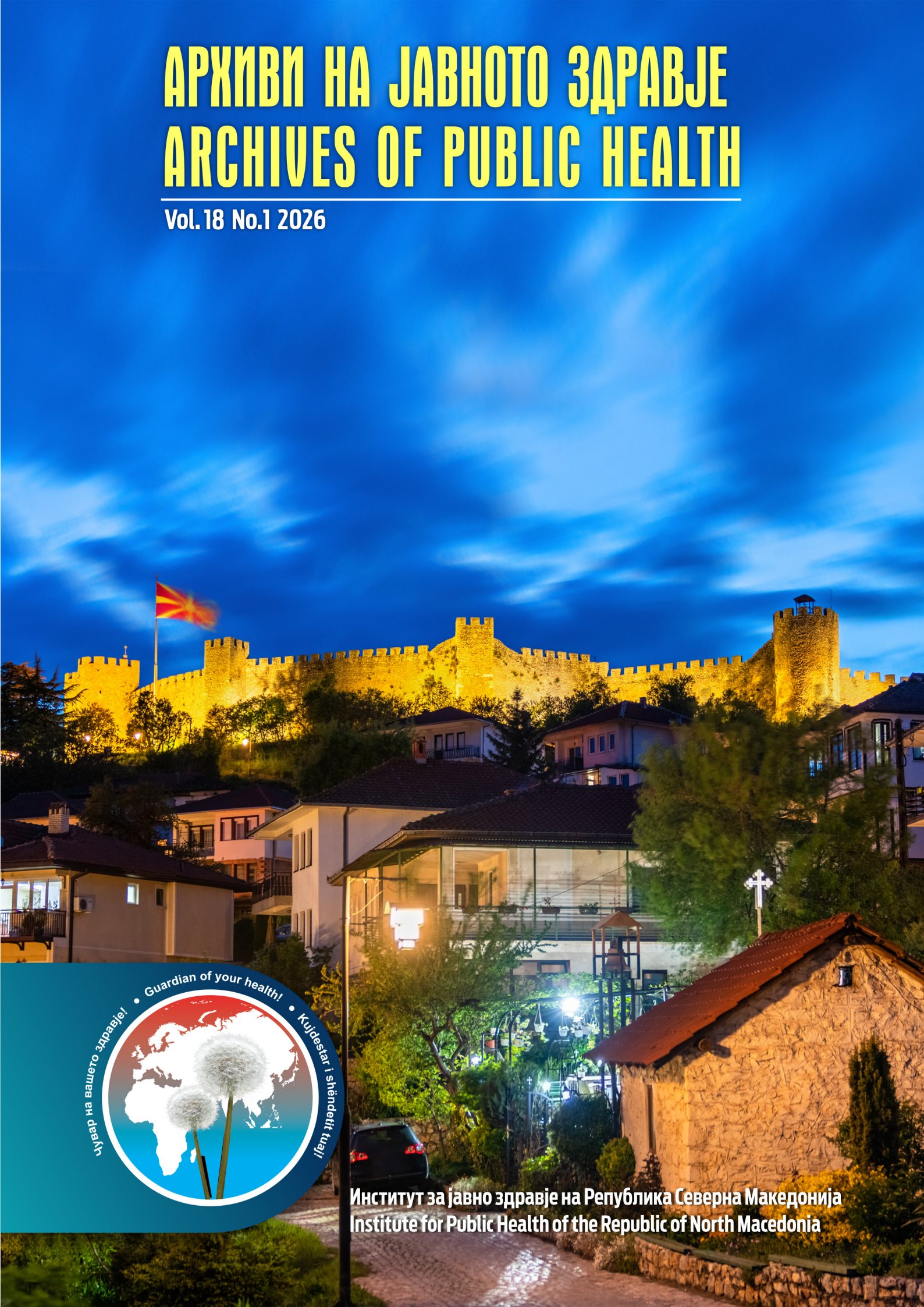
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CLINICAL SCIENCE

MORPHOLOGICAL DEVELOPMENT OF THE HIP IN NEWBORNS AND INFANTS WITH OR WITHOUT WIDE SWADDLING UP TO 8 MONTHS OF AGE

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Abstract

Developmental dysplasia of the hip (DDH) is one of the most common musculoskeletal disorders. Hip dysplasia occurs in approximately 1in 100 cases, which means it is ten times more common than hip dislocation. The physiological development of the hip during growth is determined by the central positioning of the femoral head within the acetabulum. Maintaining the hips in flexion and abduction positions in newborns is the most common recommendation for improving hip development.

The aim of this study was to assess the effects of wide swaddling on hip maturation and its morphological characteristics and development, specifically to determine whether wide swaddling influences hip maturation in the first 8 months of life. A prospective clinical stratified study was conducted, including male and female newborns and infants with type Ia, Ib, and IIa+ hips according to the Graf method. The subjects were divided into two groups. The first group consisted of 55 newborns and infants in whom wide swaddling was used (110 hips were followed). The second group consisted of 55 newborns and infants who were not swaddled (110 hips were followed). Wide swaddling consisted of an extra cloth diaper and one wide swaddle diaper.

Subjects were monitored with hip ultrasound according to the Graf method during the first weeks of life and every two months until eight months of age. For the bony roof, the results showed a natural improvement in the bony shape in infants without wide swaddling, which may indicate a positive trend in the development. The results indicated that even without wide swaddling, there was a natural improvement in bony shaping in a certain percentage of infants. For the bony rim, the results showed a natural improvement in infants without wide swaddling, which may indicate a natural developmental process. In both groups, progress was being made in the development of the ossification nucleus, indicating a natural process of improvement.

Improvement in the morphological characteristics of the hip was observed in the first months of follow-up of both groups, indicating spontaneous progression and maturation of hip

КЛИНИЧКИ ИСТРАЖУВАЊА

МОРФОЛОШКИ РАЗВОЈ НА КОЛКОТ КАЈ НОВОРОДЕНЧИЊА И ДОЕНЧИЊА СО И БЕЗ ШИРОК ПОВОЈ ДО 8-МЕСЕЧНА ВОЗРАСТ

Марина Комненовиќ[1], Зоран Божиновски[2], Милена Богојевска-Доксевска[2], Дејан Дамјановиќ[2], Игор Атанасовски[2]

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Клучни зборови: ехосонографија, развојна дисплазија на колк, широк повој

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Печатарски права: ©2026 Марина Комненовиќ, Зоран Божиновски, Милена Богојевска-Доксевска, Дејан Дамјановиќ, Игор Атанасовски. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираа оригиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Развојната дисплазија на колкот (РДК) е едно од најчестите заболувања на мускуло-скелетниот систем. Дисплазијата на колкот се јавува кај 1од 100 новороденчиња, што значи дека е 10 пати почеста од дислокацијата на колкот. Физиолошкиот развој на колкот за време на растот е детерминиран од централната поставеност на феморалната глава во ацетабулумот. Задржувањето на колковите кај новороденчињата во положба на флексија и абдукција е најчестата препорака за подобрување на развојот на колкот. Беше спроведена проспективна клиничка стратифицирана студија во која беа вклучени машки и женски новороденчиња и доенчиња со тип Ia, Ib и IIa+ колк според методот на Граф. Испитаниците беа поделени во две групи: прва група од 55 новороденчиња и доенчиња кај кои беше користен широк повој (беа следени 110 колкови) и втора група од 55 новороденчиња и доенчиња кај кои не беше користен широк повој (беа следени 110 колкови). Широкиот повој се состоеше од дополнителна тетра пелена и една шведска пелена. Испитаниците беа следени со ултразвук на колковите според методот на Граф во првите недели од животот и на секои два месеци до осуммесечна возраст. За коскеното обликување, резултатите покажаа природно подобрување на коскениот кров кај децата без широко повивање, што може да укажува на позитивен тренд во развојот. Резултатите покажаа дека дури и без широко повивање има природно подобрување во обликувањето на коскениот кров кај одреден процент од доенчињата. За коскениот агол, резултатите покажуваат природно подобрување кај децата без широко повивање, што може да укажува на природен процес во развојот. Во двете групи беше забележан значителен напредок во развојот на осификационото јадро што укажува на природен процес на подобрување. Подобрување на морфолошките карактеристики на колкот беше забележано во првите месеци од следењето кај двете групи, што укажува на спонтана прогресија и созревање на колкот.

Introduction

Developmental dysplasia of the hip (DDH) is one of the most common disorders of the musculoskeletal system. Hip dysplasia occurs in 1in 100 newborns, which means that it is ten times more common than hip dislocation and is the result of abnormalities in the size, shape, orientation, and development of the femoral head or the acetabulum.[1,2] The femoral head and the acetabulum influence each other during growth and development, starting already in the prenatal period. The physiological development of the hip during growth is determined by the central positioning of the femoral head within the acetabulum. Maintaining the hips of newborns and infants in flexion and abduction is the most common recommendation for improving hip development.[3]In newborns, there is a certain degree of hip laxity after birth, and therefore swaddling in adduction and extension should not be used. Instead, safe swaddling with the lower extremities in abduction should be used.[4–9]

In 1959, Judet and Gielis placed all newborns preventively in hip flexion and abduction up to the age of 4 months. With hip flexion of 100°, intra-acetabular pressure decreases, and the dislocating force of the hamstrings is reduced. It is necessary to pay attention to the so-called Ramsey safe zone, which means that hip abduction should not exceed 70° so as not to interrupt the blood supply to the femoral head, thereby increasing the risk of avascular necrosis (AVN) of the hip. By positioning the hips in abduction and flexion, the femoral head becomes centered and acts as a stimulatory factor for the development of the acetabulum. Some abduction orthoses have a low rate of AVN but a high rate of skin ulcers due to pressure on the soft tissues. Wide swaddling allows free movement of the lower extremities while still improving the position of flexion and abduction required for better hip development and maturation, but it cannot be used as a treatment for an unstable hip.[10]

There are not many studies investigating the effect of wide swaddling on hip maturation. The aim of this study was to evaluate the effect of wide swaddling on morphological hip development.

Material and methods

A prospective clinical stratified study was conducted, including newborns and infants with type Ia, Ib, and IIa+ hips according to the Graf method. Subjects were divided into two groups. In the group that used wide swaddling, 55 newborns and infants (19 male and 36 female), with a total of 110 hips (right and left) were followed. In the group without wide swaddling, 55 newborns and infants (25 male and 30 female), with a total of 110 hips (right and left) were followed. In both groups, the progression of the appearance of the ossification nucleus and the morphological characteristics of the hip were assessed. Follow-up examinations were performed every two months until the age of 8 months.

Wide swaddling consisted of one additional cotton (tetra) diaper and a wide diaper placed over the standard hygienic diaper, and parents were instructed on its proper use. Subjects withoutwide swaddling, continued to

use only the basic hygienic diaper.

For each subject, a clinical history was taken, including fetal position during pregnancy, postural anomalies of the fetus, birth weight, and vitamin D_3 prophylaxis. Subjects who met the inclusion criteria, i.e. those with type I or type IIa+ hips according to the Graf method, were instructed to use wide swaddling 24 hours a day. The swaddle was removed only for changing the hygienic diaper and for bathing. Any subject, who after the age of 3 months, remained type IIa – according to the Graf method, or progressed to type IIb, was excluded from the study and treated according to standard protocols.

Inclusion criteria were:

- Newborns and infants with hip types Ia, Ib, and IIa+ according to the Graf method.
- Singleton pregnancy, cephalic presentation of the fetus, and full-term newborns.
- Newborns and infants younger than three months.
- Normal birth weight (2,500–4,000 grams).
- Negative family history of developmental hip dysplasia.
- Negative clinical findings for hip instability, including no adductor contractures and negative Ortolani and Palmén tests.
- Vitamin D_3 prophylaxis on a regular basis.
-

Exclusion criteria were:

- Newborns and infants who on hip sonographic examination were type IIb, IIc, IId, or type III or IV hips according to the Graf method.
- Twin pregnancy, breech positioning of the fetus, or premature birth.
- Newborns and infants older than three months.
- Low birth weight (under 2,500 grams).
- Positive family history of developmental hip dysplasia.
- Positive clinical findings for hip instability, adductor contractures, and positive Ortolani and Palmén tests.
- Subjects that did not take vitamin D_3 prophylaxis on a regular basis.

Evaluation of hip position, range of motion and clinical tests for hip instability (positive Ortolani and Palmen/Barlow tests) were made.

Hip range of motion, the angle of passive flexion and abduction of the hips in the supine position were measured in both groups. Ultrasound follow-up and measurements according to the Graf method were performed using a Resona I9 ultrasound device with a linear probe of 2.5–9 MHz, and hips were classified into the appropriate Graf type. The Alpha and beta angles were measured in each subject.

The morphological characteristics of hip development were also noted at each visit.

The first ultrasound examination according to the Graf method was carried out in the first weeks after birth. After that, newborns and infants were followed every 2 months until they progressed to type I hips according to Graf, i.e., up to 8 months of age.

The Graf method and classification also include a description of the anatomical structures of the hip. The

first structure described is the shape of the bony roof, which can be good, adequate, deficient, severely deficient, or poor. The second structure described is the bony rim, formed at the point where the bony roof changes from concavity to convexity; it can be angular, blunt/rounded, and flat.

The third structure described is the cartilaginous roof, which can be covering or displaced cranially or caudally. The fourth structure described is the presence of an ossification nucleus of the femoral head, which can be present or absent.

The time interval to hip maturation (transition from IIa to type I hip according to Graf) was measured, and the exponential development of the hip was followed up to 8 months of age. Type IIa+ hips according to Graf are physiologically immature hips, which in some cases achieve spontaneous evolution and maturation, but in other cases progress to type IIa-.

Results

The two groups were compared to determine whether there was a significant difference in hip development.

Table 1. Baseline characteristics by fixation type

Bony roof - good	First exam	15	6	15	6
	Second exam	14	22	14	22
Bony roof adequate	First exam	25	34	25	34
	Second exam	26	18	26	18
McNemar test		p=0.000	p=0.000	p=0.000	p=0.000

There was a significant improvement in bony shaping between the first and second examinations on both sides (right and left). Some subjects who were in the “adequate” category at the first examination progressed to the “good” at the second examination. The results indicated that even without a wide swaddling there was natural improvement in bony shaping in a certain percentage of infants.

Table 2. Baseline characteristics by fixation type

		Without swaddle right	With swaddle right	Without swaddle left	With swaddle left
Bony rim - rounded/ blunt	First exam	19	18	19	18
	Second exam	2	12	2	11
Bony rim - sharp	First exam	21	12	21	12
	Second exam	38	28	38	29
McNemar test		p=0.000	p=0.000	p=0.000	p=0.000

There was a significant improvement in the status of the bony rim between the first and second examinations on both sides (right and left). A large proportion of infants progressed from the "rounded" category to the "sharp" category. The results showed natural improvement in the bony rim in infants without wide swaddling, which may indicate a positive trend in the development.

Table 3. Progression of the ossification of nucleus

		Without swaddle right	With swaddle right	Without swaddle left	With swaddle left
Absent ossification nucleus	First exam	36	36	35	35
	Second exam	13	17	11	16
Present ossification nucleus	First exam	4	4	5	5
	Second exam	27	23	29	24
McNemar test		p=0.000	p=0.000	p=0.000	p=0.000

There was a significant improvement in the formation of the ossification nucleus between the first and second examinations on both sides (right and left) in both groups. This was confirmed by McNema test (p = 0.000). There was significant progress in the development of the ossification nucleus in both groups, which may indicate a natural process of improvement.

Discussion

Type IIa+ hips according to Graf are physiologically immature hips, which in some cases achieve spontaneous evolution and maturation, but in other cases progress to type IIa. According to Graf, these physiologically immature hips must be followed by ultrasound until they progress to type I hips. The question remains whether, in this type of hip, preventive interventions can achieve faster development and maturation, since a certain degree of flexion and abduction has a stimulatory effect on hip development. With the application of wide swaddling, greater hip flexion and abduction are achieved, allowing better positioning of the femoral head in the acetabulum and actin as a stimulus for its development. The study by Raba A.A. *et al*. focused particularly on type IIa hips, pointing out that it is not possible to determine which hips will deteriorate and which will have spontaneous evolution, and this requires further investigation. However, as an independent warning factor, they emphasized that if the alpha angle at the first examination was less than 55 degrees, the hip had a negative predictive value.[11]

By introducing a protocol of ultrasound examinations according to the study by Bialik V, it becomes possible to distinguish two types of pathological hips: hips that will develop normally in the following months and hips that will progress to true dysplasia, potentially up to dislocation of the hip joint.[12]

In the study by Klisic *et al.*, the benefit of wide diapering was particularly emphasized, with a reduction in prevalence within 4 years, as well as a reduction in the incidence of surgical treatment. [13–15]

According to the results of the study by Wei Chun Lee *et al.*, in which 33 subjects used a wide diaper and 37 did not, it was concluded that the wide diaper had an effect on hip development in physiologically immature hips, while the effect of wide diapering in true dysplasia was not proven. The effect of the wide diaper has not been fully verified, since to prove that hip development is not due to natural spontaneous evolution and maturation, more than 31 subjects in each group are needed to achieve statistical significance > 0.8.1

According to the study by Harcke *et al.*, conducted on 30 newborns with suspected and documented DDH, it was shown that in subjects swaddled in adduction and extension, hip instability or dislocation progressed. In contrast, in subjects who were swaddled in a safe position, i.e., with a wide diaper, there was no change in hip stability.[16]

The study by Watanabe *et al.*, based on 18 years of clinical experience with DDH, showed that the use of diapers that hold the hips in flexion not only reduced the incidence but also the severity of DDH in childhood, indicating their effectiveness in preventing DDH.[17]

In this study, type I hips were included to determine whether the use of wide swaddling would lead to better hip maturation, while type IIa+ hips, which are physiologically immature, were selected to see whether the use of wide swaddling would lead to faster and better hip development. The results obtained so far have indicated that in both groups hip development shows progressive growth, i.e., spontaneous evolution.

Regarding morphological characteristics and the appearance of the ossification nucleus, it was determined that in most subjects the ossification nucleus was already present at the second examination, regardless of which group they belonged to, with significant further progress, indicating that the appearance of the ossification nucleus was also an independent, spontaneous process of hip maturation over time. In terms of the bony roof and bony rim, there was a higher percentage of better maturation in the group using wide swaddling, especially in the first months of its use. However, it cannot be excluded that this might have been spontaneous progression and hip maturation, since a similar progression was seen in the group without wide swaddling. All these results indicate that there is spontaneous maturation of type IIa+ hips over time, as well as spontaneous maturation in type Ia and Ib hips over time, and that this progression is similar for both types of hips. According to the study by Pellegrin M. *Et al.*, wide swaddling did not improve the position of abduction and flexion of the hips and therefore did not influence hip development, while the “caretaker’s side” carrying position of the newborn (baby-wearing in a sling with hips abducted 60 degrees and flexed 100 degrees) had a greater effect on hip development.4 Swaddling in extension and adduction of the lower extremities increases the rate of hip instability.[4] In the study by Sandeep Vaidya *et al.*, two groups of patients were compared: one swad-

dled in a so-called restrictive swaddle in extension and adduction, and the other swaddled in a so-called safe position. The results showed that using the restrictive position, the incidence of developmental dysplasia increased, whereas in the safe position, the incidence of DDH decreased.[5]

In the study by Bing Liu *et al.*, it was found that there was a progressive hip maturation in the first 3 months of life, whereas between 4–6 months there was a stagnation in hip development, i.e., reaching a plateau; it was also noted that hip development showed sex-related differences.[18]

Tegnander A. *et al.* conducted a study in which they followed a group of newborns and infants for 3 years who had normal clinical findings but suspicious-looking ultrasound findings for hip dysplasia. The conclusion of this study was that these patients did not require immediate treatment, because there was spontaneous resolution of hip dysplasia in most of them. Delaying treatment in some subjects with persistent dysplasia did not affect the outcome.[19-20]

The process of natural evolution and progression of developmental hip dysplasia as assessed by ultrasound were established by a population study in which subjects were followed using the Graf ultrasound method. The study determined that hips noted as healthy on the first ultrasound examination remained type I in almost 100% of cases, though development of dysplasia is still possible; whereas hips noted as physiologically immature at 4 weeks of age later progressed to type I without treatment.[21]

The degree of femoral head coverage and the age of the patient at the time of the first ultrasound examination have a significant impact on the decision about further treatment.

Conclusion

The ossification nucleus showed spontaneous appearance in both groups. In relation to the bony roof and bony rim, the results were similar in both groups, indicating independent hip maturation. An improvement in the morphological characteristics of the hip was observed in the first months of follow-up in both groups.

These results show that hip maturation is an independent process of progression during the first months of life, and that wide swaddling does not affect it.

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CLINICAL SCIENCE

POLYETHYLENE WEAR AND PAPROSKY MAP: AGE DRIVEN ACETABULAR BONE LOSS IN CEMENTED AND CEMENTLESS THA REVISIONS

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Abstract

Objective: To evaluate acetabular bone loss patterns, classified by the Paprosky system, in cemented and cementless acetabular components revised for polyethylene wear–related aseptic loosening, and to determine whether age, time to revision, and body mass index (BMI) predict greater defect severity. Methods: A retrospective cohort study was conducted involving 60 acetabular revision total hip arthroplasties, divided into cemented (n=30) and cementless (n=30) fixation groups. All revisions were undertaken for aseptic loosening attributed to polyethylene wear, with primary cups implanted within the Lewinnek "safe zone". Cases with developmental dysplasia, inflammatory arthropathy, or prior infection were excluded. Baseline variables were age, sex, BMI, and time to revision. Acetabular bone loss was graded radiographically using the Paprosky classification (I, IIA, IIB, IIC, IIIA, IIIB). Group differences in Paprosky subtype distribution were tested with chi-square analysis. Ordered logistic regression was employed to examine predictors of increasing Paprosky rank, and multivariable logistic regression to evaluate predictors of severe defects (Paprosky III vs. I–II), with BMI as the primary exposure and adjustment for fixation type, age, sex, and time to revision. Results: The Paprosky subtype distribution did not differ significantly between cemented and cementless cups (p=0.26). Higher age at revision was independently associated with more severe Paprosky categories (OR 1.08 per year, p=0.036), whereas fixation type showed only a non-significant trend toward higher severity for cementless components. BMI was not associated with severe acetabular defects, and cementless fixation showed a non-significant trend toward Paprosky III defects. Conclusions: In patients with polyethylene wear–related aseptic loosening, acetabular defect severity according to Paprosky classification appears more closely related to patient age - and, by implication, cumulative time in situ - than to fixation concept or BMI. Cemented and cementless acetabular components showed similar Paprosky defect distributions, and BMI was not an independent predictor of severe bone loss. These findings underscore the central role of long-term wear and osteolysis in acetabular bone loss and support development of models that integrate time-dependent wear exposure, key implant characteristics, and advanced imaging-based assessment to guide timing and strategy of revision total hip arthroplasty.

КЛИНИЧКИ ИСТРАЖУВАЊА

ПОЛИЕТИЛЕНСКО АБЕЊЕ И PAPROSKY КЛАСИФИКАЦИОНЕН СИСТЕМ: ВРЕМЕНСКИ-ЗАВИСНО АЦЕТАБУЛАРНО ГУБЕЊЕ НА КОСКЕНОТО ТКИВО УВИДЕНО КАЈ РЕВИЗИИ НА ЦЕМЕНТНА И БЕЗЦЕМЕНТНА ТОТАЛНА ЕНДОПРОТЕЗА НА КОЛК

Дарко Талевски[1], Јасминка Нанчева[2], Јасмин Циривири[1], Ненад Атанасов[2], Зоран Несторовски[1], Тоде Вранишкоски[1], Ненад Петков[1], Александар Каревски[1], Зорица Вангеловска[1], Душко Циривири[1], Александра Јованова[1]

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Цитирање: Талевски Д, Нанчева Ј, Циривири Ј, Атанасов Н, Несторовски З, Вранишкоски Т, Петков Н, Каревски А, Вангеловска З, Циривири Д, Јованова А. Полиетиленско абење и Paprosky класификационен систем: Временски-зависно ацетабуларно губење на коскеното ткиво увидено кај ревизии на цементна и безцементна тотална ендопротеза на колк. Арх Ј Здравје 2026;18 (1) 13-25.

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Клучни зборови: артропластика, протеза на колк, коскена ресорпција, разлабавување на протеза

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Печатарски права: ©2026 Дарко Талевски, Јасминка Нанчева, Јасмин Циривири, Ненад Атанасов, Зоран Несторовски, Тоде Вранишкоски, Ненад Петков, Александар Каревски, Зорица Вангеловска, Душко Циривири, Александра Јованова. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираа торигиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Цел: Да се процени моделот на ацетабуларно губење на коската класифицирано според Paprosky кај цементни и безцементни ацетабуларни компоненти ревидирани поради асептично олабавување поврзано со полиетиленско абење, и да се утврди дали возраста, времето до ревизија и индексот на телесна маса (ИТМ) предвидуваат поголема тежина на дефектот. Методи: Спроведовме ретроспективна кохортна студија на 60 ревизии на тотална ендопротеза на колк, поделени во цементна (n=30) и безцементна група (n=30). Сите ревизии беа поради асептично олабавување припишано на полиетиленско абење, со примарни чашки вградени во „безбедната зона" според Lewinnek. Беа исклучени случаите со развојна дисплазија, воспалителна артропатија или претходна инфекција. Основните варијабли беа: возраст, пол, BMI и време до ревизија. Ацетабуларното губење на коската беше радиографски класифицирано според Paprosky (I, IIA, IIB, IIC, IIIA, IIIB). Разликите во дистрибуцијата на поттиповите помеѓу групите беа тестирани со хи-квадрат тест. Со ординална логистичка регресија се испитуваа предикторите на зголемена Paprosky класификациона тежина, а со мултиваријантната логистичка регресија се анализираа предикторите за сериозни ацетабуларнидефекти (Paprosky III vs. I–II), со BMI како примарна изложеност и прилагодување за фиксација, возраст, пол и време до ревизија. Резултати: Немаше значајна разлика во дистрибуцијата на Paprosky поттиповите помеѓу цементните и безцементните чашки (p=0,26). Поголемата возраст при ревизија беше независно поврзана со повисоки Paprosky категории (OR 1,08 по година; p=0,036), додека типот на фиксација покажа само несигнификантен тренд кон поголема тежина кај безцементните компоненти. BMI не беше поврзан со сериозни ацетабуларни дефекти, а безцементната фиксација покажа несигнификантен тренд кон Paprosky III дефекти. Заклучоци: Кај пациенти кај кои постои асептично олабавување поврзано со полиетиленско абење, екстензивноста на ацетабуларниот дефект според Paprosky е повеќе поврзана со возраста и кумулативното време in situ отколку со типот на фиксација или BMI. Цементните и безцементните ацетабуларни компоненти покажаа слична распределба на Paprosky дефектите, а BMI не беше независен предиктор за опсежно губење на коската. Овие наоди ја нагласуваат примарната улога на долготрајното абење и остеолизата и укажуваат на потреба од предиктивни модели што ќе интегрираат временски зависна изложеност на абење во зависност од времето, карактеристики на имплантот и напредна дескриптивна проценка заснована на радиолошки иследувања за оптимално планирање на ревизиска тотална ендопротеза на колк.

Introduction

Total hip arthroplasty (THA) is widely regarded as one of the most effective surgical interventions for relieving pain, restoring function, and improving quality of life in patients with degenerative and post-traumatic pathology of the hip joint. Its utilization has risen steadily across the globe, in parallel with population aging and expanding indications in younger, more active individuals[1]. Aseptic loosening of the acetabular component remains the most common indication for revision THA and represents a major clinical and economic burden[2]. The extent and pattern of acetabular bone loss at the time of revision surgery strongly influence reconstructive complexity, implant choice, and the risk of subsequent re-revision, highlighting the importance of understanding how acetabular defects develop and progress[3,4].

The dominant driver of late aseptic loosening is periprosthetic osteolysis induced by particulate wear, most frequently from polyethylene liners[5,6]. Wear particles disseminate throughout the effective joint space and elicit a chronic foreign-body reaction in which macrophages phagocytose debris and release pro-inflammatory mediators that stimulate osteoclast-mediated bone resorption. This process leads to progressive periacetabular bone loss and the formation of a fibrous membrane at the bone–implant interface, ultimately compromising mechanical stability and resulting in loosening[5,7]. Historically, such changes were attributed to "cement disease," but long-term studies have shown that extensive osteolysis occurs around both cemented and cementless components, indicating that polyethylene wear and expansion of the effective joint space, rather than the presence of cement per se, are the principal etiologic factors[8,9]. In cemented constructs, debris can propagate along the cement–bone and cement–implant interfaces, whereas in cementless designs, particles may migrate along the porous surface, screw holes, and modular junctions, but in both settings' patient-related factors such as activity level and body mass index, and implant-related factors such as design and positioning, modulate wear and osteolysis patterns[10,1]. Consequently, the severity of acetabular bone loss at revision has profound implications for postoperative function, complication risk, and the likelihood of further revision[3,4].

Accurate characterization of acetabular bone loss is therefore essential for preoperative planning, selection of reconstruction strategy, and prognostic assessment in revision THA[11,12]. The Paprosky classification is the most widely used system for grading acetabular defects and is based on radiographic evaluation of hip center migration, integrity of the anterior and posterior columns and acetabular walls, and the presence of cavitary or segmental defects[13–15]. By stratifying bone loss into ordered categories from minimal to massive deficiency, it provides a common language for describing defects, comparing cohorts, and guiding the choice between hemispherical cups, augments, cages, and custom implants 16. However, despite its widespread adoption, the Paprosky system shows only fair to moderate interobserver agreement in many studies, reflecting the difficulty of translating complex three-dimensional bone loss into two-dimensional radiographic

categories and the frequent obscuration of key landmarks by the radiopaque cup[17–19]. Standardized training and structured radiographic analysis can improve reliability, but there remains a need to better link radiographic grading with actual defect morphology and clinical risk 15,20. Moreover, conventional radiographic classifications may underestimate the true complexity of periprosthetic bone loss, motivating the exploration of advanced techniques such as statistical shape modeling to enhance quantitative assessment and reproducibility[21].

Within this context, relatively few studies have specifically examined how polyethylene wear–related osteolysis translates into distinct Paprosky defect patterns in cemented versus cementless acetabular components[16]. By comparing the distribution and severity of Paprosky types between fixation modalities and correlating these patterns with clinical parameters such as implant survival time and body mass index, this investigation aims to identify characteristic modes of bone loss and potential predictors of more advanced defects[22-24,25].

Materials and Methods

Study design and cohort

This was a retrospective cohort analysis of 60 acetabular revision total hip arthroplasty procedures. Cases were divided into two fixation groups (cemented vs. cementless; 30 cases per group). In all cases, the acetabular liners were second-generation ultra-high molecular weight polyethylene (UHMWPE) articulating with a 28-mm cobalt–chromium (CoCr) femoral head.The indication for revision was constant across the cohort: aseptic loosening of the acetabular component attributed to polyethylene wear. Inclusion criteria were: (1) revision of a primary total hip arthroplasty for aseptic loosening of the acetabular component attributed to polyethylene wear, and (2) primary acetabular components implanted within the Lewinnek “safe zone” for cup orientation on standard radiographs[26]. We excluded patients with developmental dysplasia of the hip, inflammatory or autoimmune hip arthritis, and any history of periprosthetic joint infection in order to avoid the confounding effects of abnormal native acetabular morphology, systemic inflammatory disease, or infection-related bone loss on defect patterns.

Variables

Baseline variables included age at revision (years), sex, body mass index (BMI; kg/m^2), year of implantation, year of revision, and time to revision (years, derived as year of revision minus year of implantation). The primary outcome was acetabular defect severity categorized by the Paprosky classification (I, IIA, IIB, IIC, IIIA, IIIB)[25]. For ordinal regression, Paprosky categories were coded into an ordered rank from 1 (I) to 6 (IIIB). For binary regression, severe defects were defined as Paprosky III (IIIA/IIIB) and compared against non-severe defects (I/IIA/IIB/IIC).

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics (version 30.0; IBM Corp., Armonk, NY, USA). Continuous variables are summarized as mean (SD) and median [IQR] as appropriate. Between-group com-

parisons (cemented vs. cementless) were performed using Welch's t-test for mean differences and Mann–Whitney U tests for nonparametric comparisons. Categorical comparisons were analyzed using Fisher's exact test. Differences in Paprosky subtype distribution by fixation were evaluated using the chi-square test. Association between predictors and increasing Paprosky severity was evaluated using ordered logistic regression (proportional odds model), reporting odds ratios (OR) with 95% confidence intervals (CI). Association between predictors and severe defects (Paprosky III) was evaluated using multivariable logistic regression with BMI as the primary exposure. Models report OR with 95% CI; two-sided $p<0.05$ was considered statistically significant.

Results and Interpretation

The results of this study are presented as baseline comparisons and time-to-event analyses stratified by fixation type, followed by adjusted models evaluating associations with defect severity. Collectively, these findings summarize the observed group differences and the independent effects after accounting for potential confounders.

Table 1 summarizes baseline characteristics by fixation type; Table 1b reports p values for between-group comparisons. In this cohort, patients in the cemented group were older at revision and had longer time to revision. BMI differed between groups statistically.

Ordered logistic regression results are shown in Table 3. Age at revision was associated with higher

Table 1: Baseline characteristics by fixation type

Variable	Group	Value
n	cemented	30
Age, mean (SD)	cemented	76.4
BMI, mean (SD)	cemented	25.4
n	cementless	30
Age, mean (SD)	cementless	64.9
BMI, mean (SD)	cementless	27.7

Table 1b: P values for group comparisons

Variable	Test	p value
age	t-test	0.0
body mass index	t-test	0.0075
time to revision	t-test	0.0
severe defect (Paprosky III)	chi-square	0.4216

Table 2 and Figure 1 describe Paprosky subtype distribution by fixation type. The overall distribution did not differ significantly between groups (Chi-square test: $\chi^2(5)=6.47$, $p=0.2627$).

Table 2: Paprosky subtype distribution by fixation type

Paprosky subtypes	cemented	cementless
1	3	1
2A	3	4
2B	5	8
2C	9	4
3A	6	6
3B	2	7

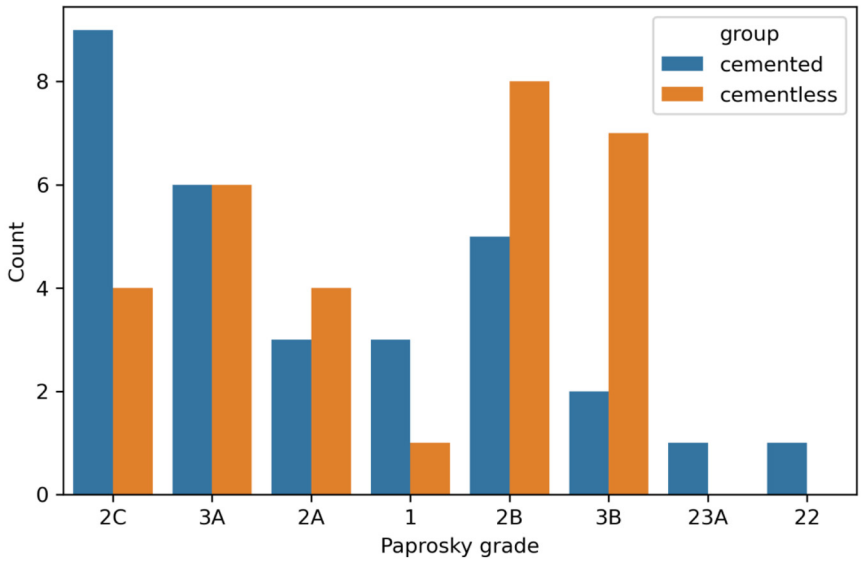


Figure 1: Paprosky subtype distribution by fixation type

Paprosky severity (OR 1.08, 95% CI 1.01–1.16, p=0.0356).

Fixation type showed a directional trend: cementless (vs. cemented) was associated with higher severity, but this did not reach statistical significance (OR 3.91, 95% CI 0.79–19.5, p=0.0958). The wide CI suggests limited power and/or substantial variability.

Multivariable logistic regression for severe defects (Paprosky III vs. I–II) is shown in Table 4. BMI was

Table 3: Ordered logistic regression for higher Paprosky rank (OR with 95% CI)

	coef	OR	CI low	CI high	p
Group	1.3647	3.9144	0.758	19.4996	0.0958
BMI	0.013	1.0131	0.8514	1.2054	0.8836
Time to revision years	0.0027	1.0027	0.84	1.197	0.976
Age/revision	0.0772	1.0803	1.0052	1.1609	0.0356
Female	0.4687	1.598	0.5041	5.0656	0.4259

not associated with severe defects (OR 1.03, 95% CI 0.84–1.26, p=0.7813). Fixation type showed a non-significant trend toward severe defects for cementless vs. cemented group (OR 4.59, 95% CI 0.73–28.92, p=0.1045). Table 4b provides the unadjusted BMI-only model for comparison.

Figure 3 visualizes time to revision by fixation type. The cemented group demonstrated a longer

Table 4: Logistic regression for severe defects (Paprosky III vs. I–II).

	coef	OR	CI low	CI high	p
Const	-8.3797	0.0002	0.0	4.0873	0.0933
BMI	0.029	1.0295	0.8386	1.2638	0.7813
Group	1.5244	4.5922	0.7291	28.924	0.1045
Time to revision years	-0.0132	0.9869	0.8043	1.2111	0.8997
Age revision	0.0856	1.0894	0.9873	1.2021	0.0881
Female	0.5393	1.7149	0.4357	6.7491	0.4404

Table 4b: Unadjusted logistic regression for severe defects with BMI only

	coef	OR	CI low	CI high	p
Const	-1.8086	0.139	0.0026	10.1831	0.3907
BMI	0.0447	1.0457	0.897	1.219	0.5681

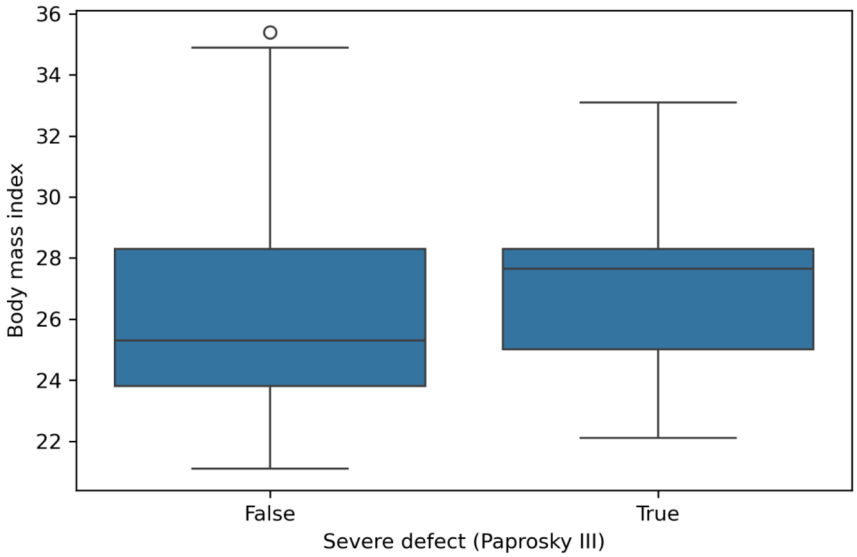


Figure 2: Body mass index by defect severity (Paprosky III vs I–II)

time to revision, consistent with the baseline comparisons. Because the groups differed at baseline, a simple unadjusted comparison of defect severity could be misleading; therefore, we used adjusted models.

Discussion

Age at revision emerged as the only clinical factor independently asso-

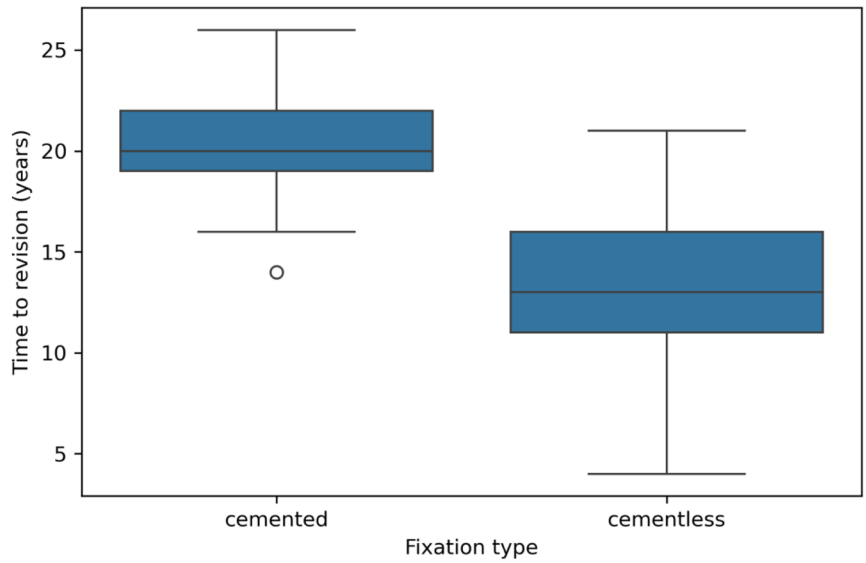


Figure 3: Time to revision by fixation type

ciated with higher Paprosky defect severity, pointing to a strong influence of cumulative time in situ on acetabular bone loss. In contrast, fixation concept (cemented vs cementless) did not materially alter the distribution of Paprosky subtypes, and BMI showed no association with severe Paprosky III defects. Taken together, these results suggest that polyethylene wear over time, rather than fixation type or patient body habitus, is the primary driver of advanced acetabular defects in this revision cohort.

This study examined how acetabular bone loss, graded by the Paprosky classification, presents in cemented and cementless acetabular components revised for polyethylene wear–related aseptic loosening, and whether clinical factors such as age, time to revision, and BMI predict more severe defects. Overall, fixation type did not significantly change the distribution of Paprosky subtypes, and BMI was not associated with severe Paprosky III defects, whereas age at revision emerged as an independent predictor of higher defect severity. These findings support the central role of polyethylene wear and time in situ as the main drivers of osteolysis and bone loss and highlight the limitations of relying on simple clinical variables or fixation concept alone to anticipate complex acetabular defects[2,27,28].

The absence of a statistically significant difference in Paprosky distribution between cemented and cementless cups suggests that, under the common pathway of polyethylene wear, both fixation concepts are vulnerable to similar patterns of acetabular bone loss. This observation is consistent with long-term series showing that extensive osteolysis and large cavitary or segmental defects occur around both cemented and cementless implants when wear is high and implants remain in situ for prolonged periods 29. In this context, the non-significant trend toward more severe

defects in cementless components, with wide confidence intervals in our regression models, should be interpreted as hypothesis-generating rather than definitive and may reflect differences in implant longevity, particle migration pathways, or unmeasured design features. Our data therefore do not support fixation type as a dominant independent determinant of Paprosky class but rather emphasize the need to view fixation as one element within a more complex construct-level analysis[2].

By contrast, the finding that older age at revision correlates with higher Paprosky severity is consistent with the concept that cumulative exposure to wear and osteolytic activity over time drives progressive bone depletion. Previous work has demonstrated strong associations between polyethylene wear rate, implant time in situ, and the development of major acetabular defects requiring complex reconstruction. In our cohort, cemented cases showed longer time-to-revision but not systematically more severe defects, suggesting that fixation mode and implant design may modify how cumulative wear translates into structural loss. This nuance supports a more sophisticated view: time and wear are necessary but not sufficient, and the specific construct (cup design, liner thickness, articulation, and possibly stem mechanics) modulates the final defect pattern[1,2,30].

The lack of association between BMI and severe Paprosky defects in adjusted models is also clinically relevant. Although obesity has often been assumed to increase wear and complications, several contemporary studies report that BMI is not a strong independent predictor of polyethylene wear or liner/head migration when implant placement and bearing characteristics are optimized[27,28]. Our results are consistent with this evidence and suggest that BMI, taken in isolation, should not be used as a surrogate marker for severe acetabular bone loss in polyethylene wear–driven revisions. Rather, BMI likely interacts with technical factors such as visualization, positioning, and activity patterns, and should be incorporated into broader, multifactorial models rather than treated as a standalone risk factor.

An important implication of our work is the central role and the limitations of the Paprosky classification in current practice. Using Paprosky types as the primary outcome reflects its status as the most widely adopted framework for describing acetabular bone loss and guiding reconstructive strategy in revision THA. However, variability in interobserver agreement and discrepancies between preoperative radiographic grading and intraoperative findings have been repeatedly reported, especially for complex three-dimensional defects and posterior/ischial bone loss obscured by the cup[12,16,19,31]. This classification noise may partially attenuate observable associations with clinical predictors, while the robust association with age suggests that only larger effects are detect-

able through this variability. At the same time, our data demonstrate that even with these limitations, meaningful patterns—such as the effect of age and time in situ—are identifiable, supporting the continued use of Paprosky while underscoring the need for improved imaging and classification tools.

From a broader perspective, our research is important because it directly addresses two pressing clinical needs: earlier identification of patients at risk of catastrophic acetabular bone loss and more individualized planning of revision strategies. Our findings show that simple stratification by fixation type or BMI is insufficient and point towards more nuanced, model-based approaches that integrate time in situ and generation of wear (including liner material and thickness, head size, and articulation), precise component positioning and biomechanics, and patient factors beyond BMI alone. This naturally leads to the concept of predictive models for acetabular defects in both cemented and cementless implants. Existing data on wear thresholds and their relationship to severe bone loss suggest that longitudinal measurements of wear and component position could be combined with patient and implant characteristics to estimate the probability of progressing to Paprosky III defects[21,30]. Our study contributes to this agenda by clarifying which readily available clinical parameters (age and time to revision) carry more predictive value and which (BMI, fixation type alone) are less informative, thereby helping to define the variable set that future models should prioritize.

A further strength of our concept is the explicit recognition that the femoral stem and its biomechanical behaviour may influence acetabular wear and osteolysis, even though our current dataset is acetabular-focused. Stem geometry, offset options, neck-shaft angle, stiffness, and fixation (cemented vs cementless) alter joint reaction forces and load transfer, which in turn affect polyethylene contact mechanics at the acetabular liner[32,33]. Certain stem designs may predispose to higher edge loading or altered pelvic tilt and thus to characteristic patterns of acetabular wear and defect formation. By framing future research around the total construct rather than the cup in isolation, we provide a rationale for studies that stratify Paprosky patterns by stem design and employ finite-element or gait-based models to mechanistically link femoral biomechanics to acetabular osteolysis. Finally, our study underscores the need for continued basic and translational research on osteolytic lesions themselves: how particles are generated and transported within the effective joint space, how local bone–immune interactions evolve over time, and why some patients develop extensive silent lesions while others do not. As advanced CT-based 3D reconstruction and statistical shape modeling become more widely available, integrating these tools with Paprosky grading, clinical variables, and implant de-

sign offers a promising path toward more accurate prediction, earlier intervention, and more bone-preserving revision strategies[20,21,31]. In this sense, our current findings are not an endpoint but a foundation: they identify key clinical signals, expose the limits of conventional predictors, and clearly map the trajectory for future research aimed at understanding and ultimately preventing severe acetabular bone loss in total hip arthroplasty.

This study has several limitations. It is a retrospective, single center analysis with a relatively small sample size, which limits generalizability. Acetabular bone loss was classified using standard radiographs and the Paprosky system, which may not fully capture three dimensional defect morphology or avoid interobserver variability. We also lacked direct measurements of polyethylene wear and detailed data on implant design and patient activity, so residual confounding cannot be excluded. This may also have introduced selection and information bias, meaning that the observed associations between age, fixation type, and defect severity should be interpreted with appropriate caution.

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CLINICAL SCIENCE

ASSOCIATION BETWEEN METABOLIC SYNDROME AND MENOPAUSAL SYMPTOMS IN PERIMENOPAUSE

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Abstract

The perimenopausal transition is characterized by hormonal fluctuations that trigger physical and psychological symptoms while simultaneously increasing the risk of metabolic syndrome. Understanding the link between these physiological shifts is crucial for preventing long-term cardiovascular and endocrine complications. Aim of the study was to determine the prevalence of metabolic syndrome (MS) in perimenopausal women and evaluate the association between the severity of menopausal symptoms and MS components. Materials and methods: This prospective cohort study was conducted over a one- year period (2021-2022) at the University Clinic for Gynaecology and Obstetrics. The study included 100 perimenopausal patients (aged 45–50) with abnormal uterine bleeding, categorized by BMI: group I (BMI > 30), group II (BMI up to 30), and a control group (n=40) of asymptomatic women. Data were collected via the Menopause Quick 6 assessment tool and laboratory biochemical analyses (lipid status, glycemia, blood pressure, and anthropometric measurements). Results: The prevalence of metabolic syndrome was significantly higher in patients of group I (80.3%) and group II (41.2%) compared to the control group (17.5%). While MS prevalence was similar between premenopausal (52.9%) and perimenopausal (52.8%) patients, specific symptoms showed strong statistical correlations. In group I ($p < 0.05$), metabolic syndrome and hot flashes, insomnia, and bone pain were significantly associated. In group II, insomnia remained significantly associated with MS ($p = 0.0326$). Hot flashes were the most prevalent symptom in group I (93.9%), while insomnia predominated in group II (73.5%). Conclusion: The study demonstrates a significant link between the intensity of menopausal symptoms - particularly vasomotor symptoms and sleep disturbances - and the prevalence of metabolic syndrome. These findings suggest that severe menopausal symptoms may serve as early clinical indicators of metabolic risk. An integrated clinical approach addressing both hormonal shifts and metabolic health is essential for reducing long-term cardiovascular and diabetic risks in perimenopausal women.

КЛИНИЧКИ ИСТРАЖУВАЊА

АСОЦИРАНОСТ ПОМЕЃУ МЕТАБОЛИЧКИОТ СИНДРОМ И СИМПТОМИТЕ НА ПЕРИМЕНОПАУЗА

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Клучни зборови: перименопауза, метаболички синдром, симптоми на менопауза.

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Печатарски права: ©2026 Анета Сима, Ана Данева-Маркова, Слаѓана Симеонова-Крстевска, Весна Ливринова, Драге Дабески. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираа торигиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Менопаузалната транзиција - перименопауза се карактеризира со хормонални флуктуации кои предизвикуваат физички и психолошки симптоми, а истовремено го зголемуваат ризикот од метаболички синдром. Разбирањето на врската помеѓу овие физиолошки промени е клучно за превенција на долгорочни кардиоваскуларни и ендокрини компликации. Цел на трудот е да се утврди преваленцијата на метаболичкиот синдром (МС) кај жени во перименопауза и да се процени поврзаноста помеѓу интензитетот на менопаузалните симптоми и компонентите на МС. Материјали и методи: Оваа проспективна кохортна студија беше спроведена во текот на една година (2021-2022) на Универзитетската клиника за гинекологија и акушерство. Студијата вклучуваше 100 пациентки во перименопауза (на возраст од 45–50 години) со абнормално крварење од матката, категоризирани според BMI: група I (BMI > 30), група II (BMI до 30) и контролна група (n=40) од асимптоматски жени. Податоците беа собрани преку алатката за проценка – модифициран прашалник Menopause Quick 6 и лабораториски биохемиски анализи (липиден статус, гликемија, крвен притисок и антропометриски мерења). Резултати: Преваленцијата на метаболички синдром беше значително поголема кај пациентките од групата I (80,3%) и групата II (41,2%) во споредба со контролната група (17,5%). Преваленцијата на МС, пак, беше слична кај пациентките во пременопауза (52,9%) и перименопауза (52,8%). Специфичните симптоми на перименопауза покажаа силни статистички корелации. Во групата I беа пронајдени значајни асоцијации ($p < 0,05$) помеѓу метаболичкиот синдром и брановите на топлина, несоницата и болката во коските. Во групата II, несоницата покажа значајна поврзаност со МС ($p = 0,0326$). Брановите на топлина беа доминантен симптом кај пациентките од групата I (93,9%), додека несоницата преовладуваше во групата II (73,5%). Заклучок: Студијата покажа значајна корелација помеѓу интензитетот на менопаузалните симптоми - особено вазомоторните симптоми и нарушувањата на спиењето - и преваленцијата на метаболичкиот синдром. Овие наоди сугерираат дека тешките менопаузални симптоми можат да послужат како рани клинички индикатори за метаболички ризик. Интегриран клинички пристап кој се однесува и на хормоналните промени и на метаболичкото здравје е од суштинско значење за намалување на долгорочните кардиоваскуларни и дијабетогени ризици кај жените во перименопауза.

Introduction

The perimenopausal transition is a critical phase in a woman's life, marked by significant hormonal fluctuations that often result in a variety of physical and psychological symptoms. Common menopausal symptoms, including hot flashes, night sweats, sleep disturbances, and mood changes, can severely impact quality of life [1,2]. At the same time, this period is also associated with an increased risk of metabolic disorders and metabolic syndrome, which includes factors like abdominal obesity, insulin resistance, hypertension, and dyslipidemia [3,4,5].

Several studies have indicated a possible link between the physiological changes occurring during perimenopause and the onset of metabolic syndrome [6, 7, 8]. However, the precise mechanisms behind this association remain poorly understood. Hormonal shifts, particularly declines in estrogen, are believed to play a crucial role in the development of both menopausal symptoms and metabolic syndrome. Still, other factors, including lifestyle, genetics, and pre-existing conditions, may also contribute [9, 11, 12].

Given the growing population of women experiencing perimenopause and the known risks associated with metabolic syndrome - such as cardiovascular disease and type 2 diabetes - understanding the relationship between these two conditions is of paramount importance [3,8,10].

This study aimed to explore the association between menopausal symptoms and metabolic syndrome in perimenopausal women, highlighting potential pathways and implications for clinical management and preventive care.

The primary aim of this study was to determine the prevalence of metabolic syndrome in women undergoing perimenopause and to find an association between metabolic syndrome and the severity of menopausal symptoms, including vasomotor symptoms (hot flashes, night sweats), sleep disturbances, mood disorders, sexual dysfunction, etc.

Materials and methods

This was a prospective cohort study, conducted at the University Clinic for Gynecology and Obstetrics in a 1-year period (2021-2022). A total of 100 patients with abnormal uterine bleeding in the perimenopausal period were included, aged 45-50 years, who were divided into two groups according to BMI. The control group consisted of 40 patients.

a) First group - patients with BMI> 30 (obese patients),

b) Second group - patients with BMI up to 30 (increased body weight),

c) Control group (40) - asymptomatic patients, with regular gynecological findings (without pathological findings and normal BMI).

A complete gynecological and ultrasound examination was performed (with transvaginal ultrasound, vaginal probe DE10-3E, device type Mindray DC-70). Further interventions had been done where indicated, which were not included in this study.

Here, we only included laboratory analyses and data from the Menopause Quick 6 assessment tool questionnaire - ultrasound examination - with transvaginal ultrasound (vaginal probe DE10-3E, device type Mindray DC-70). Laboratory analyses were

performed at the University Clinic for Biochemistry (blood pressure, glycemia, lipid status, waist circumference, waist/hip ratio, BMI).

Blood pressure (on 3 occasions with an interval of 1 hour between measurements, in a sitting position) was measured using the device OMRON M3 Comfort.

Measurement of body weight and height was done with a digital body scale (type GIMA Pegaso electronic body scale), barefoot, without clothes, only in underwear), electronic online calculator for BMI. Waist and hip circumferences were measured using a tape measure; waist circumference was measured at the level of the navel, before the end of expiration, and hip circumference was measured at the level of the trochanters of the femur. Glycemia and lipid status were measured by spectrophotometric method (Albott Architect C 80).

Results

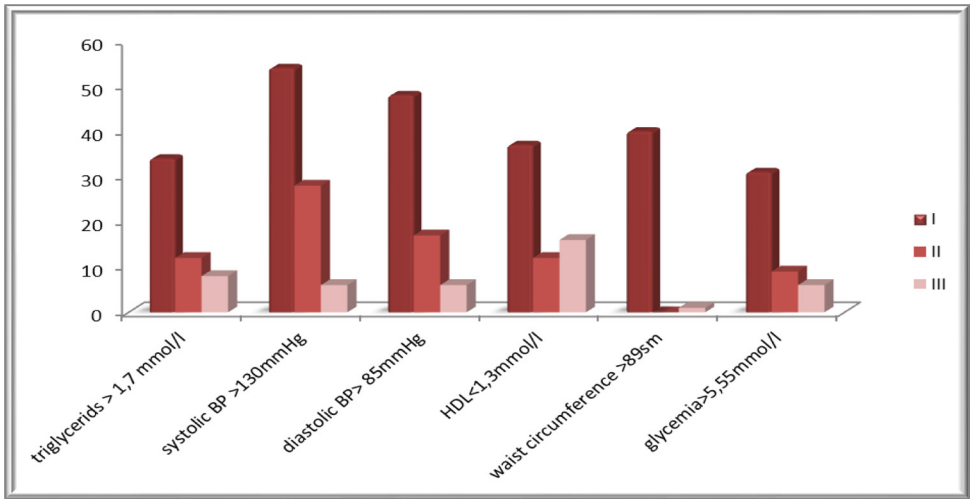


Figure 1: Patients who met the AHA criteria of metabolic syndrome.

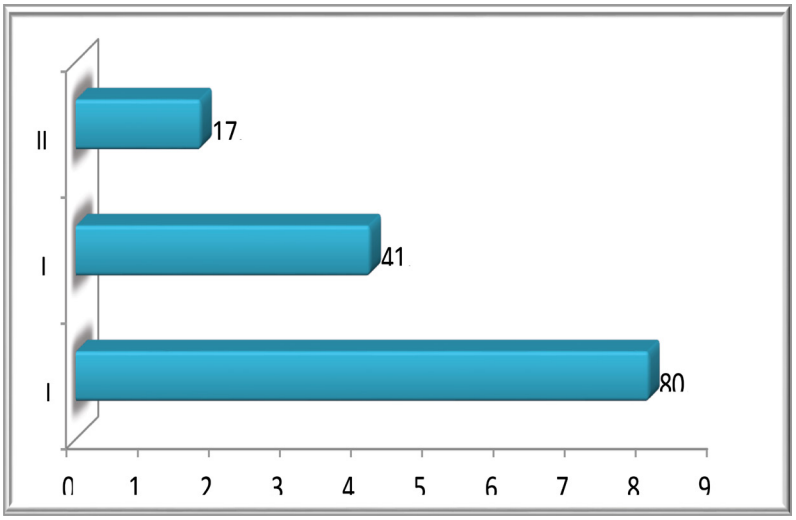


Figure 2: Prevalence of metabolic syndrome in pre/perimenopausis

The prevalence of MS in the three studied groups showed the highest value in the first studied group - high 80.3%: in the second group it was 41.2%, and in the control group it was the lowest, 17.5% (Figure 1).

The prevalence of metabolic syndrome (MS) in patients showed a similar value. It was 52.9% in premenopausal, and 52.8% in perimenopausal women (Figure 2).

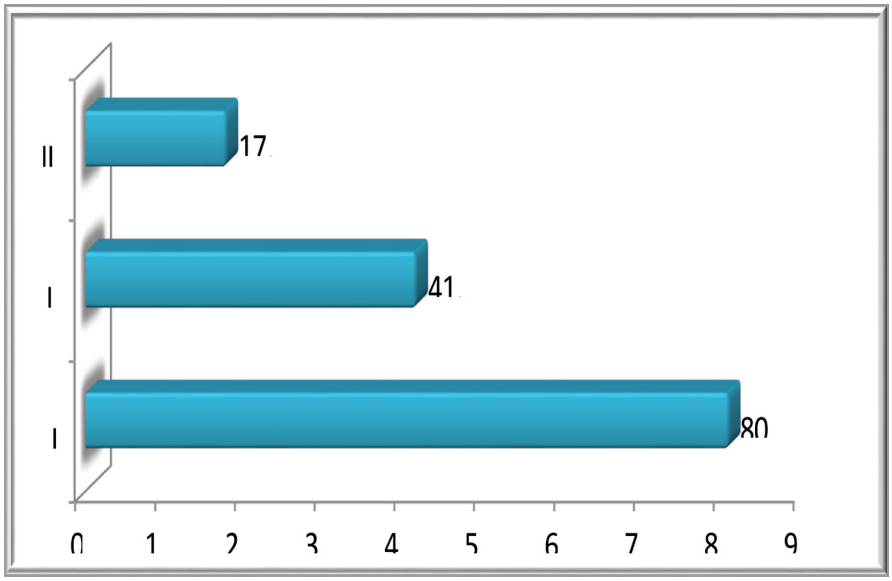


Figure 3: Menopausal symptoms in all groups

In the first examined group, the highest percentage of menopausal symptoms were hot flashes - 93.9%, followed by emotional instability - 75.8%, elevated TT - 71.2%, insomnia (disturbed sleep) - 65.2%, sexual dysfunction - 63.6%, therapy - 56.1%, bone pain - 36.4%, and the lowest percentage was dysuric complaints - 31.8%.

In the second examined group, the highest percentage of menopausal symptoms was insomnia - 73.5%, followed by hot flashes - 58.5%, emotional instability, therapy - 52.9%, sexual dysfunction - 47.1%, bone pain - 20.6%, elevated TT - 17.6%, and the lowest percentage was dysuric complaints - 14.7%.

In the third control group, the highest percentage of menopausal symptoms was elevated TT - 65.0%, followed by hot flashes - 60.0%, emotional instability - 50.0%, insomnia - 45.0%, sexual dysfunction - 37.5%, therapy and dysuric complaints with 22.5%, and the lowest percentage was bone pain - 17.5% (Figure 3).

Table 1. Baseline characteristics by fixation type

Group	Variable	Pearson Chi-square ($\chi 2$)	p-value	Significance ($p<0.05$)
First Group	Hot flashes	4.2809	0.0385	Yes
	Insomnia	8.4289	0.0037	Yes
	Therapy	7.1499	0.0075	Yes
	Bone pain	5.7509	0.0165	Yes
Second Group	Insomnia	4.5679	0.0326	Yes

An association was observed between metabolic syndrome and the presence of hot flashes in the first group ($p<0.05$) (Pearson Chi-square: 4.28091, p=.038543).

An association was found between metabolic syndrome and the presence of insomnia in the first group ($p<0.05$) (Pearson Chi-square: 8.42893, p=.003693), and the use of therapy in the first group ($p<0.05$) (Pearson Chi-square: 7.14987, p=.007497).

An association was registered between metabolic syndrome and the presence of bone pain in the first group ($p<0.05$) (Pearson Chi-square: 5.75088, p=.016480).

An association was observed between metabolic syndrome and the presence of insomnia in the second group ($p<0.05$) (Pearson Chi-square: 4.56787, p=.032577) (Table 3).

Discussion

The findings of this study suggested a significant association between menopausal symptoms and the development of metabolic syndrome during perimenopause. The hormonal changes that characterize this transition, particularly the decline in estrogen, appear to play a pivotal role in the co-occurrence of these conditions. Our results align with previous studies that have demonstrated a link between estrogen deficiency and increased risk factors for metabolic syndrome, such as insulin resistance, central obesity, and dyslipidemia [13, 14, 16].

The data indicate that the severity of vasomotor symptoms, including hot flashes and night sweats, is strongly correlated with the presence of metabolic syndrome markers. This relationship suggests that women experiencing more intense menopausal symptoms may be

at greater risk of developing metabolic syndrome. This supports the hypothesis that vasomotor symptoms may be a clinical indicator of underlying metabolic disturbances, potentially driven by common hormonal mechanisms [10, 11].

Furthermore, sleep disturbances and mood changes, which are also prevalent in perimenopause, were found to be associated with key components of metabolic syndrome.

Sleep disruption, often linked to vasomotor symptoms, may exacerbate metabolic dysfunction by altering cortisol levels and insulin sensitivity, thus contributing to weight gain and hypertension. Mood disturbances, such as anxiety and depression, may similarly influence metabolic health by affecting lifestyle choices, including physical activity and diet.

The findings underscore the importance of considering the metabolic health of women experiencing menopausal symptoms during perimenopause. Early identification and management of these symptoms may provide an opportunity to mitigate the risk of developing metabolic syndrome. Clinicians should be aware of the potential for co-occurring metabolic and menopausal symptoms, and a comprehensive approach to management - addressing both hormonal and lifestyle factors - may be key to improving outcomes [15, 16, 17].

Limitations and Future Research

While this study adds valuable insight

into the relationship between menopausal symptoms and metabolic syndrome, several limitations should be acknowledged. The cross-sectional nature of the study limits the ability to infer causality between these conditions. Future research would benefit from longitudinal studies that track the progression of menopausal symptoms and metabolic changes over time. Additionally, the study population may not fully represent the diversity of perimenopausal women, as factors such as ethnicity, socioeconomic status, and pre-existing health conditions were not extensively controlled for. Future studies should aim to explore how these variables may influence the association between menopausal symptoms and metabolic syndrome.

Conclusion

Women experiencing more severe vasomotor symptoms, such as hot flashes and night sweats, were found to be at a heightened risk for developing metabolic syndrome. Additionally, other symptoms like sleep disturbances and mood changes also demonstrated strong associations with key components of metabolic syndrome, including abdominal obesity, insulin resistance, and hypertension. Recognizing that severe menopausal symptoms may signal a higher risk of metabolic syndrome can lead to early intervention strategies. Addressing both hormonal imbalances and metabolic risk factors could help reduce the long-term health risks associated with cardiovascular disease and type 2 diabetes in this population.

Further research, particularly longitudinal studies, is needed to clarify the causal relationships between symptom severity and metabolic changes. However, monitoring and managing metabolic health in women with severe menopausal symptoms is a critical step toward improving their overall well-being during the perimenopausal transition.

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ORAL HEALTH

LASER APPLICATION FOR ROOT CANAL DISINFECTION DURING ENDODONTIC THERAPY

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Abstract

Effective cleaning, irrigation, and sterilization of root canals are essential criteria for successful endodontic treatment of infected root canal systems. Conventional chemomechanical procedures for root canal debridement cannot reliably ensure complete disinfection of the entire endodontic space, particularly in anatomically complex areas such as the apical delta and accessory canals. Following mechanical instrumentation, approximately 35% of the dentinal walls remain covered with bacterial biofilm, and even after the application of antimicrobial agents, root canals are not completely disinfected. Considering that sterility of the root canal system is a key factor for successful treatment of apical periodontitis, continuous efforts have been made to identify more effective disinfection methods. Over the past decade, the use of lasers for root canal disinfection and cleaning has increased significantly, although their full potential is still under investigation.

The aim of this study was to explain the fundamental principles of laser–tissue interaction within root canals and to compare laser-assisted endodontic treatment with conventional irrigation using 3% sodium hypochlorite and ultrasonic activation in teeth diagnosed with chronic apical periodontitis. This in vivo study was conducted on 60 teeth diagnosed with chronic apical periodontitis, which were randomly divided into three groups. Mechanical preparation of the root canals was performed using a standardized protocol with nickel–titanium rotary instruments, followed by continuous irrigation with 2.5% sodium hypochlorite (NaOCl) in combination with 17% ethylenediaminetetraacetic acid (EDTA). After completion of chemomechanical preparation, the following disinfection protocols were applied: (1) 2.5% NaOCl in combination with EDTA, (2) 2.5% NaOCl with sonic activation using an endoactivator, (3) Application of a diode laser for sterilization of the root canal system. Treatment effectiveness was assessed through radiographic evaluation of the periapical status. Radiographic examinations were performed at three-time intervals: before treatment, at 3 months, and at 6 months follow-up. The results of this study demonstrated that all applied disinfection protocols led to a reduction in periapical lesions: over the observation period. However, the most pronounced decrease in Periapical Index (PAI) values was observed in the group treated with laser-assisted disinfection.

ОРАЛНО ЗДРАВЈЕ

ПРИМЕНА НА ЛАСЕРИ ЗА ДЕЗИНФЕКЦИЈА НА КОРЕНСКИ КАНАЛИ ВО ТЕК НА ЕНДОДОНТСКА ТЕРАПИЈА

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Клучни зборови: ласери, ендодонтски третман, стерилизација на канали на корени, радиографска анализа.

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Печатарски права: ©2026 Марина Ефтимоска, Василка Ренџова. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираа оригиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторите изјавија дека немаат конкурентски интереси.

Извадок

Добрата обработка, иригацијата и стерилизација на коренските канали се важни предуслови за успешен ендодонтски третман кај инфицирани коренски канали. Традиционалните процедури за хемиско-механичко чистење на коренскиот канал не можат со сигурност да обезбедат комплетна успешна дезинфекција на целиот ендодонтски простор, особено во областите на апикалната делта, како и акцесорните канали. По механичката инструментација, околу 35% од ѕидот на дентинот останува покриен со бактериски биофилм, но и по примена на антимикробни агенси коренските канали не се целосно дезинфицирани. Имајќи предвид дека за успешен ендодонтски третман на апикалните пародонтити клучен фактор е стерилноста на каналниот систем, се прават постојани напори од страна на експертите да се најде најуспешен начин за тоа. Последнава декада употребата на ласери за дезинфекција и чистење на коренските канали е интензивирана, а нејзиниот потенцијал сè уште се истражува. Целта на овој труд беше да се објаснат основните принципи на интеракција на ласерите со ткивата во коренските канали, да се спореди ендодонтскиот третман со помош на ласер, наспроти конвенционалната употреба на 3% натриум хипохлорит и ултразвучната обработка на каналите кај заби со хроничен апикален периодонтитис. Испитувањето го реализиравме во in vitro услови на 60 заби со дијагностициран хроничен пародонтитис кои ги поделивме во три групи. Механичката подготовка на коренските канали ја спроведувавме со стандардизиран протокол на инструментализација со никел-титаниумски ротирачки инструменти, проследено со континуирана иригација со 2,5% натриум хипохлорит (NaOCl) во комбинација со 17% етилендиаминтетраоцетна киселина (ЕДТА). По завршување на механичко-медикаментозната обработка, ги применивме следните протоколи за дезинфекција: 1. 2,5% NaOCL во комбинација со ЕДТА, 2. 2,5% NaOCL во комбинација со ендоактиватор (UltraX, Eighteeth), 3. Употреба на соодветен мекоткивен ласер за стерилизација на ендодонтски третираните коренски канали. Ефективноста на третманот ја проценувавме преку радиографска анализа на периапикалниот статус, а радиографските снимки ги изработувавме во три временски интервали: пред почетокот на третманот, по 3 месеци, по 6 месеци. Резултатите од ова истражување покажаа дека сите применети протоколи за дезинфекција на коренско-каналниот систем доведуваат до намалување на периапикалните лезии во текот на периодот на следење. Сепак, најизразено намалување на PAI (Periapical Index) вредностите беше забележано кај групата третирана со ласерска дезинфекција.

Introduction

Endodontic therapy represents a fundamental discipline in dentistry, primarily aimed at preserving the natural tooth through elimination of infection from the root canal system and prevention of reinfection. Apical periodontitis is an inflammatory response of the periapical tissues, most commonly caused by microbial infection of the pulp space, in which microorganisms and their by-products play a crucial role in the pathogenesis of the disease[1,2].

Microbiological investigations have demonstrated that root canal infections are polymicrobial in nature and predominantly composed of anaerobic bacteria organized in biofilms. Biofilms represent complex microbial communities that provide protection to bacteria and significantly increase their resistance to antimicrobial agents, thereby contributing to the persistence of infection and treatment failure[3,4].

The foundation of endodontic treatment relies on chemomechanical preparation of the root canal system, which includes mechanical instrumentation combined with the use of antimicrobial irrigants. Sodium hypochlorite (NaOCl) is considered the gold standard irrigant due to its potent antimicrobial and proteolytic properties[5]. However, despite its effectiveness, NaOCl does not ensure complete elimination of microorganisms, particularly in the deeper layers of dentin and within anatomically complex regions of the root canal system 6. This limitation is largely attributed to relatively high surface tension of NaOCl, which restricts its ability to penetrate into narrow isthmuses, lateral canals, and dentinal tubules, preventing adequate contact with bacteria residing in these areas. Furthermore, the capillary forces within the intricate microchannel network of dentin are insufficient to draw the solution deeply enough to exert a meaningful antimicrobial effect, leaving residual biofilm and necrotic tissue beyond the reach of conventional irrigation.

The complex anatomy of the root canal system—including lateral canals, isthmuses, and apical deltas—poses a significant challenge for complete disinfection. Studies have shown that a considerable portion of the canal walls remains untouched after mechanical preparation, allowing the survival of microorganisms[7]. Additionally, the formation of the smear layer reduces the penetration and effectiveness of irrigants[8].

Contemporary endodontic approaches include the activation of irrigants using ultrasonic and sonic systems in order to enhance their penetration and hydrodynamic behavior. These techniques have demonstrated improved efficacy, particularly in the apical third and in anatomically complex regions; however, they still do not achieve complete sterilization of the root canal system[5, 6, 9,37].

From the early 1990s, laser-activated irrigation has increasingly been introduced as an adjunctive method for disinfection in endodontics. Lasers emit coherent and monochromatic light energy that interacts with biological tissues through photothermal and photochemical mechanisms, resulting in microbial

destruction and protein denaturation[10].

One of the principal advantages of laser application is its ability to penetrate deeply into dentinal tubules, where conventional irrigants have limited effect. Studies have demonstrated that laser therapy can reduce more than 99% of bacterial load within the root canal system and is particularly effective against resistant species such as Enterococcus faecalis [11,12].

Recent clinical and systematic studies have confirmed that laser therapy, especially when combined with sodium hypochlorite, leads to a significant reduction in bacterial load and enhances root canal disinfection. This combined approach demonstrates superior outcomes compared to conventional methods alone [13]. Furthermore, randomized clinical trials suggest that diode laser application may contribute to improved periapical healing during follow-up periods[14].

Despite these advantages, systematic reviews indicate that laser therapy cannot replace conventional chemomechanical preparation but should be considered an adjunctive method that enhances the effectiveness of root canal disinfection[15]. Additional well-designed clinical studies with standardized protocols and long-term follow-up are required to establish its definitive clinical efficacy[16].

The aims of this study were:

- to explain the fundamental principles of laser–tissue interaction within the root canal system;
- to compare laser-assisted endodontic treatment with conventional irrigation using 3% sodium hypochlorite and ultrasonic activation in teeth diagnosed with chronic apical periodontitis;
- to radiographically evaluate, over a follow-up period of 3 and 6 months, the reduction of periapical lesions after the application of three different irrigation and disinfection techniques in root canal therapy.

Materials and methods

To achieve the objectives of this study, the investigation was conducted under in vivo conditions on a total of 60 teeth diagnosed with chronic apical periodontitis. The study was carried out at the Clinic for Restorative Dentistry and Endodontics,

Faculty of Dentistry – Skopje, Ss. Cyril and Methodius University in Skopje during a period of 18 months.

Inclusion Criteria

- Permanent teeth with clinical and radiographic diagnosis of chronic apical periodontitis
- Teeth with necrotic pulp
- Presence of a periapical radiolucent lesion on radiographic examination
- Single-rooted or multi-rooted teeth with negotiable root canals.

Exclusion Criteria

- Patients who had received antibiotic therapy within the previous 3 months

- Teeth with previous endodontic treatment
- Teeth with vertical root fractures
- Patients with systemic diseases that could affect the healing process
- Third molars were not included.

Following initial selection, the teeth were randomly assigned into three experimental groups (n = 20), according to the applied irrigation and disinfection protocol.

Clinical Endodontic Protocol

The tooth was isolated with a rubber dam, and a straight-line access cavity was prepared to expose all canal orifices. The canals were located to confirm patency prior to rotary instrumentation.

Orifice shaping was performed with ProTaper SX to eliminate coronal interferences and improve straight-line access to the apical third.

Working length was determined using an apex locator (iPexII), with a size #10 or #15 file placed and confirmed via periapical radiograph. The working length was set at the point of apical constriction, approximately 0.5–1 mm short of the radiographic apex.

A reproducible glide path was confirmed to full working length using a #15–#20 hand file, reducing the risk of file separation and canal transportation in the curved molar canals.

A sequential crown-down technique was employed. Each file was used with a light in-and-out pecking motion (2–3 mm amplitude), with no more than 2–3 seconds of continuous engagement per file:

Table 1. List of files, tip size and function

File	Tip size (D0)	Function
S1 (Shaping 1)	0.17 mm	Coronal/middle third shaping
S2 (Shaping 2)	0.20 mm	Extended shaping toward apical third
F1 (Finishing 1)	0.20 mm	First apical finishing file
F2 (Finishing 2)	0.25 mm	Second apical finishing file
F3 (Finishing 3) (as needed)	0.30 mm	Used for wider canals

Recapitulation with a #10–#15 hand file was performed between each rotary file to maintain patency and remove debris. Irrigation was carried out after every instrument change. The final apical size was selected based on the initial canal diameter and tactile resistance at working length. Narrower, curved canals were finished at F1–F2, while wider or straighter canals were taken to F3 or beyond.

This was accompanied by continuous irrigation with 2.5% sodium hypochlorite (NaOCl) in combination with 17% ethylenediaminetetraacetic acid (EDTA).

Sodium hypochlorite (NaOCl), 2.5–5.25%, (10–20 mL per canal) was used as the primary irrigant, delivered with a side-vented needle positioned 2–3 mm short of working length, using slow, passive delivery to avoid apical extrusion.

A 17% EDTA solution was applied for 1 minute in the final stage to remove the smear layer, followed by a final NaOCl flush. A final rinse with saline or sterile water was performed to neutralize residual chemicals before obturation.

After accomplishment of chemomechanical preparation, the following disinfection protocols were applied:

Group 1 – Conventional Irrigation

Irrigation with 2.5% sodium hypochlorite (NaOCl) combined with 17% EDTA was performed to remove the smear layer and enhance chemical disinfection of the root canal system.

Group 2 – Activated Irrigation

Irrigation with 2.5% NaOCl activated using an EndoActivator (UltraX, Eighteeth) was applied to improve irrigant penetration and fluid dynamics within complex anatomical areas, including lateral and accessory canals.

Group 3 – Laser Disinfection

Root canal disinfection was performed using a soft-tissue diode laser, (Woodpecker – Smart Laser Blue) applied according to the manufacturer's protocol, aiming to achieve photothermal reduction of microorganisms and disruption of the bacterial biofilm within the root canal system.

Intracanal Medication and Obturation

Following disinfection, the canals were dried with sterile paper points and filled with an inter-appointment calcium hydroxide [$Ca(OH)_2$]-based intracanal medicament, which was left *in situ* for 15 days. The access cavity was temporarily sealed with glass ionomer cement.

In the absence of clinical symptoms, a second visit was scheduled. During this appointment, the $Ca(OH)_2$ paste was removed using 5 mL of 2.5% NaOCl and a Hedström file. The canals were then dried with sterile paper points and obturated using gutta-percha and AH26 sealer (Dentsply, Konstanz, Germany) employing the single-cone technique.

A glass ionomer base was placed over the obturation, followed by a composite restoration using a total-etch adhesive technique.

Radiographic Evaluation

Treatment effectiveness was assessed by radiographic evaluation of the periapical status. Radiographs were obtained at three-time intervals:

- before treatment (baseline),
- after 3 months,
- after 6 months.

Changes in the periapical region were evaluated based on the reduction of periapical radiolucency using the Periapical Index (PAI) (37).

Table 2. Periapical Index (PAI) Scoring System

PAI Score	Radiographic Findings
1	Normal periapical structures
2	Small changes in bone structure
3	Changes in bone structure with some mineral loss
4	Well-defined radiolucent area
5	Severe periodontitis with exacerbating features

Results

Statistical analysis

In this clinical study, a total of 60 teeth with periapical lesions were analyzed, divided into three groups according to the applied root canal disinfection protocol. Each group consisted of 20 teeth.

Radiographic evaluation was performed using the Periapical Index (PAI) before treatment, at 3 months, and at 6 months. All groups showed a gradual reduction in PAI values during the follow-up period, indi-

Table 3. List of files, tip size and function

Group	Baseline Mean (± SD)	Mean at 3 Months (± SD)	Mean at 6 Months (± SD)	p-value (ANOVA)
Conventional irrigation	4.15 ± 0.72	3.40 ± 0.65	2.55 ± 0.60	<0.001*
Sonic-activated irrigation (UltraX)	4.20 ± 0.70	3.10 ± 0.58	2.05 ± 0.52	<0.001*
Laser-assisted disinfection	4.25 ± 0.68	2.85 ± 0.55	1.60 ± 0.48	<0.001*

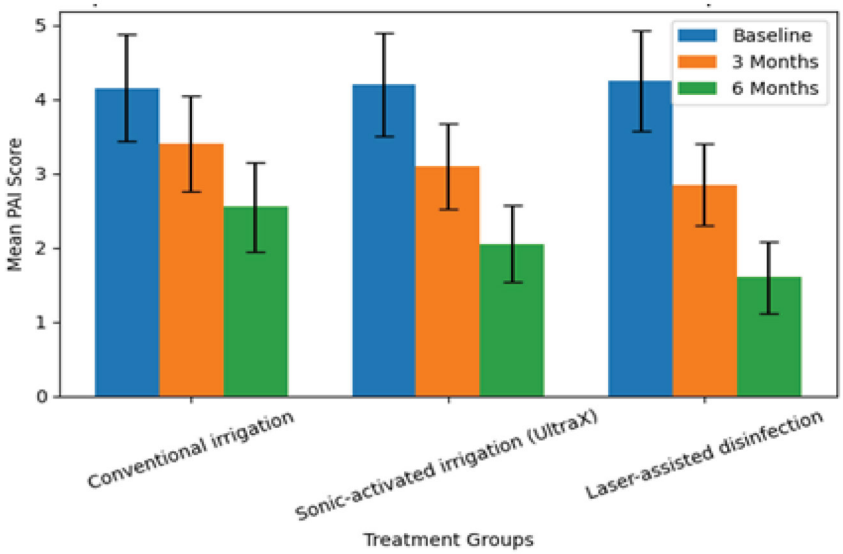


Figure 1: Comparison of PAI score reduction in treatment groups during the evaluation period

cating progressive periapical healing.

As shown in Table 1 and Figure 1, all three groups demonstrated a continuous decrease in mean PAI values throughout the evaluation period. The most pronounced reduction in PAI values was observed in the laser-assisted disinfection group. The average PAI in this group decreased from 4.25 ± 0.68 at baseline to 2.85 ± 0.55 at 3 months and 1.60 ± 0.48 at 6 months.

In the sonic-activated irrigation group, the average PAI decreased from 4.20 ± 0.70 to 3.10 ± 0.58 at 3 months and 2.05 ± 0.52 at 6 months.

The conventional irrigation group also showed a reduction in PAI values, although to a lesser extent, from 4.15 ± 0.72 at baseline to 3.40 ± 0.65 at 3 months and 2.55 ± 0.60 at 6 months.

At baseline, no statistically significant differences were observed between the groups ($p > 0.05$), indicating homogeneity. At 3 months, a trend of decreasing PAI values was observed in all groups, with the most pronounced reduction seen in the laser group.

At 6 months, the laser group showed the lowest mean PAI value (1.60 ± 0.48), followed by the sonic-activated irrigation group (2.05 ± 0.52), while the highest value was observed in the

Table 4. Clinical outcomes at 6 months

Group	Total Teeth	Complete Healing	Partial Healing	Unsuccessful Healing
Conventional irrigation	20	9 (45%)	7 (35%)	4 (20%)
Sonic-activated irrigation (UltraX)	20	12 (60%)	6 (30%)	2 (10%)
Laser-assisted disinfection	20	15 (75%)	4 (20%)	1 (5%)

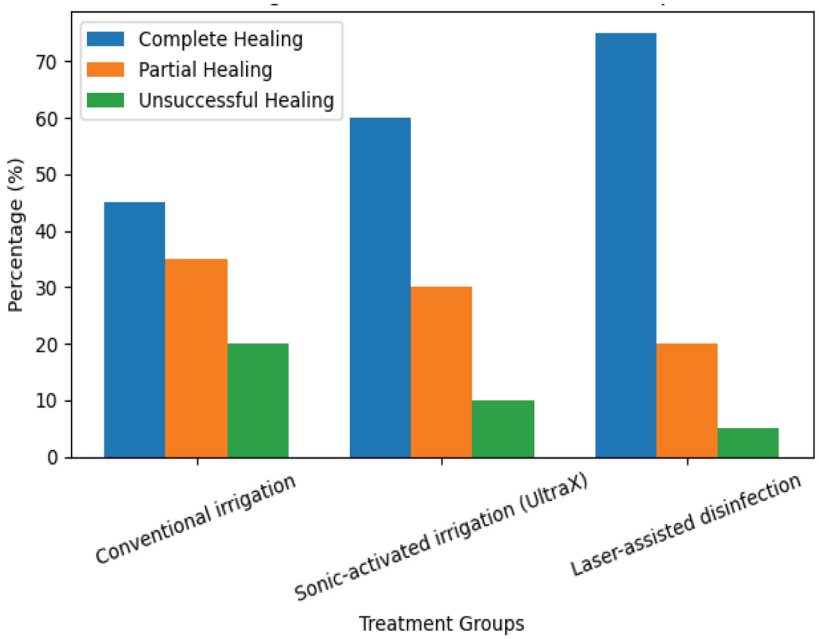


Figure 2: Healing outcomes across treatment groups

conventional irrigation group (2.55 ± 0.60). ANOVA analysis revealed statistically significant differences between groups ($p < 0.001$).

Clinical evaluation at 6 months (Table 2, Figure 2) indicated that:

- The highest rate of complete healing was observed in the laser group (75%).
- Sonic-activated irrigation achieved 60% complete healing.
- Conventional irrigation showed the lowest rate (45%).

Regarding unsuccessful cases, the highest rate was observed in the conventional group (20%), while the lowest was in the laser group (5%). Chi-square test revealed a statisti-

Table 5. List of files, tip size and function

PAI Score	Conventional Irrigation (n=20)	Sonic-activated Irrigation (UltraX) (n=20)	Laser-assisted Disinfection (n=20)
PAI 1	5 (25%)	7 (35%)	10 (50%)
PAI 2	4 (20%)	5 (25%)	5 (25%)
PAI 3	5 (25%)	4 (20%)	3 (15%)
PAI 4	4 (20%)	3 (15%)	1 (5%)
PAI 5	2 (10%)	1 (5%)	1 (5%)

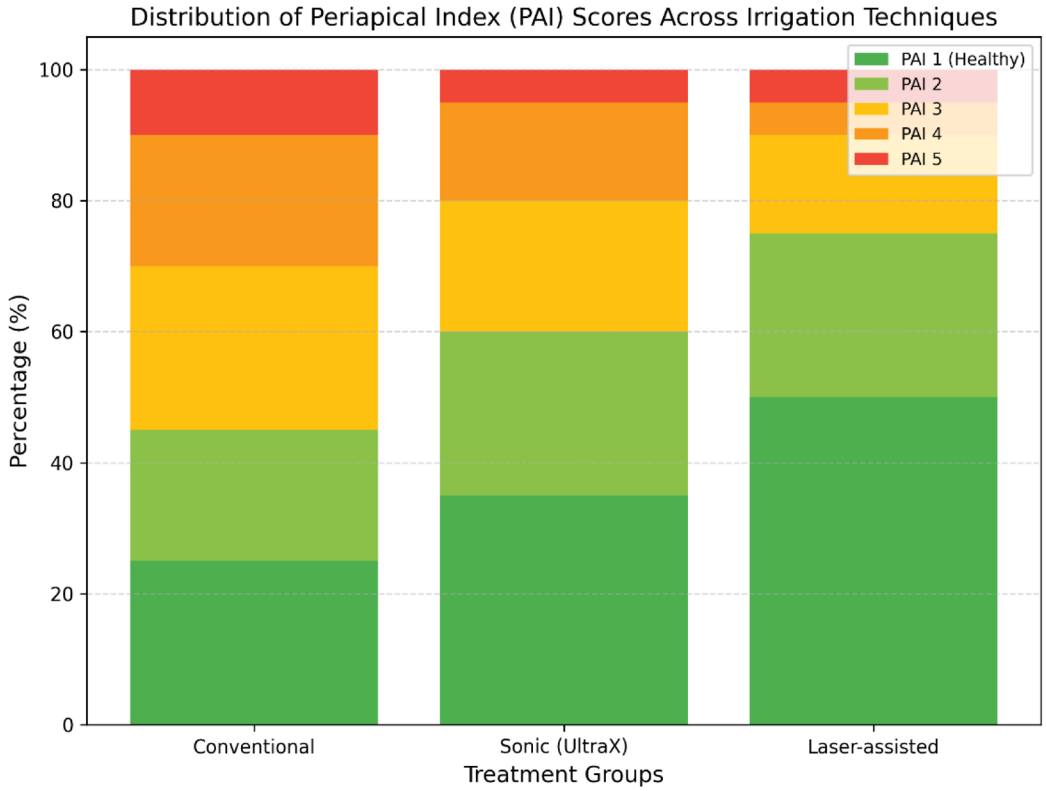


Figure 3: Distribution of PAI scores at 6 months

Table 5. Intergroup comparison of PAI values at 6 months

Group	Mean ± SD	Difference vs. Conventional	p-value (post-hoc Tukey)
Conventional irrigation	2.55 ± 0.60	–	–
Sonic-activated irrigation (UltraX)	2.05 ± 0.52	↓ 0.50	0.01*
Laser-assisted disinfection	1.60 ± 0.48	↓ 0.95	<0.001*

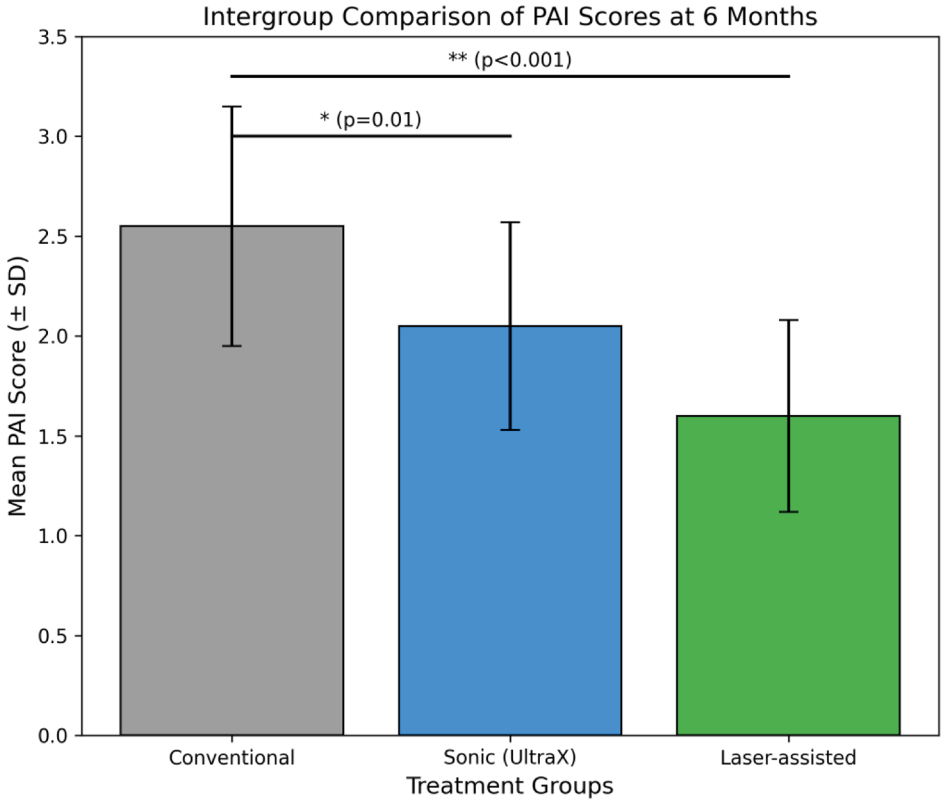


Figure 4: Intergroup comparison of PAI values at 6 months

cally significant difference between the groups (χ^2 = 6.85; p = 0.03), indicating that the choice of disinfection method significantly affects treatment outcomes.

Post-hoc analysis (Tukey test) demonstrated that:

- Sonic-activated irrigation resulted in significantly better outcomes compared to conventional irrigation (p = 0.01).
- Laser-assisted disinfection was superior to both other groups (p < 0.001).
- These results indicate a higher effectiveness of disinfection protocols using laser-assisted therapy.

Discussion

The results of this study demonstrated that all three applied root canal disinfection protocols—conventional irrigation, sonic activation, and laser-assisted disinfection—led to a measurable reduction in periapical lesions in the follow-up period. How-

ever, the most pronounced reduction in Periapical Index (PAI) values was observed in the laser-assisted disinfection group, suggesting a superior antimicrobial efficacy of laser application in endodontic therapy[17,18].

The enhanced outcomes in the laser group can be attributed to the specific mechanisms of laser-tissue interaction. Diode and other endodontic lasers generate photothermal energy that induces direct bacterial cell destruction and enables deeper penetration into dentinal tubules, where residual microorganisms often persist despite conventional chemomechanical preparation[19,20]. This deeper penetration is particularly relevant for complex root canal anatomies, including apical deltas and accessory canals, which are frequently inaccessible to standard irrigants and ultrasonic activation[21,22].

Furthermore, laser activation improves irrigant dynamics within the root canal system by inducing microstreaming and cavitation-like effects, thereby enhancing the circulation of disinfecting solutions into lateral and accessory canals. This contributes to more effective elimination of the bacterial biofilm, which is critical for the resolution of periapical inflammation and subsequent bone healing[23,24].

The sonic-activated irrigation group also demonstrated superior outcomes compared to conventional irrigation. This improvement can likely be explained by enhanced fluid dynamics, allowing better irrigant penetration and removal of smear layer and microbial biofilm, particularly in the apical third of the root canal[25,26]. The observed differences between sonic activation and conventional irrigation align with previous studies that reported increased bacterial reduction and improved PAI outcomes when mechanical energy is applied to the irrigant[27,28].

Despite these positive results, it is important to emphasize that laser-assisted disinfection should not be considered a replacement for conventional chemomechanical root canal preparation. Instead, it should be viewed as an adjunctive technique that enhances the overall effectiveness of endodontic therapy[29,30]. The combination of thorough mechanical instrumentation, chemical irrigation, and laser or sonic activation appears to offer the most predictable clinical outcomes in teeth affected by chronic apical periodontitis.

Several limitations of the present study should be considered. The follow-up period of six months is relatively short, and periapical healing may continue beyond this interval. Long-term clinical studies with follow-up periods of 12–24 months are warranted to fully assess the durability of the observed treatment outcomes[31,32]. Additionally, the sample size of 60 teeth, while sufficient to detect significant differences in PAI reduction, may not fully capture variations related to root canal morphology, patient age, or systemic health, which can all influence healing outcomes[33].

Future research should focus on comparing different laser wavelengths, power settings, and activation protocols to optimize clinical efficacy while minimizing the risk of thermal damage to periapical tissues. Moreover, combining laser

disinfection with novel irrigation solutions or nanoparticles may further enhance microbial elimination, particularly in resistant biofilm-associated infections[34,35]. The integration of three-dimensional imaging, such as cone-beam computed tomography (CBCT), could provide more precise evaluation of periapical healing and improve the objectivity of outcome assessment in future clinical trials[36,37].

In conclusion, the findings of this study support the clinical utility of laser-assisted root canal disinfection as an effective adjunct to conventional chemomechanical preparation. Both laser and sonic activation techniques offer measurable benefits in reducing periapical pathology and promoting healing. Nevertheless, comprehensive mechanical preparation and chemical irrigation remain essential, and long-term studies are necessary to confirm the sustained advantages of laser use in endodontic therapy.

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CASE REPORT

APPENDICEAL NEUROENDOCRINE TUMOR IN A PEDIATRIC PATIENT – A CASE REPORT

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Competing Interests: The author have declared that no competing interests

Abstract

Appendiceal neuroendocrine tumors (NETs) are the most common appendiceal neoplasms but remain rare in the pediatric population. They often present with clinical features mimicking acute appendicitis and are therefore usually diagnosed incidentally on histopathological examination after appendectomy. Prompt identification is crucial, as tumor characteristics determine management and prognosis. We report a case of a 13-year-old girl presenting with clinical and radiological signs of acute appendicitis due to fecalith obstruction and a right ovary cyst. Laparoscopic appendectomy and ovarian cystectomy were performed without intraoperative suspicion of malignancy. Histopathological analysis revealed a well-differentiated neuroendocrine tumor measuring 1.5 cm localized near the tip of the appendix. The lesion infiltrated all the layers of the appendix wall and penetrated the serosa, without lymphovascular invasion or mesoappendiceal extension. Immunohistochemical staining confirmed the diagnosis. Multidisciplinary tumor board decision guided further management and the patient remains disease-free at twelve-month follow-up. Outcome was promising with no recurrence, metastasis, complications, or need for additional therapy observed during follow-up. The discussion section emphasizes the critical role of histopathological analysis of appendectomy specimens and gives further recommendations for efficient management of appendiceal NETs in children, depending on tumor size and histological risk features. Appendectomy alone is usually sufficient for tumors less than 2 cm without invasion. This case underscores the critical role of histopathological vigilance and multidisciplinary care in pediatric surgical oncology.

ПРИКАЗ НА СЛУЧАЈ

НЕВРОЕНДОКРИН ТУМОР НА АПЕНДИКСОТ КАЈ ПЕДИЈАТРИСКИ ПАЦИЕНТ - ПРИКАЗ НА СЛУЧАЈ

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Клучни зборови: невроендокрин тумор на апендикс, детска хирургија, лапароскопска апендектомија, карциноиден тумор, педијатриска онкологија.

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Печатарски права: ©2026 Лазо Јовчески, Тони Ристески, Биљана Андоновска-Доковска, Александар Степановски, Сања Ѓорић, Славица Литајковска, Шабан Мемети, Ален Деаровски, Андријана Андреевска-Степановска. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираа торигиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Невроендокрините тумори (НЕТ) претставуваат најчести неоплазми на апендиксот, но исклучително ретко се јавуваат во детска возраст. Се манифестираат со клиничка слика за акутен апендицит и најчесто се откриваат случајно при хистопатолошка анализа на отстранетиот апендикс. Навременото поставување на дијагнозата е од суштинско значење, бидејќи морфолошките и хистолошките карактеристики на туморот ги одредуваат понатамошниот третман и долгорочната прогноза. Во нашиот труд прикажуваме случај на 13-годишно девојче примено на нашата клиника со позитивни клинички и радиолошки знаци за акутен апендицит, предизвикан од опструкција со копролит, и придружна циста на десниот јајник. Беше направена лапароскопска апендектомија и цистектомија на јајникот, при тоа интраоперативно не се постави сомнение за постоење на малигна болест. Хистопатолошката анализа откри постоење на добро диференциран невроендокрин тумор со димензија од 1,5 см, локализиран во предел на дисталниот дел (врвот) на апендиксот. Туморот ги инфилтрира сите слоеви на апендикуларниот ѕид со зафаќање на серозата, но без присуство на лимфоваскуларна инвазија или екстензија во мезоапендиксот. Дијагнозата беше потврдена со имунохистохемиска анализа. Понатамошното лекување беше дефинирано врз основа на одлука на мултидисциплинарен онколошки конзилиум. По дванаесетмесечно следење, пациентката е без знаци за активна болест, рецидиви, метастатска дисеминација, постоперативни компликации или потреба од дополнителен третман. Во дискусијата се нагласува значењето на задолжителната хистопатолошка анализа на сите апендектомиски препарати; исто така се даваат и препораки за оптимален хируршки третман на невроендокрините тумори на апендикс кај деца, и тоа во зависност од големината на туморот и од присуството на хистолошки фактори на ризик. Кај тумори помали од 2 см, без високоризични карактеристики, апендектомијата вообичаено е доволна како единствен третман. Овој случај ја истакнува важноста на хистопатолошката анализа и мултидисциплинарниот пристап во третманот на невроендокрините тумори на апендиксот во педијатриската онколошка хирургија.

Introduction

Acute appendicitis remains one of the most common indications for emergency abdominal surgery in children[1]. While the overwhelming majority of appendectomy specimens confirm acute inflammation, a small percentage reveal unexpected findings, including neoplastic conditions2. Among these, appendiceal neuroendocrine tumors (NETs), previously referred to as carcinoid tumors, are the most frequently encountered neoplasms of the appendix[3,4].

Despite their relative frequency among appendiceal tumors, NETs remain rare in children, with an estimated incidence between 0.1% and 0.5% of pediatric appendectomies[2,4]. These tumors typically arise from enterochromaffin cells within the distal third of the appendix and are often small, slow-growing and asymptomatic[5].

Most pediatric cases present with symptoms indistinguishable from uncomplicated appendicitis, making preoperative diagnosis virtually impossible[6,7]. Imaging studies rarely detect these tumors, particularly if small and intraoperative findings are often non-suspicious2,6. As such, most NETs are identified only through postoperative histopathological examination. Because these tumors are rare in children, treatment recommendations are often based on adult data, highlighting the value of pediatric-specific case reports and registries[3,8]. This report presents a case of a 13-year-old girl whose appendiceal NET was discovered incidentally following appendectomy for suspected acute appendicitis. We discuss the clinical features, histopathology, surgical management, prognosis and the broader implications for pediatric surgical practice.

Case report

A 13-year-old girl presented to the emergency department of our clinic, complaining of right-sided lower abdominal pain that had started one day before, without associated nausea or vomiting. She was afebrile and her vitals were within normal limits. Abdominal examination revealed tenderness in the right iliac fossa. The pain was constant and progressing. Abdominal ultrasound showed a right ovarian cyst and small amount of free fluid in the pouch of Douglas. The patient was admitted to the hospital for further evaluation. Blood analysis were in normal range, except for an elevated C-reactive protein level (30.9 mg/L). Due to the non-conclusive ultrasound findings, a contrast-enhanced abdominal and pelvic computerized tomography (CT)-scan was indicated. The CT scan showed fecalith obstruction of the appendix and a right ovarian cyst. A clinical diagnosis of acute appendicitis and right ovarian cyst was made and she underwent an explorative laparoscopy, which revealed an inflamed appendix and a right ovarian cyst, with no other abnormalities and without any intraoperative suspicion of malignancy (Fig. 1). Laparoscopic appendectomy with right ovarian cystectomy was made. The resected specimens were sent for histopathological examination. Routine intravenous fluids, antibiotics and analgesics were given in the postoperative period. The patient was discharged from hospital

on postoperative day 3 with regular follow-up over the next two weeks.

The resected appendectomy specimen measured 6.5 cm in length. The cut surface revealed a yellow tumorous lesion of 1.5 cm size in its widest diameter and localized in the distal portion near the tip of the appendix (Fig. 2). The lesion infiltrated all the layers of the appendix wall and penetrated the serosa. Microscopy showed small sized round and oval tumor cells with a moderate amount of finely granular, eosinophilic cytoplasm and round nuclei with "salt and pepper" chromatin, arranged in nests. Mitotic rate was 0–1 per 10 high-power fields. A mild perilesional lymphocytic infiltrate was also described. The regional lymph nodes could not be assessed, as they were not submitted. Immunohistochemical staining was positive for neuroendocrine markers, including chromogranin, synaptophysin and neuron-specific enolase (NSE), with a Ki-67 proliferative index of < 2%. Based on these findings, a diagnosis of a well-differentiated Grade 1 neuroendocrine tumor of the appendix was reached. Follow up examination including PET scanning revealed normal results, with no regional or distant metastatic deposits detected.

The case was reviewed by a multidisciplinary tumor board, and given the favorable features, no further surgical intervention was recommended. The patient is currently undergoing monthly follow-up at the pediatric oncology department. At 12-month follow-up, the patient remains asymptomatic with no evidence of disease recurrence.

Figures

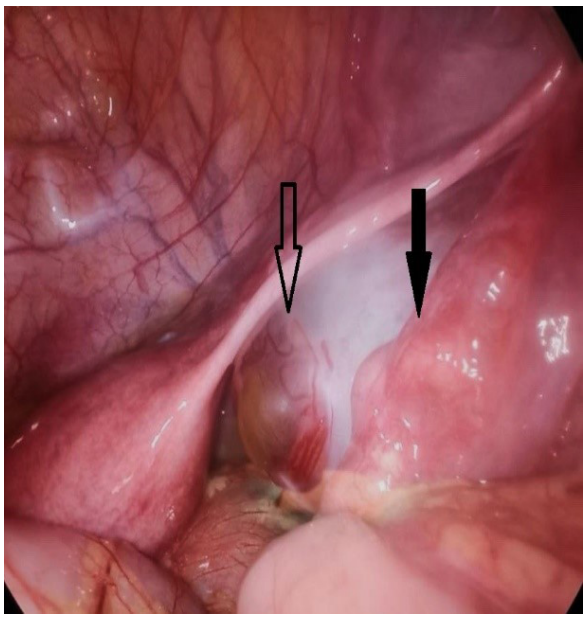


Figure 1:
Cyst of the right ovarium (hollow arrow); Inflamed vermiform appendix (solid arrow)

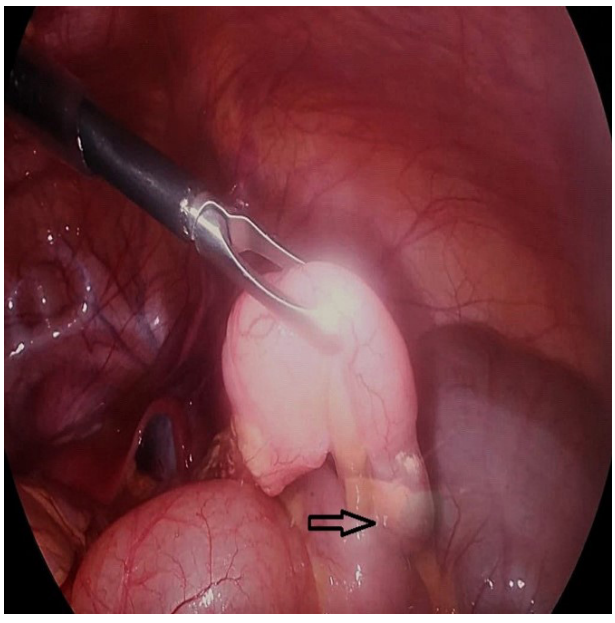


Figure 2:
Neuroendocrine tumor at the tip of the vermiform appendix (hollow arrow)

Discussion

Appendiceal NETs account for nearly 80% of all appendiceal tumors but occur infrequently in children[3,4]. Their estimated incidence in pediatric appendectomy specimens ranges from 0.1% to 0.5%, with a slight female predominance and a peak incidence in early adolescence[4]. Unlike many pediatric malignancies, there are no known genetic or hereditary syndromes commonly associated with appendiceal NETs in children. The tumors are usually sporadic and risk factors remain undefined[9]. Pediatric-specific data remain limited and treatment recommendations often reflect adult protocols[3].

Surgical excision remains the primary and definitive treatment for appendiceal neuroendocrine tumors (NETs) in pediatric patients[1,5]. Because these tumors are most often discovered incidentally during appendectomy performed for suspected acute appendicitis, as in our case, the initial surgical approach depends on the acute clinical presentation rather than oncologic suspicion[2,6]. Laparoscopic appendectomy is the preferred method in children, offering minimal invasiveness, reduced postoperative pain, shorter stay in the hospital and faster recovery. Improved visualization and the routine use of specimen retrieval bags contribute to safe tumor removal, even when malignancy is not suspected intraoperatively[1].

Intraoperative identification of appendiceal NETs is uncommon; however, features such as focal thickening, firm nodules at the appendiceal tip, or regional lymphadenopathy may raise suspicion. When available, intraoperative frozen section analysis can assist in immediate surgical decision-making, although definitive management is typically guided by postoperative histopathological findings[5]. Current recommendations stratify treatment according to tumor size and histologic risk factors. Appendectomy alone is considered curative for tumors smaller than 1 cm. For tumors measuring 1–2 cm, additional surgery may be considered in the presence of high-risk features, including mesoappendiceal invasion greater than 3 mm, lymphovascular invasion, elevated Ki-67 index, or positive surgical margins. Tumors larger than 2 cm generally warrant right hemicolectomy due to an increased risk of lymph node and distant metastasis[3,5,8]. In the present case, despite a tumor size of 1.5 cm, the absence of unfavorable histopathological and immunohistochemical features supported appendectomy as the sole definitive treatment.

Similar pediatric cases have been published recently, including a 16-year-old adolescent who presented with signs of non-typical appendicitis and was later found to have an appendiceal NET; a 14-year-old male with a well differentiated NET who required subsequent hemicolectomy after staging; and a 13-year-old female with an inflamed but not perforated appendix and a NET of 7 mm size located at its tip[2,4,7].

When indicated, right hemicolectomy involves resection of the terminal ileum, cecum, ascending colon and associated lymphatic drainage. In pediatric patients, the surgical approach, laparoscopic or open, is individualized based on tumor characteristics and surgical expertise,

with the aim of balancing oncologic clearance while minimizing long-term impact on overall growth and gastrointestinal function[1,3,5].

Postoperative surveillance is tailored to tumor risk profile and typically includes regular clinical evaluation, abdominal imaging and selective biomarker monitoring. Follow-up intervals generally range from every 6 to 12 months, particularly in intermediate risk cases and may extend for at least five years[10]. Prognosis for pediatric appendiceal NETs is excellent when management guidelines are followed, with recurrence being exceedingly rare[7,9]. Despite favorable outcomes, the psychological burden of an unexpected tumor diagnosis in a child should not be underestimated. Families may experience significant anxiety even in the setting of low-grade disease. A multidisciplinary approach involving pediatric surgeons, oncologists, radiologists and psychosocial support services is therefore essential to ensure comprehensive care[9,10]. This case highlights how a routine appendectomy can uncover a clinically silent malignancy and underscores the importance of meticulous histopathological examination and coordinated, patient-centered management to optimize both medical and emotional outcomes.

Conclusion

Appendiceal neuroendocrine tumors in pediatric patients, although rare, are clinically significant and are frequently discovered incidentally. They often mimic acute appendicitis, making preoperative diagnosis unlikely. This case reinforces the necessity of routine histopathological evaluation of all appendectomy specimens. Appendectomy alone is curative in most children with tumors smaller than 2 cm and without high-risk features. Surgical management should be guided by tumor pathology and aim to balance oncologic safety with preservation of quality of life. With multidisciplinary care, pediatric patients can achieve excellent long-term outcomes.

This case of a young patient reminds us that rare but significant conditions may lie quietly beneath common presentations, reinforcing the need for sustained clinical vigilance. It is our clinical attentiveness, precision and compassion that ensure these silent sentinels are not missed and that each child receives care as unique and resilient as they are.

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CASE REPORT

PEDIATRIC PROTEUS SYNDROME: A RARE CASE REPORT WITH FOCUS ON CLINICAL MANAGEMENT AND LONG-TERM OUTCOMES

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Key words: Proteus syndrome, AKT1 mutation, overgrowth disorder, vascular anomalies, multidisciplinary management.

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Abstract

Proteus syndrome (PS) is a rare mosaic genetic disorder caused by a somatic mutations in the AKT1 gene, resulting in asymmetric overgrowth of skin, skeleton, soft tissues, and internal organs. Progressive tissue expansion and vascular anomalies increase the risk of functional impairment and thromboembolic complications. Aim of the paper was to describe the clinical presentation, diagnostic evaluation, and management of a pediatric patient with PS, highlighting the role of multidisciplinary care. Case report: A 4-year-old girl presented with right upper limb overgrowth and a soft-tissue mass in the pectoral region. Diagnosis was confirmed via clinical assessment, radiologic imaging, and genetic testing for AKT1 mutation. Surgical excision of hypertrophic tissue was performed, and histopathology confirmed a benign lipomatous lesion. A two-year follow-up included monitoring of functional outcomes and disease recurrence. Postoperative recovery was uneventful, with primary wound healing. Progressive hypertrophy necessitated a second surgical intervention. Multidisciplinary follow-up facilitated timely management of emerging complications without major adverse events. Conclusion: PS requires early diagnosis and individualized, multidisciplinary management. Surgical interventions improve function, but long-term surveillance is essential due to the progressive nature of the disorder.

ПРИКАЗ НА СЛУЧАЈ

ПРОТЕУС СИНДРОМ ВО ПЕДИЈАТРИСКА ВОЗРАСТ: ПРИКАЗ НА СЛУЧАЈ СО ФОКУС НА КЛИНИЧКИ ПРИСТАП И ДОЛГОРОЧНИ ИСХОДИ

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Цитирање: Соколова Р, Јовчески Л, Мемети Ш. Протеус синдром во педијатриска возраст: приказ на случај со фокус на клинички пристап и долгорочни исходи. Арх Ј Здравје 2026; 18 (1) 54-60.

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Клучни зборови: Протеус синдром, AKT1 мутација, мозаичен раст, васкуларни аномалии, мултидисциплинарен пристап

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Печатарски права: ©2026. Розета Соколова, Лазо Јовчески, Шабан Мемети. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираа торигиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Протеус синдромот (ПС) е ретко, мозаично генетско заболување предизвикано од соматска мутација на генот AKT1, кое резултира со асиметричен и диспропорционален раст на различни ткива и органи. Прогресивната хипертрофија и васкуларните аномалии го зголемуваат ризикот од функционални нарушувања и тромбоемболички компликации. Цел на трудот е да се прикаже клиничкиот тек и пристапот кон третманот на пациент со ПС, со посебен акцент на мултидисциплинарната грижа. Прикажуваме случај на четиригодишно девојче со хипертрофија на десниот горен екстремитет и мекоткивна маса во пекторална регија. Дијагнозата е потврдена преку клиничка евалуација, радиолошко снимање и генетско тестирање за AKT1. Извршена е хируршка ексцизија на хипертрофичното ткиво, а хистопатологијата покажа бенигна липоматозна лезија со лимфатична малформација на пекторална регија. Двогодишното следење вклучуваше следење на функционалните исходи и рецидивот на болеста. Постоперативното закрепнување беше без компликации, со примарно заздравување на раните. Прогресивната хипертрофија бараше втора хируршка интервенција. Мултидисциплинарното следење го олесни навременото справување со новите компликации без поголеми несакани ефекти. Заклучок: ПС бара рана дијагноза и индивидуализиран мултидисциплинарен пристап, со долгорочно следење поради прогресивниот тек на болеста

Introduction

Congenital vascular and tissue malformations represent a heterogeneous group of disorders involving abnormal growth and development of blood vessels, bones, and soft tissues. The International Society for the Study of Vascular Anomalies (ISSVA) recently updated its globally accepted classification of vascular anomalies (2025), which refines the division of vascular tumors and malformations and incorporates new genetic and clinical insights into vascular anomalies[1].

Proteus syndrome (PS) is one of the rarest disorders within this group. It is a mosaic, somatic mutation-driven genetic condition caused by spontaneous, non-hereditary mutations in the AKT1 gene (10q23.3), leading to asymmetric and disproportionate overgrowth of various tissues and organs. First described by Cohen *et al*. in 1979, the syndrome is named after the Greek sea god Proteus, symbolizing its marked phenotypic variability. The estimated incidence is approximately 1 in 1,000,000 live births. Its clinical presentation is diverse and progressive, affecting multiple tissues including skeleton, skin, adipose tissue, and internal organs. Recent systematic reviews of clinical reports (Rostagni et al., 2025) have documented the spectrum of associated benign tumors, the timing of clinical onset, and characteristic features that inform early recognition and multidisciplinary management of affected children[2].

Clinically, PS is characterized by disproportionate, asymmetric overgrowth, which may affect the skin, subcutaneous tissue, skeleton, and internal organs. Cutaneous manifestations include vascular malformations, lipomas, hyperpigmentation, and various nevi, with cerebriform connective tissue nevi considered highly characteristic. Skeletal abnormalities commonly involve hyperostosis of the skull, long bones of the arms and legs, and the hands and feet, while internal organ involvement may include enlargement of the spleen, thymus, colon, or other tissues. Overgrowth is typically mosaic, presenting as patchy areas of affected and unaffected regions. A proportion of patients exhibit neurological abnormalities and progressive visual impairment.

Progressive vascular anomalies increase the risk of potentially life-threatening thromboembolic complications, including deep vein thrombosis and pulmonary embolism. The complex, multisystemic presentation underscores the need for early recognition. Its progressive and unpredictable course requires multidisciplinary management and long-term follow-up.

The differential diagnosis includes macrodystrophia lipomatosa, neurofibromatosis type 1, Parkes Weber syndrome, haemangiomatosis, Maffucci syndrome, and other rare disorders. Proteus syndrome is also known by several other names, such as partial gigantism, nevi hemihypertrophy macrocephaly syndrome, and Wiedemann syndrome. Treatment is mainly symptomatic and surgical, accompanied by genetic evaluation of affected individuals. Approximately 25% of patients with Proteus syndrome are beyond the age of 22-29 years.

Case Presentation

We present the case of a 4-year-old female patient referred to the University Clinic for Pediatric Surgery due to a soft-tissue swelling in the right pectoral and axillary region. The patient experienced pain during movement, without discomfort at rest.

The child was born from an uncomplicated first pregnancy (Apgar score 9/10) and had no family history of hereditary, degenerative, or autoimmune diseases. No abnormalities were noted at birth. On inspection, an elongated face with an open mouth and a soft tissue mass in the area of the right chest wall was noted. The mass was painless, soft on palpation, poorly demarcated, not adherent to the surrounding tissues, and no palpable lymph nodes were detected.

During the second year of life, progressive enlargement of the small finger and forearm of the right arm was observed, accompanied by the development of a soft-tissue mass in the right pectoral region.

Comprehensive clinical, radiological, and genetic assessments were performed, revealing a mutation in the AKT1 gene, consistent with the diagnosis of Proteus syndrome.

Under general anesthesia with endotracheal intubation, surgical excision of the tumorous mass was performed. A passive drain was placed intraoperatively to manage any postoperative fluid accumulation.

Histopathological examination revealed a benign lipomatous lesion with hyperplastic features. No evidence of malignancy was found.

During the postoperative period, mild wound moisture was observed due to a pre-existing lymphatic malformation. The drain initially produced a yellowish, clear, odorless fluid. After several days, the secretion stopped, and the drain was removed. The wound healed per *primam intentionem*.

During a two-year follow-up period, progressive hypertrophy of the fingers of the right hand and limited range of motion were observed, necessitating a second surgical reduction of the hypertrophic tissue.

The child underwent surgery under general anesthesia with endotracheal intubation. Fatty tissue was excised down to the fascia and musculature. Postoperatively, the wound healed well without any signs of infection. A mild asymmetry in forearm volume was observed, with the right forearm measuring 2 cm larger than the left.

The patient remains under regular follow-up with the orthopedic surgeon, geneticist, and pediatrician.

Long-term multidisciplinary monitoring is recommended due to the progressive nature of Proteus syndrome.

Clinical examination, radiographic imaging, laboratory tests, and histopathological analysis were performed. The diagnosis of Proteus syndrome was made according to the established diagnostic criteria. The patient met all general criteria, one criterion from Group B, and two criteria from Group C, including vascular malformations and a characteristic facial phenotype.



Figure 1:
Asymmetric overgrowth of the right thoracic region



Figure 2:
Macrodactyly and asymmetric enlargement of the fingers of the right hand, consistent with Proteus syndrome

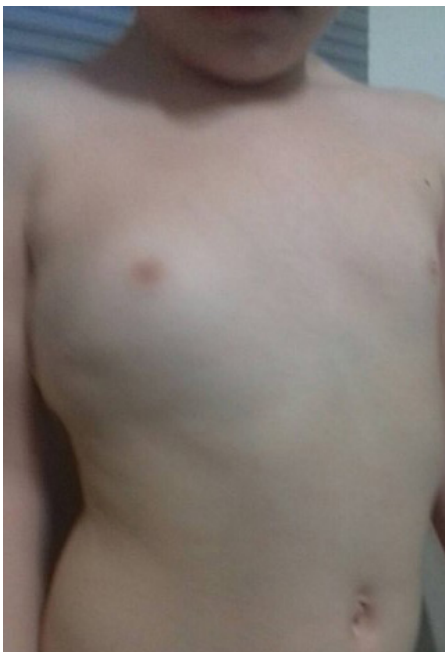


Figure 3:
Asymmetric overgrowth of the right chest wall and axillary region in a pediatric patient with Proteus syndrome

Histopathological examination of the excised tissue showed fatty tissue consistent with a benign lipomatous lesion. During follow-up, the child showed normal development and had no difficulties with the school curriculum. Abdominal ultrasound revealed no abnormalities in the urogenital system. All findings are summarized in Table 1.

General Criteria
Mosaic Distribution Progressive Course Sporadic Occurrence
Specific Criteria
Category A
Cerebriform connective tissue nevus
Category B
Linear epidermal nevus
Asymmetric, disproportionate overgrowth of two of:
Limbs, skull, external auditory canal, vertebrae, or viscera
Specific tumors in the first decade of life:
Bilateral ovarian cystadenomas
Monomorphic parotid adenomas
Category C
Dysregulated adipose tissue
Vascular Malformations
Capillary, venous, and/or lymphatic
Lung bullae
Facial phenotype:
Long face, dolichocephaly, down-slanted palpebral fissures, low nasal bridge, wide or anteverted nares, open mouth at rest
The diagnosis of Proteus syndrome requires all three general criteria, plus one criterion from category A, or two criteria from category B, or three criteria from category C. (Adapted from Biesecker, 2006)

Figure 1:
Diagnostic criteria for Proteus syndrome: general and specific (categories A–C) criteria applied in the presented case

Discussion

Proteus syndrome (PS) was initially described by Cohen and Hayden in 1979. Contemporary clinical reviews demonstrate a broad phenotypic spectrum. Skeletal overgrowth is reported in approximately 95% of patients, cerebriform connective tissue nevi in 65%, dysregulated adipose tissue in 39%, and vascular malformations in 32%[3]. These data highlight the marked clinical heterogeneity of the disorder. They also emphasize the importance of confirming a somatic *AKT1* mutation and implementing a multidisciplinary approach to long-term management.

Historical reassessment of John Carey Merrick, the "Elephant Man," revealed asymmetric overgrowth of the right arm and hand, macrodactyly affecting multiple fingers, and cerebriform connective tissue nevi involving the scalp and plantar surfaces. These findings are more consistent with Proteus syndrome than with neurofibromatosis type 1[4]. Subsequent modern clinical analyses further identified venous and lymphatic malformations, disproportionate lower limb growth, and asymmetric truncal adipose tissue distribution. All of these features align with the diagnostic spectrum of PS[5].

Clinically, Proteus syndrome manifests with a wide range of skeletal, cutaneous, soft-tissue, vascular, and internal organ abnormalities. Skeletal involvement commonly includes limb asymmetry, macrodactyly, and hyperostosis. Cutaneous features may include cerebriform connective tissue nevi, hyperpigmentation, and Blaschko's lines. Overgrowth of adipose and connective tissues is frequent. Vascular anomalies may involve venous, lymphatic, or mixed components. Internal organ involvement has also been reported. Importantly, patients with PS have a significantly increased risk of thromboembolic events, which remain a leading cause of morbidity and mortality [6].

Accurate diagnosis of Proteus syndrome requires detailed clinical assessment and radiological evaluation, including magnetic resonance imaging and ultrasonography. Molecular genetic testing is essential to identify a somatic activating mutation in the *AKT1* gene. Due to the mosaic nature of the disorder, genetic confirmation remains the definitive diagnostic criterion. Prenatal and postnatal studies have shown that pathogenic *AKT1* variants can be detected through exome sequencing of affected tissues. This underscores the importance of targeted molecular analysis in patients with segmental overgrowth[7]. The differential diagnosis includes neurofibromatosis type 1, which is characterized by café-au-lait macules and neurofibromas caused by *NF1* mutations. Clinical overlap with other overgrowth syndromes necessitates an integrated diagnostic approach combining clinical, imaging, and genetic data.

The present case illustrates the characteristic progressive and mosaic nature of Proteus syndrome. No abnormalities were observed at birth. Progressive macrodactyly of the right hand and soft-tissue overgrowth of the right thoracic and axillary regions developed during early childhood. This pattern is consistent

with previously reported segmental involvement in PS[3,6]. The identification of a benign lipomatous lesion associated with a lymphatic malformation reflects the known predisposition of patients with PS to adipose and vascular tissue dysregulation. Surgical intervention was required due to functional impairment and progressive enlargement. This mirrors the recurrent need for staged surgical procedures described in the literature. Despite adequate excision, disease progression continued and necessitated repeat surgery. This finding highlights the chronic and relapsing course of the syndrome and reinforces the importance of long-term multidisciplinary follow-up[8, 9].

Management of Proteus syndrome is primarily symptomatic and surgical. The main goals are to improve function, alleviate pain, and correct deformities. Therapeutic options include surgical excision or reduction of hypertrophic tissue, orthopedic correction, and physical therapy. Conventional medical therapies provide limited benefit. As a result, novel targeted treatments are under investigation. The AKT inhibitor miransertib (ARQ092, MK-7075) has demonstrated acceptable safety and tolerability in patients with PS and PIK3CA-related overgrowth spectrum disorders in phase 1/2 trials. Ongoing studies are evaluating its efficacy in reducing overgrowth and improving quality of life[8].

Experimental therapies such as sirolimus, an mTOR inhibitor, have shown modest reductions in pathological tissue volume in related overgrowth syndromes. However, their effects in classical Proteus syndrome are limited and variable. This is likely due to feedback activation within the PI3K/AKT signaling pathway, as suggested by case series and pilot studies.

Given the progressive and unpredictable nature of Proteus syndrome, comprehensive multidisciplinary care is essential. This approach should involve pediatrics, genetics, orthopedics, radiology, and pathology. Close follow-up is particularly important to monitor tumors across multiple organ systems. Such tumors are reported in nearly one-fifth of patients, with a median diagnosis age of about 15 years[9]. Regular imaging, thorough clinical examinations, and tailored preventive strategies, including periodic abdominal ultrasonography, are recommended. These measures facilitate early detection of neoplasms and reduce the risk of complications. Management should also prioritize optimization of quality of life and minimization of pain and functional limitations through coordinated, patient-centered care.

Conclusion

This case highlights the progressive and heterogeneous nature of Proteus syndrome in early childhood. Surgical management of benign soft-tissue overgrowth was successful, yet disease progression required repeated interventions. Early diagnosis, genetic confirmation, and long-term multidisciplinary follow-up are essential to optimize function and monitor disease evolution.

Associated vascular and adipose malformations underscore the need for regular imaging and clinical sur-

veillance. Coordinated care from pediatrics, genetics, orthopedics, and radiology is critical for timely intervention. This report reinforces the importance of individualized treatment plans and adds clinical insight to the limited pediatric Proteus syndrome literature.

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CASE REPORT

NASOPALATINE DUCT CYST- DIAGNOSIS AND SURGICAL MANAGEMENT: A CASE REPORT

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Abstract

A nasopalatine duct cyst (NPDC) is a fluid-filled sac in the roof of the maxilla, near the incisive foramen, usually between the roots of the maxillary central incisors. It is one of the most common nonodontogenic cysts of the oral area. The aim of this article was to present a case of an unusually large nasopalatine duct cyst in a 35-year-old female patient with chief complaint of painless swelling over the palate and anterior maxilla. The swelling was gradually increasing in size over the past 3 months without associated displacement of maxillary central incisors. There was no associated history of trauma, loose teeth, previous treatment or pain in the region. After the clinical examination and the radiographic diagnosis of NPDC, a surgical enucleation under i.v. sedation and local anesthesia was undertaken, and the specimen was sent to the Institute of Pathology in Skopje. Histopathological examination confirmed the diagnosis of a NPDC. Recovery was uneventful, with primary healing of the incision site. Although NPDC is a rare clinical entity, it is an important consideration in the differential diagnosis of anterior maxillary radiolucency.

ПРИКАЗ НА СЛУЧАЈ

ЦИСТА НА НАЗОПАЛАТИНАЛНИОТ КАНАЛ – ДИЈАГНОЗА И ХИРУРШКИ ТРЕТМАН: ПРИКАЗ НА СЛУЧАЈ

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Клучни зборови: циста на назопалатинален канал, дијагноза, хируршки третман

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Печатарски права: ©2026 Марко Зафировски, Александар Илиев, Антонио Кирков, Александар Стаматоски, Зоран Шушак, Гордана Петрушевска. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираа ториганалниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Назопалатиналната циста (НПДЦ) претставува цистична лезија исполнета со течност, сместена во базата на максилата, во близина на инцизивниот форамен помеѓу корените на максиларните централни инцизиви. Таа е една од најчестите неодонтогени цисти во оралната регија. Целта на овој труд беше да се прикаже случај на невообичаено голема циста на назопалатиналниот канал кај 35-годишна пациентка со безболен оток над палатумот во предната третина. Отокот постепено се зголемувал во последните 3 месеци без последователно поместување на максиларните централни инцизиви. Во медицинската историја на пациентката немаше информации за потврдена траума, расклатени заби, претходен стоматолошки третман или болка во истата регија. По клиничкиот преглед и радиографската дијагноза на НПДЦ (ОПГ и ЦБЦТ скен), беше изведена хируршка енуклеација на цистата со и.в. седација и локална анестезија, а примерокот беше испратен на Институтот за патологија во Скопје. Хистопатолошкиот наод ја потврди дијагнозата на НПЦ. Закрепнувањето одеше непречено, со примарно заздравување на местото на инцизијата. НПДЦ иако е редок клинички ентитет, треба да се има предвид во диференцијалната дијагноза на предната максиларна радиолуценција.

Introduction

A nasopalatine duct cyst is a fluid-filled sac in the roof of the maxilla that arises from embryologic remnants present in the nasopalatine duct. It is one of the most common nonodontogenic cysts of the oral area occurring in about 1 % of the population and it was first described by Meyer in 1914[1]. The nasopalatine duct cyst (NPDC) occurs in the median of the palate, usually anterior to first molars, near the incisive foramen, usually between the roots of the maxillary central incisors. It is seen as radiolucency, between central incisors and must usually be larger than 6 mm to distinguish cyst from incisive foramen, which is a normal anatomical feature. Root resorption and tooth displacement may be present. Radiographically, it may often appear as a solitary well-defined, oval or round unilocular heart-shaped radiolucency if the anterior nasal spine is superimposed. NPDCs are usually symmetrical, although some may be displaced to one side. The cyst can be distinguished from a normal but widened canal and from periapical granuloma or radicular cyst associated with the roots of anterior teeth. These cysts are not cancerous, and their removal can reduce the risk of progressive enlargement that could lead to displacement of teeth. Its removal also prevents the cyst from becoming infected and causing discomfort or pain. Patients may be asymptomatic and discovered on routine radiographic examination. If one or more symptoms are present, complaints are often found to be associated with secondary infection of a previously asymptomatic nasopalatine duct cysts and include primarily swelling, drainage, and pain[2]. A correct diagnosis can only be made after proper clinical, radiographic, and histopathologic examination. Treatment, if required, is surgical and consists of local curettage. This almost inevitably requires the sacrifice of the nasopalatine vessels and nerves, which results in a small area of anesthesia over the anterior palate behind the upper incisor teeth. Some patients (particularly more elderly patients) find this particularly troublesome in the articulation of some words. Recurrence rate is very low after treatment[3].

Case report

A case of a nasopalatine duct cyst in a 35-year-old female patient with chief complaint of painless swelling over the palate and anterior maxilla is presented. CBCT scan in the three references planes - sagittal, axial and frontal (coronal) - showed a well-defined, round radiolucency in the region of incisive canal, measuring 2.2 cm × 1.5 cm × 0.4 cm, with corticated margins in the midline and between the central incisors. These were the typical radiographic features of NPDC (Fig. 1).

Clinical examination revealed a palatal expansion on the anterior hard palate. The swelling was gradually increasing in size over the past 3 months without associated



Figure 1: Preoperative CBCT scan in sagittal, axial and frontal (coronal) reference planes showing a well-defined radiolucency in the anterior maxilla.

displacement of maxillary central incisors. There was no associated history of trauma, loose teeth, previous treatment or pain in the region. After the clinical examination and the radiographic diagnosis of NPDC, a surgical enucleation under i.v. sedation and local anesthesia was undertaken, and the specimen was sent to the Institute of Pathology in Skopje.



Figure 2: Intraoral photo of the surgical cavity after cyst removal.

Histopathological examination confirmed the diagnosis of an NPDC. Gross examination revealed a whitish, soft consistency fragment measuring 2.2 cm × 1.5 cm × 0.4 cm (Fig. 3). The recovery was uneventful, with primary healing of the incision site.

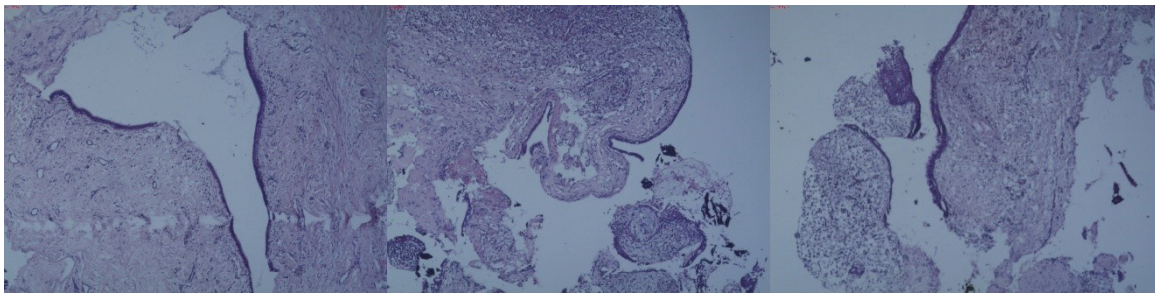


Figure 3: IHistologic features of the biopsy specimen.

Discussion

NPDC is the most common non-odontogenic cyst developing from the proliferation of embryological epithelial remnants of nasopalatine duct[4]. Most studies show a higher incidence of NPDC among males than females[5]. NPDCs are usually central or unilateral with no prevalence of side occurrence. Radiographically, they are seen as well-defined round or oval radiolucencies in the midline, although some lesions may appear heart-shaped[6], either because

they become notched by the nasal septum during their expansion or because the nasal spine is superimposed on the radiolucent area. Due to similar signs and symptoms, the NPDC may be easily misdiagnosed by the clinicians as a periapical lesion. This is why many authors believe that its prevalence is actually higher than presented in the literature[7]. Most of these cysts are asymptomatic or cause such minor symptoms being tolerated for very long periods. Nearly 40 % of the cases are totally asymptomatic and found only during routine clinical examination. In one study, the authors reported that 87 % of cases were asymptomatic[7]. Our patient reported few symptoms despite the size of the lesion. If this lesion was left untreated for an extended period, it could have abnormal growth. NPDC may be delined by a variety of different types of epithelium that ranges from stratified squamous to pseudostratified columnar, or a combination of these. A reported 71.8 % of NPDCs have squamous, columnar, cuboidal, or some combination of these epithelial types; respiratory epithelium has been found in only 9.8 %[8,9]. The connective tissue wall contains small arteries and nerves, representing the nasopalatine neurovascular bundle. Collections of mucous glands and scattered chronic inflammatory cell infiltrate are frequently present. In this case, the squamous epithelium was present with stratification. A correct diagnosis can only be made after proper clinical, radiographic, and histopathologic examination[10]. General imaging differential considerations include: periapical granuloma /periapical cyst, schwannoma in the incisive canal region, nasolabial cyst, median palatine cyst and enlarged nasopalatine duct. The present case had typical clinical, radiographic, and histopathological features of a nasopalatine duct cyst. The importance of this case lies in the diagnosis of NPDC, as these lesions can easily be misinterpreted as periapical cysts and inadvertent root canal therapy of adjacent vital teeth can be avoided. The treatment of choice is enucleation. Excision must be total to avoid relapse, and postoperative long term follow-up is essential. Marsupialization may be recommended for a large cyst without bony architecture, which has the risk of developing a postsurgical permanent fistula. Recurrence rate is low and ranges from 0% to 11%, depending on the study. Paresthesia of anterior palate may occur in fewer than 10 % of the cases, which can happen when branches of nasopalatine nerve are removed during surgery. Only after histological examination, the definitive diagnosis can be established[11-13].

Conclusion

Nasopalatine duct cysts are the most common nonodontogenic cysts of the oral cavity seen in the general population. In the case of asymptomatic apical radiolucency located in the anterior maxilla, differential diagnosis must distinguish NPDC from other maxillary

anterior radiolucencies. Vitality testing of teeth adjacent to or involved with a cyst-like lesion is mandatory and the final diagnosis could only be performed after histological analysis. It is important that practitioners are aware of the features of the NPDC.

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