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The Effect of Local and Systemic Administration of L-Thyroxine on Rate of Regeneration and Cytokine Secretion in Experimental Burn Wound Model

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ABSTRACT

BACKGROUND: Thermal skin injuries are among the most common traumatic lesions in humans; however, overall treatment outcomes for deep burns remain unsatisfactory. Thyroid hormones are key regulators of cellular processes, including cell proliferation and angiogenesis, which makes them potential stimulators of regeneration in skin injuries.

AIM: The work aimed to investigate systemic and topical effects of L-thyroxine on the wound healing process in an experimental model of deep burn wounds.

METHODS: The effect of pharmacologically altered thyroid status and 10 µg/mL thyroxine-containing hydrogel on an experimental third-degree (IIIB) skin burn was studied in 74 white non-linear male rats weighing 220–257 g. A third-degree (IIIB) burn was induced in the proximal dorsal region. Seventy-two hours after burn induction, the eschar was completely excised along the border with intact skin, and a splinting ring was applied; subsequently, in groups Ib and IIIa, the investigational drugs were applied topically. On day 10 after burn induction, levels of interferon gamma (IFN-γ), alpha-defensin 1 (DEFA1), transforming growth factor β1 (TGF-β1), and fibroblast growth factor 2 (FGF2) were measured in wound exudate using enzyme-linked immunosorbent assay. Changes in burn wound area were assessed over time using the Universal Desktop Ruler software.

RESULTS: Median time to 50% epithelialization in systemic and local hyperthyroidism groups was 20 (19; 21.5) and 21 (18; 22) days, respectively, significantly shorter than in the intact control group. Median time to 75% epithelialization in all experimental groups differed significantly from both control groups: in systemic and local hyperthyroidism groups, it was 29.5 (28; 32), 30.2 ± 0.9, and 33.3 ± 0.45 days, respectively; in propylthiouracil-induced hypothyroidism group, median time to 75% epithelialization was not reached. In systemic hyperthyroidism group, IFN-γ, DEFA1, TGFβ1, and FGF2 levels in wound exudate, and in local hyperthyroidism group, FGF2 and IFN-γ levels, were significantly higher than in both control groups. In contrast, in propylthiouracil-induced hypothyroidism group, FGF2 and IFN-γ levels were significantly lower compared with control groups.

CONCLUSION: Systemic hyperthyroidism and application of thyroxine-containing gel to wound surface accelerate natural wound healing. Thyroid hormones exhibit dose-dependent effects on FGF2 and IFN-γ secretion.

Keywords: thyroid hormones; thermal skin damage; III degree burn; wound healing; hyperthyroidism; defensins.

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Влияние локального и системного введения L-тироксина на скорость регенерации и секрецию цитокинов на модели экспериментальной ожоговой раны

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АННОТАЦИЯ

Обоснование. Термические повреждения кожи относятся к одним из самых распространенных травматических повреждений человека, при этом совокупные результаты лечения глубоких ожогов остаются неудовлетворительными. Тиреоидные гормоны являются одними из ключевых регуляторов клеточных процессов, включая клеточную пролиферацию и ангиогенез, что делает их потенциальными стимуляторами регенерации при поражениях кожи.

Цель — исследовать системное и топическое влияние L-тироксина на течение раневого процесса на экспериментальной модели глубоких ожоговых ран.

Методы. В опытах на 74 белых нелинейных крысах-самцах массой 220–257 г исследовали влияние медикаментозно измененного тиреоидного статуса и гидрогеля с тироксином в концентрации 10 мкг/мл на течение экспериментального термического ожога кожи IIIB степени. Термический ожог, соответствующий IIIB степени, наносили в области проксимальной части спины. Через 72 ч после нанесения ожога рану освобождали от струпа полным его иссечением по границе с неповрежденной кожей с наложением шинирующего кольца, после чего в Ib и IIIa группах проводили аппликацию исследуемых лекарственных средств. На 10-е сутки после нанесения ожога в раневом отделяемом определяли уровни гамма-интерферона (ИНФ-γ), дефензина альфа 1 (DEFa1), трансформирующего фактора роста β-1 (TGFβ1), фактора роста фибробластов 2 (FGF2) с использованием иммуноферментного анализа. Динамику изменения площади ожоговой раны оценивали в динамике с использованием программы Universal Desktop Ruler.

Результаты. Медианы времени 50% эпителизации в группах системного и локального гипертиреоза составили 20 (19; 21,5) и 21 (18; 22) дней и были достоверно меньше интактного контроля. Медианы времени 75% эпителизации ран во всех экспериментальных группах статистически значимо отличались от обеих контрольных групп: в группах системного и локального гипертиреоза составила 29,5 (28; 32), 30,2±0,9 и 33,3±0,45 дней соответственно, при этом медиана времени до 75% эпителизации в группе индуцированного пропилтиоурацилом гипотиреоза не достигнута. Уровни ИНФ-γ, DEFa1, TGFβ1, FGF2 в раневом отделяемом в группе системного гипертиреоза и уровни FGF2 и ИНФ-γ в группе локального гипертиреоза были статистически значимо повышены в сравнении с обеими контрольными группами. В группе гипотиреоза, индуцированного пропилтиоурацилом, напротив, уровни FGF2 и ИНФ-γ демонстрировали статистически значимое снижение в сравнении с контрольными группами.

Заключение. Системный гипертиреоз и аппликации тироксин-содержащего геля на раневую поверхность приводит к ускорению «естественного течения раневого процесса». Тиреоидные гормоны демонстрируют дозозависимые эффекты в отношении секреции FGF2 и ИНФ-γ.

Ключевые слова: тиреоидные гормоны; термическое повреждение кожи; ожог III степени; раневой процесс; гипертиреоз; дефензины.

Как цитировать

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BACKGROUND

Thyroid hormones (THs) are essential regulators of cellular processes, including proliferation, differentiation, and metabolism, acting through both genomic and nongenomic mechanisms [1]. Nuclear receptor stimulation alters the expression profiles of more than 100 genes, more than half of which are tissue-specific [2]. Nongenomic mechanisms are activated by stimulation with L-thyroxine (T4) or, to a lesser extent, via direct (T3) and reverse (rT3) triiodothyronine. The latter are specific binding sites on integrin (CD51/CD61), resulting in dose-dependent activation of the mitogen-activated protein kinase (MAPK) signaling pathway, which involves the RAS/RAF/MEK/ERK pathway. Furthermore, phosphatidylinositol-3-kinases (PI3K) and serine/threonine protein kinase (STK) can be involved [3]. In malignant neoplasms, excessive TH levels cause tumor progression as a result of nongenomic effects that activate cell proliferation, angiogenesis, and immunomodulatory effects associated with modified pro- and anti-inflammatory cytokine secretion [4, 5]. However, the role of THs in regeneration and proliferation of both unaffected and affected tissues is poorly understood [6]. The available theoretical data on intracellular and tissue effects of iodothyronines support their potential use as universal proliferation and angiogenesis regulators in the treatment of various skin injuries [7]. However, the use of thyroid hormones, including topical iodothyronines, is still insufficiently studied.

This study aimed to investigate systemic and topical effects of L-thyroxine on the wound healing process in an experimental model of deep burn wounds.

METHODS

Overall Experimental Study Design

This experimental study assessed the impact of drug-induced changes in thyroid status and the topical effect of L-thyroxine on wound healing. The experiment used male nonlinear white rats weighing 184–246 g ($n = 65$). The animals were obtained from the Rappolovo husbandry (Leningrad region, Russia). Upon receipt, the animals were quarantined for at least 14 days. During the quarantine, all animals were examined twice daily (in the morning and evening) to assess their overall condition and behavior. Animals with suspected diseases and/or behavioral changes were excluded from the study during the quarantine.

Animal Housing, Study Group Formation, and Randomization

Animals ($n = 74$) were kept under standard vivarium conditions, with four rats per cage. Each rat was separated from others by a perforated partition, which facilitated communication and minimized isolation stress. Water and

feed were provided *ad libitum* to all animals. Following an experimentally induced burn, rats were randomized into five study groups, with a treatment to control ratio of 1.8:1.0. In group Ia, systemic hyperthyroidism was experimentally induced. Group Ib (local hyperthyroidism) received thyroxine-based gel applications. In group II, systemic propylthiouracil-induced hyperthyroidism was modeled by substituting water with 0.1% propylthiouracil (PTU) solution. Group IIIa served as a positive control and received dioxomethyltetrahydropyrimidine + chloramphenicol applications. Group IIIb served as an intact control (Table 1).

Drug Substances

The study used levothyroxine and PTU (Table 2); thyroxine solution was administered intraperitoneally, following a daily weighing. To make the thyroxine-based gel, thyroxine solution was mixed with sodium carboxymethyl cellulose (Na-CMC) up to 10 µg/mL. Positive controls received dioxomethyltetrahydropyrimidine + chloramphenicol applications. To ensure testing integrity and comparable stress levels, all groups except the systemic hyperthyroidism group received daily injections with 0.2 mL of 0.9% sodium chloride solution.

Thermal Burn Modeling

A thermal burn was induced using the previously described procedure [8] in the proximal back region to prevent animal snouts and paws from contacting the wound surface. Four days before the experimentally induced injury, this region was shaved and dehaired using a special cream for 15 min. After 15 min, the cream and hair were removed, the skin was rinsed with warm water, wiped dry with a paper towel, and allowed to dry. The skin at the future burn site was then marked to designate the center of thermal applicator placement. Thermal burns were induced under general anesthesia with tiletamine + zolazepam in combination with 0.01% clonidine solution (2:1) when the deep sleep phase was reached. Thermal burns were induced using a cylindrical applicator made of steel, weighing 835 g, with a flat, circular working section with a diameter of 20 mm, providing a wound surface area of 100π (314 ± 5 mm²). To induce burns, the applicator was heated to a constant temperature by immersing in boiling water (98–100 °C) for 2 min. The applicator was then used on the animal's skin for 30 s. Following that, the applicator was removed. After 72 h, the scab was removed by complete dissection along the edge of unaffected skin. Following that, the skin around the wound was sutured, with the surgical suture ends left loose. A ring splint (height 4 mm, inner diameter 25 mm, outer diameter 26.5 mm) was placed along the perimeter of the wound and fixed by suturing. The ring splint was covered with a patch that was fixed along its edges to minimize wound contamination

Table 1. Study group characteristics

Group No.	Group name	Number of animals	Group description	Method description	Administration frequency
Ia	Systemic hyperthyroidism	18	Inducing moderate drug-induced hyperthyroidism	Intraperitoneal administration at a dose of 100 µg/100 g body weight	Once daily
Ib	Local hyperthyroidism	18	Creating increased levothyroxine concentrations at the wound site	Applying 1 mL of levothyroxine-based gel (10 µg/mL)	Once daily to the wound surface
II	Systemic hyperthyroidism	18	Inducing moderate drug-induced hyperthyroidism	Substituting water with 0.1% propylthiouracil solution	<i>ad libidum</i>
IIIa	Positive control	10	Topical application of a standard drug	Applying 1.0 g of dioxomethyltetrahydropyrimidine + chloramphenicol	Once daily
IIIb	Intact control	10	Open wound management without drug therapy	–	–

Table 2. Drug substances used in the study

Substance name	Chemical name	Manufacturer	Country
L-thyroxine (levothyroxine sodium)	2-amino-3-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]propionic acid	Republican Unitary Production Enterprise Belmedpreparaty	Republic of Belarus
Propylthiouracil	2,3-dihydro-6-propyl-2-thioxo 4(1 <i>H</i>)-pyrimidinone	Wuhan Hezhong Bio-Chemical Manufacture Co., Ltd	China

and reduce topical drug loss. The splint prevented wound contraction and kept its size constant, allowing for more objective assessment of the test and control products.

Laboratory Animal Monitoring

To ensure objective assessment during all stages of the experiment, wounds were photographed using a scale ruler for subsequent wound area calculation. Wound areas were calculated in the Universal Desktop Ruler software, which uses photographs to assess wound geometry, with a preliminary calibration based on the scale ruler on the photograph. Changes in wound surface epithelization were used as complete wound healing criteria.

Enzyme-Linked Immunosorbent Assay

Resorption and thyroid status in drug-induced systemic hyperthyroidism with iodothyronine-based hydrogel application were assessed based on serum thyroid-stimulating hormone (TSH) levels. For this purpose, blood samples were collected during decapitation. The Vector-Best test system (Vector-Best, Russia) was used. Interferon gamma (IFN-γ), alpha defensin 1 (DEFA1), transforming growth factor β-1 (TGF-β1), and fibroblast growth factor 2 (FGF2) levels in wound discharge were assessed by enzyme-linked immunosorbent assay (ELISA) with Cloud-Clone Corporation reagents (USA), according to the manufacturer's instructions. Samples were collected on day 10 after inducing burns, by wound discharge absorption with sterile paper points that were applied to the wound for 60 s.

The samples were then placed in sterile tubes with 0.9% sodium chloride solution for 45 min. A multifunctional plate reader Victor X5 (PerkinElmer Inc., USA) was used.

Ethics Approval

The study followed the ethical principles of the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (adopted in Strasbourg on March 18, 1986, and updated in Strasbourg on June 15, 2006).

Statistical Analysis

Data analysis was performed using Statistica for Windows (USA), version 10.0, with generally accepted descriptive statistics procedures, taking into account the small sample size. The data are presented as a mean with standard error (SE) and standard deviation (SD), as well as a median (*Me*) with upper and lower quartiles [*Q*₁; *Q*₃], with normality testing of each variable. The Anderson–Darling test was used for normality testing in groups. The groups were compared using the Mann–Whitney *U* test, based on the distribution of a variable in each experiment. Kaplan–Meier curves were used to compare changes in wound epithelization. The curves showed the mean remaining wound surface at each time point, ranging from 100% at baseline to 0% for complete epithelization. The median time to 25%, 50%, and 75% epithelization was calculated, with a standard error calculated using the Greenwood equation. Changes in epithelization based on the distribution of the variable were assessed using the Mantel–Cox logrank test or the

Table 3. Changes in wound epithelization during the experiment (*Me* [Q_1 ; Q_3])

Integral wound healing parameters	Animal groups				
	Hyperthyroidism		Systemic hyperthyroidism (Group II)	Comparison groups	
	group Ia	group Ib		group IIIa	group IIIb
Time to 25% epithelization, days	10.0 [9.5; 11.0]	12.9 ± 0.3	15.0 [13.0; 16.5]	13.2 ± 0.4	14.6 ± 0.3
Time to 50% epithelization, days	20.0 [19.0; 21.5]*	21.0 [18.0; 22.0]*	29.5 [26.0; 32.5]	23.5 ± 0.6*	28.1 ± 0.7
Time to 75% epithelization, days	29.5 [28.0; 32.0]**	30.2 ± 0.9**	Not achieved**	32.5 [29.0; 35.0]*	36.0 [34.0; 37.0]

Note. *Significant difference from intact control; **Significant difference from standard of care (group IIIa).

Gehan–Breslow–Wilcoxon test. The significance level for the null hypothesis (no significant differences or factor effects) was 0.05.

RESULTS

Experimentally induced hyperthyroidism and/or levothyroxine-based hydrogel application (Table 3) significantly reduced the epithelization time. In contrast, drug-induced hyperthyroidism significantly increased the epithelization time.

When assessing changes in burn wound epithelization, the median time to 50% epithelization in groups that received systemic or topical iodothyronines was 20 [19; 21.5] days and 21 [18; 22] days, respectively, differing significantly from the intact control. The time to 75% epithelization in all experimental groups differed significantly from both intact and positive controls. In groups Ia and Ib, the time to 75% epithelization was 29.5 [28; 32] days and 30.2 ± 0.9 days, respectively, whereas in the induced hyperthyroidism group, this parameter was not achieved (Table 3).

When assessing the thyroid status by TSH and T4 levels, the findings accurately reflected systemic hypo- and hyperthyroidism in accordance with modern hormonal regulation concepts. Blood TSH and T4 levels in animals with topical application of thyroxine-based gels corresponded to euthyroidism, with no significant differences from thyroid hormone levels in groups IIIa and IIIb (Table 4).

All assessed cytokine and DEFA1 levels in wound discharge on day 10 of the experiment were significantly elevated in the systemic hyperthyroidism group compared to both control groups. Topical application of a thyroxine-based gel (10 µg/mL) resulted in a significant increase in FGF2 and IFN-γ levels only. In contrast, in the PTU-induced hyperthyroidism group, there was a significant decrease in FGF2 and IFN-γ levels compared to controls, indirectly indicating dose-dependent effects of iodothyronines in FGF2 and IFN-γ expression regulation (Table 5).

DISCUSSION

The role of THs in tissue regeneration and wound processes is still insufficiently studied. However, available data suggest that iodothyronines have anti-inflammatory and immunomodulatory effects [9] that reduce the cytotoxicity of immunocompetent cells while increasing pro-inflammatory cytokine expression [10, 11]. This is most relevant for IFN-γ, TNF-α, and interleukin-6 (IL-6), and to a lesser extent for CXCL9, CXCL10, CXCL11, IL-21, IL-23, and IL-37 [12]. Cytokines and DEFA1 were selected considering the role of these biologically active substances in wound regeneration. Our study used IFN-γ as a reference parameter, because numerous studies confirm its increased expression in systemic hyperthyroidism [9]. However, according to our findings, drug-induced hyperthyroidism resulted in increased secretion of all assessed cytokines and DEFA1, whereas topical iodothyronines only resulted in increased IFN-γ and FGF2 levels.

Our study showed a shorter natural history of wound healing with drug-induced systemic hyperthyroidism and topical application of a thyroxine-based gel, whereas PTU-induced hyperthyroidism resulted in prolonged epithelization, supporting topical use of iodothyronine-based drugs [7].

There are currently few experimental studies on the use of iodothyronine-impregnated wound dressings and sutures, primarily demonstrating the regenerative and proangiogenic effects of natural iodothyronines. T4-impregnated cotton wound dressings (1 µg/mL) have demonstrated high efficacy in skin wound healing in laboratory animals. Complete epithelization of superficial mechanical wounds with a diameter of 20 mm was achieved within 23 days [13]. In an experimental study, combination hydrogels containing chitosan, carboxymethyl cellulose, and hydroxyapatite, at various T4 concentrations (0.1, 0.5, and 1 µg/mL), showed dose-dependent proangiogenic activity with increasing T4 concentrations in a chicken embryo chorioallantoic membrane model [14]. A similar model demonstrated that T3-impregnated polycaprolactone fibers had a considerable proangiogenic

Table 4. Thyroid hormone levels on the last day of the experiment

Assessed hormones		Animal groups				
		Hyperthyroidism		Systemic hyperthyroidism (group II)	Control	
		group Ia	group Ib		group IIIa	group IIIb
TSH, mIU/L	mean	0.33 ± 0.07 [^]	1.53 ± 0.13 [^]	6.09 ± 0.6	1.67 ± 0.29 [^]	1.74 ± 0.2
	<i>Me</i>	0.27	1.39	5.82	1.37	1.58
	[<i>Q</i> ₁ ; <i>Q</i> ₃]	[0.14; 0.34]	[1.13; 1.72]**,###	[4.16; 6.92]*,*,*,###	[1.13; 1.84]	[1.32; 2.12]
T4, nmol/L	mean	97.98 ± 2.86	75.19 ± 2.51	56.19 ± 2.99	77.64 ± 0.2.81	74.88 ± 2.77
	<i>Me</i>	98.15	81.93	64.26	79.24	75.92
	[<i>Q</i> ₁ ; <i>Q</i> ₃]	[87.58; 108.83]*,*,*,###	[87.58; 108.83]**,###	[49.05; 64.26]*,*,*,###	[69.45; 86.5]	[66.84; 82.8]

Note. [^]Normally distributed variable; *Significant difference from group Ib; **Significant difference from group IIIa; [#]Significant difference from intact control; ^{##}Significant difference from systemic hyperthyroidism (group IIa).

Table 5. Levels of assessed cytokines and alpha defensin 1 in animals

Assessed cytokines, pg/mL		Animal groups				
		Hyperthyroidism		Systemic hyperthyroidism (group II)	Control	
		group Ia	group Ib		group IIIa	group IIIb
FGF2	mean	29.24 ± 3.12	29.9 ± 1.88	15.51 ± 1.16	21.57 ± 2.36	23.13 ± 2.07
	<i>Me</i>	27.25	28.5	16.04	20.86	21.93
	[<i>Q</i> ₁ ; <i>Q</i> ₃]	[17.43; 40.45]**,###	[23.2; 36.2]**,###	[10.86; 18.54] [#]	[16.49; 24.37]	[18.99; 28.49]
TGFβ1	mean	5.76 ± 0.62	5.31 ± 0.66	4.64 ± 0.64	4.89 ± 0.73	4.33 ± 0.72
	<i>Me</i>	5.56	4.51	4.97	4.24	4.41
	[<i>Q</i> ₁ ; <i>Q</i> ₃]	[3.59; 7.65] [#]	[3.03; 8.15]	[2.46; 6.48]	[2.87; 7.73]	[2.46; 6.13]
DEFa1	mean	0.61 ± 0.08	0.53 ± 0.08	0.41 ± 0.06	0.42 ± 0.09 [^]	0.35 ± 0.03
	<i>Me</i>	0.67	0.48	0.42	0.35	0.37
	[<i>Q</i> ₁ ; <i>Q</i> ₃]	[0.26; 0.85] ^{#,###}	[0.23; 0.83]	[0.19; 0.63]	[0.23; 0.69]	[0.26; 0.4]
IFN-γ	mean	60.58 ± 3.74	61.38 ± 3.75	37.87 ± 3.99	49.22 ± 5.76	49.25 ± 4.54
	<i>Me</i>	61.16	64.08	37.69	50.89	48.08
	[<i>Q</i> ₁ ; <i>Q</i> ₃]	[55.49; 71.67]**,###	[49.77; 71.23]**,###	[30.67; 49.58]**	[33.25; 66.86]	[42.85; 56.98]

Note. [^]Normally distributed variable; **Significant difference from group IIIa; [#]Significant difference from intact control; ^{##}Significant difference from systemic hyperthyroidism (group IIa).

effect at the application site. When placed in aortic rings in rats, this material enhanced the invasive potential of endothelial cells and increased the total cross-sectional area of capillaries [15].

CONCLUSION

Our study improves the understanding of the role of THs in wound processes and their potential use to promote regeneration. Experimentally induced systemic hyperthyroidism and thyroxine-based gel (10 µg/mL) improve wound healing in an experimental setting. Systemic hyperthyroidism promotes secretion of all assessed cytokines, whereas thyroxine-based gel applications only increase FGF2 and IFN-γ secretion.

ADDITIONAL INFO

Author contributions: A.A. Minchenko, A.R. Khasanov, A.A. Korina: investigation; A.I. Poloskov: resources; writing—original draft; A.E. Trandina, A.S. Buntovskaya: methodology; K.B. Ovanesov: formal analysis; E.M. Mavrenkov, R.I. Glushakov: writing—review & editing, conceptualization. All the authors approved the version of the draft to be published and agreed to be accountable for all aspects of the work, ensuring that issues related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. А.А. Минченко, А.Р. Хасанов, А.А. Кокорина — проведение эксперимента; А.И. Полосков — подготовка и дозирование фармакологических субстанций, написание статьи; А.Е. Трандина, А.С. Бунтовская — выполнение лабораторных исследований; К.Б. Ованесов — анализ данных; Э.М. Мавренков, Р.И. Глушаков — редактирование статьи, разработка общей концепции. Авторы одобрили версию для публикации, а также согласились нести ответственность за все

аспекты работы, гарантируя надлежащее рассмотрение и решение вопросов, связанных с точностью и добросовестностью любой ее части.

Этическая экспертиза. Проведение исследования одобрено независимым этическим комитетом ООО «Медицинские технологии» (протокол № 34 от 19.12.2023). Протокол исследований не регистрировали.

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Раскрытие интересов. Авторы заявляют об отсутствии отношений, деятельности и интересов за последние три года, связанных с третьими лицами (коммерческими и некоммерческими), интересы которых могут быть затронуты содержанием статьи.

Оригинальность. При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, данные).

Доступ к данным. Все данные, полученные в настоящем исследовании, доступны в статье.

Генеративный искусственный интеллект. При создании настоящей статьи технологии генеративного искусственного интеллекта не использовали.

Рассмотрение и рецензирование. Настоящая работа подана в журнал в инициативном порядке и рассмотрена по обычной процедуре. В рецензировании участвовали два внешних рецензента и член редакционной коллегии.

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