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ABSTRACT

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THE PREVALENCE OF ANISOMELIA AND NEUROSENSORY IMPAIRMENT AS RISK FACTORS FOR TROPHIC ULCER FORMATION IN DIABETIC PATIENTS

Introduction. Diabetic foot ulcers are a major complication of diabetes, often leading to severe outcomes such as lower limb amputation. Risk factors for their formation include vascular disease, microcirculation disorders, impaired tissue regeneration, and local infections. However, the role of leg length discrepancy or anisomelia in combination with peripheral neurosensory deficit as a modifiable risk factor remains underexplored. **This study aimed** to assess the prevalence of anisomelia and peripheral neuropathy in diabetic patients compared to healthy individuals and analyze their potential impact on trophic ulcer formation.

Methods. The study involved 200 participants, including 101 healthy individuals divided by age into two groups and 99 diabetic patients with and without trophic foot ulcers, comparable in age, sex, and body mass index. Anisomelia was measured using a device with a virtual ruler application. Neurosensory impairment was assessed with a modified Neuropathy Disability Score. Data were analyzed using SPSS 27.0, employing Student`s t-tests, Pearson`s chi-square tests, and one-way ANOVA with Bonferroni corrections.

Results. The mean values and the distribution of people with different degrees of anisomelia did not differ between students in the final stages of their growth and mature individuals with a developed skeleton ($p = 0.232$; $p = 0.412$). There was no statistically significant difference between the mean leg length discrepancy values in patients with diabetes and the healthy population ($p = 0.935$). The prevalence and severity of anisomelia among patients with diabetes mellitus did not differ significantly from the general population ($\chi^2 = 2.06$; $p = 0.356$). Neuropathy severity differed significantly between diabetic patients with and without foot ulcers ($\chi 2 = 66.6$; $p < 0.001$), with severe neuropathy predominating in individuals who suffered from trophic ulcers (74.0%). Patients with ulcers had significantly higher NDS scores (8.33 ± 1.76) compared to those without ulcers (4.47 ± 1.07).

Conclusions. The study found that leg length discrepancy was similar in prevalence and severity between healthy individuals and diabetic patients. However, even minor asymmetry in people with diabetes may trigger trophic ulcer formation. Peripheral neuropathy severity was significantly higher in diabetic patients with ulcers, suggesting that anisomelia combined with neurosensory impairment may be a key risk factor for diabetic trophic ulceration.

Keywords: diabetes mellitus, diabetic foot ulcers, anisomelia, leg length discrepancy, peripheral neurosensory deficit, neuropathy.

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ПОШИРЕНІСТЬ АНІЗОМЕЛІЇ ТА НЕЙРОСЕНСОРНИХ ПОРУШЕНЬ ЯК ФАКТОРІВ РИЗИКУ ФОРМУВАННЯ ТРОФІЧНИХ ВИРАЗОК У ХВОРИХ НА ЦУКРОВИЙ ДІАБЕТ

Вступ. Діабетичні виразки стопи – серйозне ускладнення цукрового діабету, що часто призводить до тяжких наслідків, зокрема ампутації нижніх кінцівок. Факторами ризику їх розвитку є судинні захворювання, порушення мікроциркуляції, знижена здатність тканин до регенерації та локальні інфекції. Однак роль різниці в довжині ніг (анізомелії) у поєднанні з периферичним нейросенсорним дефіцитом як модифікованого фактора ризику залишається недостатньо вивченою. **Мета цього дослідження:** оцінити поширеність анізомелії та периферичної нейропатії у пацієнтів із цукровим діабетом порівняно зі здоровими особами та проаналізувати їхній потенційний вплив на розвиток трофічних виразок.

Матеріали та методи. У дослідженні взяли участь 200 осіб, зокрема 101 здорова людина, яких поділили на дві вікові групи, та 99 пацієнтів із цукровим діабетом (з трофічними виразками та без них), співставних за віком, статтю та індексом маси тіла. Анізомелію вимірювали за допомогою пристрою, обладнаного віртуальною лінійкою. Нейросенсорний дефіцит оцінювали за модифікованою шкалою оцінки нейропатії (Neuropathy Disability Score). Дані аналізували за допомогою SPSS 27.0, використовуючи t-тест Стьюдента, χ^2-критерій Пірсона та однофакторний дисперсійний аналіз (ANOVA) з поправкою Бонферроні.

Результати. Середні значення та розподіл осіб із різними ступенями анізомелії не відрізнялися між студентами на фінальному етапі їх росту та дорослими людьми зі сформованим скелетом ($p = 0,232$; $p = 0,412$). Не було виявлено статистично значущої різниці між середніми значеннями різниці довжини ніг у пацієнтів із діабетом та здорових осіб ($p = 0,935$). Поширеність і тяжкість анізомелії серед пацієнтів із цукровим діабетом не відрізнялися від загальної популяції ($\chi^2 = 2,06$; $p = 0,356$). Тяжкість нейропатії суттєво відрізнялася між пацієнтами з діабетом, які мали трофічні виразки, та тими, хто їх не мав ($\chi^2 = 66,6$; $p < 0,001$), при цьому тяжка нейропатія переважала серед осіб із трофічними виразками (74,0%). Пацієнти з виразками мали значно вищі показники NDS (8,33 ± 1,76) порівняно з діабетичними хворими, у кого виразок не було (4,47 ± 1,07).

Висновки. Дослідження показало, що різниця в довжині ніг має подібну поширеність і ступінь вираженості серед здорових людей та пацієнтів із цукровим діабетом. Однак навіть незначна асиметрія у людей із діабетом може стати тригером для розвитку трофічних виразок. Тяжкість периферичної нейропатії була значно вищою у пацієнтів із виразками, що вказує на можливу роль анізомелії в поєднанні з нейросенсорним дефіцитом як важливого фактора ризику розвитку діабетичних трофічних виразок.

Ключові слова: цукровий діабет, діабетичні виразки стопи, анізомелія, різниця довжини ніг, периферичний нейросенсорний дефіцит, нейропатія.

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ABBREVIATIONS: DFUs – diabetic foot ulcers; LLD – leg length discrepancy; DM – diabetes mellitus; NDS – Neuropathy Disability Score; BMI – body mass index; HbA1c – glycated hemoglobin

INTRODUCTION / ВСТУП

Diabetic foot ulcers (DFUs) remain a significant health problem, often leading to lower limb amputation and an increase in morbidity and mortality [1]. The main pathogenetic factors in developing such lesions are peripheral artery disease, microcirculation disorders, reduced tissue regenerative capacity, and local infectious complications [2]. Studies also indicate that the characteristics of reparative processes in trophic ulcers in patients with diabetes mellitus may play a significant role in their progression and healing [3]. While various risk factors of diabetic foot ulcers may have been identified in previous research, the effectiveness of early pathogenetically based diagnosis, treatment, and prevention is still low [4]. That is why scientists have recently focused more and more on additional modifiable risk factors.

The role of leg length discrepancy (LLD) or anisomelia as a risk factor for the formation of trophic ulcers in patients with diabetes mellitus (DM) remains insufficiently studied [5]. According to various researchers, LLD affects about 70–90% of the general population [6, 7]. Anisomelia is considered significant if it is greater than 2 cm. This condition occurs only in 0.1% of the world's population and can influence the person's quality of life by affecting several functional activities such as posture, balance, walking, and running [8]. Many people may accommodate 1 cm LLD and do not seem to have any clinical symptoms by a combination of kinematic changes at the pelvis, knee and ankle. However, in some diseases like diabetes mellitus, where the foot may be affected by vascular changes or neuropathic disorders, any amount of anisomelia may need to be corrected as it can cause complications [7].

The potential impact of the peripheral neurosensory deficit on the ability of people with diabetes to effectively modify their gait, compensating for the impairments caused by anisomelia, remains underexplored. Additionally, there is limited data on whether the prevalence and degree of LLD differ significantly between diabetic patients and the general population. Understanding the relationship between anisomelia, neurosensory impairment, and trophic ulcer formation in diabetes may offer new approaches to early diagnosis and targeted prevention strategies.

The aim of the study was to assess the prevalence of anisomelia and neurosensory impairment as risk factors for the formation of trophic ulcers in patients with diabetes mellitus compared to healthy individuals.

MATERIALS AND METHODS

The study involved 200 participants. The control group consisted of 101 practically healthy individuals (group 1; 52.5% female; age [±SD] – 33.9 ± 19.5 years). It was divided by age into the groups 1a (n=55; 58.2% female; age [±SD] – 19.1 ± 1.9 years) and 1b (n=46; 45.7% female; age [±SD] – 51.5 ± 16.0 years). The study also included 99 patients with diabetes mellitus: 53 patients without trophic ulcers (the group 2; 50.9% female; age [±SD] – 54.8 ± 14.4 years) and 46 patients with unilateral plantar trophic ulcers (the group 3; 52.2% female; age [±SD] – 64.1 ± 7.5 years). Table 1 shows the main clinical, age, gender, and anthropometric characteristics of the patients in the comparison groups.

All participants were examined at the clinical bases of the Department of Internal and Family Medicine of Sumy State University – the Sumy Laser Clinic and the Sumy Regional Clinical Hospital. Inclusion criteria for the study participants of groups 2 and 3 were diabetes mellitus type 1, 2 moderate or severe

compensated stage (mean glycated hemoglobin (HbA1c) < 7%), and a body mass index (BMI) ≤ 25 km/m^2. Patients with musculoskeletal disorders or decompensated comorbidities were excluded from the study. The distribution of patients by diabetes type did not significantly differ between the 2nd and 3rd groups (p = 0.812). Patients of the group 3 were additionally diagnosed with diabetic foot syndrome I–II according to the E. Wagner classification [9].

Table 1 *– Clinical characteristics of the comparison groups*

Indicator	Control group (n=101)	Group 1a (n=55)	Group 1b (n=46)	Group 2 (n=53)	Group 3 (n=46)	p
Age, years ± SD, (min-max)	33.9 ± 19.5 (17–78)	19.1 ± 1.9 (17–22)	51.5 ± 16.0 (25–78)	54.8 ± 14.4 (25–82)	64.1 ± 7.5 (45–76)	p_{1a-1b} < 0.001 p_{1b-2} = 0.822 p_{1b-3} = 0.051 p_{2-3} = 0.053
Sex, f/m, %	52.5 / 47.5	58.2 / 41.8	45.7 / 54.3	50.9 / 49.1	52.2 / 47.8	p_{1a-1b} = 0.209 p_{1b-2} = 0.532 p_{1b-3} = 0.362 p_{2-3} = 0.151
BMI, kg/m^2 ± SD	23.3 ± 0.6	20.5 ± 0.4	23.8 ± 0.6	24.5 ± 0.5	24.0 ± 0.7	p_{1a-1b} = 0.275 p_{1b-2} = 0.335 p_{1b-3} = 0.429 p_{2-3} = 0.735
HbA1c, % ± SD	4.8 ± 0.8	4.0 ± 0.5	5.2 ± 0.6	6.8 ± 0.5	6.9 ± 0.3	p_{1a-1b} = 0.065 p_{1b-2} = 0.009 p_{1b-3} = 0.006 p_{2-3} = 0.835

Note: f- female; m – male; BMI – body mass index; HbA1c – glycated hemoglobin; SD – standard deviation; p – the statistical significance of differences between the groups; categorical variables were compared using the χ2 test, quantitative variables – using One-way ANOVA

All of the participants provided informed consent to participate in the study, according to the Ethical Principles for Medical Research Involving Human Subjects, WMA Declaration of Helsinki, 2013.

A clinical examination was performed to assess neuropathic changes in the feet of participants. A modified NDS (Neuropathy Disability Score) scale was used to quantify sensory impairment. It includes the ankle reflex, vibration sensitivity (128 Hz tuning fork), pin-prick, and temperature (cold tuning fork) sensation, with a maximum score of 10 points. The severity of neuropathy was graded as follows: mild (scores 3–5), moderate (scores 6–8) and severe (scores 9–10) [10].

Lower limb length was measured using a device consisting of a platform equipped with a 1 m rail positioned at a 45° angle to its longer side. One end of the rail was fixed to the platform's midpoint. The other end had a tripod to hold a mobile phone with a "virtual ruler" application. The platform was placed flush against a vertical wall. Patients were standing upright on it, so their heads, shoulder blades, buttocks, and heels touched the wall. The anterosuperior iliac spine was palpated and marked as the proximal landmark on both sides of the patient's body. The distal landmark was identified as the most prominent part of the tibial bone's outer surface on the right and left. The virtual ruler application was used to fix the first measurement point on the proximal landmark. Then, the mobile phone was moved down to align with the distal landmark, tracing its intersection with the horizontal plane (the floor). There, the second measurement point was fixed. This process recorded the measurement between the two landmarks, displayed on the mobile device screen, and documented with a photo for further calculations. Measurements were repeated for the other leg, and the difference in leg length was calculated. Each limb was measured three times. The average value was used for analysis [11].

Data analysis was conducted using the SPSS version 27.0 (USA). Quantitative variables were presented as mean ± standard deviation for normally distributed data and percentage values. Percentages were used for categorical data. The Shapiro–Wilk test was applied to assess the normality of distribution for quantitative variables. Student`s t-test was employed to compare the quantitative variables of the two groups, while Pearson`s chi-squared test (χ^2) assessed the relationship between categorical variables and their distribution. One-way ANOVA with the Bonferroni multiple comparisons correction was used to compare the mean

values of the three groups. A *p*-value of <0.05 was considered statistically significant.

RESULTS

A limb length discrepancy was determined with a distribution in the following ranges: less than 0.5 cm, 0.5 to 1.5 cm, and more than 1.5 cm, to investigate the prevalence of anisomelia in the study groups. Due to technical and anthropometric measurement errors, a mean leg length discrepancy of less than 0.5 cm was considered statistically and clinically insignificant.

The control group 1 consisted of 101 practically healthy individuals. The average difference between the right and left limbs in the control group was 0.96 ± 0.79 cm. No LLD was found in 21.8% of the subjects. 78.2% of people had a difference between both limbs. 61.4% of them had a slight difference of 0.5–1.5 cm, and 16.8% had a difference of greater than 1.5 cm.

This group was divided into the 1sta and 1stb groups according to age. The group 1a consisted of 55 healthy students of Sumy State University in the final stages of their growth and skeletal development. Their age ranged between 17 and 22 years. The group 1b consisted of 46 mature, virtually healthy individuals with a developed skeleton, aged from 25 to 78 years. There was no difference in the distribution of sex (p = 0.209), HbA1c (p = 0.065), or BMI (p = 0.275) between the groups 1a and 1b.

The mean difference between the right and left limbs of the subjects in the group 1a was 0.93 ± 0.66 cm. No difference in leg length was found in 18.2% of the students. The LLD between the two limbs, equal to the 0.5–1.5 cm range, was determined in 67.3% of them and greater than 1.5 cm – in 14.5% of the subjects.

The average LLD in the 1stb group was 1.0 ± 0.93 cm. There was no difference in the leg length in 26.1% of practically healthy individuals in group 1b. The data analysis showed that 54.3% of them had a difference between the two limbs of 0.5–1.5 cm and 19.6% – greater than 1.5 cm.

There was no difference between the mean values of LLD in the 1sta and 1stb groups (p = 0.232). Furthermore, the distribution of people with different degrees of anisomelia did not differ by age (χ^2 = 1.775; p = 0.412).

The average leg length discrepancy in diabetic patients of the 2nd group was 0.98 ± 0.88 cm. No difference in the leg length was found in 30.4% of participants. 69.6% of patients had a difference between the two limbs. A slight difference equal to 0.5–1.5 cm was established in 52.2% of them, and 17.4% had an LLD greater than 1.5 cm.

The average difference between the right and left extremities in the group 3 was 0.92 ± 0.68 cm. There was a difference of less than 0.5 cm in leg length in 28.3% of patients. A slight difference, equal to 0.5–1.5 cm, was found in 50.0% of them and greater than 1.5 cm – in 21.7%.

The next task was to analyze whether there is a difference in the prevalence of anisomelia between the patients with diabetes mellitus and the healthy population, we compared the 1stb, 2nd, and 3rd groups, comparable in age, gender, and body mass index (p > 0.05). There were no differences in the level of the glycated hemoglobin (HbA1c) between the 2nd and 3rd groups (p = 0.835), but its level was significantly higher compared to the 1stb group ($p_{1b\text{-}2}$ = 0.009; $p_{1b\text{-}3}$ = 0.006). There was no statistically significant difference between the mean anisomelia values of the 1stb, 2nd, and 3rd groups (p = 0.935). In addition, the distribution of people with different degrees of LLD did not differ between the three groups (χ^2 = 2.06; p = 0.356). Thus, the prevalence and severity of anisomelia among patients with DM do not differ from those in the general population (Table 2).

All the participants in the 1st group didn`t have any neurological disorders. The following results were obtained when assessing the status of peripheral neurosensory impairment in diabetic patients. No patients were without neurological symptoms (0–3 NDS points) in the 2nd and 3rd groups. In the 2nd group, 48 patients (90.6 %) had mild severity of neuropathy disability. 5 patients (9.4 %) of the group 2 had moderate severity of neuropathy. There were no patients with the severe stage of neuropathy. In contrast, the distribution of patients in the group 3 by the severity of neurological disorders was as follows: mild – 6 patients (13.0 %), moderate – 6 patients (13.0 %), and severe – 34 patients (74.0 %). Thus, the distribution of patients by severity of peripheral neuropathy significantly differed between the groups 2 and 3 (χ2 = 66.6; p < 0.001) (fig.1). The mean NDS score in the patients of the group 2 was 4.47 ± 1.07, in the group 3 – 8.33 ± 1.76. Diabetic patients with trophic foot ulcers had a significantly higher average NDS score than those without ulcers (p < 0.001).

Table 2 *– The prevalence of anisomelia in the studied groups*

Indicator	Control group (n=101)	Group 1a (n=55)	Group 1b (n=46)	Group 2 (n=53)	Group 3 (n=46)	p
Δl < 0.5; n (%)	22 (21.8%)	10 (18.2%)	12 (26.1%)	16 (30.4%)	13 (28.3%)	p_{1a-1b} = 0.412 (χ^2 = 1.775) p_{1b-2} = 0.888 (χ^2 = 0.24) p_{1b-3} = 0.679 (χ^2 = 0.775) p_{2-3} = 0.835 (χ^2 = 0.36)
Δl = 0.5-1.5; n (%)	62 (61.4%)	37 (67.3%)	25 (54.3%)	28 (52.2%)	23 (50.0%)	
Δl > 1.5; n (%)	17 (16.8%)	8 (14.5%)	9 (19.6%)	9 (17.4%)	10 (21.7%)	
Average LLD ± SD, cm	0.96 ± 0.79	0.93 ± 0.66	1.00 ± 0.93	0.98 ± 0.88	0.92 ± 0.68	p_{1a-1b} = 0.232 p_{1b-2} = 0.869 p_{1b-3} = 0.455 p_{2-3} = 0.157

Note: Δl – the value of the difference between the lengths of the lower extremities; SD – standard deviation; p – statistical significance of differences; categorical variables were compared using the Pearson's chi-squared (χ2) test, quantitative variables – using one-way ANOVA with the Bonferroni multiple comparisons correction

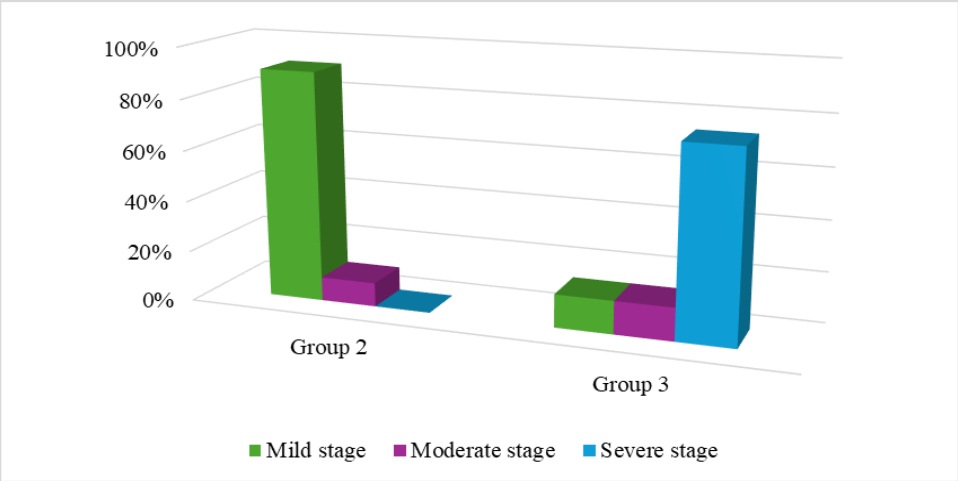

Figure 1 – The prevalence of neuropathy by severity

DISCUSSION

In a study performed by the American Academy of Orthopedic Surgeons, among the 600 military recruits, 32% had a difference between the length of their legs 1/5–3/5 inches (0.5–1.5cm). LLD of > 1.5 cm was measured in 4% of cases [12]. The results of our study confirm that anisomelia is a quite common condition. We also proved that the prevalence of anisomelia among people with diabetes did not differ significantly from the general population (fig. 2).

Individuals with LLD often develop some compensatory mechanisms to maintain balance and reduce vertical displacement of the body's center of mass [6]. Some studies suggested that the shorter leg experiences increased pressure, while others reported that the longer leg bears a greater load [13, 14]. However, it is clear that even minor anisomelia can lead to some changes in gait mechanics, resulting in uneven weight distribution and increased pressure on specific areas of the foot [7]. This is especially relevant for patients with diabetes mellitus and neuropathy, in whom even a slight artificially induced LLD could significantly affect plantar pressure distribution, as was investigated by Nahas et al. [15].

Distal symmetric polyneuropathy is one of the most common chronic complications of diabetes, with an estimated prevalence of more than 50% in people with diabetes [16]. It is a significant risk factor for diabetic

foot ulceration, which is associated with a 5-year lower limb amputation rate of 10% and a mortality rate of 40% [17]. While neuropathy is often a symmetrical process, diabetic foot ulcers frequently occur unilaterally. Therefore, it can be assumed that the presence of neurosensory impairment can significantly aggravate the effects of anisomelia. The sensory deficits impair the ability of patients with diabetes to recognize pain and pressure changes, making it difficult for individuals to detect and adapt to abnormal loads [18]. Despite the symmetrical character of the neuropathy, individual variations in gait, foot structure, and weight distribution can predispose specific areas of the foot to higher pressure and increased risk of ulceration [19].

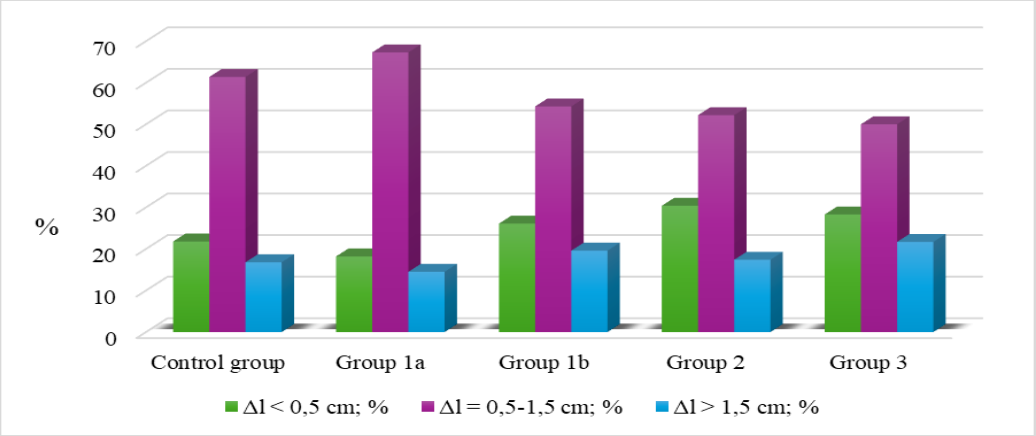

Figure 2 – The prevalence of anisomelia in patients with diabetes mellitus and healthy population; Δl – the value of the leg lengths discrepancy

As follows, anisomelia, especially in combination with neurological deficits, can increase the risk of unnoticed injuries contributing to subsequent ulceration. However, the mechanisms of this influence require further research, which will help to develop more effective strategies for the prevention and treatment of diabetic foot ulcers.

Our study has several limitations, including a relatively small sample size and the inclusion of only patients with compensated diabetes. Additionally, the study did not assess other important risk factors for diabetic foot ulcers, such as peripheral arterial disease, smoking, and glycemic control. Further research with larger sample sizes and a more comprehensive assessment of risk factors is necessary to fully clarify the complex relationship between anisomelia, neuropathy, and foot ulcer development in diabetic patients. Conducting a larger-scale multicenter study similar to this could lead to the establishment of a diabetic foot risk stratification system.

CONCLUSIONS

The results of the study demonstrated that the prevalence and severity of leg length discrepancy were comparable between healthy individuals and diabetic patients, regardless of age or sex. However, an insignificant asymmetry, which in healthy people does not manifest itself, can become a trigger for trophic ulcer formation in the case of diabetes. In contrast, the presence of peripheral neuropathy significantly differed, with the highest severity observed in diabetic patients with trophic ulcers. These findings suggest that anisomelia, in combination with peripheral neurosensory impairment, may be one of the most important risk factors for the formation of diabetic trophic ulcers.

PROSPECTS FOR FUTURE RESEARCH / ПЕРСПЕКТИВИ ПОДАЛЬШИХ ДОСЛІДЖЕНЬ

Further researches are needed to determine the long-term impact of leg length discrepancy on the unilateral character of the diabetic foot ulcers development and progression.

AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ

All authors substantively contributed to the drafting of the initial and revised versions of this paper. They take full responsibility for the integrity of all aspects of the work.

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The authors declare no conflict of interest.

ARTIFICIAL INTELLIGENCE DISCLOSURE / ВИКОРИСТАННЯ ШТУЧНОГО ІНТЕЛЕКТУ

No artificial intelligence technologies were used during manuscript writing or editing.

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