrealistic concept of beauty, the prevalence of eating disorders is only expected to rise. Together with an increasing incidence of IDDM, we can expect see more patients with diabulimia presenting to EDs. The role of the EP is therefore not only to diagnose and treat the acute complications of IDDM, but also to recognize those at risk of eating disorder and to ensure timely referrals for comprehensive mental health treatment.

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## Conflicts of interest

None to report.

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REVIEW ARTICLE

# Advances in understanding, diagnosis and targeting ATTR cardiomyopathy: a review

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## Abstract

Transthyretin amyloidosis (ATTR) manifests as wild-type (ATTRwt) and hereditary/mutant (ATTRv) forms and can lead to heart failure due to cardiac amyloidopathy. Diagnosing ATTR, particularly in asymptomatic carriers of pathogenic variants, remains challenging despite the advances. Complex and multi-aspect management involves a limited range of well-examined conventional therapies to address the heart failure and frequently coexisting arrhythmias and valvular issues. Disease-modifying treatment, RNA-based treatments, CRISPR-Cas9 gene editing and monoclonal antibodies targeting amyloid deposits are recent and promising innovations. This review explores the diagnostic intricacies, therapeutic dilemmas and emerging solutions in ATTR cardiomyopathy. The significance of early detection and precise, targeted approaches to enhance patient outcomes is underscored.

**Keywords:** cardiomyopathy · amyloidosis · transthyretin

## Citation

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## Introduction

Amyloidosis is a diverse group of diseases whose pathogenesis involves the deposition of insoluble protein deposits of various origins that impair the function of internal organs, including the heart. Vast majority (95%) of cardiac amyloidosis (CA) cases are light chain amyloidosis (AL) and transthyretin amyloidosis (ATTR) [1]. These are rare diseases, but their estimated prevalence in the European population is 3/1000 [2] and in recent years the incidence of ATTR-CA has increased several-fold [3] and might be underestimated [4-5]. Transthyretin (TTR) is a protein produced in the liver, involved in the transport of thyroid hormones and vitamin A in the blood, its defective spatial conformation causes the formation of deposits in ATTR.

ATTR is divided into the wild type (ATTRwt) associated with aging and the mutant or hereditary type (ATTRv), which is characterized by a single amino acid substitution in the chain of 127 amino acids that make up the protein. It can occur familially, although up to 50% of patients with this type have no confirmed cases among relatives [6-7].

ATTRv with polyneuropathy is estimated to affect 5000--10000 people worldwide [8]. It can be divided into late-onset (after age 50) and early-onset ATTRv, the former of which is usually sporadic and has a more aggressive course with predominant peripheral neuropathy [9]. More than 130 pathogenic variants of TTR are known [6]. Some variants (e.g. p.Leu131Met) manifest complete penetrance in a specific age range, but most have incomplete penetrance [3, 10] and the chance of revealing clinical features increases with age [11]. The most common variant is p.V142I – named after the amino acid substitution site. Carriers of this mutation are 3-4% of the global population of African ancestry and in the United States it may account for about 23% of ATTR-CA cases [12]. Therefore, it is suspected that it may be a founder mutation or codon 142 could be a mutational hotspot [3, 13]. In European population-based studies, the frequency of the mutant type among patients with ATTR-CA was just a few percent [3, 13]. Most patients with ATTRv were of African and Caribbean descent and usually carried the p.V142I mutation [13-14].

The hereditary form of ATTR is distinguished by the onset of symptoms at a younger age [3] and usually a co-occurrence of cardiac and neurological symptoms [15]. At the same time, the occurrence of ATTRv is associated with increased mortality and a more severe course of the disease [16]. Hence, genetic screening tests for ATTRv have been advocated for all patients with a diagnosis of ATTR and genetic testing was included in the diagnostic protocol for hypertrophic cardiomyopathy [17-18], whose clinical picture may resemble ATTR-CA.

Wild-type ATTR is more common and associated with aging, usually affecting white males around the age of 80, hence it is sometimes called "senile amyloidosis." Cardiac manifestation (restrictive cardiomyopathy with diastolic heart failure) in this type of AL is often overlooked and underestimated due to the overlap of concomitant diseases in this age group, e.g. hypertension, valvular defects, heart failure (HF) due to ischemic disease, hypertrophic cardiomyopathy. ATTR-CA was detected in about 13% of patients hospitalized with HFpEF (heart failure with preserved ejection fraction) and about 16% with severe aortic stenosis undergoing transcatheter aortic valve implantation (TAVI) [6, 19]. Diagnostic vigilance should be increased when other systemic manifestations of amyloidosis occur, often preceding cardiac involvement by several years [20], e.g. carpal tunnel syndrome (almost always bilateral), spinal canal stenosis or rupture of the biceps tendon [5-6].

The aim of our study was to explore the diagnostic intricacies, therapeutic dilemmas, and emerging solutions in ATTR cardiomyopathy, underscoring the significance of early detection and precise, targeted approaches to enhance patient outcomes.

## Materials and methods

A comprehensive literature search in PubMed and Google Scholar was conducted to identify relevant studies pertaining to ATTR cardiomyopathy. The search was performed using electronic databases including. The following search terms were used: "ATTR cardiomyopathy," "transthyretin," "diagnosis," "amyloidosis," "treatment," "genetic mutations," and "clinical trials" and their equivalents in Polish. The search was limited to articles published in English and Polish. Studies were included if they focused on any aspect of ATTR cardiomyopathy, including its pathophysiology, clinical manifestations, diagnosis, treatment modalities, genetic mutations and recent advances. Both human and animal studies were considered. After excluding 57 abstracts that were duplicated or not directly related to ATTR cardiomyopathy or amyloidosis, a total of 93 reviews, case reports, original research articles and clinical trials were included in this review.

## Results and discussion

### Pathogenesis of myocardial damage

Deposition of TTR occurs most often interstitially (around the myocytes) and leads to restrictive cardiomyopathy (due to increased stiffness and thickness of both chambers of the heart) [4]. If the deposits are more intramural, occupying the interventricular or interatrial septum, they may also cause features of hypertrophic cardiomyopathy, ultimately leading to HFpEF [15]. Due to low wall compliance, relatively higher

incoming blood pressure is needed to fill the ventricles, leading to left ventricular (LV) diastolic failure [21]. During the progression of the disease, stroke volume, compliance and minute volume gradually decrease [6], resulting in increased mortality [22]. Furthermore, there is laboratory evidence that TTR oligomers induce specific cellular abnormalities to the cultured cardiomyocytes leading to reduction in their survival time and may lead to alterations within the electrical function of cardiomyocytes resulting in arrhythmias [23].

Cardiac involvement at diagnosis is usually asymptomatic. The first symptoms of the disease are nonspecific, therefore can contribute to misdiagnosis e.g. exertional dyspnea and atrial fibrillation (with possible embolic complications) lower limb edema and ascites [4-5].

## Atrial fibrillation

The most common persistent arrhythmia in ATTR-CA is atrial fibrillation (AF) [6]. It is more common in ATTRwt (incidence 27-71%) than in ATTRv (5-28%) [24] and is characterized by a higher propensity for thrombosis than in the general population. Up to about 30% of the patients had a cardiac thrombus [25] of which up to 87% were taking anticoagulants, thus marginalizing the role of the CHA2DS2-VASc score in this group of patients [26] and suggesting the use of systemic anticoagulation in all cases of AF in ATTR-CA. Also, patients with preserved sinus rhythm in ATTR-CA have a higher risk of embolization due to impaired left atrial function [4, 27].

No differences in survival have been demonstrated between patients with pharmacologically restored sinus rhythm (amiodarone) and those treated according to the heart rate (HR) control strategy [28]. Sinus rhythm restoration and ablation are more effective when used in the initial phase of the CA [29-30]. Despite the efficacy of cardioversion being comparable to other groups, the rate of AF recurrence after one year in this group of patients is high [31]. Also, recurrences after ablation are common (58% recurrence rate after 39 months) [29].

Regarding HR rate control strategy, cautious use of beta-blockers in persistent AF or non-dihydropyridine calcium channel blockers is recommended at the lowest possible dose and with frequent monitoring of the patient's condition due to the risk of hypotension and potential enhancement of amyloid accumulation [24]. A possible alternative in patients at high risk of hypotension is digoxin [32]. It should be remembered that the use of digoxin and calcium blockers is contraindicated if the LV outflow tract is narrowing in the course of hypertrophic cardiomyopathy.

## Bradyarrhythmias

Amyloid deposition can cause conduction system dysfunction, ranging from atrio-ventricular (A-V) block I° (20%) to III°. Since left bundle branch block and complete heart block are more common in ATTR-CA than in AL-CA [4], pacemakers are routinely implanted in ATTRwt, but it has proven reasonable to implant them also in patients with familial amyloidosis who have a high risk of A-V block: bundle-branch His-ventricular (HV) interval ≥ 70 ms, HV interval > 55 ms (if associated with bundle-branch block), Wenckebach point ≤ 100 beats/min [33]. In patients with particularly high pacing rates, who are at risk of pacing-induced cardiomyopathy [34] (which would worsen HF), cardiac resynchronisation therapy implantation can reduce HF symptoms while increasing left ventricular ejection fraction (LVEF) and survival [35].

## Ventricular tachycardias

Cardiac death in the setting of ATTR-CA is rare [6]. Implantable cardioverter-defibrillator (ICD) implantation should be considered in patients with syncope and complex non-fixed ventricular arrhythmias [36], although many reports do not demonstrate increased survival compared with CA patients without ICDs [24]. The European Society of Cardiology (ESC) recommendations state that there is insufficient evidence for the efficacy of ICD use in the primary prevention of sudden cardiac death in CA [37]. The decision about ICD implantation should be made individually for every patient, particularly in patients with syncope of unknown origin and suspected proarrhythmogenic state [38].

## Valvular diseases

Aortic stenosis often co-occurs with ATTR-CA, particularly in older men, who are at risk for both diseases. The best treatment option is TAVI, which has a lower procedural risk than traditional surgical valve replacement (AVR) [19, 39]. Unfortunately, patients with CA after TAVI have a higher risk of hospitalization for HF [40] and an almost 2 times higher risk of death within 1.7 years compared to patients without additional burden [19].

Mitral and tricuspid valves are typically involved in ATTR-CA, often thickened and remodeled together with the interatrial septum [41], however the valve disease is most often hemodynamically insignificant. In a study of tissues obtained during mitral valve surgery, < 1% showed coexistence of ATTR-CA (more often ATTRwt type) [42]. In studies of small groups, percutaneous surgery was not associated with an increased risk of complications in these patients [43]. Notwithstanding, the importance of corrective interventions for tricuspid regurgitation is controversial, as it appears to be sec-

ondary to RV remodeling rather than resulting from primary valve dysfunction [44].

## Transplantation as a therapeutic option

The majority of plasma TTR is synthesized in the liver, making orthotopic liver transplantation (OLT) a treatment option for TTR amyloidosis to halt the production of variant TTR in the blood. This procedure was reported beneficial for patients with the Val30Met mutation and neuropathy, particularly when qualified for the procedure in well-nourished state, early-stage and early-onset of the disease. However, clinical reports have indicated that cardiomyopathy and neuropathy can still progress in patients with TTR mutations other than Val30Met, as well as in some Val30Met patients following OLT. This information suggests that even after OLT, wild-type TTR produced by the new liver can still accumulate in the heart as amyloid. In cases where a patient undergoes combined heart and liver transplantation, amyloid deposition in the heart graft typically does not occur. However, there have been observations of progression of amyloid deposition in other organ systems following this procedure, making the genetic screening important prognostic tool for identification of higher risk patients with TTRwt mutation [33, 45-46].

## Disease-modifying treatment

The latest treatment strategies for ATTR-CA are based on two mechanisms: spatial stabilization of TTR and silencing of the genes responsible for its production [47]. The group of stabilizing drugs includes Diflunisal, Tafamidis and Acoramidis. The former is a non-steroidal anti-inflammatory drug that binds to the tetraiodothyronine binding site on the TTR tetramer, thereby limiting its abnormal folding into amyloid by slowing its dissociation time. When used at a low dose (250 mg twice daily), it is usually well tolerated and results in slowing the progression of HF in ATTR-CA [48]. Tafamidis is a benzoxazole derivative, used in oral form, that reduces all-cause mortality by 13.4% and the risk of hospitalization for cardiovascular reasons in patients in the New York Heart Association (NYHA) Classification class I or II by 32% at 30-month follow-up. The greatest mortality reduction benefit was demonstrated at 18 months after treatment implementation. Unfortunately, patients in NYHA class III showed an increased risk of hospitalization compared to placebo, while other side effects were not observed [49-50]. In preclinical trials there is also Acoramidis, which resembles in structure the p.T139M variant of TTR, which in patients who are heterozygotes for the p.V50M showed a protective effect and prevented familial amyloid polyneuropathy [51]. It seems that it could be more effective than the above-mentioned drugs, because it binds TTR in a more selective manner, provides stronger stabilization of both the p.V142I TTR variant and TTRwt [52].

Two genetic methods of silencing TTR production are available: antisense oligonucleotides (ASOs) and short interfering RNAs (siRNAs). The ASOs bind to proteins in the serum, on the cell surface and in its interior, where they start a chain of messenger ribonucleic acid (mRNA) degradation by incorporation with the target mRNA in the nucleus and activation of endonucleases [53]. Examples of ASOs include Inotersen and AKCEA-TTR-LRx. The former, which is a first-generation drug administered by weekly subcutaneous injections, stabilizes neuropathy and improves quality of life in ATTRv patients with polyneuropathy, regardless of myocardial involvement. As for the effect on the heart, during the 2-year follow-up an improvement in exercise tolerance in the 6-minute walk test by 20.2 meters and a decrease in mean LV mass in cardiac magnetic resonance (CMR) imaging by 8.4% were observed, and these positive results persisted after another year of follow-up [54]. However, the side effects of this drug require expanded studies, as it has been shown that it can induce glomerulonephritis and severe thrombocytopenia (PLT < 25,000/mL) in up to 6% of subjects [55], while the NEURO-TTR study (NCT01737398) did not confirm these reports and tolerability in the study group was good. AKCEA-TTR-LRx, on the other hand, is a second-generation drug, which in a phase 1 study (NCT03728634) proved more effective in lowering serum TTR levels by 85.7% (51-fold higher efficacy with 27-fold lower drug dose), what's more, it can be administered by monthly subcutaneous injections and so far has not shown serious side effects [56].

The siRNAs are double-stranded oligonucleotides with a sense strand acting as a drug carrier and an antisense strand constituting the active molecule. The antisense strand binds to the target sequence present in all types of ATTR and forms a complex that silences the gene sequence in the process of RNA interference with subsequent degradation of TTR mRNA in the liver and reduction of TTR concentration in plasma [33, 53]. The first generation of siRNAs is Patisiran, which reduces TTR levels in both wild-type and mutant ATTR [57]. Clinical benefits achieved after 18 months of use include reduced NT-proBNP, global longitudinal strain (GLS) and mean LV wall thickness, in addition to a 46% reduction in hospitalization and all-cause mortality compared with the placebo group. Unfortunately Patisiran has not been approved for the treatment ATTR-CA, because it has not yet been shown to influence cardiovascular outcomes in the other studies [58]. The second-generation drug in this group is Vutrisiran, which in the long-term (for 90 days) reduced TTR levels by 83% 6 weeks after use in phase 3 clinical trials (NCT04153149 and NCT03759379) which will be completed in December 2026 [59].

In 2018, the United States Food and Drug Administration approved both Patisiran and Inotersen for the treatment of genetically mediated ATTR polyneuropathy. Initial data from the studies mentioned above, were obtained from patients with ATTR polyneuropathy who also had symptoms of cardiomyopathy, suggest that we may expect equally beneficial treatment effects in patients with ATTR-related heart disease. Consequently, studies of both drugs are ongoing in phase 3 clinical trials in the population of patients with ATTR-related heart disease. Tafamidis is the first and so far the only drug with documented efficacy in a randomized study for treating ATTR-related heart disease. In the 2021 ESC guidelines regarding the diagnosis and treatment of acute and chronic HF, Tafamidis is designated as a Class I medication for ATTR-CA. Inotersen and Patisiran are recommended for consideration in cases of genetically mediated ATTR polyneuropathy [60].

| |
|---|
| 1. Neuropathic pain of unknown origin |
| 2. New diagnosis of hypertrophic cardiomyopathy (or aortic stenosis) with low flow and pressure gradient in an elderly patient |
| 3. Postural hypotension (sometimes combined with erectile dysfunction) due to autonomic neuropathy |
| 4. Hypertensive cardiomyopathy with normal blood pressure and no valve abnormalities |
| 5. Difficulty tolerating β-blockers or ACE -inhibitors |
| 6. Deposits in the vitreous body |
| 7. Enlarged tongue |
| 8. Periorbital purpura |

**Figure 1. "Red flags" suggesting the diagnosis of ATTR-CA**

## Diagnostic problems

Since ATTR-CA manifests late, usually already in the advanced stage of HF, when treatment is no longer effective, much emphasis is placed on diagnostic possibilities in asymptomatic patients from at-risk groups (e.g. carriers of pathogenic variants with incomplete penetrance [6]) or in the early stage of the disease. As described above, some extracardiac manifestations of ATTR can be helpful in guiding towards the appropriate diagnostic pathway for CA, but there are other symptoms that can serve as "red flags" for the diagnosis of ATTR-CA: intolerance to beta-blockers or angiotensin-converting-enzyme inhibitors (ACEIs), low or normal blood pressure in hypertensive patients, a new diagnosis of hypertrophic cardiomyopathy or aortic stenosis with low flow and gradient in an elderly patient [4] (Figure 1). Recent studies have proven both the positive and the negative predictive value of some of the parameters mentioned and proposed the T-AMYLO scale simplifying the diagnostic process of ATTR-CA by identifying high-risk patients requiring further diagnostics and allowing ATTR-CA to be excluded in up to 30% of suspected patients with LV hypertrophy without the need for performing additional imaging tests (Figure 2). This seems to be a step towards non-invasive screening of patients at risk [40]. Known markers of HF, e.g.

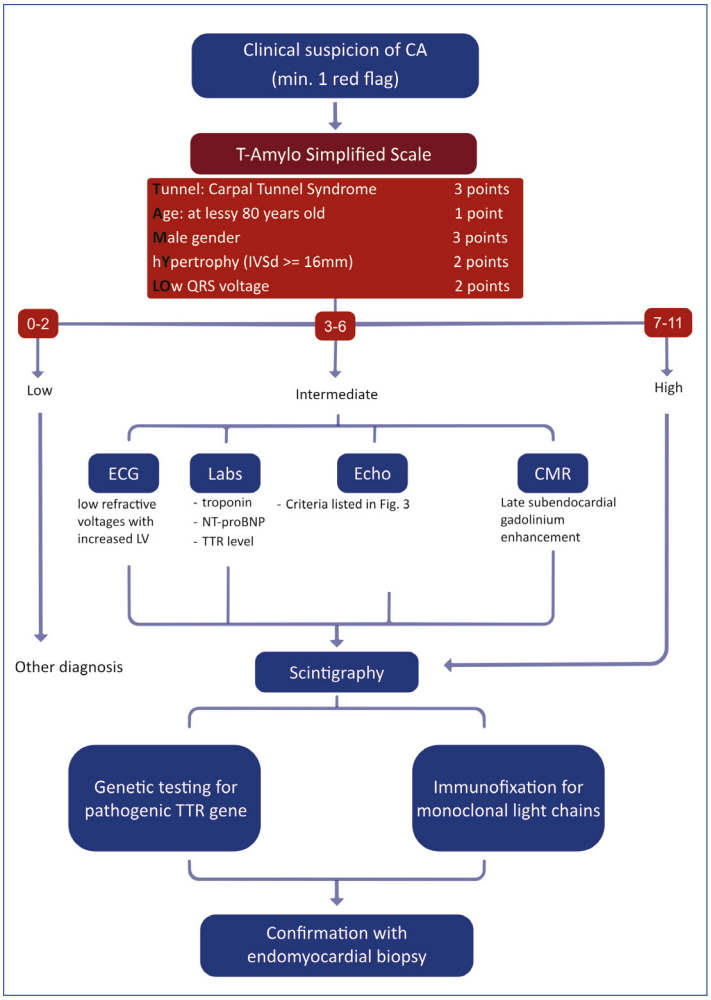


**Figure 2. Simplified ATTR-CA diagnostic algorithm**

| Main criterion: |
|---|
| Ventricular wall thickness ( > 12 mm) with reduced fractional shortening ( < 30%) in the absence of any other plausible causes of LV hypertrophy |
| Additional criteria: |
| 1. Early diastolic dysfunction |
| 2. Low myocardial tissue velocities |
| 3. Atrial enlargement and dysfunction |
| 4. Thickened valves |
| 5. Pericardial effusion |
| 6. Reduced LV systolic thickening and cardiac output with normal or small cavity size or signs of raised filling pressures |
| 7. Right ventricular and interatrial septal thickening |
| 8. Decrease in tricuspid annular plane systolic excursion |
| 9. Decreased tissue Doppler systolic velocity and longitudina strain despite generally maintained normal ejection fraction and radial shortening |

**Figure 3. Echocardiographic parameters of ATTR amyloidosis**

troponins (cTn) or N-terminal prohormone of brain natriuretic peptide, can be helpful for staging assessment and have been included in the new ATTR staging guideline [16], but do not identify asymptomatic carriers of TTRv in whom they tend to remain normal [61].

Adipose tissue biopsy can be used as an adjunct method in the diagnosis of ATTR-CA, but this method is invasive, has limitations related to the diverse localization of amyloid and does not definitively determine the etiology of CA [62].

The electrocardiogram (ECG) has negligible diagnostic [63] and prognostic value [6] in ATTR-CA, although low refractive voltages with increased LV wall thickness may suggest amyloidosis, which is more characteristic of AL-CA [64].

Echocardiography (echo) with Doppler assessment of myocardial strain is currently the leading method for assessing the progression and diagnosis of ATTR-CA even though it is not sufficient to alone diagnose CA [11, 65]. Some authors suggest over-reliance on planar imaging (echo, CMR), particularly in the context of asymptomatic patients in whom cardiac lesions may not be present or detectable [65]. Although no formal system for evaluating echocardiographic parameters in ATTR-CA has been established and lesions do not clearly distinguish ATTR from AL [6], several useful negative prognostic parameters have been identified. Of particular diagnostic importance is typical ventricular wall thickness (> 12mm) with reduced fractional shortening (< 30%) in the absence of any other plausible causes of LV hypertrophy [66] leading to early diastolic dysfunction with low myocardial tissue velocities. Other suggestive features are biatrial enlargement and dysfunction, thickened valves, pericardial effusion, reduced LV systolic thickening and reduced cardiac output with normal or small cavity size or signs of increased filling pressures (Figure 3).

The right ventricle is commonly influenced by both the direct presence of amyloid in its tissue and the increased pressure from pulmonary hypertension, leading to right ventricular and interatrial septal thickening, a decrease in all 3 parameters: TAPSE, tissue Doppler systolic velocity and LS, of which decreased LS is most typical feature of CA in a tissue Doppler imaging. Despite these deviations ejection fraction is generally maintained and there are no variations in radial shortening [65]. In both AL-CA and ATTR-CA, despite preserved LVEF, there is an early reduction of LS in the basal and middle segments of the heart cavity with typical sparing of the apex, which is not present in other causes of increased LV wall thickness [4]. Based on this feature, an equation was developed to distinguish ATTR-CA:

$$\frac{\text{mean LS of the apex}}{\text{(mean LS of the base + LS of the center of the left ventricle)}}$$

a result of 1.0 is the cutoff value for ATTR-CA [67]. To increase specificity, a multi-parameter diagnosic criteria has been proposed that includes, in addition to GLS with typical apical sparing and relative wall thickness, TAPSE and ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/E') assessment [4].

CMR is a useful adjunct method to echo, in which the most diagnostically relevant is late subendocardial gadolinium enhancement (LGE) indicative of amyloid deposits that increase extracellular volume [65, 68]. CMR with LGE has a 93% sensitivity in detecting CA, but does not differentiate AL from ATTR-CA. Myocardial T1 mapping, a pixel-based reconstruction of measured longitudinal relaxation times, supplements the use of LGE in diagnosing CA via CMR. Besides its diagnostic usefulness, it can be utilized for monitoring and tracking myocardial amyloid infiltration and thus disease severity. Unlike LGE, native myocardial T1 (a measure of T1 time before the administration of contrast) offers an objective quantitative measurement rather than a subjective qualitative one. Native T1 demonstrates similar diagnostic performance in both AL and ATTR CA, often showing elevation in the early stages of CA before the onset of biventricular thickening or detectable LGE [69].

In AL-CA, testing for free light chains in serum is a highly sensitive biomarker, however at this time there are no tests based on TTR oligomer blood levels. However, high free light chain concentration might not be specific for AL-CA, particularly in patients over 65 years of age. Monoclonal gammopathy of undetermined significance (MGUS) affects up to 5% of people in this age group, potentially leading to misdiagnosis with ATTR-CA. Also, in chronic kidney disease, increased free

light chains from impaired renal filtration might mask ATTR-CA. Coming back to TTR, its normal range in the serum is 18-45mg/dl and depends on age, sex, ethnicity and nutritional status. It can also vary due to infectious processes and inflammatory states (it correlated with c-reactive protein, sedimentation rate, albumin levels). More importantly, regardless of these factors, lower levels of TTR have been shown to be associated with increased mortality and worsening cardiac function in ATTRwt suggesting that it can be useful as disease progression indicator. In the same study 1- and 2-year follow-up was conducted in which the comparison was made between patients treated and not treated with diflunisal. Unchanged TTR in the not treated group corresponded with increased cTn-I (cardiac troponin I) and decreased LVEF [4, 70-71].

## Differentiation with AL-CA

In the entire initial diagnostic process of CA, it is crucial to consider its most common subtype (70-80%), which is AL. This is particularly important due to the difficulty (or rather the inability) to differentiate it from ATTR-CA in basic imaging studies such as echo or CMR, as mentioned earlier. The misdiagnosis rates between hereditary TTR and AL amyloidosis can reach 7%, with the catastrophic possibility of performing a bone marrow transplant instead of an OLT or vice versa. Furthermore, the course of AL is more aggressive, with a median survival of < 6 months in untreated symptomatic patients, compared to 2-6 years in ATTR-CA [72].

The faster progression of AL amyloidosis may result from the proven cytotoxic effects of human amyloidogenic light-chain oligomers. Accumulation of these oligomers in the cardiac muscle leads to impaired cardiomyocyte contractility through oxidative stress. This has been confirmed in a study comparing AL-CA, ATTRwt-CA and ATTRv-CA, where despite lower amyloid accumulation in the LV wall measured using LGE in AL patients, similar decreases in LS and overall greater impairment of LV function were observed compared to patients with higher LGE in the TTR mutation groups. Early identification of patients with AL amyloidosis is also essential for initiating treatment, which is more readily available and can significantly help a large proportion of patients, unlike in the case of ATTR-CA, where drugs are still in the research phase and the therapeutic path is not as clearly defined [73].

Currently, a diagnostic protocol based on single-photon emission computed tomography (SPECT) with both 99mTc-PYP and 99mTc-DPD is used for non-invasive differentiation of these two diseases. This imaging has a 99% negative predictive value and 86% positive predictive value. The lower specificity was associated with slight tracer uptake in individuals with AL, hence a combination of this method with immunofixation of monoclonal protein in blood or urine was proposed, raising the specificity to 100%. Additionally, a 4-point scale based on visual marker assessment in bone, heart, and soft tissues has been introduced to facilitate the description of the SPECT imaging [74].

Conventional histopathology and amyloid typing are still necessary in cases of uncertainty (e.g., suspicion of MGUS or chronic kidney disease coexisting with ATTR-CA, overlapping characteristic clinical features of both CA subtypes) despite the methods used or their inaccessibility. The highest sensitivity is seen with kidney or liver biopsies (90%). Other less invasive procedures perform worse, for example biopsies of skin (70-80%), abdominal fat tissue (60-80%), rectum (50-70%) or bone marrow (50-60%). The biopsy of abdominal fat tissue is often preferred for screening due to its high availability and ease of procedure when more accurate methods are not accessible. Endomyocardial biopsy, which carries greater risks, is reserved for heart-related angiography or suspected cases of isolated CA. If an endomyocardial biopsy does not reveal the characteristic microscopic pattern, it can help rule out heart involvement in amyloidosis. In that cases TTR amyloidosis is diagnosed by identifying a TTR gene mutation, along with Congo red staining and anti-TTR antibody labeling of an endomyocardial or extracardiac biopsy sample. Whereas, diagnosis of AL amyloidosis involves detecting high levels of monoclonal protein in serum and/or urine, along with Congo red staining and labeling with specific anti-k or anti-l light-chain antibodies on an endomyocardial or extracardiac biopsy. TTRwt amyloidosis is diagnosed when an endomyocardial biopsy shows both red Congo staining and labeling with anti-TTR antibodies, or positive staining on an extracardiac biopsy associated with significant cardiac uptake of technetium 99 bisphosphonate during scintigraphy in the absence of any TTR mutation [75].

## Possibilities of rapid diagnosis of asymptomatic patients

As for the timing of screening, it is recommended to start screening 10 years before the estimated age of onset of symptoms (the estimate takes into account the typical age of onset of ATTR-CA and the age of diagnosis of ATTR-CA in the family) [76]. ATTR-CA is the only form of CA in which the diagnosis can be made non-invasively [8]. At this point, the most sensitive screening test is cardiac scintigraphy (SPECT) with tracers such as 99mTechnetium-pyrophosphate (99mTc-PYP), 99mTechnetium-3,3-diphosphono-1,2-propanodicarboxylic (99mTc-DPD), 99mTechnetium hydroxymethylene diphosphonate (99mTc-HMDP), in which tracer uptake has been observed in asymptomatic patients [77-78]. The method has proven sensitive and has made it possible to distinguish AL-CA from ATTR-CA, as uptake is almost non-existent in the former [39], although it is not completely specific for ATTR-CA [79]. According to the algorithm for non-invasive diagnosis of amyloidosis, the absence of clonal proliferation along with high

99mTc-PYP/DPD/HMDP uptake in SPECT suggests ATTR-CA with high probability, without the need for endomyocardial biopsy [80].

Another imaging study to identify asymptomatic patients is CMR with LGE, which can show characteristic deposits even before the thickening of the ventricular wall. Combining this method with T1-mapping imaging [81] and extracellular volume measurements can identify patients at risk of developing ATTR-CA with 80-93% sensitivity and specificity [82-83].

The role of genetic testing in identifying pre-penetration carriers of TTR variants cannot be overlooked [84]. If detection of the variant itself by mass spectroscopy is not sufficient (or the result is negative), and there is a high clinical suspicion of ATTR-CA, then deoxyribonucleic acid (DNA) sequencing is used. Sometimes the sequence of actions taken before the biopsy can be reversed depending on availability of diagnostic techniques and clinical case [4].

## Uncertainties about conventional treatment

Another challenge is effective treatment to both prevent the development of HF and improve the condition of patients with ATTR-developed heart failure. Little is known about the benefits of conventional HF therapy in patients with ATTR-CA and most recommendations are based on expert opinion. Many reports focus on the increased risk of hypotonia in patients with ATTR-CA due to the reduced ability to maintain stroke volume by increasing the volume and force of ventricular contractility. Therefore, these patients' cardiac output largely dependent on heart rate and caution is advised when administering beta blockers which are indicated only when atrial arrhythmias coexist and at the lowest possible dose [41].

Also, the use of angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor/neprilysin inhibitors and sodium-glucose co-transporter-2 (SGLT2) inhibitors raises concerns about symptomatic hypotension, particularly with autonomic neuropathy co-occurring with ATTR-CA [85-86]. A solution in such cases may be the use of midodrine or droxidopa and compression stockings [87].

Although the use of loop diuretics is the mainstay of maintaining fluid balance in patients with ATTR-CA and their intravenous use reduces hospital and emergency department admissions [88], one should avoid aggressively forcing diuresis, as there is a high risk of organ hypoperfusion and consequent acute kidney injury [85]. The first-line drug is usually furosemide, whereas torasemide or bumetanide is recommended if there is no response. Synergistic aldosterone antagonists or thiazides may be added as a next step [6]. There is an increased need for diuretics as HF progresses and the need for high doses is an unfavorable prognostic factor [89]. Similarly, the use of vasopressors has been associated with a particularly high mortality rate, which may be due to the cardiogenic shock these patients are usually admitted with [90].

Because of the difficulty in establishing adequate fluid balance, the narrow therapeutic window, and the increased risk of hypotony and hypoperfusion in patients with ATTR-CA treated with standard HF medications, a strategy based on remote monitoring might be beneficial in this group [91]. In light of recent reports and recommendations on the treatment of HF [92], it seems important to further investigate the effect of SGLT2-inhibitors on the course of ATTR-CA.

## Future therapies

CRISPR-Cas9 is a genetic engineering method consisting of two components. First, guideRNA recognizes a target sequence in the cell's genome and guides the Cas9 enzyme to it, which activates the "cutting" process. A defective DNA fragment with a pathogenic mutation can be "cut out" or a repair-like process can be induced by homologous recombination based on the provided RNA template. NTLA-2001 is a drug using this mechanism and it caused a > 97% decrease in TTR in mice after a single application over 12 months [93].

Another strategy is to degrade or extract amyloid using specific monoclonal antibodies. PRX-004 is an antibody that binds only to abnormally folded TTR, thus it may improve the macrophagal removal of amyloid accumulated in the myocardium [94]. In a phase I study (NCT03336580), PRX-004 shows efficacy and a good safety profile. A phase II trial (NCT05442047) is currently underway to focus specifically on patients with ATTR-CA, and the results of this trial are to be published by May 2025 [95]. Another antibody in phase I clinical trials with a similar mechanism is NI006, which, after 12 months of us, caused a decrease in radio tracer uptake in cardiac scintigraphy and extracellular volume in CMR [96].

A type of recombinant antibody targeting the plasma amyloid P component (SAP) is Miridesap. SAP is synthesized in the liver and binds to all types of amyloid fibers and administration of Miridesap was associated with a > 90% decrease in serum SAP and activation of complement-dependent phagocytosis of amyloid deposits [97]. It also showed a reduction of the amyloid deposit burden in liver and kidneys over 6 weeks of therapy, but patients with cardiac involvement were not included in the study [98]. A subsequent phase 2 clinical trial failed to show a positive effect on cardiac amyloid deposits with ATTR-CA, and further studies of Miridesap were abandoned [99].

If there is a high load of amyloid deposits, the process of deposition of native TTR in tissues and organs on preformed amyloid fibrils can continue despite its stabilization. In such a case, the protein association inhibitor TabFH2, which binds to the F- and H- ends of beta-strands and blocks the process of TTR deposition, may be helpful [100]. There are also oth-

er inhibitors of TTR aggregation – a study of 19 patients with ATTR-CA taking epigallocatechin gallate (EGCG), a polyphenol that in vitro shows the ability to inhibit the formation of amyloid deposits [101], for 12 months showed a 12.5% decrease in mean LV mass, a 9% increase in mean mitral annular velocity and no disease progression [102]. However, a later retrospective study on a larger group found no effect of EGCG on mortality [103]. Also, curcumin administered chronically to mice with the human TTR p.V50M variant slowed tetrameric dissociation and reduced deposition of amyloid deposits, moreover, it seems to be able to dissolve the deposits [104]. Unfortunately, it is poorly tolerated at high doses, has a short half-life and poor bioavailability [6], hence the need for its pharmacokinetic modification if it were to be applicable to this indication. The available and currently investigated treatment methods are summarized in Figure 4.

## Conclusions

Amyloidosis includes diseases like AL and ATTR, with an increasing diagnosis of ATTR cardiomyopathy (ATTR-CA). ATTR is divided into wild-type (ATTRwt) and variant (ATTRv), with p.V142I being common. Genetic screening is crucial due to higher mortality and severe symptoms in ATTRv. ATTR-CA results in restrictive cardiomyopathy and diastolic heart failure, leading to complications like atrial fibrillation, bradyarrhythmias, and occasionally ventricular tachycardias, necessitating interventions such as pacemakers, anticoagulation, and ICDs. Diagnosing ATTR-CA involves echocardiography, cardiac scintigraphy and CMR with LGE. Differentiating it from AL amyloidosis is challenging, requiring comprehensive diagnostics. Treatments like liver transplantation are beneficial, especially for Val30Met mutation patients. Disease-modifying therapies,

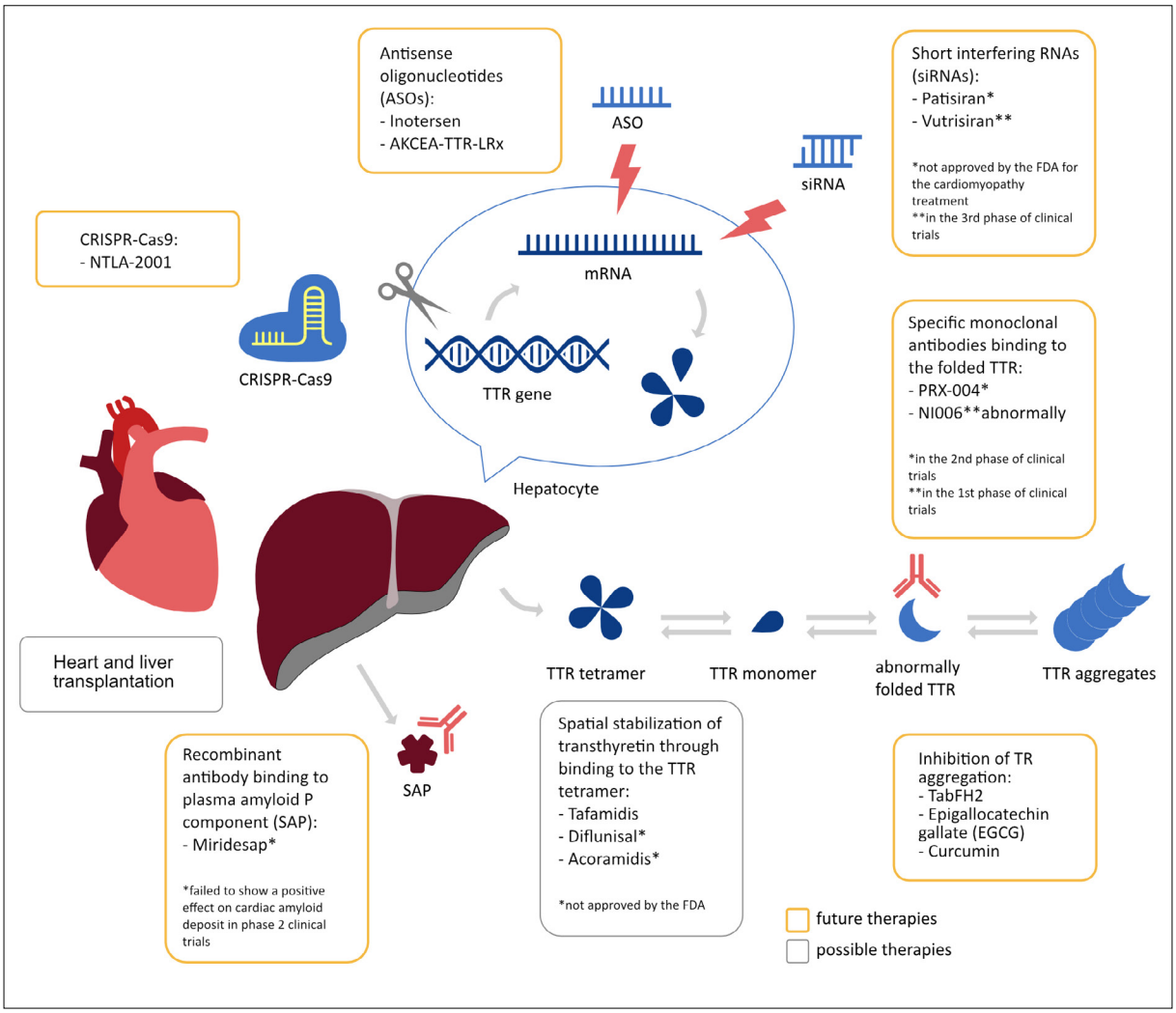


**Figure 4. Summary of ATTR treatment methods and their mechanisms of action**

including Tafamidis, antisense oligonucleotides and siRNAs, show promise. Future treatments explore CRISPR-Cas9, monoclonal antibodies, protein association inhibitors and natural compounds like EGCG and curcumin.

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REVIEW ARTICLE

# Comparison of the use of non-antibiotic drugs with antibiotics in postoperative circumcision wound healing: a systematic review

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## Abstract

Circumcision is one of the most commonly performed operations. It is common to use of antibiotics to prevent complications after circumcision. However, as awareness of antibiotic resistance increases, it is necessary to consider using other prophylactic drugs. This review aims to evaluate non-antibiotic drugs for wound healing after circumcision. We conducted a literature search in accordance with the PRISMA guidelines using Google Scholar, PubMed, and ScienceDirect search engines to find treatment intervention studies comparing circumcision wound healing outcomes and adverse effects after non-antibiotic topical drugs and antibiotics. A total of 2 studies with 636 participants matched our inclusion criteria. 2-octyl cyanoacrylate and nanosilver gel (AgNPs) were used for post-circumcision wound treatment. The group with topical non-antibiotic drugs had a lower healing rate. There was no significant difference between wound healing and significant adverse effects between drug comparisons. Antibiotic resistance tests between intervention and control groups were not included in these studies. Data comparing non-antibiotic drugs and antibiotics for post-circumcision wound healing are still limited. Further studies conducted in various settings are needed to assess the efficacy of non-antibiotic topical agents for post-circumcision wound healing and reducing antibiotic resistance.

**Keywords:** antimicrobial resistance · antibiotic · circumcision · postoperative management · topical agents

## Citation

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## Introduction

Circumcision, one of the most ancient surgical procedures known to humanity, has been performed for a variety of cultural, religious and medical reasons [1]. Circumcision is often performed on male children because of lower risks and costs, less postoperative discomfort and a shorter healing period compared to adults [1]. In the uncircumcised condition, the prepuce (commonly referred to as foreskin) is a warm and moist environment where pathogens can potentially survive and reproduce [1]. The foreskin can be subject to micro abrasion, which increases the risk of acquisition and transmission of pathogens [1]. Although circumcision can reduce the risk of infection in children, in adults this procedure can have an impact on sexual function and lead to male body dysmorphia [2]. More studies are needed regarding the benefits of circumcision in various background conditions [2].

Possible complications following circumcision include bleeding, infection, excessive skin removal, recurring phimosis, epithelial inclusion cysts, penile adhesions and meatal stenosis [3]. Some complication such as bleeding, ring device removal and infection are more common in non-therapeutic circumcision, while meatal stenosis and adhesion are common in therapeutic circumcision [4]. Effective approaches to reduce the risk of complications include strict asepsis during surgery, avoiding the risk of contact with non-communicable diseases, pre-operative and post-operative therapy after circumcision and providing a sterile and hygienic environment [3]. Circumcision is considered a clean surgical procedure with a low risk of wound infection, but in some parts of the world antibiotics are prescribed as prophylaxis despite the additional costs and lack of guidelines [5]. It is noteworthy that antibiotics are indicated for patients with urological abnormalities such as vesicoureteric reflux (VUR), who are undergoing circumcision [6].

While the surgical aspects of circumcision are well-documented and standardized, the post-operative care and the use of topical treatments for wound healing and prevent complications continue to be areas of ongoing research and clinical interest [4]. In recent years, there has been an increasing focus on the use of creams in post-circumcision care [7]. Nevertheless, there is a lack of specific data regarding the avoidance of topical antimicrobials after this procedure. Improper use of antibiotics can contribute to antibiotic resistance, therefore the use of non-antibiotic products has been explored [8]. This systematic review aims to thoroughly examine the existing body of literature to assess the effectiveness and safety of medication options for post-circumcision treatment, with a particular focus on both antibiotic and non-antibiotic creams. Through a critical analysis of available evidence, our goal is to offer insights for healthcare providers, patients and researchers.

## Material and methods

We conducted a literature search using the PubMed, Google Scholar and ScienceDirect databases between September 2023 and October 2023, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline [9]. We used the following keywords: “ointment”, “wound healing,” “after circumcision”, “comparative studies” and “post circumcision”. Combine keywords using “AND” and “OR” to expand or narrow the search. The literature search was based on the following PICO framework: Patient (elective circumcision patients), Intervention (ointments other than antibiotics), Comparison (with antibiotic ointments) and Outcome (the wound healing outcomes reported in the particular study).

The inclusion criteria applied in this search were: intervention studies (randomized and non-randomized), full-text articles written in English language, published within the last 10 years, elective circumcision regardless of surgical method, a comparison of topical treatment for circumcision wounds and reporting relevant clinical outcomes (e.g. wound infection rates, wound closure time, wound complications and patient-reported outcomes). Conversely, the exclusion criteria were: review articles, systematic reviews, meta-analyses, lack of full-text articles, non-intervention studies, duplicate publications or overlapping data from the same study population and any other publications not in English, animal studies, lacking clear comparison between topical non-antibiotic drugs and antibiotics, treatment with oral antibiotics and insufficient data on wound healing outcomes.

We extracted the following data from the articles: study type, year of publish, study location, language, sample size, follow-up period, patients (sex, number, mean of age, inclusion-exclusion criteria, comorbidities), intervention (length of study, type of intervention and control, route of administration and dosage), comparison (antibiotic versus non-antibiotic drug) and outcome (time to recovery, quality of recovery, infection rate, closure time and patient-reported outcomes and adverse outcomes). After all data were extracted, we assessed the risk of bias of the study using Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB-2) [10]. When there were differing results, two authors discuss the study together.

## Results

In the literature search we identified a total of 319 studies. Out of these, 314 studies were excluded due to various reasons, e.g. the unavailability of full-text articles, study type (reviews, systematic reviews, meta-analyses, case studies). Most of the studies retrieved were focused on human sub-

jects and discussed the effects observed after the intervention. Following a comprehensive review, we found two studies that met the inclusion criteria (Figure 1).

Of the 2 studies that were included, Alemayehu et al. compared 2-octyl cyanoacrylate in the United States [11] and Balzarro et al. compared nanosilver gel (AgNPs) in Italy [12]. Total 636 participants were included in the 2 studies. When examining the timeframe required for wound healing, no significant difference between control and intervention groups was reported. Characteristics and outcomes of each study are presented in Table 1.

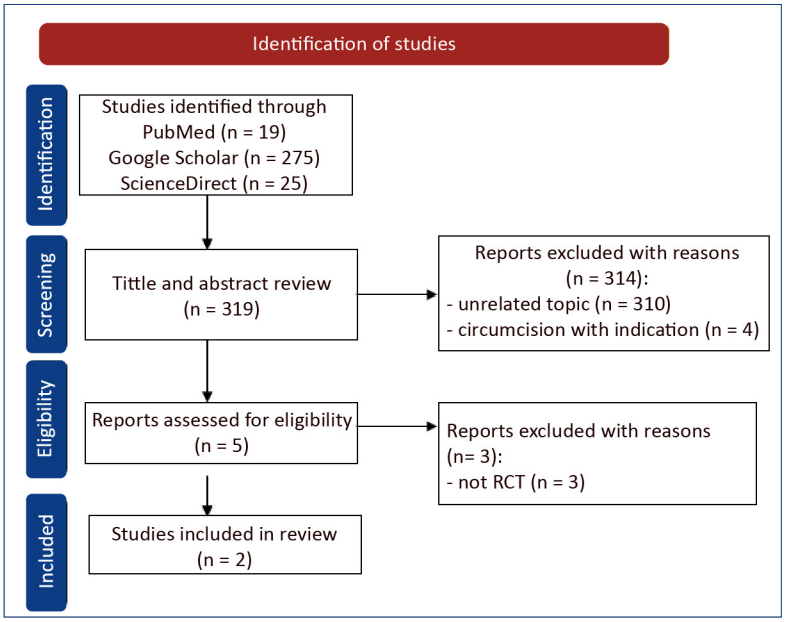


**Figure 1. PRISMA flowchart of our systematic review**

## Adverse effects

Alemayehu et al. reported that the number of adverse effects using the 2-octyl cyanoacrylate group was greater than that of the antibiotic group (bacitracin), including the incidence of respiratory distress. Meanwhile, Balzarro et al., reported adverse effects in the antibiotic group (gentamicin) in the form of reactions to deep or severe wound infections with or without tissue damage accompanied by hematomas that required aspiration (Southampton Scoring System (SSS) Grade V).

## Risk of Bias

The results of the risk of bias assessment based on the RoB-2 tool are shown in Figures 2A and 2B. In study conducted by Balzarro et al., "high" concerns are related to the lack of randomization process and the measurement of outcomes. In the study by Alemayehu et al., "some" concerns are caused by the bias in reported results due to the loss of some of

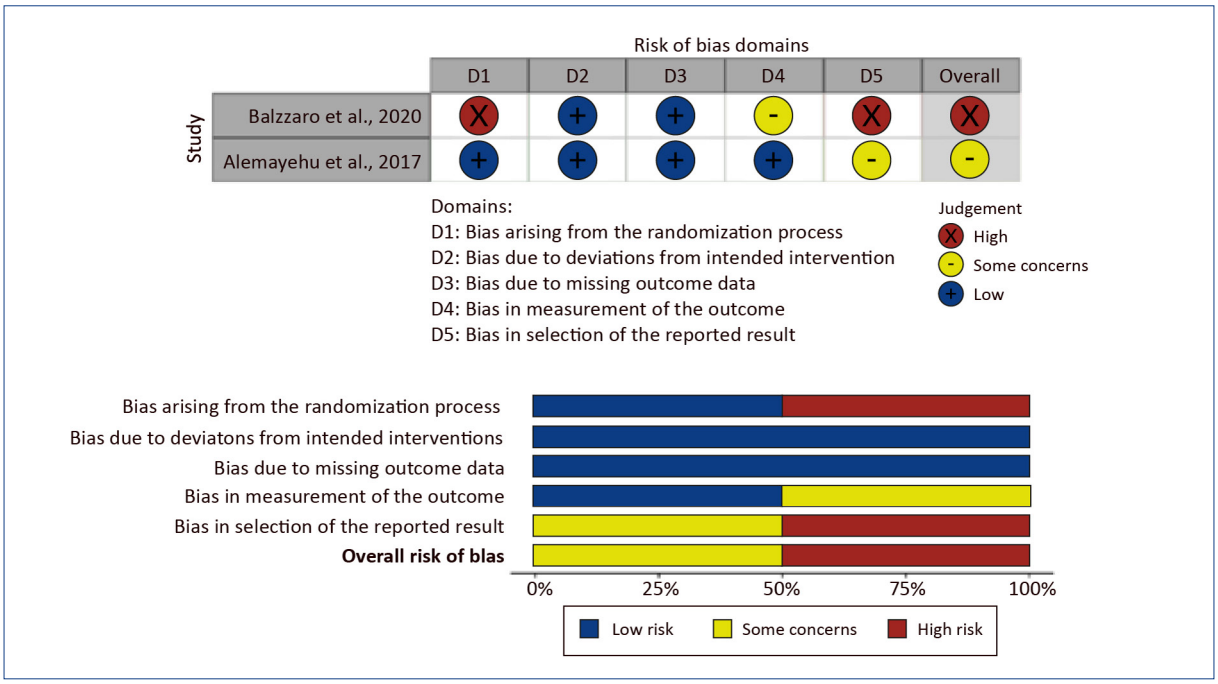


**Figure 2. Domain of risk of bias assessment (A) and the overall result of risk of bias (B)**

**Table 1. Summary of included studies**

| Author | Alemayehu et al. [11] | Balzarro et al. [12] |
|---|---|---|
| Study design | Prospective, randomized trial | Multicenter, non-randomized study |
| Number of sample | 244 patients (125 in the GLUE arm and 119 in the NO GLUE arm) | 392 patients (194 in intervention group, and 198 in control group) |
| Treatments | 2-octyl cyanoacrylate (GLUE group) with the skin adhesive | A hydrogel cream containing AgNPs, titanium dioxide, hyaluronic acid, and aloe vera |
| Antibiotic comparison | Bacitracin ointment | Gentamicin cream |
| Endpoint | The number of adhesions in the GLUE group was greater than controls (16.8 vs 15.1%) | In 10-days early follow-up post circumcision, the AgNPs group showed a slower healing rate. At the 30-day follow-up, the difference normal healing between the two groups was not significant |
| Statistics | p = 0.86 | 49.5% vs 58% (p = 0.45) in 10-days follow-up and and 97.4% vs 98.4% (p = 0.45) in 30-days follow-up |
| Adverse outcome | Intervention group: 13 cases (bleeding, infection, wound dehiscence, fever, and respiratory distress) \| Bacitracin group: 10 cases. | In antibiotic group, there were 7.6% patients (15/198) with pus discharge (SSS grade IV) |
| Conclusion | 2-octyl cyanoacrylate skin does not decrease the rate of penile adhesions after circumcision | AgNPs led to a late but safer healing, they were non-inferior to the antibiotic cream wound dressing efficacy |

patients are loss to follow-up. The concerns reported in each of these studies are related to the outcomes reported in the existing studies.

## Discussion

Circumcision is generally a sterile surgical procedure, but topical antimicrobial agents may be indicated in some situations [13]. Increasing awareness of antimicrobial resistance resulting from decades of antibiotic overuse has made therapeutic options increasingly limited [14]. However, patients with poor hygiene and vulnerable socioeconomic conditions, antibiotics are still prescribed antibiotics as prophylaxis after surgical procedures with open wounds or with a high risk of exposure to infection [15]. In addition, antibiotics are an easy-to-use and affordable prophylactic treatment for infections [16]. Therefore, alternative antimicrobial options need to be developed to reduce antibiotic use and antibiotic resistance.

Alemayehu et al. found that 2-octyl cyanoacrylate glue did not decrease the rate of recurrent penile adhesions after circumcision. This agent is composed of cyanoacetate and formaldehyde which can polymerize from exposed skin tissue and has the ability to bind strongly with water, blood and body tissues [17]. The development of 2-octyl cyanoacrylate makes it more bio-tolerant and induces less inflammation [17]. 2-octyl cyanoacrylate has been widely used in plastic surgery because it produces minimal wounds with a healing rate that is not much different from suturing [18]. This condition may be due to inadequate retraction of the foreskin after the glue sloughed off. However, most patients with adhesions were able to be treated with manual retractions. The use of 2-octyl cyanoacrylate is also reported to have minimal adverse effects compared to circumcision with suturing [19]. Therefore, the use of 2-octyl cyanoacrylate can be a better and safer choice than suturing for wound closure after surgery.

There was no significant difference between the adverse effects of using 2-octyl cyanoacrylate and bacitracin. Bacitracin works by targeting peptidoglycan inhibition and bacterial cell wall formation, thereby preventing bacterial adhesion on the surface [20]. Bacitracin is more effective against gram-positive bacteria, whereas the majority of infections in the pubic area are caused by gram-negative bacteria [21-22]. However, in vitro studies by Lemnaru (Popa) et al. also demonstrated the efficacy of bacitracin against gram-negative bacteria such as *Escherichia coli* [20]. 2-octyl cyanoacrylate has antimicrobial properties by forming an effective barrier against gram-positive and gram-negative bacteria [23]. Although the Park et al.

(2021) study reported the risk of allergic contact dermatitis due to 2-octyl cyanoacrylate, such risk level tends to be low [24]. Due to few adverse effects and outcomes that are not significantly different, 2-octyl cyanoacrylate can be an alternative to antibiotics for circumcision wounds

A study by Balzarro et al. found that AgNPs gel was effective in healing circumcision wounds, but that healing time was longer compared to gentamicin cream. Adibhesami et al. reported that administering gentamicin combined with AgNPs can accelerate the wound healing rate compared to AgNPs alone in an animal model [25]. Gentamicin is one of the most commonly used antibiotics for post-surgical wounds because it is effective against gram-positive and gram-negative bacteria, particularly in high infection-risk locations e.g. colorectal and perineal [26]. Also, gentamicin interacts with skin keratinocytes by increasing laminin α3 and β3 expression [27]. Although it is known that AgNPs can heal wounds by inhibiting the expression of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), tumor growth factor-β1 (TGFβ1) and IL-6, while the expression of anti-inflammatory cytokines such as IL-10, vascular endothelial growth factor (VEGF) and interferon-λ (IFN-λ) increases, thereby influencing inflammatory cytokines and proliferation of keratinocytes [25].

Existing literature demonstrates that silver nanoparticle (AgNPs) gel is an effective and safe alternative to antibiotic cream for wound healing after circumcision. While AgNPs gel may lead to a longer healing process, it is less likely to cause side effects compared to antibiotics. Components of antibiotics that interact mediated by the immune system can index hypersensitivity reactions that cause various symptoms such as angioedema, urticaria, or in more severe cases such as acute tubular necrosis [28]. Although AgNPs also have a risk of allergies, several approaches include modifying particle size, surface functionalization and preparing AgNPs components that have lower inflammatory effects to reduce the negative impact on cells [29]. In this study, the wound healing rate in the AgNPs group was lower, although Balzarro et al. also reported that the antibiotic group caused adverse effects. The healing rate in each group was also not significantly different. However, this difference in healing ability needs to be investigated further regarding their interaction at the cellular level so that AgNPs can be a safer alternative to antibiotics.

The prevalence of antibiotic use is decreasing along with increasing awareness of antibiotic resistance. Several programs have shown positive outcomes in reducing the over prescription of antibiotics [30]. Inappropriate use of antibiotics is most frequent in cases of upper respiratory tract infections (sore throat and cough), otitis media and sinusitis [31]. The prescription of antibiotics to patients undergoing obstetric and gynecological, gastrointestinal, and orthopedic surgery is reported to be far below the guidelines for antibiotic use [32]. Several studies show that continuation of postoperative antibiotics does not provide more benefits if compliance with antibiotic use was good according to the recommendations [33]. However, the prescription of antibiotics as prophylaxis still occurs, especially in outpatients [34]. Therefore, it is necessary to develop appropriate strategies for the prescribing antibiotics in various clinical situations, including circumcision. In our investigation, we encountered a lack of data regarding antibiotic resistance in postoperative circumcision cases. However, there were instances, such as those involving atopic dermatitis patients treated with bacitracin, where high levels of resistance were observed [35]. Additionally, there were 3 documented occurrences of gentamicin-resistant infections among patients undergoing peritoneal dialysis during each respective study period [36].

Our study has several limitations. The sample size we analyzed is limited due to the design and study centers we included, so studies with similar aims in broader and more diverse populations are needed. Our literature search strategy led us to exclude similar studies published in other languages. In addition, both of the analyzed studies were conducted in developed countries (USA and Italy) where hygiene conditions are different than in low- and middle-income countries. More data are needed before non-antibiotic treatment alternatives can be accepted in clinical settings to reduce the level of antimicrobial resistance. Neither of the studies provided data about bacterial resistance, thus highlighting the potential for future research to explore the implications of non-antibiotic drug utilization on resistance risk among circumcision and other postoperative patients. Furthermore, non-antibiotic ointments are typically more expensive compared to antibiotics, thus prompting questions about their cost-effectiveness.

## Conclusions

The use of non-antibiotic drugs as a substitute for antibiotics for post-circumcision wound healing is still limited. Non-antibiotic agents have a more fewer adverse effects with no significant differences in healing rates. The included studies are limited to small sample size and high-income country settings that have good hygiene infrastructure. Larger studies are needed to determine the healing effectiveness and safety of non-antibiotic drugs as an alternative to antibiotic treatment after circumcision.

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## Conflict of interest

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REVIEW ARTICLE

# Gamma knife radiosurgery in psychiatry: a review

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## Abstract

Gamma knife radiosurgery (GKRS) is a minimally invasive technique frequently employed in neurosurgery or oncology, and it has applications in psychiatric patients as well. While it is commonly used in conditions like obsessive-compulsive disorder, GKRS also has efficacy in treating major depression disorder, generalized anxiety disorder, autism spectrum disorder and anorexia nervosa. Promising outcomes have been observed, particularly in cases resistant to conventional treatment, leading to significant improvements in the patients' quality of life. Severe adverse effects from GKRS procedures are rare. To enhance our understanding of the utilization of GKRS in psychiatry, further extensive research, especially through double-blinded studies involving larger cohorts, is imperative. Determining the ideal volume and radiation dose for radiosurgical capsulotomy remains a key topic of research. When it comes to psychiatric neurosurgical procedures, the decision-making process should be personalized for each patient, taking all relevant factors into consideration.

**Keywords:** psychiatry · radiosurgery · gamma knife · neurosurgery

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## Introduction

The incidence of mental disorders in the present century is increasing and the effectiveness of treatment of mental disorders is a significant clinical problem, as the therapy mechanisms are not fully discovered [1-2]. A wider knowledge of the neurophysiology and the influence of stereotactic procedures on neural tissue, coupled with advances in modern neuroimaging, has resulted in increased interest in radiosurgery [3]. Stereotactic radiosurgery (SRS) was created in the mid-20$^{th}$ century and involves the administration of a high dose of single ionizing radiation through the intact skull into a critically located small intracranial target [4]. Radiosurgery has been developed over decades by clinicians, physicists and engineers [5]. SRS involves exposing the intracranial target to focused radiation beams from many angles using the exact correlation of the virtual target visible on radiological images. The gamma knife (GK) procedure is a stereotactic method based on frames with Cobalt-60 sources. It combines high precision of convergence of numerous gamma rays emitted by multiple sources of Cobalt-60 with image guidance [4]. The final effective dose rate is predictable because the activity of each Cobalt-60 source at the time of manufacture and its deterioration over time are well-estabilished [6]. GK radiosurgery (GKRS) has clinical application including both benign and malignant tumors of the brain and skull base, functional and psychiatric disorders and vascular malformations [1, 7]. The radiological diagnosis is vital before starting treatment with GKRS [4].

Lars Leksell invented the GK and first used it clinically in 1967 to treat a patient with craniopharyngioma in 1967 [5]. The first use of GKRS in psychiatry was also described by Leksell in 1985: he treated a 29 years old male with resistant obsessive-compulsive disorder. Researchers used a maximum radiation dose of 100-120 Gy and the results after one month were unsatisfactory [8]. Currently, GKRS is being explored as a potential treatment method, for the severe and treatment-resistant cases of obsessive compulsive disorder (OCD), major depression disorder, generalized anxiety disorder (GAD) and autism spectrum disorder (ASD). The main GKRS procedures performed in psychiatry are anterior capsulotomy (making small changes to the anterior cingulate gyrus and the anterior limb of the internal capsule), subcaudate tractomy (disrupting the continuous white matter fibers found in the corpus callosum) and cingulotomy [1-2]. Main aim of such psychosurgery is improvement of the patient's quality of life, reducing compulsions, obsessions, anxiety and depression by delivering precise and targeted radiation to specific brain areas [1]. Severe complications in SRS procedures are rare [9]. While research is ongoing and its long-term effects are still being studied, this innovative approach underscores the evolving intersection between technology and psychiatric care.

The aim of this study was to summarize current knowledge regarding the use of GKRS in patients with psychiatric indications.

## Material and methods

To conduct this review, we searched the PubMed and Google Scholar databases for articles related to application of GK use in psychiatry. We used key words such as 'gamma knife psychiatry', 'radiosurgery psychiatry', 'gamma knife OCD', 'gamma ventral capsulotomy'. Our focus was on articles published in between 2017 and 2023, including their references, as we wanted to focus on most recent publicatons. We assessed the papers by titles, abstracts and full texts, with the main inclusion criteria being that they addressed the use of GKRS in psychiatry. Among 83 papers from databases, after removing duplicates, 35 articles were identified, including review articles, case series and case reports from the field of neurosurgery and psychiatry. After evaluation, 14 papers were included to the paper, as they were raising the problem of the use of GK surgery in psychiatric disorders, while 16 publications were excluded. The most important criteria of exclusion was if the paper is describing radiosurgery methods with GK device implementation, as majority of the works described other methods of radiosurgery. Accepted papers were divided into two groups: 10 articles about GK use in the treatment of OCD and 4 articles describing 5 studies about its use in other psychiatric conditions.

## Results

Despite the fact that GK surgery in psychiatry is most commonly used in treatment of OCD, we found reports about the implementation of this method in the treatment of generalized anxiety disorder (GAD), autism spectrum disorder (ASD) and major depressive disorder (MDD). Studies show that GKRS is in most cases implemented in long-lasting conditions resistant for pharmacological treatment [10]. For clarity, all the introductory information about the particular psychiatric conditions is presented here in the Results section, together with the outcomes of using GKRS in their treatment.

### Obsessive-compulsive disorder

Obsessive-compulsive disorder (OCD) is based on recurring, unwanted thoughts (obsessions) or reiterative actions (compulsions) designed to reduce or prevent fear and anxiety [11-12]. It is estimated that this disorder affects between 1% and 3% of the population worldwide, with symptoms of varying severity. Drug treatment and the use of behavio-

ral therapy is ineffective in 3-5% of patients with OCD [13]. Drug resistance may be caused by both environmental factors and personality disorders. Other treatment methods include deep-brain stimulation, neurosurgical ablation or transcranial magnetic stimulation [14-16]. It is important to remember that OCD varies in severity and drug resistance can have different easons, e.g. psychiatric psychiatric comorbidity or environmental factors [13]. In such cases, radiosurgical methods can be used, including the use of GK and its anterior capsulotomy (GVC) approach, but it is important to remember that this method is still experimental and may need further research or ethics comittees approval in some countries. This procedure involves creating tiny lesions in the ventral part of the anterior limbic internal capsule (ALIC), whose fibers transmit information from the prefrontal cortex to the structures of the basal ganglia structures [12-13, 17-20]. GVC outcomes can be measured using the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). It consists of two parts – for obsessive thoughts and for compulsive behavior. The minimum score that can be obtained is zero, while the maximum score is 40. It is possible to interpret the Y-BOCS score as follows: 1) < 8 (subclinical symptoms), 2) > 16 (clinically significant symptoms), 3) ≥ to 24 (moderately severe OCD) [17-18]. Patients are considered responsive to GVC if there is a ≥ 35% reduction Y-BOCS scores after treatment [17, 19].

Due to the large number of reports on the implementation of GK in the management of refractory OCD, selected cases described in ten papers are briefly described in Table 1 [11-13, 17, 19, 21-25].

A randomized study by Lopes et al. included 16 patients with resistant OCD, who were randomly divided into active and sham group, both containing 8 patients [19]. After 1 year, the median Y-BOCS score was 23.5 in the active group and 31 in the sham group. At month 12, the two groups were not statistically different in terms of anxiety (assessed using the Beck Anxiety Inventory, BAI) and depression (via the Beck Depression Inventory (BDI)). At month 24 after GVC three additional patients responded [19].

The paper by Rasmussen et al. presents the results of a follow-up study in patients with refractory OCD after GVC using the Leksell Gamma Knife [13]. The subjects were divided into two groups, which consisted of 15 and 40 patients. Patients in the first group were subjected to repeated single shots. The target site of the second stage (also a repeated single shot) was set directly ventral to the first stage shot. The second group of subjects received two shots bilaterally. Thirty-one patients (56%) improved by more than 35% over the 3-year follow-up period using the Y-BOCS scale [13]. The study used the Sickness Impact Profile to compare baseline and follow-up measures of functional status and quality of life. After three years, improvements were noted in emotional behavior and social interactions in the group that received repeated single injections. Nonetheless, there were improvements observed in the second group in terms of emotional behavior, recreational activities, sleep and rest, home management, mobility, and work. At 6 months, the group, which included 15 patients, showed no significant improvement in the Y-BOCS, Clinical Global Impression Scale (CGI-I), or Global Assessment of Functioning (GAF) scales. The group that received the double injection showed improvement in OCD symptoms (based on the Y-BOCS), depressive symptoms (based on the Hamilton Depression Scale) and anxiety (based on the Hamilton Anxiety Scale) [13].

A study by Bouvens van der Vlis et al. analyzed magnetic resonance (MR) images of 8 OCD patients with at least 3 years of follow-up after GVC surgery [11]. The strongest correlation with a reduction in symptom severity was found for a reduction in left ventral diencephalon volume. The largest decrease in Y-BOCS scores was observed between 6 months and 1 year, of -7.1 ± 5.6. The mean total reduction in Y-BOCS was 19.6 after 3 years of follow-up, with equal reductions for obsessions and compulsions [11].

A retrospective study by Pattankar et al. included patients with refractory OCD [11]. The following psychiatric comorbidities were present in the study group: generalized anxiety disorder (55.6%), depression (44.4%), and the occurrence of self-destructive ideations was confirmed by 33.3% of the patients. The mean Y-BOCS score at the last follow-up was 23.8 ± 7.7. Four patients showed a complete or fractional response (≥ 25% reduction in Y-BOCS score) at last follow-up. For GVC, 4 out of 5 patients with moderate or severe OCD presented favourable outcomes, while all of the three patients with extreme cases of OCD remained nonresponders (< 25% reduction in Y-BOCS score) [12]. One patient after cingulotomy remained resistant to treatment (< 25% reduction in Y-BOCS score) [12].

The study described by Spatola et al. involved patients whose previous treatment had been unsuccessful. Comorbidities in this group included bipolar disorder, depression, generalized anxiety disorder, personality disorder and tics. Before radiosurgery using GKRS, the mean Y-BOCS score was 32.7 ± 4.8 (17.3 ± 1 for obsession score; 16.3 ± 3.6 for compulsion score). Seven patients presented positive effects of GVC and two were classified as non-responders. The mean score of Y-BOCS was 14.7 ± 8.8 [23]. It is noteworthy that bipolar disease as a comorbidity is an important limitation.

A retrospective study by Ertek et al. (2021) included patients who underwent radiosurgery with Elekta Gamma-Knife between 2005 and 2020 [24]. GVC was performed on both sides, with a maximum radiation dose varying from 140 to 180 Gy. The mean Y-BOCS score decreased from 32.3 to 20.5 at 6 months after surgery. Half of the patients met the criteria for achieving a full response, which is typically defined in the

**Table 1. Summary of selected studies regarding GVC in OCD treatment**

| Study | Participants | Average age of patients, in years | Treatment | Observation period, in months | Effects |
|---|---|---|---|---|---|
| **Rasmussen et al. (2018) [13]** | 55 (22 F; 35 M) | 33.6 ± 10.5 | GVC | 36 | reduction in Y-BOCS score by ≥ 35% in 56% of patients<br>reduction in OCD symptoms (56% of patients)<br>reducing symptoms of co-occurring depression and anxiety |
| **Bouvens van der Vlis et al. (2022) [11]** | 8 | 35 ± 7.5 | GVC | 36 | reduction in Y-BOCS scores of 19.6 points on average (by 51%)<br>response rate 63% |
| **Pattankar et al. (2022) [12]** | 9 (1 F, 8 M) | 30.1 ± 9.4 | GVC (8 patients)<br>Cingulotomy (1 patient) | 3-192 | 55.6% of respondents report an improvement in overall functioning |
| **Spatola et al. (2018) [23]** | 10 (5 F, 5M) | 41.2 ± 10.7 | GVC | 6-116 | reduction in Y-BOCS scores of 53% on average<br>reduction of symptoms of depression and anxiety |
| **Ertek et al. (2021) [24]** | 12 (7 F, 5 M) | 30.75 ± 4.92 | GVC | 6 | reduction in Y-BOCS scores by an average of 11.8 points |
| **Lopes et al. (2014) [19]** | 16 (ST: 3 F, 5 M, AT: 3 F, 5 M) | ST: 34.1 ± 10.1<br>AT: 32.1 ± 10.6 | GVC | 54.5-56.5 | reduction in Y-BOCS score by 28.6% in the active treatment group |
| **Peker et al. (2020) [25]** | 21 | 32.8 ± 7.61 | GVC | 38-149 | reduction in Y-BOCS scores by an average of 20.4 points, reduction in symptoms of co-occurring depression |
| **Gupta et al. (2019) [17]** | 40 (16 F, 24 M) | 42.5 ± 13.3 | GVC | 9-36 | reduction in the Y-BOCS score down to ≤ 16 in 40% of patients, reduced symptoms of anxiety, improved general functioning |
| **Rück et al. (2008) [22]** | 25 (14 F, 11 M) | 41 ± 11 | GVC | avg. 131 | reduction in the average Y-BOCS score from 34 (before surgery) to 18 (after surgery) |
| **Batistuzzo et al. (2015) [21]** | 17 | 34.4 ± 10.6 | GVC | 12 | reduction in the average Y-BOCS score from 32.9 (before surgery) to 21.4 (after surgery) |

AT – active treatment, F – female, GVC – gamma ventral capsulotomy, M – male, OCD – obsessive-compulsive disorder, ST – sham treatment, Y-BOCS – Yale-Brown Obsessive-Compulsive Scale

literature as an improvement of more than 35% in the Y-BOCS score [24].

A single-centre retrospective study performed by Peker et al. included patients with OCD unresponsive to current treatment [25]. A bilateral single shot or a bilateral double shot technique was used. The radiation was between 140 and 150 Gy. Fifteen patients (75%) achieved a complete positive reaction and five were described as non-responders. The final status of one of the patients is not known because he was not followed up after 6 months. The mean pre-GVC Beck Depression Inventory-II scale score of 35.1 reduced to 13.8 after 36 months of follow-up [25].

An international, multicentre, retrospective cohort study was performed by Gupta et al. A group of patients with Y-BOCS scores ≥ 24 (for this group: 35 ± 3.6) underwent GVC using 1 or 2 isocentres with a dose between 120 and 180 Gy [17]. The range of Y-BOCS test values after GVC was 27.5 ± 10.8. According to the authors, eighteen patients (45%) were considered responsive to the applied treatment and 16 (40%) of them were in remission at the last post-event check. Nineteen patients (47.5%) remained stable with Y-BOCS in the range of 26-36 after GVC and three patients (7.5%) had worse Y-BOCS scores [17].

Brief description of GK radiosurgery outcomes in patients suffering from diseases other than OCD is presented in Table 2 [8, 26-29].

## Generalized anxiety disorder

Generalized anxiety disorder (GAD) is a mental condition typically presenting with persevering and uncontrollable fear about various aspects of life. Patients suffering from GAD experience worry or fear to an extreme and it significantly limits their daily functioning and overall mental state [30]. According to Mindus et al., the results of GKRS in GAD were not satisfactory and unfortunately were not specified [30]. The primary point made by Mindus et al. is that magnetic resonance imaging could assist in establishing a radiation threshold that

**Table 2. Brief summary of selected cases of GKRS in psychiatric disorders other than OCD**

| Study | Patient's details (number, age, sex) | Disease details | Treatment | Follow-up period in months | Effects | Comments |
|---|---|---|---|---|---|---|
| **Mindus et al. (1987) [28]** | 5 F (37-47 years); 2 M (25 and 40 years) | GAD | Bilateral anterior capsulotomy; maximum dose of radiation 102-160 Gy | 72-96 | satisfactory (3 patients); fair (2 patients); very unsatisfactory (2 patients) | 5-25 years-long history of GAD |
| **del Valle Ramiro et al. (2006) [29]** | 3 F \|(13-52 years); 6 M (14-49 years) | GAD, Heteroagression (in one case in comorbidity with OCD) | Anterior capsulotomy / limbic leucotomy / subcaudate tractotomy | 12-36 | fair to good results 0 | |
| **Torres et al. (2021) [26]** | 10 M, mean age of 25 years, | < 0.001 | Capsulotomy / amygdalotomy / cingulotomy / lesions of stria terminalis; maximum dose of radiation 120 Gy | < 24 | improvement of symptoms, increased activity of patients | |
| **Park et al. (2017) [27]** | F, 49 years | MDD | Subcaudate tractotomy maximum dose of radiation 130 Gy | 4 | improvement of patient's condition, limited symptoms of depression, discontinuation of medication intake. | 30 years-long history of depression |

GAD – generalized anxiety disorder, F – female, M – male, MDD – major depressive disorder, OCD – obsessive-compulsive disorder

is effective for clinical purposes in radiosurgery. This information would be valuable for designing future studies related to GK capsulotomy. More recently, del Valle Ramiro et al. also evaluated patients with GAD [29]. Reseachers focused on different mental conditions, including GAD, OCD and schizophrenia, but their work faced criticism, as indications was unclear and controversial, with no evauation based on clinical scales presented, technique was not described and there were no follow-up reports stated, what should be considered as an important limitation [8].

### Major depressive disorder

Major depressive disorder (MDD) is a mental health condition characterized by constant feelings of sadness, hopelessness, and a lack of interest or pleasure in activities that were once enjoyable. It feels more severe than normal feelings of sadness, but it is vital to remember that presentation may differ significantly from one individual to another [31-32]. MDD can significantly impact daily life and functioning of the patient [32-33]. While GK treatment is initially used for various neurological and mental conditions, its application in treating depression is not as common as pharmacotherapy, psychotherapy, electroconvulsive therapy, magnetic seisure therapy, direct current stimulation (DCS), vagus nerve stimulation (VNS), deep brain stimulation (DBS), transcranial magnetic stimulation (TMS), phototherapy and relaxation or meditation techniques [34]. A potential patient must fulfill clinical criteria related to the severity, chronicity and treatment resistance as determined by a multidisciplinary team's decision-making process [27]. Severity may be assessed with scales such as HAMD-17, BDI or MADRS [35]. Case report narrated by Park et al. was based on subcaudate tractotomy in case of a long-term, refractory depression followed by nine suicidal attempts [27]. Other surgical method for patients with resistant MDD may be cingulotomy, but case studies and evidence are limited [27]. Their case revealed that depression burden decreased after GKRS, with discontinuation of pharmacotherapy 4 months postoperatively [27].

### Autism spectrum disorder

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder affecting communication skills, social interactions, behavior and motor or sensory experiences with a wide range of symptoms and levels of severity [26, 36-37]. Management methods can be based on a combination of behavioral therapy, speech and language therapy, occupational therapy and social skills training [36-37]. Treatment methods for pediatric and adult patients vary and their further description exceedes the scope of this paper [36-37]. The main aim is to help patients develop essential life and social skills, as it will increase their quality of life and level of independence [26, 36-37]. Torres et al. described the implementation of radiofrequency and GKRS on patients with ASD, who were refractory to traditional treatment. After the procedure, patients were evaluated in three behavioral scales: The Overt Aggression Scale (OAS), Parental Concern Questionnaire (PCQ), Children's Yale-Brown Obsessive Compulsive Scale for Autism Spectrum Disorder (CYBOCS-ASD). MR scans were obtained (at 6 months and one year after the procedure, then once a year for the next 5 years post-surgery). Results were positive, with improvement in every patient since the first week after the procedure. The symptoms of the 10 patients showed a notable decrease (PCQ 39.9 to 33, OAS 11.8 to 5, CYBOCS-ASD 30.4 to 20) both before the surgery and at the latest follow-up. In all cases there was an almost total reduction of agressiveness and significant decrease of restrictive-repetitive actions, which was confirmed by patient's caregivers The authors did not specify examples of improvement in the functioning of patients with autism, other than improvement according to the mentioned scales [26].

## Discussion

Modern psychosurgery is significantly safer and more effective than invasive procedures from the past, e.g. leucotomy, lobotomy, lesioning surgeries of the hypothalamus or amygdala [26, 38-39]. Ablative techniques are connected with lower costs and no need to implement artificial devices. Also, as craniotomy is not necessary, the risk of infection or hemorrage are excluded, as far as the risks connected with anaesthesiological procedures [38]. The unsatisfactory results of previous OCD treatment with GK capsulotomy led to a change in the initial treatment target to the most ventral part of the internal capsule and the ventral part of the striatum [20]. Based on the studies presented in this paper, it can be concluded that GKRS is a safe and effective procedure that can be implemented in selected cases of resistant OCD [12-13, 25]. However, it is not possible to predict clinical outcome after GVC treatment in patients with refractory OCD. This is suggested by the variability of ALIC fibre organization between patients, which can be detected by neuroimaging studies, allowing the precise target of the treatment to be determined [11, 20]. It is noteworthy that patients undergoing GVC showed significant reduction of symptoms such as depression, anxiety, followed by improvement of the quality of life and better overall functioning [13]. Creating and implementing strict guidelines for using surgical methods in the treatment of psychiatric disorders is crucial and should be taken under consideration.

Adverse effects after GVC are rare and patients tolerated the procedure well. Rasmussen et al. observed transient oedema (9% of patients), cysts (5%) and radiation necro-

sis leading to a state of minimal consciousness (1.8%) [13]. Adverse effects observed by Peker et al. included transient headache (14.3% of patients), persistent headache (9.5%), and brain cyst (10%) [25]. No clinically significant abnormalities on neurological examination were reported in this group. For the group studied by Gupta et al., mood disorders occurred after GVC in 25% of patients, neurological complications in 7.5% and one patient developed radiation necrosis [17]. In contrast, Ertek et al. described the occurrence of headaches in 16.7% of patients [24]. Placebo effect seems to be absent or weak, according to the literature [8].

Among the neuropsychiatric adverse effects one can distinguish cognitive decline, insomnia or anxiety. It is important to remember that unsatisfactory treatment results, combined with inadequate pharmacological management, may lead to suicidality. In light of this, it seems justified to maintain pharmacological treatment and optimize it to prevent suicidal tendencies in patients [27].

Implementation of GKRS in psychiatric disorders other than OCD seems to have promising outcomes. Studies held in the 1980s revealed unsatisfactory results, but modern evaluations have results ranging from fair to good. The main reason for this difference is the improvement in GKRS techniques and the associated increased safety of these procedures [8, 10, 26-27, 40]. Randomized controlled trials (RCT) with GK are potentially possible, because patients may not be aware whether they are being treated or not (they may not be informed if they are receiving radiation doses while in the operating room). The major limitation of RCTs using GK is the radiation exposure, which creates additional technical obstacles for researchers. So far, only one RCT using GK was conducted among psychiatric patients: a 2014 study by Lopes et al. regarding patients with OCD [19, 41]. It is vital to remember that modern GK devices seem not to emit radiation, as its sources remain covered. This fact may create an opportunity to widening the research using tools such as randomized clinical trials [41]. Double-blinded studies of larger cohorts are needed to extend the knowledge about psychiatric use of GK.

In spite of improvements in GK technology and radiological imaging techniques over time, the optimal volume and dose of radiation appropriate for radiosurgical capsulotomy remains a subject of research. Currently, two major trends in these issues stand out; lowering the radiation dose accompanied by a decrease in adverse events and the use of more refined analytical techniques to draw conclusions (incidence of adverse events, radiation dosage, location) [20, 42]. In view of this, further research is needed on the effective radiation dose and targeting methods that maximize the effectiveness of GVC and reduce the risk of adverse effects [13]. Furthermore, a reduction in the severity of OCD symptoms may result not only from direct modulation of neuronal pathways, but also from the increased efficacy of pharmacological and psychological therapies acting synergistically with GVC [42].

## Conclusions

Decision-making regarding neurosurgical procedures to treat a mental illness should be individualized for each patient. Many factors should be considered, such as patient preferences and attitudes, risks, psychosocial support, quality of life (current and anticipated), comorbidity, socio-economic situation and follow-up. The role of the multidisciplinary team is to assist patients in deciding on treatment options. It should include clinicians specialized in all therapies under consideration. Restricted access to the centers experienced in performing GKRS procedures is an important limitation. More data from randomized clinical trials, preferrably from multiple centers, are needed to extend the use of GKRS in psychosurgery. More research is needed regarding effective radiation doses.

## Conflicts of interest

None to report.

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REVIEW ARTICLE

# Physical activity in type 2 diabetes mellitus: a review

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## Abstract

**Introduction:** This literature review explores the role of physical activity (PA) in managing and preventing type 2 diabetes mellitus (T2DM), synthesizing the latest guidelines for all T2DM patients. Following PRISMA guidelines, it identifies specific areas for further research. **Methods:** Indexing services (PubMed and Scopus) were used to identify relevant studies, emphasizing original research, review articles, and updated institutional guidelines spanning 2017-2023. The following keywords were used: diabetes, physical activity, type 2 diabetes mellitus, PA, and exercise. Proposal and opinion articles, non-English papers (or those lacking full-text translation), studies involving non-human subjects, pediatric populations or with skewed gender distribution were excluded. **Results:** PA improves quality of life, BMI, glycemic control and well-being. Effects vary by activity domain, such as work or leisure time. Recommendations suggest 60 daily minutes of exercise for children, 150 weekly minutes of moderate intensity exercise for adults, and screening for adverse events. A "sit-less" approach is proposed for those unable to maintain regular activity, with glycemic monitoring for those with variability. **Conclusion:** PA is crucial in T2DM management. Conflicting findings regarding glycemic control warrant further investigation to ascertain causes, whether related to bias or other factors.

**Keywords:** physical activity · diabetes · T2DM · diabetes mellitus · exercise

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## Introduction

For quite some time it has been known that lifestyle changes have been the primary intervention in type 2 diabetes mellitus (T2DM) [1]. The implementation of physical activity (PA) or exercise into daily life has been the preferred method of achieving adequate glycemic control, losing weight and lowering the body mass index (BMI) [1]. Although a lot of research supports the fact that an exercise regimen in patients with diabetes helps to achieve more favourable outcomes, these results are vastly heterogeneous. Intriguingly, some recent studies have shown the lack of a relationship between exercising and achieving adequate glycemic control (see the "Contradictory results" subsection) [2-5]. Nonetheless, an exercise regimen is still recommended in diabetes-related guidelines all around the world. The aim of this review was to condense the newest, most relevant studies and guidelines to guide clinicians in their formulation of individual management plans for their patients. Further aim was to temper expectations and accurately define what exactly can be expected as a result of implementing PA in terms of glycemic control and overall morbidity.

## Methods

Indexing services PubMed and Scopus were used to find studies that were relevant, factually important and recent. The search was conducted using the following keywords: physical activity, diabetes, PA, T2DM, type 2 diabetes mellitus, exercise, graded regimen. Newer articles were prioritised and only those from 2017-2023 were included in the review. Articles not published in English (or without a full-text English version), research on a non-human population, research focusing entirely on a paediatric population, opinion pieces and proposals were excluded. Duplicate articles were removed. This literature review includes original research, review papers, meta analyses and institutional guidelines. The basis of this shortlisting was to not only provide the most detailed narrative with the newest information but also to discuss some interesting contradictory results found as of late. No papers with significant biases were included in this review. However, articles with potential for bias were included in the "Contradictory results" subsection, for the purpose of initiating a discussion regarding not only the direction for further research but also the initiation of similar studies to either prove or disprove said results. This review was conducted in accordance with the PRISMA 2020 guidelines.

## Results

The initial search retreived a total of 11733 abstracts. Upon implementation of the exclusion criteria and removal of duplicates, 1074 abstracts remained. After screening the full-texts, a total of 46 articles were chosen for analysis in this review (Figure 1).

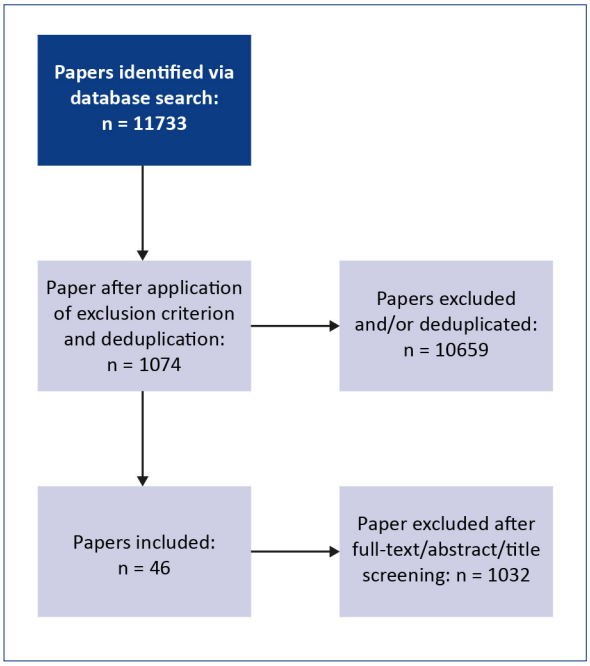


**Figure 1. PRISMA flow diagram**

## Discussion

It is well-known that regular exercise/PA is one of the foundations to a healthy lifestyle. It was found that patients with T2DM and low PA level had a shorter life expectancy with higher risk of chronic diseases than their counterparts with moderate to high PA levels [1]. Additionally, it has been demonstrated that individuals with higher levels of weekly PA are at a significantly lower risk of developing diabetes than their counterparts with lower levels of weekly PA. It was shown that individuals who managed 150-300 minutes, 300--600 minutes and > 600 minutes of weekly PA as compared to individuals with < 150 minutes, were respectively at a 49%, 62% and 71% lower risk of developing diabetes [6].

PA has also been shown to improve the common comorbidities that are expected in a majority of patients with T2DM. Exercise improves endurance, provides a therapeutic effect in musculoskeletal and cardiovascular comorbidities as well as reduces weight and BMI [7-8]. Exercise also improves endothelial dysfunction in patients independent of their glyce-

mic state [9]. This cardiovascular benefit of a 3-month exercise regimen is shown to reduce adverse events up to 24 months later, even despite cessation of exercise after 3 months [9].

PA has also been shown to improve glycosylated hemoglobin (HbA1c) levels, BMI, quality of life and waist circumference in patients on long-term regimina [10]. It was in fact found that "improve activity" was by far the most effective lifestyle intervention in the prevention of T2DM, even ahead of "promote healthy diet" or "control smoking" [11].

In addition to lowering weight and BMI in those as required, PA (both short-term and long-term) has also been shown to improve the 24-hour glycemic control in patients with T2DM [12]. It has also been shown that PA can reduce the time spent in hyperglycemia in these patients [12]. That being said, there was a high amount of heterogeneity observed in the results, as reported in a meta-analysis from 2020 [13].

## Demographics

It was shown that sex can not be considered separate from the discussion of PA in diabetes and might be a confounding factor in studies that have heterogeneous results [14]. Studies that included primarily men showed much different results than those that featured a diverse group of participants from both sexes. Similarly, sex, not BMI or age was found to have the most significant changes to 24-hour glycemic control [13].

Additionally, it has also been shown that women might experience a more dynamic set of barriers (including perceived barriers) to exercise as compared to men [15]. This was primarily found to be the case due to a perceived lack of time, societal or personal opinions about the benefits or reasons for exercise or family discouragement [16]. It was in fact shown that there is a strong correlation between a barrier to PA and the presence of children at home, however the number of children did not seem to increase this perceived barrier [17]. This is further affirmation that this perceived barrier is in line with the perceived lack of available time. It was also found that working women faced the same perceived barriers whether they were from higher or lower socioeconomic backgrounds with the primary ones being a lack of energy and a lack of time [18]. This is an important finding as it could imply that these barriers are perceptual and not necessarily a negative driving force as there is a homogeneity in experience between working and non-working women. Clinicians must therefore tailor their approaches to a holistic psychosocial model for each patient and understand their perceptions of own health as well as their attitudes towards the suggested treatment plan.

It was also shown that exercise carried out during leisure time was inversely related with the development of diabetes [19]. On the contrary, PA carried out domestically or at work was shown to have an astonishing additive effect to the risk for developing diabetes [20]. This is an immensely important finding with more research warranted as it may require clinicians to be more precise with their weekly exercise recommendations since equivalent amounts of exercise have a seemingly opposite effect depending on the context and setting in which they are performed [20]. Additionally, it has been shown that although leisure-time PA shows an inverse relationship with the development of diabetes, so called "transport physical activity" (the PA involved in going from one place to another) only shows this inverse relationship in men and not in women [21]. This study was carried out in a Korean cohort. As has been shown in previous studies, there is something to be said for the heterogeneity in the response of cohorts of different ethnicities and their respective glycemic responses to glucose loads implying a potential fundamental processing difference [22].

There is therefore an evident need for clinical recommendations made with domain-specific PA in mind, tailored to each individual. Clinicians must also keep this in mind whilst inquiring about patients' average weekly mobility and amount of exercise, and must strive to organize the respective times into domain-specific categories.

## Recommendations

As mentioned, patients face a variety of perceived barriers to PA. Therefore, patients should feel like an active member of the decision-making team so that they are invested in the management plan and are more likely to follow it. Additionally, the exercise regimen that unanimously chosen by the patient and clinician should be specifically tailored to suit individual needs so as to not overwhelm the patient physically or psychologically. It is shown that this is a key factor especially in the first 6 weeks of starting a training regimen and is the most likely cause behind the subsequent discontinuation [23]. Additionally, elderly patients may especially benefit from a PA regimen that places an emphasis on not just exercise but also flexibility and stretching due to their reduced age-related or comorbidity-related functional capacities [24].

It has been shown in multiple studies that patients using insulin to manage their diabetes may benefit from rigorous monitoring of their glycemia before, during and after exercise in order to prevent adverse events related to hypoglycemia [24]. Continuous glucose monitoring systems (CGMS) may be an appropriate intervention for patients with diabetes who wish to pursue an exercise regimen, as they have been shown to not only lead to lesser hypoglycemic events but also increase a patients' time-in-range (TIR) or the time that a patient spends in a euglycemic state [25]. The use of such devices can further help individual patients by allowing them to monitor the variations in their glycemia and use this data to appropriately modify their daily diet.

It has been shown that PA has been an effective intervention in improving the severity of depression symptoms [26]. Intriguingly, it was found that on the contrary, in patients who have both T2DM and depression, exercise was not an adequate intervention in providing significant or even sufficient glycemic control [27]. Interestingly, exercise was still found to be an appropriate lifestyle intervention to reduce the severity of depression in patients with coexisting depression and diabetes. Unfortunately there is a severe lack of literature on this particular topic and more research is needed.

## Sitting

It was noted that there was an increased risk of cardiovascular disorders as well as diabetes in individuals who spent longer periods during the day sitting [28]. Interestingly, the risk for the development of diabetes was not diminished even after correcting for time spent daily engaging in PA, however the risk for cardiovascular disorders was diminished all the same [29]. This is important because it is essential for the clinician to understand that there are certain factors that not even exercise can mitigate and these must be discussed and kept in mind whilst making recommendations to patients.

It was also found in a cohort of Europeans that there was a causal relationship between television viewership, a sedentary lifestyle and the development of T2DM. Conversely, there was no causal relationship between computer usage and the development of diabetes. It was also shown that being seated whilst driving was in fact not associated with an increased risk for developing diabetes [30]. This might be explained by various mechanisms including the observed differences in the health ramifications between the sedentary activities that are mentally passive versus mentally active [31].

It was also noted that interrupting sitting time with light-intensity exercise may attenuate postprandial hyperglycemia even more effectively than a continuous bout of moderate exercise, particularly in patients with insulin resistance and a higher BMI [32]. This is important as it may be an alternative regimen for patients that are unable or not motivated enough to partake in continuous exercise.

## Contradictory results

Intriguingly, a meta-analysis of 28 studies showed that although PA improved 24-hour glucose concentrations in short-term studies, this effect was not statistically significant in long-term studies [2]. Although 24-hour glucose levels were not significantly improved compared to the control cohort, they were improved compared to the pre-exercise levels of the same cohort. That being said, there was a high degree of heterogeneity in these results. Although the limitations of that analysis are not completely understood, it must be stated that there is a high possibility of bias in the trial methodologies (when accounting for sex, intensity of exercise and time of day when exercise is performed), as well as the methodology used to analyse these trials [3]. A follow-up study showed that 50 minutes of walking at 3 different times of day in fact did not improve 24-hour glucose profiles in patients with T2DM [2].

Another study found that only exercise interventions in the evening had a positive impact on 24-hour glucose levels as opposed to no exercise or exercise interventions in the morning [4]. Even more interestingly, a recent study had contradictory results to the aforementioned: in a cohort of 73 patients who took part in short term PA in the form of 50 minutes of walking before dinner, it was found that there was no significant improvement in 24 hours glucose concentrations [5]. Once again, there was a high degree of heterogeneity in the results. The reasons for this contradictory finding are not understood clearly.

## Guidelines

It has been shown that lack of PA negatively affects the lives of patients, particularly those with T2DM [33]. Patients need to therefore be educated and made aware about this fact so that they are more likely to actively engage with proposed therapies. PA has additionally also been shown to decrease HbA1c levels, blood pressure and lipid levels in patients [34-35]. Therefore guidelines suggest adopting a holistic, multi-factorial therapeutic approach to diabetic patients.

The International Society for Pediatric and Adolescent Diabetes suggests that children and adolescents with diabetes must be encouraged to obtain at least 60 minutes of moderate to intense aerobic PA daily [36]. Moderate PA entails activities such as walking, cycling, running, hiking etc. Moderate to intense activity may involve sports such as football, basketball, cricket and so on. Conversely, very high intensity and anaerobic exercises may cause unwanted spikes in blood glucose as seen with activities such as weightlifting and sprinting [37]. This is important because patients on insulin therapy that partake in very high intensity or anaerobic exercises might not benefit from a therapeutic pre-exercise dose reduction and may instead require a post-exercise hyperglycemic correction. Patients on insulin therapy that partake in aerobic exercise however may benefit from a pre-exercise dose reduction and this may be evaluated on a case-by-case basis. High-intensity exercise is also contraindicated in patients with recurrent adverse sequelae of diabetes or with advanced retinopathy [36]. Additionally, an episode of severe hypoglycemia in the past 24 hours or recurrent episodes of hyperglycemia may be seen as contraindications to exercise until the underlying basal metabolic status is rectified.

Further, combined nutrition, PA and behavioral therapy is recommended to patients with diabetes [38-40]. This is

particularly true for patients who are overweight or obese. This regimen is to be accompanied by frequent counseling sessions (as many as 16+ sessions in 6 months) to ensure adherence and eventual accomplishment of a caloric deficit of more than 500 kcal per day [41].

The American College of Sports Medicine also recommends that individuals with diabetes that wish to or are recommended to incorporate an exercise regimen into their daily life may benefit from medical screening, particularly individuals with macrovascular disorders, cardiac dysfunction etc. The screening would take into account their current level of PA, as well as any cardiovascular, metabolic or renal pathologies [42]. Although the results of such a screening may not necessarily disqualify an individual from a PA regimen, it may guide clinicians in modifying their recommendations with respect to total time spent and intensity of said regimen.

A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommends that adults obtain a weekly minimum of 150 minutes of moderate intensity anaerobic exercise [43] (classified as any activity that can be carried out whilst maintaining an uninterrupted conversation) and reduce sedentary time and break-up prolonged sitting time. Additionally, those individuals that opt to partake in aerobic activity should supplement this with 2-3 weekly sessions of resistance, flexibility or balance training (the last of which is particularly beneficial for the elderly with limited mobility) [43].

Similarly, the 2023 guidelines published by the ADA recommend that adult patients with diabetes partake in a minimum of 150 minutes of weekly moderate to vigorous intensity anaerobic exercise whilst also focusing on reducing sedentary time and breaking up prolonged seated time [44]. This weekly activity target may be spread over 3 days [45-46]. Resistance exercises in conjunction with moderate aerobic activity, particularly in the same session, were found to have an additive effect in the lowering of glycemic levels and may therefore be safely recommended to patients. It is recommended that resistance exercises be carried out at least 2 days a week [45]. Exercises that aid in increased flexibility may help older patients with diabetes that are experiencing varying forms of functional disability. Exercise-related recommendations to patients ought to be as specific as possible, mentioning the type, duration and intensity of recommended weekly activities. Such recommendations must be customized to each individual patient on the basis of their comorbidities and physical ability.

## Discussion

It is therefore evident that PA is an essential intervention in the clinicians' tool chest for patients with T2DM. An appropriate amount of weekly aerobic exercise may not only allow for better glycemic control, but may even reduce time spent in hyperglycemia [8]. Additionally, patients show improved BMI, a better quality of life and lower waist circumference, all further improving glycemic control as well as their overall health [10].

Recent studies have shown that there is some variability in the performance of exercise in different domains of life. Notably, leisure-time PA was found to have the expected directly proportional relationship to glycemic control whereas work-time PA or even transportation PA were either not shown to exhibit this same effect or even had an inversely proportional relationship [21]. Therefore, clinicians must be specific in their recommendations as well as questioning of patients whilst trying to determine current and potential future weekly activity levels.

According to the American Diabetes Association, adolescents and children would benefit from at least 60 minutes of moderate aerobic exercise daily whereas adult patients should look to striving for closer to a minimum of 150 minutes of weekly aerobic exercise interspersed with resistance training [43-46]. All individuals who are to be prescribed an exercise or activity regimen would benefit from a screening to ensure that there is minimal risk for adverse events [42]. Additionally, patients who frequently experience variability in glycemic levels may benefit from CGMS and potential dose adjustments [25]. Elderly patients may benefit from the addition of exercises that enhance flexibility thereby increasing functional mobility.

Patients who are unable to stick to an exercise regimen due to functionality or motivational issues may benefit from a "sit-less" intervention that has been shown to reduce insulin resistance in patients significantly [32].

Patients with diabetes, particularly those treated with insulin and sulfonylurea, face a heightened risk of hypoglycemia during and after exercise [24]. Engaging in PA can enhance the glucose-lowering effects of these medications, potentially leading to hypoglycemia. It is therefore imperative for individuals taking these medications to monitor their glucose levels closely before and during exercise. CGMS offer a valuable tool for real-time glucose monitoring, facilitating timely adjustments to insulin doses as needed [25]. Although some intriguing and contradicting results have been noted in recent studies, there is a lack of understanding as to whether these are a result of bias or an occult underlying phenomenon. These heterogenic results ranged from meta analyses unable to reciprocate the beneficial effects of PA in diabetes over a long period of time [2], to a lack of improvement in 24 hour glucose concentrations after implementation of a PA regimen [4-5]. Further investigation is warranted to better understand the pathophysiological mechanisms governing these findings.

## Conclusion

PA has been shown to improve quality of life, BMI, overall morbidity and glycemic control. Adults with T2DM must aim to achieve at least 150 minutes of moderately intense aerobic exercise per week, interspersed with resistance training sessions. Children and adolescents with T2DM must aim to achieve at least 60 minutes of moderately intense aerobic exercise daily. All patients may benefit from a medical screening before prescription of an exercise regimen. The domain in which PA is conducted (ie. in the workplace, at leisure, during transportation, etc.) has shown a variability in results with respect to glycemic control. Patients must be advised to undertake leisure-time PA and not count work-time PA towards their weekly activity goals. Conflicting findings regarding glycemic control warrant further investigation, whether related to bias or other factors.

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## Conflicts of interest

There are no conflicts of interest to declare.

## Data availability

No datasets were generated or analysed during the current study.

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RESEARCH ARTICLE

# Quality of life and mental state of women trying to conceive using the in vitro method

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## Abstract

**Background:** the process of treating infertility using the in vitro method can affect both physical and mental health. The study aims to determine the impact of trying to conceive using the in vitro method on the quality of life and psychological well-being of women. **Material and methods:** respondents completed an online questionnaire. The experiment was conducted from July to December 2023 and 100 women involved. It was based on an questionnaire created by the authors and questionnaire tools: Fertility Quality of Life, Patient Health Questionnaire (PHQ-9), and selected subscales from Berlin Social Support Scales (BSSS). **Results:** Among the respondents, 85% of women do not have children. The average age of the women studied was 34 years, while the average number of years of infertility treatment was 6 years. Respondents rate their quality of life the best in the area of relationship, but the worst in the area of emotions. More than 80% of respondents were at risk of developing depressive disorders of varying severity. Nevertheless, the vast majority are satisfied with the support they receive. **Conclusions:** negative emotions that accompany women during in vitro process significantly affect their quality of life. They also contribute to an increased risk of mental disorders.

**Keywords:** quality of life · depression · infertility · in vitro fertilization

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## Introduction

The World Health Organization (WHO) indicates that on average 1 in 6 people of reproductive age worldwide experience infertility, which constitutes approximately 17.5% of the entire population [1-2]. The failure of natural conception may lead couples to use alternative reproductive methods, such as in vitro fertilization (IVF). In its report, the Polish Society of Reproductive Medicine and Embryology announced that in 2019, a total of approximately 22000 embryo transfers took place in Poland, resulting in over 8000 pregnancies [3]. Despite its popularity, trying to conceive via IVF may involve a number of emotional and mental challenges for women going through the process. Women may experience various emotional difficulties and sometimes even psychological problems such as anxiety, depression, eating disorders or low self-esteem. In the long term, social isolation, reduced communication and relationship difficulties between partners may occur [4]. The IVF process itself is not simple and includes challenges for women such as systematic visits and medical examinations, hormonal stimulation, ovarian puncture and embryo transfer [5].

The aim of our study was to determine the extent to which participation in the IVF procedure affects the quality of life and mental state of the respondents. We assessed whether this particular group of women is at risk of mental disorders and to what extent they need support from their partner, friends or family. There are many reports regarding the quality of life of women struggling with infertility in such countries as China, Hungary, Italy, Jordan and Kazakhstan [6-10]. The analysis of the literature indicates the niche nature of Polish reports in this area, which mentions the justification for continuing the research in the future.

## Materials and methods

Using the Google Forms website, we developed a survey consisting of 66 questions divided into 4 sections. The first one contained general questions about socioeconomic data and the duration of infertility treatment, the number of embryo transfer attempts made, the number of children, miscarriages, stillbirths and the current costs incurred in connection with the IVF procedure. The second section contained the Fertility Quality of Life (FertiQol) questionnaire, an instrument used to assess the quality of life of people struggling with fertility problems [11]. The FertQol consists of two parts: basic and treatment. The basic part, consisting of 24 questions, was divided into 4 subscales: "Emotional," "Mind and Body," "Relational" and "Social." The part regarding the treatment process contains 10 questions and focuses on two subscales: "Treatment Environment" (describing the medical environment) and the "Treatment" subscale (patient's tolerance to treatment). Based on the results of the 6 subscales of the FertiQol, it is possible to assess the respondent's quality of life ("Core", the first part of the questionnaire) and treatment ("Treatment", the second part), as well as obtain a general score in the assessment of health, quality of life and treatment ("Total score"). The higher the score, the higher the quality in the particular area of life. The third section of our survey consisted of questions from Patient Health Questionnaire (PHQ-9), to assess the risk of depression in the study group. The last section contained questions from selected subscales of the Berlin Social Support Scales (BSSS): "Perceived available support," "Need for support" and "Looking for support."

The study design assumed the participation of non-pregnant women during the IVF procedure. Due to significantly high number of women struggling with the problem of infertility, no upper age limit was set for the respondents. We shared our survey on social media groups associating women who were undergoing the IVF procedure. Participation in our study was voluntary and anonymous. We conducted our study from July to December 2023. Approval to conduct this project was obtained from the Independent Bioethics Committee for Scientific Research at the Medical University of Gdańsk (KB/386/2023). Statistical analysis of the obtained data was carried out using the Statistica software-version 13.1 PL (StatSoft Inc., Tulsa, USA) and Microsoft Excel (Microsoft, Redmond, USA).

## Results

A total of 100 women participated in our study. The average age of the respondents was 34 years (x = 33.89), while the average declared duration of infertility treatment was approximately 6 years (x = 5.54). More details are presented in Table 1. The majority (85%) of the surveyed women did not have children, while the remaining 15% (n = 15) had experience with motherhood. Of the surveyed women, 13 (13%) had one child, and 2 (2%) had two children. More than half of the respondents (53%, n = 53), had never experienced a miscarriage. Whereas, 28 women (28%) once experienced the loss of a child before the 22$^{nd}$ week of pregnancy, 9 women (9%) admitted that such an event occurred twice, while 10 respondents (10%) experienced it three times or more. Among the respondents, 7% of them (n = 7) declared the experience of stillbirth, including six women (6%) once, and one woman (1%) experienced it twice. In the survey we asked about the number of attempts to transfer an embryo or embryos. Nearly 1/3 of women (n = 28, 28%) did not have such a procedure, which may indicate the initial stage of the IVF procedure. Almost half of the surveyed women (n = 45, 45%) have had

**Table 1. Analysis of sociodemographic data of the respondents**

| | | |
|---|---|---|
| **Age** | < 30 | 19% |
| | 30-35 | 49% |
| | 36-40 | 19% |
| | > 40 | 13% |
| **Education level** | Vocational school | 2% |
| | Secondary | 18% |
| | Higher | 80% |
| **Place of residence** | Village | 32% |
| | City < 50000 residents | 16% |
| | City 50-250 thousand residents | 39% |
| | City 250-500 thousand of residents | 13% |
| **Financial situation** | Bad | 1% |
| | Average | 24% |
| | Good | 53% |
| | Very good | 22% |

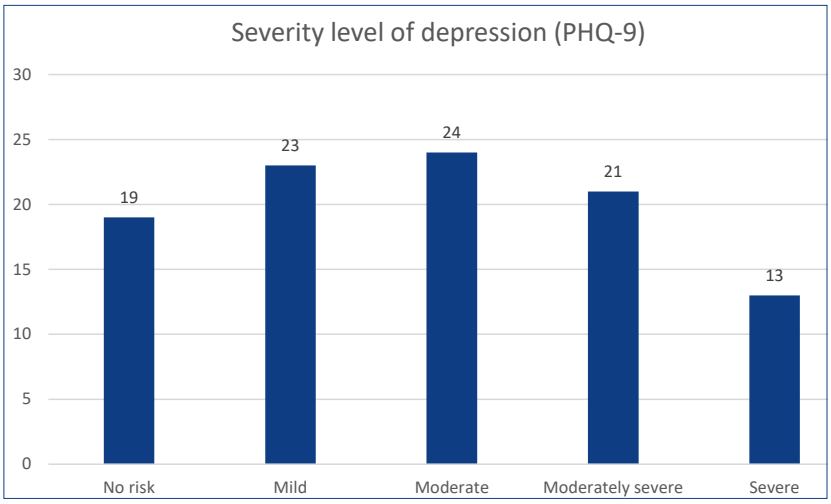


**Figure 1. Results obtained by respondents in the Patient Health Questionnaire (PHQ-9)**

1 or 2 attempts, 21 women (21%) completed 3-4 attempts and 6 (6%) completed at least 5 attempts.

Basic statistics of the results obtained by the study group in the FertiQol are presented in Table 2. The respondents obtained the highest average score in the "Relationships" subscale, which may indicate that, in their opinion, fertility problems do not have a negative impact on the relationship or partnership in terms of sexuality, communication and commitment. The lowest average score concerned the "Emotional" subscale, which in turn suggests that negative emotions, (e.g. sadness and jealousy), significantly reduce the quality of life and mental state of women.

In our study group, the vast majority of women (n = 81, 81%) obtained results indicating the possibility of depression, with varying degrees of severity. Of the surveyed women, 23% (n = 23) obtained a result indicating the likelihood of mild depression, 24% (n = 24) – moderate depression, 21% (n = 21) – moderately severe depression and 13% (n = 13) – to a severe degree. A detailed analysis of the severity of depression dictated by the results obtained by the respondents is presented in Figure 1. Moderately severe and severe depression concerned over 1/3 of the respondents (n = 34, 34%), while only 19 women (19%) obtained a "no risk" result, indicating a probable lack of depression diagnosis. It should be emphasized that Patient

**Table 2. Basic statistical analysis of the results obtained using the FertiQol questionnaire**

| FertiQol | N | A | Me | Min | Max | SD |
|---|---|---|---|---|---|---|
| **Emotional subscale** | 100 | 36.25 | 35.42 | 4.17 | 83.33 | 19.96 |
| **Body and Mind subscale** | 100 | 43.58 | 41.67 | 0.00 | 91.67 | 20.14 |
| **Relationships subscale** | 100 | 60.25 | 62.50 | 20.83 | 83.33 | 14.24 |
| **Social subscale** | 100 | 48.17 | 50.00 | 0.00 | 95.83 | 18.87 |
| **Treatment Environment subscale** | 100 | 60.00 | 62.50 | 12.50 | 95.83 | 15.28 |
| **Treatment subscale** | 100 | 47.81 | 50.00 | 0.00 | 87.50 | 17.60 |
| **Quality of Life Assessment (CORE)** | 100 | 47.06 | 47.92 | 14.58 | 81.25 | 14.68 |
| **Treatment evaluation (TREATMENT)** | 100 | 55.13 | 55.00 | 17.50 | 85.00 | 13.08 |
| **Total assessment of health status, quality of life and treatment (TOTAL SCORE)** | 100 | 49.43 | 50.37 | 15.44 | 82.35 | 12.87 |

N – number of respondents; A – average; Me – median; Min – minimum value; Max – maximum value; SD – standard deviation

**Table 3. Basic statistical analysis of the results obtained using the selected Berlin Social Support Scales (BSSS)**

| BSSS | N | A | Me | Min | Max | SD |
|---|---|---|---|---|---|---|
| **Perceived available support** | 100 | 26.25 | 27.00 | 8.00 | 32.00 | 5.69 |
| **Demand for support** | 100 | 11.89 | 12.00 | 5.00 | 16.00 | 2.63 |
| **Looking for support** | 100 | 13/04 | 13.00 | 5.00 | 20.00 | 3.90 |

N – number of observations; A – average; Me – median; Min – minimum value; Max – maximum value; SD – standard deviation

Health Questionnaire (PHQ-9) is a screening tool, therefore it is advisable to consult with a specialist in order to confirm or rule out a diagnosis of depression.

We used selected subscales from the Berlin Social Support Scales (BSSS) assessing social support from the perspective of the respondent. The descriptive statistics of the results obtained by the respondents in these subscales are presented in Table 3. The "Perceived available support" subscale consists of 8 questions and the maximum possible number of points to be scored was the highest of all selected subscales. The surveyed women obtained low average scores (x = 11.89) in the "Need for support" subscale and high average scores (x = 26.25) in the "Perceived available support" from close relatives' subscale.

## Discussion

According to the report of by Statistics Poland, as of 2020 the average age of women at the time of delivering their first child in Poland was 28.5 years, compared to 22.7 years in the 1990s [12]. The average age of women in our study group was 34 years (x = 33.89). The results obtained may indicate that Polish women are trying to have their first child increasingly later in life. Nowadays, there is a trend related to the changes in the role of women in the society: increasingly more often women decide to give up the exclusive role of a caregiver at home in favor of independence, resourcefulness and personal development, which in turn may contribute to delaying the decision about motherhood [13]. Wylęgły determined the causes of the so-called "late motherhood" (parenthood after the age of 35): the importance of education and professional

career in the lives of many young people and the lack of financial stability [14].

Mikołajczyk et al. reported about the increasing number of Polish women with higher education [15]. Our results are in line with that observation: over 80% (n = 80) of our respondents declared having higher education, which may be one of the factors indirectly contributing to late motherhood. The report by Statistics Poland emphasizes that in 2018--2022 women were better educated compared to men. In the 30-34 years of age group, 47% of people (predominantly women) have higher education [16]. People of this age often feel more stable financially and in life, which may cause some women to consciously decide to become mothers at a later age, when they feel more ready to take on this challenge [17].

Every fifth respondent declared her place of residence in the countryside, while approximately 76% (n = 76) in areas considered urban. Most of the assisted reproduction centers are located in large agglomerations, which may be to the advantage of people living in cities, facilitating their access to treatment methods [18]. Environmental and lifestyle factors can also affect fertility [19].

When starting the IVF procedure, it is not possible to clearly determine how many months or years infertility treatment will last. The average duration of therapy declared by the respondents in the study was nearly 6 years (x = 5.54). Nearly half of the respondents, 47% (n = 47), declared having > 5 years of treatment for infertility. During this time, over 70% of respondents (n = 72) attempted to transfer an embryo or embryos. Most of them, 45% (n = 45) had only 1 or 2 attempts. The success rate of getting pregnant after the first embryo transfer is approximately 35%, but with age this probability declines [20]. Sharma et al. reported that the first ineffective IVF cycle may result in couples deciding to discontinue treatment due to the financial burden and existing mental and emotional problems [3].

Chanduszko-Salska compared ineffective infertility treatment to the loss of a loved one. The mourning process, strong emotions and stress, loss of faith in one's own body and fertility, lack of faith in the possibility of having a child after numerous losses are factors that may have a significant impact on both the quality of life and the mental state of women [21]. Of the respondents, 28% (n = 28) had experienced a miscarriage, while 7% (n = 7) had a stillbirth. The loss of a longed-for offspring can cause strong reactions both somatic and psychological. Women can be afraid of getting pregnant again, thinking that they will lose it too [22]. Difficult psychological consequences indicate the need to consider psychological help dedicated to women at every stage of the IVF procedure. Psychological assistance should also be provided to women who have experienced a miscarriage or stillbirth.

The Public Opinion Research Center stated in its announcement that the assessment of the financial situation and income has the greatest impact on improving life satisfaction [23]. Slightly more than half of the respondents assessed their financial situation as "good." Only 22% of respondents (n = 22) declared their financial situation as very good, and 24% (n = 24) as "average." In the first quarter of 2023, the average household income per person in Poland was 7124.26 PLN [24]. The surveyed women were asked about the costs incurred in connection with the in vitro procedure. Nearly 60% of them (n = 59) chose the answer "over 20000 zł" (the option referring to the largest financial costs). One of the respondents commented that "one zero is missing" in the answer choices. The high costs of the IVF procedure result from numerous tests interfering with the woman's body, ultrasound examinations, specialist consultations and the number of attempts to conceive the desired child [25]. Despite significant costs, not only financial ones, some women want to have biological offspring because it is a condition for them to feel stable and fulfilled in life [4].

"Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" [26]. The WHO emphasizes that mental health is an integral and necessary component of health. Warzecha showed that 87% of women did not seek the help of a psychologist before starting the IVF procedure. Only 6% of respondents admitted to consulting with a psychologist in the clinic where the procedure was to take place, and the reason for such a consultation was not specified [27].

The results obtained in the FertiQol confirmed that negative emotions have the greatest impact on the quality of life of women trying to conceive using the IVF method (the mean score of the "Emotional" subscale was x = 36.25). The obtained results confirm that difficulties with getting pregnant may contribute to a significant increase in stress, thus significantly increasing the risk of depression [28]. Wdowiak et al. compared 3 infertility treatment methods (assisted reproductive technology (ART), intrauterine insemination (IUI) and IVF), and observed that the women undergoing the IVF procedure obtained the highest result in the emotional domain [29]. Our results are opposite and this discrepancy may be due to the size of the study group, thus more research is needed. Wdowiak et al. also demonstrated that the choice of treatment method affects the assessment of the health status of women struggling with infertility, which may be an additional factor justifying providing psychological care to this group [29].

## Limitations of the study

Our research has some limitations. Only 100 women took part in the study and the size of this study group limits the possibility to observe the trends that exist in the entire population. The short duration of the study (July to December

2023) could also affect the collected data. Moreover, our survey was made available only online on websites associating women trying to conceive using the IVF method. It would be justified to conduct further research in the future, modified to overcome the above-mentioned limitations.

## Conclusions

The negative emotions that women experience during the IVF procedure significantly reduce their quality of life and may contribute to an increased risk of mental disorders. It is extremely important to receive support from one's loved ones during this time. Women should be assured that they can receive specialist help from gynecologists, midwives, nurses and psychologists. Properly conducted psychoeducation could help women undergoing IVF understand the validity of the performed procedures, reduce the feeling of negative emotions and increase the level of knowledge and sense of control. Infertility is a global issue, therefore more in-depth studies are needed that include follow-up assessing the mental state of women undergoing the IVF procedure.

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## Conflicts of interest

The authors report no conflicts of interest.

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