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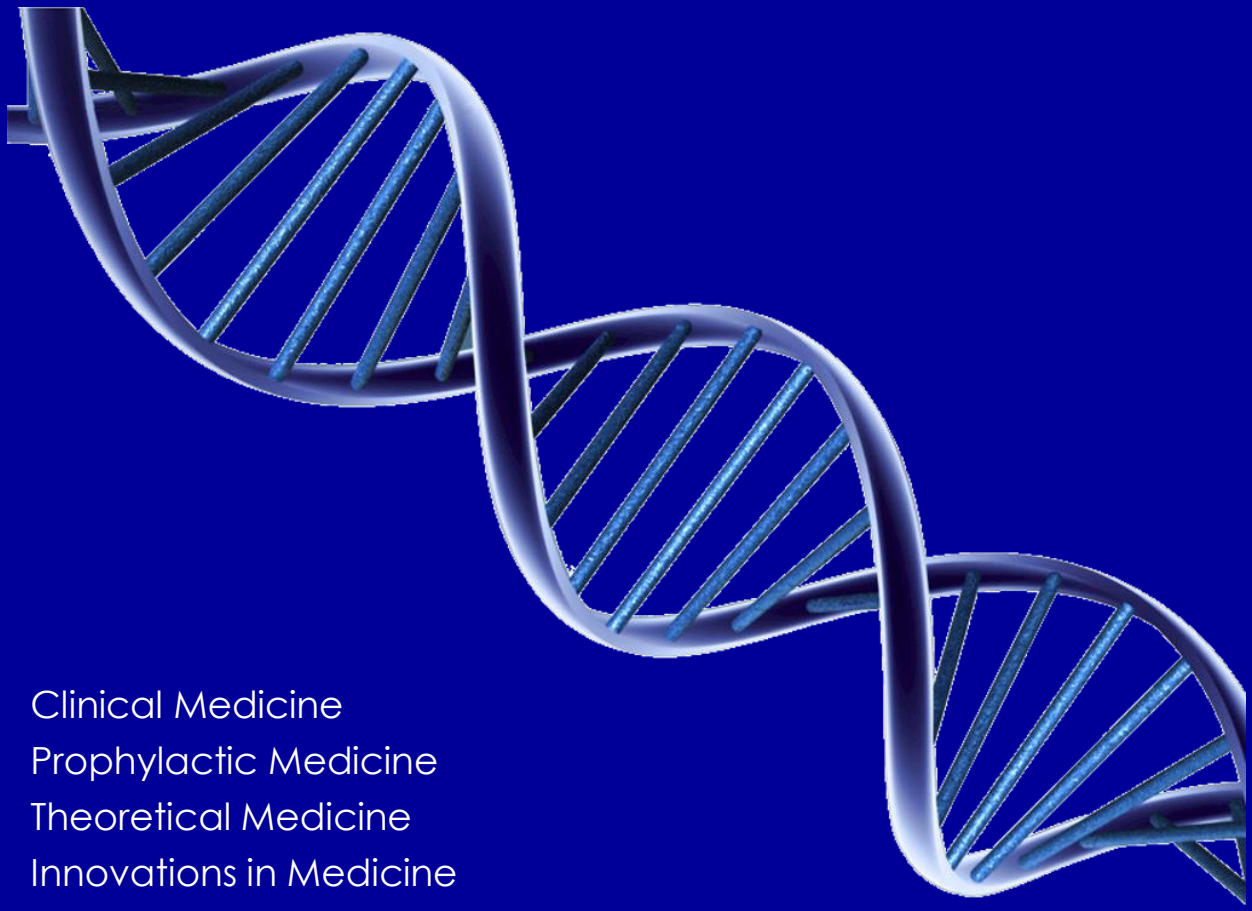

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POSTOPERATIVE PAIN AND MULTIMODAL ANESTHESIA IN BARIATRIC SURGERY

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ABSTRACT

Any rational anesthesia strategy should focus on intraoperative and postoperative pain control. Adverse effects of opioids on the course of the early postoperative period are known.
The aim of our study is to determine the correlations of acute postoperative pain with different types of anesthesia.
Methods: 203 patients who underwent bariatric surgery were under our observation; 113 (55.67%) of them are women and 90 (44.33%) are men.
Standard anesthesia with opioids was administered to 49 (24.14%) patients - group I, multimodal + partial use of opioids - group II: 76 (37.44%), multimodal anesthesia - 78 (38.42%) - group III.
Results: During anesthesia with opioids, compared to the second and third groups, the pain in the operative area, as well as in the head, throat, waist and ears is significantly higher.
During multimodal anesthesia, pain is reliably less in all cases, and pain in the throat was not noted.
Correlation analysis showed that opioid anesthesia was significantly correlated with postoperative pain,: Pain in the operated area - $r=0.504^{**}$,$p<0.001$; Head pain - $r=0.395^{**}$, $p<0.001$; Throat pain - $r=0.301^{**}$, $p<0.001$Waist pain$r=0.320^{**}$, <0.001Muscles pain - $r=0.422^{**}$, $p<0.001$
whereas multimodal anesthesia was significantly negatively correlated with all types of postoperative pain.
In the second phase, in the opioid anesthesia group, compared to the second group, there is significantly more pain in the lower back and muscles, and in the third group, there was no pain at all.
The frequency of patients who did not require medical treatment during the intrahospital stage is not significantly different from each other, and the pain requiring non-opioid treatment is significantly less after multimodal anesthesia - Group I - 28(57.14%), Group II - 25(32.89%), Group III - 2(2.56)($p<0.0001$). Pain requires opioid medication - Group I - 20(40.82)Group II – 19(25.00%), ($p<0.0001$). No patient in this group required opioid treatment.
In the ambulatory stage, no patient in the multimodal anesthesia group needed medical treatment, and significantly fewer patients in group II needed non-opioid treatment.
Conclusion: Multimodal anesthesia reduces perioperative pain and the need for perioperative opioid use.
Keywords: Postoperative pain, Multimodal anesthesia, perioperative opioid use.

The use of bariatric surgery to treat severe obesity has several benefits in terms of sustained weight loss, improvement or resolution of several metabolic comorbidities in terms of improvement [1].

Cognition is defined as the brain's ability to acquire, process, store, and retrieve information. Pain is described as an unpleasant sensory or emotional experience, and in order to consciously experience pain, cognitive processing is necessary[2]. The pain pathway consists of transduction, transmission, modulation and perception [3].

Any rational anesthesia strategy should focus on intraoperative and postoperative pain control[4]. Adverse effects of opioids on the course of the early postoperative period are known. In addition to the traditional side effects of rats (depression of consciousness, excessive sedation, nausea, etc.), they have the ability to create opioid-induced hyperalgesia, immunosuppressive effects and reduce the effect of local anesthetics; In addition, opioid analgesia prevents accelerated postoperative rehabilitation of patients. The concept of multimodal analgesia allows refusing the use of opioid analgesics or reducing their dose to a minimum in the perioperative period. Multimodal analgesia involves the simultaneous administration of two or more drugs that affect different levels of acute pain syndrome formation[5].

The use of traditional methods of general anesthesia and postoperative analgesia with a combination of narcotic and non-narcotic analgesics is accompanied by an increase in hemodynamic parameters - both during the operation and during the four days of the postoperative period [6].

Management strategy, anesthetic choice and anesthetic doses must be adapted to the needs of the individual patient [7]

The aim of our study is to determine the correlations of acute postoperative pain with different types of anesthesia.

Methods

203 patients who underwent bariatric surgery were under our observation; 113 (55.67%) of them are women and 90 (44.33%) are men.

Standard anesthesia with opioids was administered to 49 (24.14%) patients - group I, multimodal + partial use of opioids - group II: 76 (37.44%), multimodal anesthesia - 78 (38.42%) - group III.

1 group

Propofol - potentiator of GABA A receptors, Fentanyl - opioid (narcotic analgesic), Sevoflurane - inhalation drug, Morphine - opioid (narcotic analgesic), Promedol - opioid (narcotic analgesic).

2 groups

Propofol - potentiator of GABA A receptors, Fentanyl - opioid (narcotic analgesic), Sevoflurane - inhalation drug,

Dexmedotomidine is a selective agonist of alpha 2 receptors, Locoregional analgesia (lidocaine, naropin, bupivacaine - sodium channel blockers).

3 groups

Propofol - potentiator of GABA A receptors, Sevoflurane - inhalation drug, Dexmedotomidine is a selective agonist, of alpha 2 receptors, Locoregional analgesia (lidocaine, naropin, bupivacaine - sodium channel blockers),

Dosing was done according to the individual characteristics of the patient.

Statistical Analysis

Categorical variables are expressed as frequencies and %. variables were compared with the use of the Fisher's Exact Test. Correlation analysis between categorical variables was performed by Spearman correlation analyses, p value <0.05 was considered as statistically significant. All statistical analyses were performed using SPSS version 23.

Results

The localization of pain after surgery is given in Table 1.

Table 1. Distribution of pain according to localization and type of anesthesia

Phases of postoperative care	localization of pain	Group I (With opioids) n=49		Group II (With partial use of multimodal opioids) n=76		Group III (multimodal) n=78		F	p
		n	%	n	%	n	%		
Phase I	in the operated area	47	95.92	43	56.58	14	17.95	58.12	<0.0001
	head	19	38.78	9	11.84	1	1.28	20.94	<0.0001
	throat	10	20.41	4	5.26	0	0.00	10.94	<0.0001
	waist	20	40.82	14	18.42	4	5.13	14.17	<0.0001
	muscles	25	51.02	15	19.74	2	2.56	26.98	<0.0001
Phase II	Pain in the lower back	9	18.37	3	3.95	0	0.00	10.38	0.0001
	Pain in the muscles	11	22.45	8	10.53	0	0.00	9.77	0.0001

Post-anesthetic pain after bariatric intervention in Phase I of post-anesthetic care was distributed as follows:

As we can see, pain in the operated area is the most common, while throat pain is the rarest.

During anesthesia with opioids, compared to the second and third groups, the pain in the operative area, as well as in the head, throat, waist and ears is significantly higher.

During multimodal anesthesia, pain is reliably less in all cases, and pain in the throat was not noted.

Correlations between type of anesthesia and pain during bariatric surgery are shown in table 2.

Table 2. Correlations between type of anesthesia and postoperative pain:

Factors		Anesthesia with opioids	With partial use of multimodal+opioids	Multimodal anesthesia
Pain in the operated area	r	0.504**	0.083	-0.526**
	p	<0.001	0.240	<0.001
Head pain	r	0.395**	-0.054	-0.294**
	p	<0.001	0.444	<0.001
Throat pain	r	0.301**	-0.050	-0.215**
	p	<0.001	0.480	0.002
Waist pain	r	0.320**	-0.006	-0.275**
	p	<0.001	0.933	<0.001
Muscles pain	r	0.422**	-0.018	-0.353**
	p	<0.001	0.797	<0.001
* - p<0.05,** - p<0.01				

Correlation analysis showed that opioid anesthesia was significantly correlated with postoperative pain, whereas multimodal anesthesia was significantly negatively correlated with all types of postoperative pain.

In the second phase, in the opioid anesthesia group, compared to the second group, there is significantly more pain in the lower back and muscles, and in the third group, there was no pain at all.

The distribution of patients according to the intensity of pain in phase II is given in diagram 1.

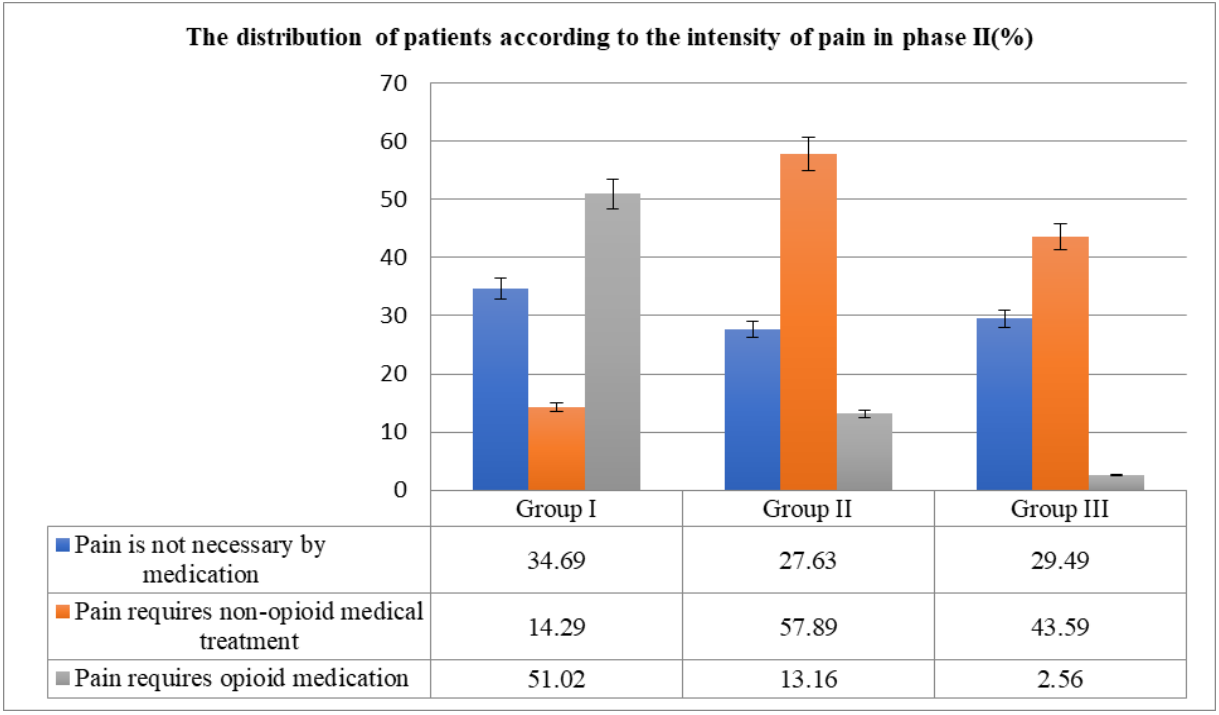

Diagram N1

No significant difference between the groups was observed in the frequency of patients who did not require medication for pain relief after surgery, the need for non-opioids was significantly higher in group II, and the need for opioids was significantly higher in group III.
The degree of pain in intra-hospital and post-hospital stages is given in Table 3.

Table 3. Assessment of pain quality at intrahospital and posthospital stages:

Post intensive stages	degree of pain	Group I (With opioids) n=49		Group II (With partial use of multimodal opioids) n=76		Group III (multimodal) n=78		F	P
		n	%	n	%	n	%		
Intrahospital stage	Pain (discomfort) is not necessary by medication	1	2.04	4	5.26	4	5.13	30.51	<0.0001
	Pain requires non-opioid medical treatment	28	57.14	25	32.89	2	2.56	20.78	<0.0001
	Pain requires opioid medication	20	40.82	19	25.00	0	0.00	30.51	<0.0001
Ambulatory stage	Pain (discomfort) does not require medical treatment	7	14.29	5	6.58	3	3.85	2.48	0.0865
	Pain requires non-opioid medical treatment	18	36.73	9	11.84	0	0.00	21.15	<0.0001

As can be seen from the table, the frequency of patients who did not require medical treatment during the intrahospital stage is not significantly different from each other, and the pain requiring non-opioid treatment is significantly less after multimodal anesthesia. No patient in this group required opioid treatment.
In the ambulatory stage, no patient in the multimodal anesthesia group needed medical treatment, and significantly fewer patients in group II needed non-opioid treatment.

Discussion

Multimodal anesthesia (MMA) refers to the use of additive or synergistic combinations of analgesics to achieve clinically necessary analgesia, with the goal of minimizing the significant side effects associated with higher doses of a single aquagenic medication, such as opioid analgesics[8], especially since a patient's first exposure to opioids often occurs in the perioperative setting, a vulnerable time when multimodal therapy can play a major role in reducing opioid exposure[9].
The importance of multimodal anesthesia is particularly emphasized in patients who may be prone to opioid-related side effects, such as patients with obstructive sleep apnea. Healthcare systems can also benefit from implementing effective MMA, as fewer opioid-related side effects can improve patient outcomes, lead to faster recovery, and rational use of resources [10].
Our study showed that there is a reduction in postoperative pain under multimodal anesthesia. Opioid-free anesthesia allows us to avoid their use in the perioperative period. According to our

study, the frequency of need for postoperative use of opioids is dramatically reduced in the multimodal anesthesia group.

Prevention of postoperative pain should begin immediately after planning the operative treatment. A multidisciplinary group of doctors, based on the conclusion made after assessing the patient's condition and risk factors, will draw up a perioperative plan for pain relief [12].

Conclusion: Multimodal anesthesia reduces perioperative pain and the need for perioperative opioid use.

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BOTOX COMPILATION

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ABSTRACT

Botulinum neurotoxin is a toxin produced by the anaerobic Clostridium botulinum bacteria. While Botox is used in many diseases thought to be caused by excessive contraction of striated and smooth muscles, it has also become popular with its use in the cosmetic field. When the toxin is injected into the muscles, it affects the nerve cells and creates partial and temporary paralysis, thus preventing the muscle from contracting too much. Botulinum toxin, which started to be applied in the perioral region for therapeutic purposes, is used in various areas such as temporomandibular joint disorders, bruxism, gummy smile, masseter hypertrophy, salivary gland problems. Although the therapeutic effect of Botox is temporary and relatively safe, it is essential to have knowledge of the relevant anatomy and the systemic and local side effects of drugs applied to the face.

Introductıon

Treatment options in dentistry are changing day by day, and non-conventional options like the use of botulinum toxin (Botox) are becoming increasingly popular. Botox (BTX) is a reversible, minimally invasive, and safe treatment option for numerous disorders in the maxillofacial region. Even though Botox has been known as an aesthetic treatment option used to eliminate facial wrinkles, it has long been used in medicine and dentistry in different treatment indications by blocking neuromuscular activity for a certain period (1).

Botulınum toxın

2.1. Mechanism of Action

Botox has eight serotypes (A, B, C1, C2, D, E, F, G), and all serotypes have a similar structure and molecular weight (2). When botulinum toxin is administered to muscles with high activity, paralysis occurs in the relevant muscles, and muscle activity decreases. Botulinum toxin shows its effect by inhibiting the release of acetylcholine (Ach), which provides conduction in all parasympathetic and cholinergic nerve endings (1-8). The toxin irreversibly binds to the presynaptic neuron, but it takes two weeks to complete its effect. The effect duration varies between 3-6 months. With repeated injections, the duration of the toxin's effect is prolonged.

2.2. Commercial Forms

The A, B, E, and F types of toxin are active in humans. Types A and B are used for therapeutic purposes. (4). The dosage of botulinum toxin (BTX) treatment varies with the brand of toxin used. The dose given for any toxin type is valid only for the specific preparation and cannot be added or transferred to the doses of other preparation unless it is the same toxin serotype. The toxin dose

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should be adjusted precisely because different preparations have varying effects on different body parts (5).
Some trade names and countries of origin of Botox are as follows:
Botox®: It is purified BTX-A isolated through the fermentation of C.botulinum. The Allergan company commercialized the purified BTX-A under the trade name Botox in 1991. Every vial of Botox provides 5 ng (nanograms) (100 U) of air-dried toxin. The vials also contain 500 µg of albumin and 900 µg of sterile vacuum-dried sodium chloride (without preservatives). There is FDA approval in many European countries, USA and Canada (6).

Dysport®: It contains 12.5 ng (500 U) of air-dried toxin, 125 µg of albumin, and 2.5 mg of lactose. Because Dysport comes from a different type A bacterial strain, its doses are not similar to those of Botox; they are higher and diffuse more compared to Botox (7).

Xeomin®: It is purified freeze-dried BTX-A that does not contain additional helper complex proteins (hemagglutinin and nonhemagglutinin). It is less immunogenic than other BTX-A products. Moreover, it is the only BTX form that can be stored at room temperature, whereas other forms should be kept in the refrigerator (8).

Myobloc®: It is made from Serotype B and is effective in treating movement disorders rather than cosmetic use. It can be used in cases of droopy eyelids, for some wrinkles, and as an alternative treatment for cosmetic neural blockade in patients resistant to BTX-A products. 1 U of Botox is approximately equivalent to 50-100 U of Myobloc. BTX-B is in an acidic solution which may result in painful injections (8).

2.3. Toxicity
The lethal dose for 50% of a human population (weighing approximately 70 kg) exposed to type A toxin is 90-150 ng intravenously, 700-900 ng by inhalation, and 70 µg orally. Since the dose usually used in dentistry is a maximum of 5 ng and is significantly smaller than the lethal dose, overdosing is nearly impossible (5-9).

2.4. Storage Conditions
The purified and powdered neurotoxin complex is packaged in vials containing 100 U of BTX-A. It is readied for use by diluting it with saline.
It is recommended to dilute the toxin by gently stirring the vial while not shaking it and avoiding foam formation; otherwise, the toxin will denature.
Botox® can be kept in the freezer at -5°C or below and in the refrigerator at 2-8°C for 6 months without diluting. The diluted Botox® should be used within 24 hours under the condition that it is stored in the refrigerator at 2-8°C. The literature has reported that it does not lose its activity up to 6 hours, loses 44% of activity by 12 hours, and 70% of activity within 1-2 weeks. When the diluted solution becomes frozen in the deep freezer, it becomes unusable since it will crystallize (10-11).

2.5. Resistance

Botulinum toxin is a protein capable of inducing potent neutralizing antibodies. Therefore, no more than 100 units should be administered in each treatment session, and intervals between treatments should not be shorter than one month to avoid antibody formation.

Other formulations can be used following resistance development because cross-reactions against other serotypes do not occur (12).

2.6. Contraindications

1) Muscular disorders (neuromuscular diseases such as Myasthenia Gravis and Eaton-Lambert Syndrome and motor neuron diseases)
2)Presence of infection at the injection site
3)Hypersensitivity to any known substance in the formulation
4)Patients receiving aminoglycosides or drugs inhibiting neuromuscular transmission
5)Pregnancy and lactation
6) Patients with unrealistic anticipations
7) Patients with psychological disorders (10)

2.7. Side effects

1. Pain during injection
2. Local edema, erythema, and ecchymosis due to injection
3. Temporary numbness and burning sensation at the administration site
4. Reversible muscular weakness
5. Flu-like syndrome
6. Diarrhea
7. Abdominal pain
8. Hypertension
9. Headache, dizziness (2)

3. Botox Applıcatıons İn Orthodontıc Practıce

3.1. Gummy Smile

Smiling has a significant role in expressing one's emotions and facial aesthetics. Therefore, patients anticipate not only dental aesthetics but also smiling aesthetics following orthodontic treatment (13).

In orthodontics, facial aesthetics are achieved by conventional measures such as leveling the dentition, correcting the profile, and improving the smile. A beautiful smile is created by harmonizing the teeth, lips, and gums with each other in appropriate proportions. The ideal situation is that the upper lip symmetrically exposes 2-3 mm of the gingiva, and the gum line follows the upper lip contour. A gummy smile is defined as excessive exposure of the gingiva during smiling (14).

Etiologic factors may be skeletal, dental, muscular, and iatrogenic. For example, muscular hypertrophy causing excessive lip movements may lead to a gummy smile. Therefore, the treatment approaches differ depending on the etiology. (15).

The muscles elevating and laterally retracting the upper lip while smiling are the levator labii superioris muscle, levator labii superioris aleque nasi muscle, levator anguli oris, zygomaticus major, zygomaticus minor, risorius and depressor septi nasi (16) (Figure 1).

While maxillary embedding is preferred if the gummy smile is of skeletal origin, alveoloplasty and/or gingivectomy is preferred for dentogingival origin, incisor intrusion for dental origin, myectomy is preferred in the presence of short upper lip, and Botox is preferred in the correction of the hyperactive upper lip (12).

Numerous surgical procedures have been described in the literature for the gummy smile. However, postoperative swelling, infection, postoperative pain, temporary or permanent nerve damage, and surgical and orthodontic relapse have led patients to alternative treatments.

Besides surgical approaches in muscle-related conditions leading to excessive lip mobility, Botox applications are also preferred since they offer painless and rapid solutions. In addition, Botox is an effective treatment, particularly in excessive gingival exposure due to excessive contraction of the lip muscles by blockade of the levator labii superioris alaeque nasi muscle and in limitation of upper lip movements (8).

A dose of 3 U is recommended for Botox injection at the injection point known as the "Yonsei point," located at the triangle's center formed by the levator labii superioris, levator labii superioris alaeque nasi, and zygomaticus minor muscles (8) (Figure 2). The advantage of the technique is that because it is a semi-permanent, minimally invasive, and painless procedure without postoperative morbidity, it is more acceptable for patients to undergo a radical change in appearance (17).

Polo (2005) treated cases with gummy smiles caused by excessive muscle contraction by injecting BTX-A into five patients and reported that the upper lip length increased by 124% and the gingival appearance decreased significantly. Likewise, in another study, Polo (2008) applied Botox to 30 gummy smile patients with a gingival exposure of 5.2+-1.4 mm. In the post-injection second week, the patients' average gingival exposure decreased to 0.09+-1.06 mm. The gingival exposure increased from the 2nd to the 24th week. However, it did not reach its initial values until the end of the 30-32nd week. Moreover, the application's other effect is a reduction of the nasolabial fold of (8).

Mazzuco and Hexsel (2010) identified four different gummy smile types and responsible muscles in 16 patients. They defined excessive gingival exposure as anterior if it was between canine and canine, posterior if it was in the premolar and molar regions, mixed if in both anterior and posterior regions, and asymmetric gummy smile if it was unilateral. In addition, the levator labii superior aleque nasi muscle was responsible in anterior cases, zygomaticus major and zygomaticus minor muscles in posterior cases, their combination in mixed cases, and unilateral levator labii superior aleque nasi, zygomaticus major and zygomaticus minor muscles in asymmetric gummy smile cases. To treat a gummy smile, they injected Botox into the muscles. The injection points were one cm lateral and inferior to the nasal area on the nasolabial fold for the levator labii superior aleque nasi muscle, and the most lateral point on the nasolabial fold and two cm lateral to this point at the level of the tragus for the zygomaticus major and minor muscles. The researchers treated gummy smiles in all patients and reported success rates of 96% for anterior, 61.06% for posterior, 90% for mixed, and 71.93% for asymmetric cases (18).

3.2. Masseter Hypertrophy

Masseter hypertrophy is a disorder characterized by either unilateral or bilateral enlargement of the masseter muscle. This condition can lead to malocclusion, bruxism, clenching and temporomandibular joint disorders. In its etiology, bruxism, psychosomatic factors, stress, parafunction, and trauma are involved (19).

The habits of unilateral chewing and clenching in patients may cause masseter hypertrophy resulting in facial asymmetry (2).
The results obtained with Botox injected into the masseter muscles in these cases seemed reliable and effective (20).
Smyth et al. (1994) performed the first botulinum toxin injection to the masseter muscle and stated that it was a less invasive method for shaping the lower face cosmetically (21).
After Botox administration, in most patients, a reduction in masseter hyperactivity was determined to result in a reduction in total muscle size over time (maximum reduction of 35.4%) (22).
Boris Bentsianov et al. (2004) demonstrated the injection sites in the masseter hypertrophy (20) (Figure 3).
To et al. (2001) evaluated the effect of Botox in masseter hypertrophy in five cases (4 cases - bilateral and one case - unilateral) using ultrasonography and EMG. They measured the volume changes with ultrasonography and the electrical activity with EMG. They received a positive response from all of their patients (23).
Baş et al. (2010) performed BTX-A injections in a patient with masseter hypertrophy developing due to unilateral chewing habits and in another with masseter hypertrophy whose etiology could not be determined. They reported atrophy of the masseter muscle and satisfactory facial appearance in both patients after three months (24).

3.3. Bruxism

Bruxism is defined as the parafunctional activity of the masticatory muscles occurring with repetitive mandibular movements and characterized by clenching or grinding of the teeth. In severe cases, bruxism might cause headaches and masseter hypertrophy. The prevalence of this condition, which is generally considered a clenching habit that occurs in response to stress and anxiety states, is 20% in the community (26). In addition, in bruxism, the excessive force exerted by the masticatory muscles on the dentition is a risk factor for tooth abrasion, muscle or joint pain, joint locking and sounds, and prosthetic restorations (25-26). The etiological factors are categorized as peripheral and central (27) (Table 1).
Contemporary bruxism treatments focus on reducing excessive muscular activity and protecting potentially affected structures such as teeth, masticatory muscles, and TMJ. Recent studies have shown that Botox application is effective in bruxism. The therapeutic efficacy of the toxin is achieved through the reduction of masticatory muscle contraction, including masseter, anterior temporalis, and in some cases, lateral pterygoid muscles (28).
In another study, BTX-A was injected into the masseter muscles of patients with a history of severe bruxism refractory to medical and dental procedures (mean dose: 61.7 U/side; range 25-100 U), and a mean therapeutic response time of 19 weeks was reported. Injecting Botox bilaterally into the masseter muscles was documented to significantly reduce the symptom severity for an average of 19±17 weeks (29). Botox treatment was effective on bruxism, and injections at a dose of <100 U were considered safe for healthy patients (30).

3.4. Temporomandibular Joint Disorders

Temporomandibular joint disorders (TMDs) are disorders affecting the temporomandibular joint (TMJ), masticatory muscles, and associated structures (31). Symptoms may include pain in the head, face, neck, and around the ear, noise from the joint, and restricted jaw movements (1).

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In most TMD cases, secondary muscle spasticity due to bruxism is an etiologic factor (32). The traditional treatment approaches in TMDs include physiotherapy and exercise, anti-inflammatory and analgesic drugs, muscle relaxants, oral splints, acupuncture, or their combination. Recently, Botox applications have also been proven effective in relieving pain and tenderness in TMD and have started to be practiced frequently (33). With BTX-A injection, attempts have been made to overcome pain in the joints and masticatory muscles, restriction in mouth opening, recurrent joint dislocations, and hyperactivity in the masticatory muscles. Even though there is no standard protocol for the use of Botox® for TMD, case reports have shown a reduction in pain, and improved function with 25 to 100 U of Botox® injected into the masseter and temporal muscles. Furthermore, Botox injection involving the lateral pterygoid muscles has also been reported as having a favorable therapeutic effect (34).

3.5.Oro-mandibular Dystonia

Oro-mandibular dystonia (OMD) is a movement disorder characterized by involuntary spasms and muscle contractions in the muscles around the TMJ and perioral muscles. OMD is considered a subgroup of TMD because of its affected muscles (35). As a result, trismus, bruxism, involuntary jaw opening-closing, and uncontrolled tongue movements are encountered (12). Most of the publications reported on OMD have been open-ended studies; however, they all have reported improvement with Botox injections. The most comprehensive and long-term study on this subject is the study conducted by Tan and Jankovic (1999) involving 162 patients with OMD. As a result of the injection of BTX-A into the masseter muscle and/or submental region, improvements in masticatory and speech functions were reported in 67.9% of patients, and the mean duration of clinical recovery was 16.4 ± 7.1 weeks (22-29-36).

3.6. Pathological clenching/teeth grinding (Trismus)

Trismus is a phenomenon causing chronic trauma to the gums and related tissues. Low Botox doses can potentially alleviate this disorder. Similarly, patients with a deep or cross bite undergoing orthodontic treatment encounter elevated chewing force due to prolonged masticatory muscle activity. With Botox, this unfavorable situation can be prevented; thus, the orthodontic treatment duration can be reduced, and patients can be provided with more comfortable eating, speaking, and swallowing functions (1-33).

3.7. Prevention of Post-Surgical Relapse

The utilization of Botox for paralysis of the geniohyoid muscle to prevent relapse in orthognathic surgical interventions in which the mandible was anteriorized has been reported (12).
Even though the perioperative use of Botox is not considered very often, it actually accelerates postoperative wound healing by reducing muscle strength in many fields. For example, in jaw fractures where rigid internal fixation is not suitable, Botox can be used to prevent muscle movement to reduce the displacing forces on the bone fragments and provide better stabilization (12).

4. Other uses of botox in dentistry

4.1. Trigeminal Neuralgia

Trigeminal neuralgia is a neurological condition causing acute severe pain and affecting the orofacial muscles, and mainly secondary to a blood vessel's trigeminal nerve compression. The pain is sudden and sharp, like a lightning flash (3).
Botox is used in trigeminal neuralgia in patients who are unresponsive to medical treatment, in patients in whom surgery cannot be performed, or in patients whose surgical treatment has failed (37).
Zhang et al. (2014) injected different doses of Botox or saline into trigger points in 84 patients with trigeminal neuralgia and achieved successful results independent of the dose in patients treated with Botox in their randomized controlled study. In Botox use for trigeminal neuralgia, rather than systemic side effects, local side effects such as edema at the injection site and facial asymmetry due to surrounding muscles' involvement were observed. (38).
BTX has been stated as a rapid, effective, and minimally invasive method for treating trigeminal neuralgia compared to other invasive treatments (39).

4.2. Sialorrhea and Salivary Secretion Disorders

Sialorrhea (excessive salivation) is a common condition arising from poor oral and facial muscle dominance (2). Since the salivary gland cells' secretions occur by cholinergic receptor activation, BTX depresses the glands' secretory activity. Sialorrhea is particularly common in cases with cerebral palsy, Parkinson's disease, Frey syndrome, amyotrophic lateral sclerosis, or motor neuron disease. Regarding the salivary gland, Botox is utilized in various conditions such as salivary fistulas, aspiration of saliva, dysphagia, idiopathic hypersalivation, sialocele, and chronic sialadenitis (40).
When the effects of Botox on salivary glands were analyzed, it was found that injections into the parotid and submandibular glands were effective in controlling hypersecretion (30). The salivary flow decreased significantly within four weeks after 30-70 U of Botox was injected into the parotid gland (41).

4.3. Mandibular Spasm

This muscle spasm originates from the spasm of all masticatory muscles and associated mandibular muscles (20). Botox treatment applied to the masticatory musculature effectively treats hyperfunctional or spastic muscles (42).

4.4. Combination with Dental Implant Applications

Overstrain of the masticatory muscles may interfere with osseointegration of implants and calli in jaw fractures. In this regard, injecting Botox into the masticatory muscles can provide a more stable environment and therapeutic benefit for the osseointegration of implants and fractures (43).

4.5. Facial nerve paralysis

For treatment of asymmetric appearance in cases of facial paralysis, a method that induces facial symmetry by intentionally creating partial facial paralysis by injecting Botox into the patient's normal (healthy) side of the face was proposed, and it was stated that visual symmetry of the patient could be achieved in this way (44).

4.6. Growth and Development Studies

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Chemical denervation is achieved, muscle activities are reduced locally with Botox application, and muscle functions' contribution to craniofacial bone development can be identified (45).
In an animal study by Babuccu et al. (2009), a total of 4 groups were formed, including two groups in which Botox was injected into the right masseter and right temporalis muscles, a control group, and a group in which sterile saline was injected into the masseter and temporal muscles. Osteometric measurements revealed significant atrophy in the botox-injected groups' relevant muscles. The nasal bone, premaxilla, maxilla, and zygomatic arch dimensions were significantly reduced in the groups where Botox was injected into the right masseter and temporal muscles compared to the left-sided muscles. The masseter group showed no difference regarding skull dimensions and mandibular length compared to saline and control groups, whereas the decrease in skull dimensions was significant in the temporal group compared to the other groups. Therefore, it was stated that skeletal muscle denervation with Botox during the growth and development period negatively affected bone development. Researchers have even thought that with increasing utilization of BTX-A and comprehensive research that will be conducted on this subject, craniofacial development may be changed in the desired direction by manipulating muscle functions in craniofacial anomalies and deformities in the future (46).

Conclusion

Today, the use of Botox applications for aesthetic and therapeutic purposes in dental practice has become increasingly widespread. Even though more studies are needed about Botox applications in orthodontics, since its effect is reversible, it is a reliable and supportive treatment method. The correct indication and informing the patient are the issues that must be considered in practice.

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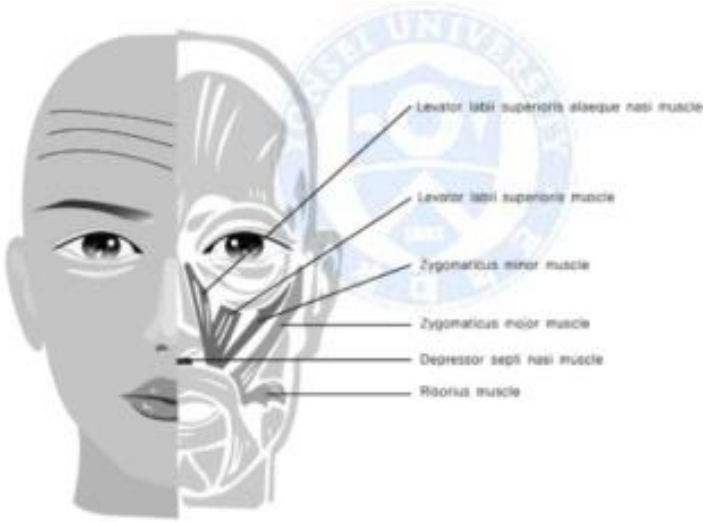

Figure 1. Muscles responsible for the gummy smile

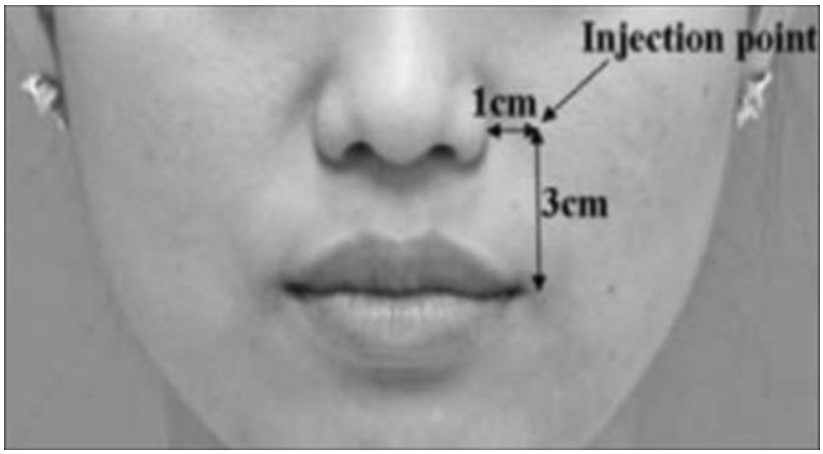

Figure 2. Yonsei point

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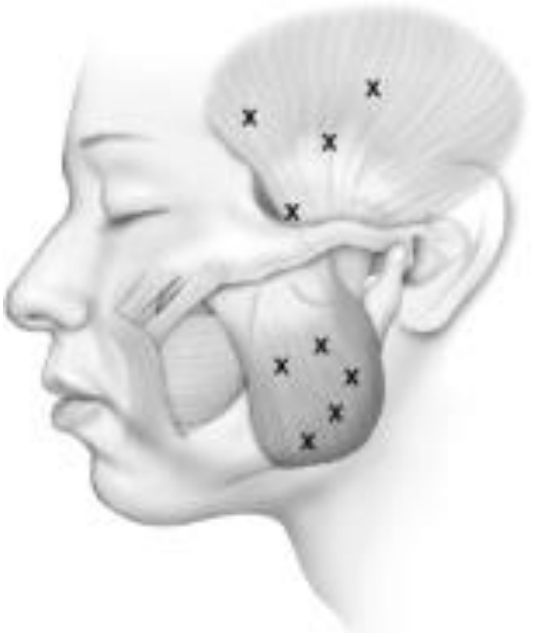

Figure 3. Injection sites

Table 1. Etiologic factors for bruxism.

Peripheral factors	Central factors	
	Pathophysiological	Psychosocial
Facial morphology	Sleep disorders	Stress
Condylar asymmetry	Alterations in brain chemistry	Anxiety
Dental arch's shape	Using various drugs	Fear
Malocclusion	Alcohol/coffee usage/smoking	Frustration
	Familial-genetic factors	Poor social support
Centric relationship-maximal intercuspidization unconformity	Nutritional deficiencies (calcium, magnesium, etc.)	Personality
Occlusal irregularities	Allergies	

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CERVİCAL THYMİC CYST: A RARE DİFFERENTİAL DİAGNOSİS İN LATERAL NECK MASSES

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ABSTRACT

A cervical thymic cyst (CTC) is a rare entity among lateral neck masses. They are usually diagnosed in early childhood and may be determined at any level of the descent of the thymus between the mandibular angle and superior mediastinum. CTC is commonly misdiagnosed as branchial cysts, lymphatic malformations, lymphadenitis, dermoid cysts, epidermoid cysts, or neoplastic masses. The exact diagnosis of cervical thymic cyst can be uncommonly made preoperatively, and histopathological examination of the surgical specimen is the only definitive diagnostic tool for most reported cases. We reported the clinical presentation and management of a cervical thymic cyst in a 9-year-old male to emphasize the importance of cervical thymic cyst in the differential diagnosis of lateral neck masses.
Keywords: Cervical thymic cyst, Lateral neck mass, Branchial cyst,

Introduction

A cervical thymic cyst is very rare, with only about 100 reported cases in the literature. (1) It is caused by the cessation of the regular embryologic migration of thymic primordium. Hsieh et al. reported that children's cervical thymic cysts accounted for 0.3 % of all congenital cervical cysts. (2) In 1901, Polloson and Piery made the first attempt at surgical cyst excision, but a total removal was succeeded in 1944. Clinical presentation and management of a cervical thymic cyst in a 9-year-old child have been reported in the literature review.

Clinical Report

A 9-year-old male presented to our department with a painless left-sided neck swelling of two months. His parents noticed the mass incidentally, increasing in size over time. The medical and family history was unremarkable. A painless, soft, semi-mobile about 9 x5 cm neck mass was palpated on physical examination. There were no overlying skin changes, weight loss, or pressure symptoms. All the hematological and biochemical tests and thyroid function tests were also normal. In the preoperative workup, ultrasonography was performed, and an isoechogenic mass with dense content on the left side of the neck was detected. Abscess or branchial cyst was taught as the primary diagnosis. Computerized tomography (C.T.) scan of the neck (Figure 1) showed a 90x40 mm fluid density hypodense lesion with septations, and the lesion was adjacent to the carotid artery and jugular vein. And Magnetic Resonance Imaging (M.R.) also had similar findings, and the primary diagnosis of the radiologists was lymphangioma (Figure 2).

Under general anesthesia, a transverse incision was taken over the cyst. It was under the sternocleidomastoid muscle adhering to the common carotid artery and jugular vein. After carefully separation from muscle and carotid sheath, the specimen was sent for histopathologic examination. The final histopathological investigation revealed multiloculated cysts lined by stratified squamous epithelium and thymic tissue in the cyst wall. Also, a parathyroid gland of about 5 mm was found in the periphery of the cyst. Six months following surgery, there was no recurrence or immunity problem.

Discussion

Thymic cysts are very rare lesions representing only about 1 % of cystic cervical masses. (3) Embryologically, the thymus is derived from the third pharyngeal pouch and descends into the mediastinum. The parathyroid gland may be found in the cyst wall, indicating the common embryonic origin from the third branchial pouch. (4) A parathyroid gland about 5 mm in size was also found in the wall of the excised cyst. Cervical thymic cysts are more common in males (males: females 3:2) and are usually present in the first decade of life. (5) Our patient was also male and nine years old. Cranially the ectopic thymic cyst passes posteromedial to the carotid sheath and ends near the pyriform sinus. Cranially and caudally, it may extend below the thyroid as far as the mediastinum. (6) Although the reported cysts vary, we found most of the cysts were about 4-5 cm in size. Craniocaudal length of our cyst was 9 cm, extending from the pyriform sinus to the upper mediastinum.

The differential diagnoses of cystic neck mass include second branchial cleft cyst, cystic hygroma/lymphangioma, thyroglossal cyst, ectopic thymic cyst, dermoid cyst, vallecular cyst, epidermoid cyst, necrotic lymphadenopathy, cystic nerve tumors, and cystic neuroblastoma. On ultrasonography, necrotic lymphadenopathy, cystic nerve tumor, or neuroblastoma have thick walls. A thin-walled cystic lesion can be due to a branchial cleft cyst, lymphangioma, thyroglossal cyst, and ectopic thymic cyst. While the thyroglossal cyst is usually in the midline, the others are in the lateral of the neck, as in our case. Exact radiological differential diagnoses of these lesions are not always obvious, but there may be some pointers. While branchial cleft cysts pass between the carotid bifurcation to end at the base of the tonsils, thymic cysts pass behind the carotid artery to terminate at the pyriform sinus. Also, thymic cysts extend more caudally, sometimes to the mediastinum; it is never seen in branchial cysts (6).

Making a preoperative diagnosis is important if it is the only functioning thymic tissue without the mediastinal thymus. Radiological techniques may provide a correct preoperative diagnosis and show the nature, extent, and relation with surrounding neurovascular structures. Preoperative CT should be obtained before surgery to confirm the normal or abnormal thymic tissue. Surgical removal of the CTC is the treatment of choice. The presence of normal thymic tissue in the cyst wall on histopathologic examination confirms the diagnosis. Removal of the lesion may leave the patient athymic. Although this is not a problem for adults, immunodeficiency problems may be seen in children. Possible complications include myasthenia gravis associated with ectopic thymic tissue or rarely developing a malignant thymoma. But there have been no reported immunodeficiency or myasthenia gravis after removing the cervical thymic cyst. Also, after six months following surgery, we have not seen any problem

Conclusion

A cervical thymic cyst is an infrequent differential diagnosis of a lateral neck mass. However, they should be considered in the investigation of cystic neck swellings. Imaging, surgical findings, and histopathological examination are essential in exact diagnosis. Our case emphasizes the need for considering cervical thymic cyst, although rare, as a differential diagnosis of a lateral neck mass.

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Figures

Figure 1. Axial CT scan showing the cyst, posterolateral to the left carotid artery and terminating at the pyriform sinüs.

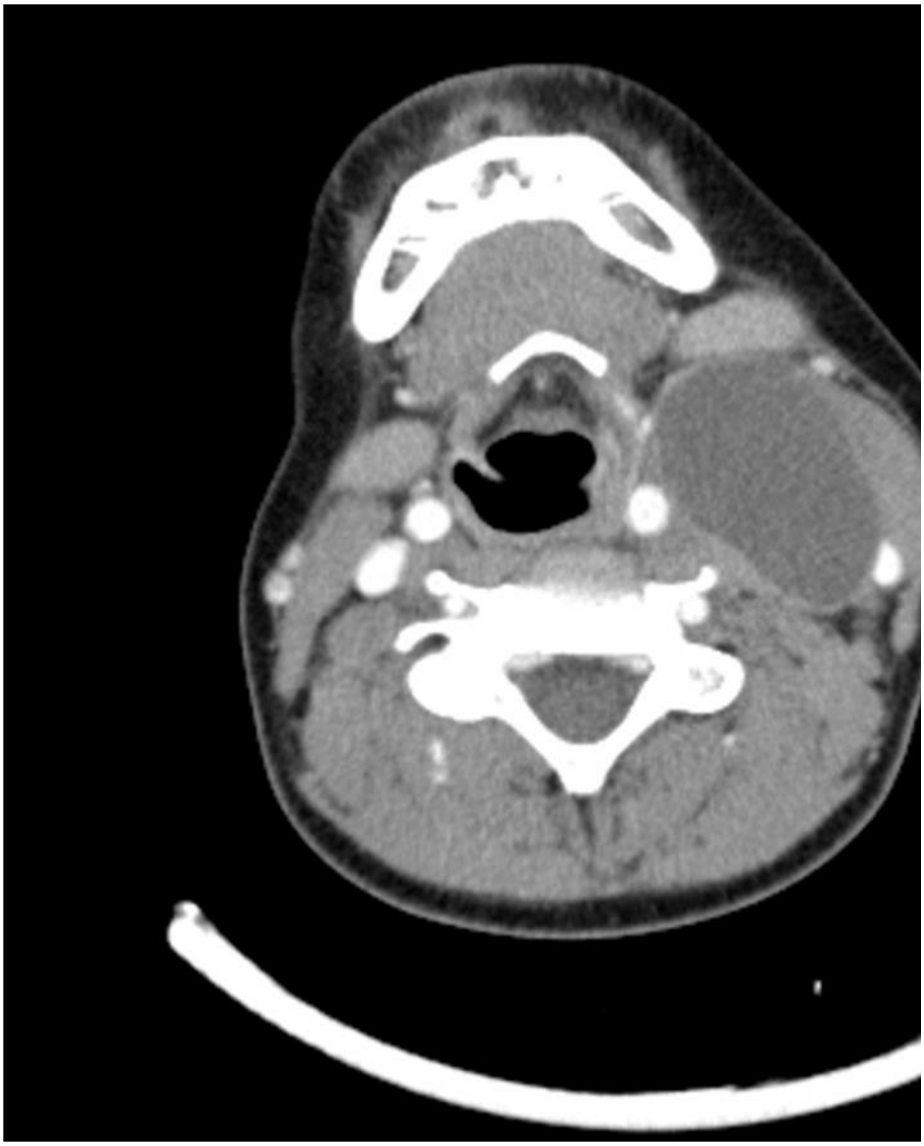

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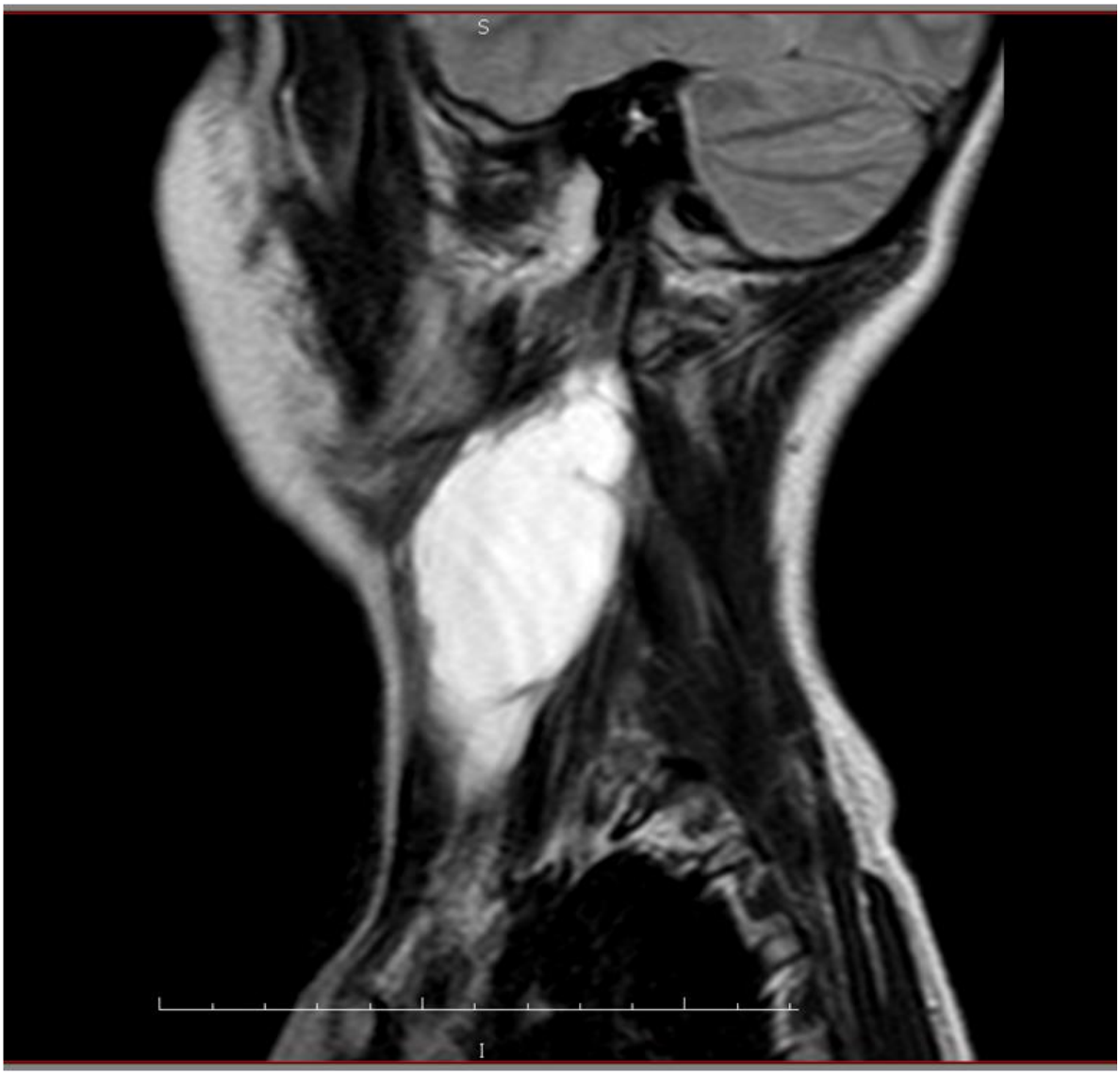
Figure 2. Sagittal MR image shows the cyst, 9 cm in length extending from pyriform sinus to upper mediastinum



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MODERN APPROACH TO THE CLINICAL VIEW, PATHOGENESIS AND TREATMENT METHODS OF ENDOMETRIOSIS

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Objective: Endometriosis is a progressive estrogendependent widely spread disease especially among women suffering of chronic pelvic pain (40-80%) and infertility (25-80%). Pathogenesis is multifactored, but ectopic dissemination of endometrial tissue with forming of endometrioid implants is doubtless. The role of stem cells in its pathogenesis is proved. The choice of therapeutic approaches is wide, however the unique approach has not been worked out yet. The management is determined with the aim of therapy (treatment of pelvic pain or infertility).
Results: Laparoscopic surgery and excision of en dometriomas are associated with decreasing pelvic pain. Therefore there is a number of patients for those surgery is the primary approach in endometriosis treatment. Bowel endometriosis is conjugated with severe pelvic pain and high risk of complicated surgery. Pharmacological agents (Gonadotrophin-Releasing Hormone analogs, progestagens, oral contraceptive pills, androgens, non-steroid anti-inflammatory drugs, etc.) are commonly applied ongoing for endometriosis of various location. They control pelvic pain syndrome effectively, but every of them has its advantages and disadvantages.
Conclusion: Elagolix treatment may become the basis of new strategy, which core is partial estrogen depression, therefore further research is required. Angiogenesis inhibition also represents a new line in endometriosis management. Sorafenib effects on stem cells proliferation, invasion and HIF-1 activation help to suppose new possibilities for its application. Anti-angiogenic drugs may show good result separate or being combined with hormone therapy and provide high efficacy of complex pharmacological approach.
Keywords: pelvic pain, endometriosis, infertility, stem cells, Gonadotrophin Releasing Hormone, oral contraceptive pills.

The relevance of the problem

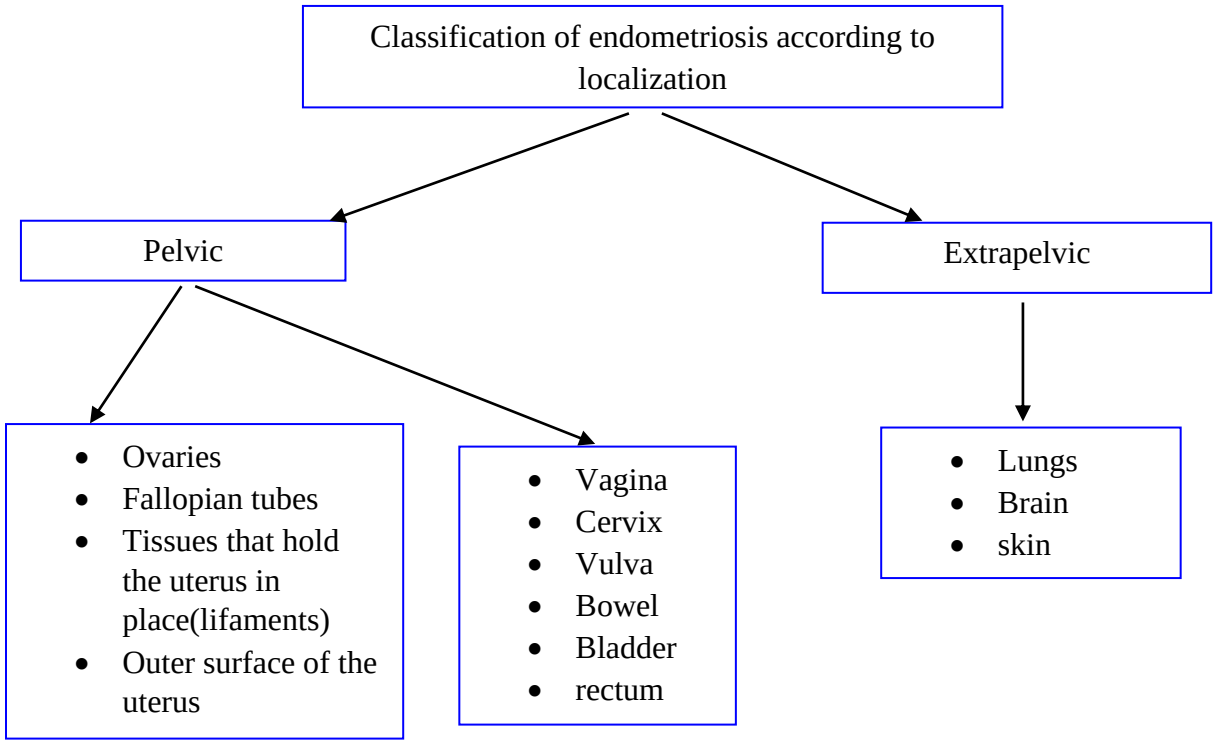
Endometriosis is an estrogen-dependent chronic progressive disease that is widespread in women with pelvic pain (40-80%) and infertility (25-80%). Although the pathogenesis of the disease is multifactorial, the spread of the endometrium to ectopic areas and the subsequent formation of endometrioid heterotopies are undeniable. The role of stem-shaped cells in this process has also been proven. Despite the wide range of treatment methods for endometriosis, a unified approach to them is not defined by specialists, and the choice of treatment method is determined individually by the goal (treatment of pelvic pain or infertility). Endometriosis remains an actual scientific and clinical problem, and its main controversial issues are: is endometriosis a disease; mechanisms of its formation and classification; genetic and immunological aspects; internal and external endometriosis and adenomyosis; diagnostic criteria, etc.

Terminology and classification

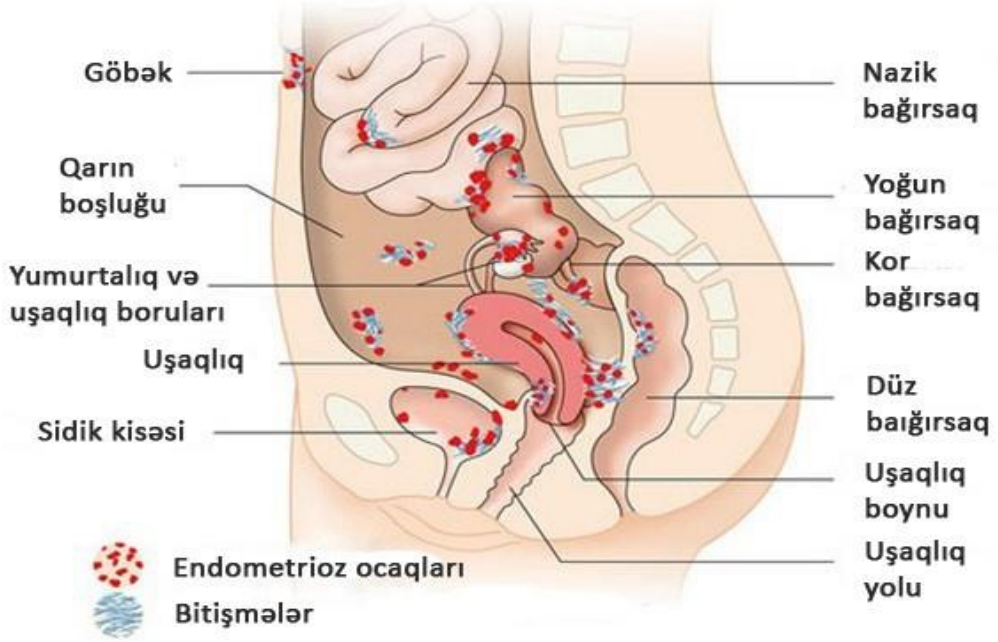
Endometriosis is a pathology characterized by the fact that endometrial tissue, normally found only in the inner lining of the uterus, is found in other membranes of this organ and other genital and extragenital organs outside the uterus. In most cases it is found in women of reproductive age

(20 to 40 years old), but it rarely occurs in postmenopausal women as well. Although it manifests itself in very frequent cases with pelvic pain and infertility, sometimes it can also be asymptomatic. It is usually found in the genitals and pelvic organs, but it can also appear in other areas. Since the endometrioid tissue contains receptors for hormones, the changes in the normal endometrium occur in that tissue and are manifested by bleeding once a month. There are several classifications of endometriosis. The most widespread classification is the one proposed by the American Veterinary Society (R-AFS) in 1979 and revised in 1985 and 1986. It is based on the calculation of the number of heterotopias expressed in points [I stage (minimal changes) - 1-5 points; II stage (moderate changes) – 6-15 points; III stage (acute changes) – 16-40 points; Stage IV (gross changes) – more than 40 points]. At the same time, clinical practice uses the classification of endometriosis based on its location. From this point of view, endometriosis is divided into two groups - genital and extragenital. Genital endometriosis can be located in the myometrium (adenomyosis), peritoneum, ovaries, cervix, uterus, and perineum. Extremal endometriosis, on the other hand, is not topographically related to the organs and tissues of the reproductive system, and mainly includes the organs of the abdominal cavity (appendix, rectum, small and large intestine), lungs and pleural cavity, skin (post-operative scars, extremities, lymphatic nodes).

Diagram 1



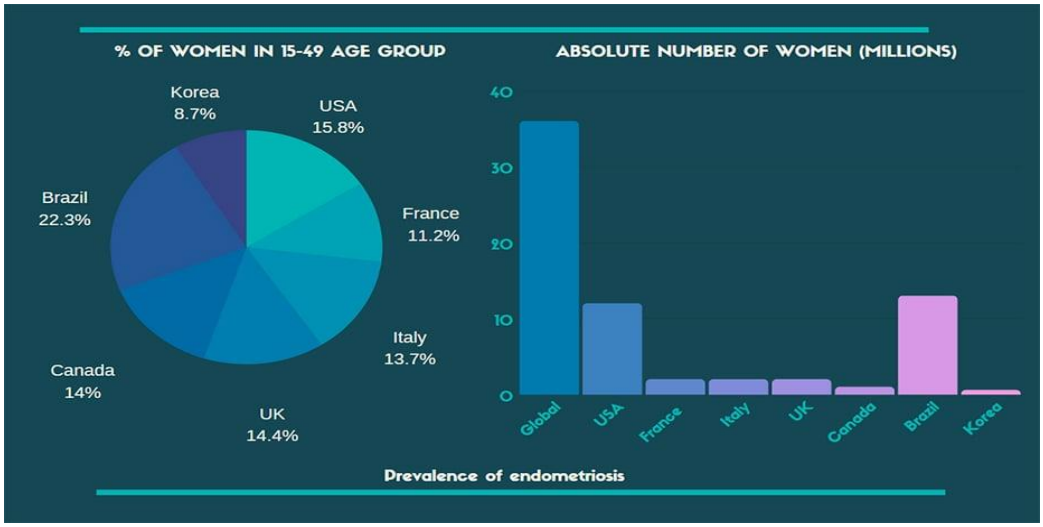
Picture 1



Epidemiology

Endometriosis ranks 3rd in prevalence after genital inflammatory diseases and uterine fibroids. It is observed in 7-50% of women. It occurs in 2-10% of women who apply for the first time, and in 30% of women who have undergone gynecological surgery. 20-50% of women suffering from infertility also have foci of endometriosis.

Picture 2. Prevalence of endometriosis in different countries



Pathogenetic factors

Hormonal disorders; immune system dysfunction and impaired biological response of endometrial cells to sex hormones; constitutional hereditary genetic predisposition; deficiency of the

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antioxidant system of the body; long-term tension of protective-adaptive reactions; prolonged use of intrauterine contraceptives; stressful situations.

Hormonal – the secretion and effect of progesterone is disturbed in patients. An elevated level of estrogens is noted, which stimulates the increased reproduction of endometrial cells. Most often, in such women, an increase in prolactin secretion and a violation of the function of the adrenal gland are observed.

Immunological – an imbalance in the growth and death of cells is characteristic. Intensified secretion of endothelial growth factor leads to the development of vessels and the spread of endometriosis foci. At the same time, the activity of killer cells decreases, apoptosis (genetically programmed death of cells) slows down. They investigated the inability of the immune system to cope with the cycle cell of retrograde mens fluid. If the immune system copes with endometriosis, then endometriosis is related to allergic and autoimmune pathologies. And the causality of this theory has not been fully investigated.

Retrograde theory (implantation theory) – it is the most widely accepted theory. It was first proposed by John Sampson. According to the theory, during menstruation, a part of the endometroid cells flows into the fallopian tubes, into the abdominal cavity, attaches to the peritoneal surface and develops there, but it appeared in women without mensis, in pre-pubescent girls (the theory did not justify itself), and endometriosis was also found in the lungs and brain, and this distanced us from this theory.
In addition, it is noted that endometroid cells differ from normal endometrial cells in their biochemistry, hormonal response and immunology. It is assumed that endometroid cells are a subset of endometrial cells.

Theory of endometrial formation – according to the theory, endometrial cells pass into the uterine wall during abortions, intrauterine diagnostic procedures, operations, that is, during manipulations accompanied by a violation of the integrity of the intrauterine mucous membrane. Moving to the muscle layer, endometrial cells begin to increase and multiply and create an endometriosis focus. This theory explains the appearance of foci of endometriosis in organs located far away by the proliferation of endometrial cells through blood vessels during operations on the uterus.

Other theories: stem-like cells; environment; müllerionosis (embryonic); coelomic metaplasia; autoimmune; oxidative stress theories. Although the exact cause of endometriosis is unknown, many theories have been presented to better understand and explain its development. These concepts do not necessarily exclude each other. The pathophysiology of endometriosis is most likely multifactorial and involves an interaction between several factors.

Symptoms of endometriosis
The course of endometriosis can be different: at the beginning the disease passes symptom-free and can be detected only as a result of preventive examinations. However, there are also acute symptoms of endometriosis. One of them is pelvic pain and is identified in about 16-24% of patients. The nature of the pain (mild, severe, spastic, stabbing pain), localization (lower back,

rectum, lower abdomen), the degree of pain does not depend on the degree and stage of proliferation of endometrioid tissue, the pain is associated with menstruation. It usually occurs 1 week before menstruation, during menstruation and 1 week after menstruation. If there is inflammation and adhesions, the pain is permanent and unrelated to menstruation, it becomes chronic. Pelvic pain has a significant negative impact on women's mental health and quality of life; especially in women suffering from pelvic pain, a high level of anxiety and depression, loss of working capacity, and restrictions on social activities are identified.

Dysmenorrhea — painful menstruation — it is found in 40-60% of patients. Most often it intensifies in the first 3 days of menstruation and is often due to bleeding into the cavity of the cyst and, as a result, its increased pressure; irritation of the peritoneum; and endometriosis bleeding from foci; are associated with compression of the blood vessels.

Dyspareunia (painful intercourse) – ain during defecation and urination. Discomfort and pain during sexual intercourse, which occurs when endometriosis is localized in the uterus, rectovaginal partition, oma-in the area of the uterine ligaments, and uterus-rectum cavity.

Menorrhagia — heavy and continuous menstruation — it is found in 2-16% of patients. It is often accompanied by adenomyosis and related diseases: uterine fibroids, ovarian polycystosis.
Infertility – it occurs in 25-40% of women with endometriosis. Gynecologists still do not know exactly what the mechanism of infertility in endometriosis is. It is assumed that inflammation and adhesions cause infertility. The main reason of infertility is the presence of adhesions in the pelvic organs, thereby the violation of normal anatomy.
Table 1. Main symptoms of localization of endometriosis.

Localization	**Symptoms**
Genital organs	Dysmenorrhea Pelvic pain Infertility Lumber-sacral pains Menstrual irregularity
Gastro-intestinal tract	Tenesmes and rectal bleeding Diarrhea, constipation
Urinary system	Hematuria (related to menstruation) Urethra obstruction
Scar area, umbilicus	Bleeding and pain associated with menstruation
Lung	Menstrual hemoptysis

Endometriosis and pregnancy
Endometriosis reduces the chances of pregnancy termination, so pregnant women with endometriosis should be constantly monitored. The probability of pregnancy after the first 6-14 months of endometriosis treatment is 15-56%. Main risks;; ectopic pregnancy; placental abruption

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- 1.5-6 times more common than other women; miscarriages; premature birth; preeclampsia according to recent evidence. In pregnant women with endometriosis, the prognosis is alleviated, the reason: an increase in progesterone level reduces the growth of endometric tissue; absence of menstruation; due to low levels of estrogen during lactation.

Diagnosis

To diagnose the disease, a gynecological examination is carried out. By means of colposcopy examination, the location and shape of the damage with endometriosis are clarified. The most valuable of radiological methods is spiral computed tomography. Because, by means of it, it is possible to accurately determine the nature of endometriosis, its localization, interaction with neighboring organs, as well as to clarify the state of the small pelvis cavity. One of the most informative research methods is magnetic resonance, which provides accurate visualization of small pelvic organs and their structure thanks to the high resolution of magnetic resonance imaging. Using this method, ovarian endometriosis is determined with an accuracy of 96%. One of the most accessible and widespread methods for diagnosing endometriosis is the ultrasound examination method. The method helps to clarify the location, dynamics, etc. of the focus under the influence of therapy.

Currently, one of the most accurate methods of diagnosing the disease is laparoscopy (puncture of the abdominal wall with the introduction of a special device - a laparoscope). For example, this method provides the diagnosis of ovarian endometriosis with an accuracy of 96%. Laparoscopy also assesses the degree of endometriosis; lesions may appear dark blue, powdery black, red, white, yellow, brown, or non-pigmented; detects the size of lesions; names endometriosis areas by various names, such as implants, lesions, or nodules. Larger lesions may appear inside the ovaries as endometriomas or "chocolate cysts", "chocolate", because they contain a thick brown liquid, mainly old blood.

The identification of various tumor markers in the blood serum is becoming increasingly important. Currently, most of the existing ones are the determination of CA-125, REA and SA 19-9 markers, as well as the RO-test (universal diagnostic test of tumor growth), carried out by the method of immunoenzyme analysis. It was determined that the concentrations of oncomarkers CA 125, CA 19-9 and REA in the blood serum of healthy people were on average 8.3, 13.3 degrees and 1.3 mg/ml, respectively. During endometriosis, these indicators are on average 27.2, 29.5 degrees and 4.3 mg/ml, respectively.

Treatment

In recent years, the treatment of endometriosis has been the most discussed aspect of the problem. The provision that is indisputable to this day — it is impossible to eliminate the anatomical substrate of endometriosis by means of any effect, except for surgical operation, at the same time, other procedures reduce the severity of disease symptoms in a limited number of patients and restore the functions of various parts of the reproductive system. The main goal of treatment — hormonal treatment aimed at preventing the growth of endometrioid cells and slowing down the progression of the process; treatment of infertility; surgical operation aimed at eliminating the hearth.

The most common variants of surgical intervention during pathology: destruction of foci in the cervix and uterus with laser, cold or electric current; removal of the uterus with or without increments; ablation (endoscopic resection) of endometriosis foci; laparoscopic removal of foci in

the ovaries and peritoneum. Most often, hormonal treatment is prescribed before and after surgery. Hormonal therapy is also prescribed at times when there are contraindications to surgery. The goal of treatment is inhibition of ovulation, lowering of estrogen level, stopping of menstrual bleeding. All this leads to the atrophy of the endometrium and the reduction of the size of endometrioid foci.

However, surgical treatment is not always appropriate or acceptable to the patient. Alternatively, it can be considered a method of treating minimal and moderate endometriosis (without diagnostic testing), or rather, symptoms that are likely to be the cause of this disease. This therapy can be accepted only after a thorough examination of the patient, provided that there are no possible causes of other (non-gynecological) symptoms, with the exception of volumetric formations in the abdominal cavity, and only by a doctor who has extensive experience in the treatment of endometriosis.

The most commonly used drugs for the treatment of endometriosis are: progestagens; estrogen-gestagenic preparations; agonists of gonadotropin-releasing hormone; antigestagens.

Symptomatic treatment of endometriosis includes the following group of drugs: non-steroidal anti-inflammatory agents: spasmolytic drugs; iron preparations for the correction of anemia.

A socially significant complication of endometriosis is infertility. For its treatment, in vitro fertilization is widely used (IVF). IVF is effective during endometriosis only in 10-20% of cases. It is most commonly indicated in women over 35 years of age, for severe disseminated forms of the disease, in severe lesions of the fallopian tubes.

Prevention

Avoid excessive physical stress during childhood and youth; taking combined oral contraceptives; reducing abortions and other intrauterine manipulations; avoiding contact between healthy and damaged tissues during surgical treatment of endometriosis.

Prognosis

Endometriosis tends to recur. During the last year's 5 years of treatment, this disease occurs in 40% of women, and in the next 5 years-in 75%. When menopause begins, the probability of recurrence of the disease decreases. In the case of radical removal of the organ damaged by the disease, the process does not progress.

Conclusion

Thus, for endometriosis, paradoxical aspects of etiopathogenesis and their clinical contrasts, the cause of which has not yet been found, are characteristic. In fact, in the benign nature of the disease, local invasion, an aggressive course with wide spread of foci is possible; minimal endometriosis is often accompanied by severe pelvic pain, large endometrioid cysts are asymptomatic; the cyclic effect of hormones causes the development of endometriosis, while continuous use stops the development of the disease. Such enigmas stimulates further deepening and expansion of fundamental and clinical research in all areas of the problem of endometriosis.

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THE IMPORTANCE OF STUDYING THE CHANGES IN BONE METABOLISM PARAMETERS IN PRE- AND POSTMENOPAUSAL WOMEN WITH DIABETES

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ABSTRACT

Determine the directionality of changes in serum bone remodeling markers and bone mineral density in pre- and postmenopausal women with this disease. The analysis included 142 women with diabetes as a case group and 43 women, as a control group. The results show that a distinctive feature in the group of patients with type 1 diabetes is a deeper violation of mineral metabolism and bone resorption accelerating with a decrease in the concentration of magnesium and calcium in the blood serum. Changes in bone metabolism in the majority of examining subjects with DM2 are associated with inhibition of bone formation and, to a much lesser extent, bone resorption accelerating during the late pre-menopause and continuing at similar rates in the early years of post-menopause with a decrease in the intensity of bone mass loss in old age. A special feature of bone metabolism in diabetes mellitus against elevated values of the parathyroid hormone is the high activity of bone remodeling with a predominance of bone resorption, as evidenced by the positive correlation between the level of the parathyroid hormone and the biochemical bone resorption marker.
Keywords: diabetes mellitus, postmenopause, bone turnover

Abbreviations:

ALP	alkaline phosphatase
b-CTx	C-terminal telopeptide of type I collagen
BMI	body mass index
BMD	bone mineral density
Ca^{2+}	ionized calcium
CT	calcitonin
DM	diabetes mellitus
DM1	type 1 diabetes mellitus
DM2	type 2 diabetes mellitus
DXA	dual-energy X-ray Absorptiometry
ELISA	enzyme-linked immunosorbent assay
FPG	fasting plasma glucose
GFR	Glomerular filtration rate
HOMA-IR	homeostatic model assessment of insulin resistance
HbA1c	glycosylated hemoglobin
K^{+}	potassium
Mg^{2+}	magnesium
Na^{+}	sodium
P^{+}	inorganic phosphorus
PINP	aminoterminal pro-peptide of procollagen type I

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PTH	Parathyroid hormone
tCa	total calcium
T-score (L1-L4)	lumbar spine area T-score
T-score (Prox.)	proximal femur areaT-score
T-score (FN)	femoral neck areaT-score
25 (OH) D	vitamin D

Introduction

Diabetes mellitus (DM) is a chronic metabolic disease that has an important impact on overall health [1,2]. Diabetes affects over 425 million adults worldwide and is projected to reach 629 million by 2045 [3]. Until recently, the list of target organs affected by diabetes did not include bone tissue. The presence of this disease in anamnesis increases the probability of fractures, predisposing to a higher incidence of falls and decreasing bone mineral density [4]. Postmenopausal remodeling of bone tissue in the older age group of patients is induced or aggravated by diabetes mellitus (DM) leading to an increased risk of femoral neck fracture with DM1 by 12 times and in patients with DM2 up to 2.5 times even those without diabetes [1]. The aim of the study was to determine metabolic bone changes associated with diabetes mellitus in pre- and postmenopausal women. Determination directionality of changes in serum bone remodeling markers and bone mineral density in the pre- and postmenopausal periods in this disease.

Materials and Method

The research was provided according to the principles of the Helsinki Declaration and was approved by the Health Research Ethics Committee of Azerbaijan Medical University. After an explanation of the aim of the study, written informed consent from each participant was received.

A cross-sectional study included 57 women with DM1 and 85 women with DM2 in the pre- and post-menopause who had previously not been diagnosed with osteoporosis. The age of surveyed women is from 40 to 68 years (56.3 ± 0.9 and 57.6 ± 6.2 years). Duration of diabetes: 17.08 ± 0.8 and 8.15 ± 4.6 years, the mean value of HbA1c was 57 ± 0.2 and 58 ± 1.6 mmol/mol, neuropathy and retinopathy were detected in 42% and 88% of patients. The control group comprised of 43 women (55.4 ± 1.2 years) without a history of diabetes.

Exclusion criteria: women who had been treated for osteoporosis or had a history of fracture, and patients with diseases of the endocrine system, liver, and kidneys of the non-diabetic nature, diabetic nephropathy of the 4-5 stage in the anamnesis.

Some subjects' characteristics were prospectively collected: BMI in kg / m2 (25.8 ± 0.3 and 30.2 ± 3.83 kg / m2) was calculated; menopausal status of surveyed women was assessed using the Cooperman index (duration of menopause averaged 13.4 ± 0.8 and 10.7 ± 0.6 years).

Blood samples were drawn before 10-hour a.m.; they were put into heparin for subsequent centrifugation, stored at -70°C, and thawed immediately before serum biomarker and hormonal analyses. Biochemistry panel, including HbA1c, sodium, potassium, magnesium (Mg^{2+}), total calcium (tCa), ionized calcium (Ca^{2+}), phosphate (P^{+}), creatinine, albumin, alkaline phosphatase (ALP), aminoterminal pro-peptide of procollagen type I (PINP), C-terminal telopeptide of type I collagen (beta-CTx) in serum, was measured using on an automatic electro-chemiluminescence analyzer (COBAS C, Roche Diagnostics GmbH Mannheim, Germany). Glomerular filtration rate (GFR) was calculated by CKD-EPI equation: (=141 x min (SCr(mg/dl)/k,1)a x max (SCr/k,1)-

1,209 x 0.993 age (x1.018 if female) (in ml/min/1,73 m^2). Commercially available human ELISA assays of insulin, parathyroid hormone (PTH), calcitonin (CT) and vitamin D (25 (OH) D) were performed according to manufacturer's instructions. Insulin sensitivity was assessed by homeostasis model assessment of insulin resistance (HOMA-IR) using the following equation: (fasting insulin (μU/ml) × fasting glucose (mmol/l) / 22.5).

All subjects underwent DXA on a densitometer (DXA HOLOGIC, Discovery QDR 4500A, USA) for the lumbar spine (L1-L4), proximal femur (Prox.) and femoral neck (FN) areas. WHO criteria for diagnosis of osteoporosis by BMD (T-score ≤ 2.5SD), osteopenia (T-score from -1 to -2.5 SD), and normal (T-score > -1).

The statistical analysis was carried out using STATISTICA 10 program. Data were presented as mean (M) and confidence interval (95% CI) unless specified otherwise. Statistical analysis was done using unpaired parametric data analyzed by Mann—Whitney U test. Spearman's rank correlation was calculated to assess the power of connection between the parameters. A value of p <0.05 was considered statistically significant.

Results

A total of 142 pre- and postmenopausal women with diabetes as a case group and 43 women, without diabetes mellitus, as a control group was recruited in this case-control study. According to the results of the study, in the women's group with DM1 and DM2, the mean value of tCa level with some tendency to lower in comparison with the control group did not significant differences (p >0.05) and corresponded to the age reference range, with the tendency to decrease in postmenopause. Values of Ca^{2+} in the DM1 and DM2 group of patients were significantly lower than the control values (p <0.05); the maximum decrease of Ca^{2+} concentration was observed in the postmenopausal subgroup of patients with DM1 and DM2 (p <0.05). In the control group, the mean P values in the serum in postmenopausal women were significantly lower than in patients with DM1 and DM2 (p <0.05). Clinical parameters of the study groups are illustrated in Table 1.

Table 1. Comparison of the parameters of bone metabolism and the T-score of the DXA with DM1 and DM2 in pre- and postmenopause in comparison with the control group

Groups / Characteristics	T1DM, n=57		T2DM, n=85		Non-DM Controls, n=43	
	T1DM premenop., n=12	T1DM postmenop., n=45	T2DM premenop., n=14	T2DM postmenop., n=71	Controls premenop., n=15	Controls postmenop., n=28
tCa, mg/dL	9,4±0,08 (9,2-9,5)		9,4±0,05 (9,3-9,5)		9,4±0,07 (9,2-9,5)	
	9,4±0,19	9,3±0,08	9,6±0,09	9,4±0,06	9,5±0,16	9,3±0,08
Ca^{2+}, mmol/L	1,06±0,01 (1,03-1,08) [a]		1,06±0,01 (1,03-1,09) [a]		1,1±0,01 (1,07-1,12)	
	1,09±0,02	1,05±0,01[a]	1,07±0,04	1,06±0,01 [b]	1,12±0,02	1,09±0,01
P, mg/dL	5,3±0,14 (5,1-5,6)		4,9±0,10 (4,7-5,1)		5,04±0,13 (4,7-5,3)	
	5,6±0,34	5,3±0,15 [a]	5,1±0,20	4,9±0,12	5,3±0,21	4,8±0,14
PTH, pg/dL	53,99±2,21 (49,5-58,48)		50,18±1,71 (46,74-53,61)		48,3±3,13 (41,8-54,79)	
	42,49±6,24	56,29±2,16 [b]	44,41±2,54	51,31±1,95	42,15±6,69	50,83±3,41
вит. D_3, ng/mL	21,85±1,6 (18,59-25,1) [a]		24,11±1,31 (21,48-26,73)		27,56±2,48 (22,45-32,66)	
	25,34±4,06	20,68±1,64	29,35±5,18	23,17±1,23	29,71±5,06	26,48±2,81
CT, pg/mL	12,54±1,43 (9,61-15,47) [a3]		10,65±0,88 (8,88-12,43) [a]		6,88±0,93 (4,94-8,83)	
	6,1±2,09	14,35±1,57 [ab]	4,9±0,87	11,83±0,94[ab]	3,36±1,65	8,43±0,92[b2]

				[2]		
ALP, IU/L	112,5±5,08 (102,35-122,71)		121,0±3,78 (113,5-128,6)		115,6±6,67 (102,1-129,03)	
	109,5±10,62	113,3±5,83	112,5±7,95	122,7±4,24	110,4±9,16	118.3±9,06
PINP, ng/mL	36,69±2,03 (32,61-40,77) [a4]		42,03±1,32 (39,41-44,65) [a]		49,72±3,14 (43,39-56,03)	
	43,59±7,12	34,85±1,71 [a2]	47,1±4,32	41,03±1,31[ab]	53,55±5,44	47,67±3,85
b-CTx, ng/mL	0,563±0,04 (0,477-0,650)		0,511±0,02 (0,460-0,563)		0,483±0,03 (0,420-0,547)	
	0,510±0,09	0,578±0,04	0,457±0,06	0,522±0,02	0,437±0,05	0,508±0,03
T-score (L1-L4)	-2,48±0,2 (-2,8; -2,1) [a3]		-1,26±0,16 (-1,5; -0,9)		-1,37±0,26 (-1,9; -0,8)	
	-2,01±0,39 [a]	-2,61±0,23 [ab2]	-0,80±0,35	-1,35±0,19	-0,81±0,3	-1,67±0,36
T-score (Prox.)	-1,87±0,18 (-2,2; -1,5) [a4]		-1,03±0,16 (-1,3; -0,7)		-0,69±0,21 (-1,1; -0,2)	
	-1,28±0,34	-1,99±0,2 [a3b]	-0,80±0,18	-1,07±0,19	-0,34±0,28	-0,86±0,27
T-score (FN)	-2,01±0,19 [a3] (-2,4; -1,6)		-1,27±0,15 (-1,5; -0,9) [a]		-0,83±0,23 (-1,3; -0,3)	
	-1,52±0,41	-2,11±0,22 [a2]	-0,94±0,28	-1,32±0,17 [a]	-0,53±0,38	-0,99±0,29

[a] - $p<0,05$; [a2] - $p<0,01$; [a3] - $p<0,005$; [a4] - $p<0,001$ compared with the control group data;
[b] - $p<0,05$; [b2] - $p<0,01$ compared with subgroup premenopausal patients;

In the control group, the mean PTH index was lower in comparison with the diabetes group, but did not significantly difference (p <0.05) and in both groups showed a rise in post-menopause. In women with long-term diabetes, the level of PTH was statistically significantly different from that in women with diabetes duration of less than 10 years (p <0.05). There was significant negative correlation between PTH levels and P1NP (r = -0.532, p = 0.001) and also a positive correlation between bone resorption marker b-CTx (r = 0.413, p = 0.002). As a result of the study of patients with DM1 and DM2, a decrease was observed below the reference mean value of vitamin D, statistically significant in comparison with the control group (p <0.05), with a decreasing trend in postmenopause in both groups. In addition, patients in the case group had correlation of Ca2+ level and vitamin D with serum levels of PTH concentration: r = -0.378, p = 0.01 and r = -0.461, p = 0.001. In a control group of postmenopausal women, the serum CT level was statistically significantly lower than in patients with diabetes (p <0.05).

The data obtained as a result of the study show an increase in serum PTH and CT levels along with a decrease in the calcium concentration allows one to assert that there is a violation of the secretion of calcium-regulating hormones and their connection with pathological bone remodeling in type 1 and type 2 diabetes mellitus. It should be noted that with the increase in the disease's duration and in the stage of decompensation, the severity of these changes is increasing.

Patients with DM1 and DM2 showed a decreasing trend in serum bone formation marker PINP levels in 35.5% and 18.3%, with sufficient statistical significance and an increase in the bone resorption marker of b-CTx in 16.6% and 5.8% of patients. At the same time, the values of the bone resorption marker b-CTx did not statistically significantly differ from the values of the subjects from the control group. In the postmenopausal subgroup of patients with DM1 and DM2, the mean b-CTx was slightly higher than in premenopausal women. However, according to the age norm, it did not go beyond the reference values. A part of women with diabetes (20%) showed a decrease in the bone formation marker PINP, against the background of unchanged bone resorption. Data from several authors in studies evaluating bone remodeling indices in diabetes also indicate a decrease in mainly bone formation markers, while bone resorption markers in most studies did not differ statistically from control ones [6].

The P1NP level was negatively correlated with HbA1c (DM1: r = -0.328, p = 0.03; DM2: r = -0.301, p = 0.02). The analysis of the data showed a statistically significant relationship between

the duration of DM and the level of b-CTx (DM1: r = 0.349, p = 0.08; DM2: r = 0.214; p = 0.04), apparently due to hyperglycemia-induced inhibition of osteoblastic function [7]. Also, the dependence of PTH and b-CTx changes in the group of patients with DM1 and DM2 were determined (r = 0.413, p = 0.002 and r = 0.507, p = 0.001).

In women with DM1 and DM2, premenopause tended to lower values of b-CTX and P1NP, reflecting a slowdown in bone remodeling compared to the control group women, regardless of age and duration of the disease. In subgroups of postmenopausal women with DM1 and DM2, compared with the control subgroup, predominant decrease in bone formation was observed, indicating that there is an inconsistency observed between bone remodeling processes.

In DM, the number of cases of reduction of BMD in the vertebrae (L1-L4) in women was 75%, in the proximal femur and femoral neck area - 39%. In 83 out of 142 women with diabetes, changes in the T-score were found only in lumbar spine area, in 32 females only in the femur. In 24 cases, a combination of changes in the two regions was determined. Thus, a part of women (n = 115) who have detected changes in only one of the studied areas the risk of misdiagnosis rises substantially if only one zone was measured.

In the control group, the number of cases of osteoporosis in the vertebrae (L1-L4) was 14%, in the proximal femur and in the femoral neck areas - 2.3% and 7%. Osteopenia in vertebrae was detected in 23% of women. In the proximal femur area, osteopenia in the control group of women was found in 26%, and in the femoral neck area in 28% of cases.

A negative correlation was observed between T-score of L1-L4 Lumbar spine and duration of diabetes (DM1: r = -0.568, p = 0.001; DM2: r = -0.267, p = 0.04). In women with diabetes in postmenopausal women, the decrease in BMD in this area is corresponding to an increase in the disease's duration with concomitant age-related changes. The mean negative correlation was also noted in the subgroup of postmenopausal women (DM1: r = -0.515, p = 0.01 and DM2: r = -0.416, p = 0.04). A statistically significant correlation was observed between the T-score of L1-L4 region and b-CTx level (DM1: r = -0.452, p = 0.002; DM2: r = -0.357; p = 0.09). This suggests that the presence of diabetes in the history of exacerbation of bone marrow homeostasis, thereby contributing to the development of osteoporosis in the later postmenopausal period.

Discussion

Analysis of data on markers of bone tissue metabolism in women showed a statistically significant relationship between the duration of DM with the level of b-CTx and the T-score measured in the lumbar spine region. This indicates that both bone metabolism markers and DXA are independent factors indicative of changes in bone tissue, which can be of great importance for early diagnosis and evaluation of the effectiveness of the therapy [7,8]. In general, the processes of bone formation and resorption are closely related, and formation markers and resorption markers tend to change in a coordinated manner. The dissociation of these processes observed with diabetes, when the formation markers are reduced, while the resorption markers do not change, may show that the markers of bone metabolism may indicate very specific changes in bone remodeling processes associated with a disruption in the metabolism of carbohydrates in diabetes. It is possible that glucose changes the concentration of markers circulating in the blood, affecting bone metabolism [6,9], which can clinically increase the bone tissue fragility in patients with diabetes.

The study showed that in most patients, altered bone metabolism is associated with inhibition of bone formation and, to a lesser extent, with bone resorption. Osteoporosis is less common in

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postmenopausal women with diabetes type 2 compared to non-diabetic patients. So, patients with type 2 diabetes had lower b-CTx values and relatively higher levels of P1NP, reflecting less pronounced bone metabolism changes compared with patients with type 1 diabetes, regardless of age and duration of the disease. In type 2 DM, a less pronounced increase in the activity of bone resorption biochemical marker was determined than in type 1 DM, while the formation marker did not differ from the values of the control group. In case of type 1 DM, according to the results of biochemical markers of bone remodeling, on the contrary, the inhibition of bone formation processes were determined and the processes of bone tissue resorption were enhanced. This indicates the different directions of the pathogenetic mechanisms of the development of diabetic osteopathy in the early stages of type 1 and type 2 diabetes. This process more pronounced in the late perimenopause and is still high during the early postmenopause with a decreased intensity of bone loss n the late postmenopausal period compared with the healthy women group.

Conclusions

The results of this study indicate that changes in bone metabolism in most of the examined patients are associated with inhibition of osteogenesis and, to a much lesser extent, with bone resorption. The processes of bone resorption accelerate in the late premenopausal period and continue at the same pace in the first years of menopause. However, in the future in postmenopause, there is a decrease in the intensity of bone loss.

This processes are associated with the duration of diabetes, as indicated by the level of b-CTx and T-score of the lumbar spine. The bone resorption marker in patients with type 2 diabetes is lower than in the case of type 1 diabetes.

Disclosures

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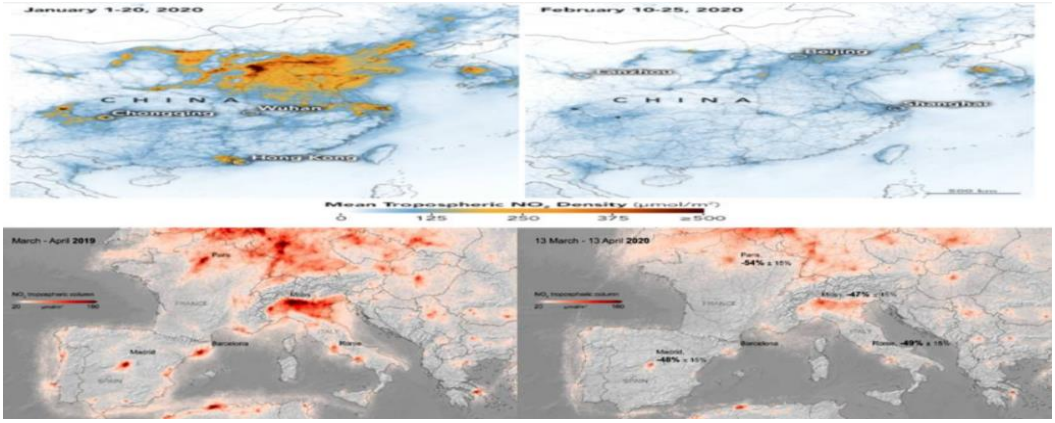

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Рукопись должна содержать аннотацию в пределах 300 слов. Рукопись должна иметь самодостаточный реферат без цитирования и кратко излагать цель исследования, методологию, основные результаты и основные выводы. Аннотация должна быть в одном абзаце с предложениями. Не используйте подзаголовки или список точек в аннотации. Кроме того, следует избегать нестандартных или необычных сокращений, но, если они необходимы, они должны быть определены при их первом упоминании в самом реферате.
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POSTOPERATIVE PAIN AND MULTIMODAL ANESTHESIA IN BARIATRIC SURGERY

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ABSTRACT

Any rational anesthesia strategy should focus on intraoperative and postoperative pain control. Adverse effects of opioids on the course of the early postoperative period are known.
The aim of our study is to determine the correlations of acute postoperative pain with different types of anesthesia.
Methods: 203 patients who underwent bariatric surgery were under our observation; 113 (55.67%) of them are women and 90 (44.33%) are men.
Standard anesthesia with opioids was administered to 49 (24.14%) patients - group I, multimodal + partial use of opioids - group II: 76 (37.44%), multimodal anesthesia - 78 (38.42%) - group III.
Results: During anesthesia with opioids, compared to the second and third groups, the pain in the operative area, as well as in the head, throat, waist and ears is significantly higher.
During multimodal anesthesia, pain is reliably less in all cases, and pain in the throat was not noted.
Correlation analysis showed that opioid anesthesia was significantly correlated with postoperative pain,: Pain in the operated area - $r=0.504^{**}$,$p<0.001$; Head pain - $r=0.395^{**}$, $p<0.001$; Throat pain - $r=0.301^{**}$, $p<0.001$Waist pain$r=0.320^{**}$, <0.001Muscles pain - $r=0.422^{**}$, $p<0.001$
whereas multimodal anesthesia was significantly negatively correlated with all types of postoperative pain.
In the second phase, in the opioid anesthesia group, compared to the second group, there is significantly more pain in the lower back and muscles, and in the third group, there was no pain at all.
The frequency of patients who did not require medical treatment during the intrahospital stage is not significantly different from each other, and the pain requiring non-opioid treatment is significantly less after multimodal anesthesia - Group I - 28(57.14%), Group II - 25(32.89%), Group III - 2(2.56)($p<0.0001$). Pain requires opioid medication - Group I - 20(40.82)Group II – 19(25.00%), ($p<0.0001$). No patient in this group required opioid treatment.
In the ambulatory stage, no patient in the multimodal anesthesia group needed medical treatment, and significantly fewer patients in group II needed non-opioid treatment.
Conclusion: Multimodal anesthesia reduces perioperative pain and the need for perioperative opioid use.
Keywords: Postoperative pain, Multimodal anesthesia, perioperative opioid use.

The use of bariatric surgery to treat severe obesity has several benefits in terms of sustained weight loss, improvement or resolution of several metabolic comorbidities in terms of improvement [1].

Cognition is defined as the brain's ability to acquire, process, store, and retrieve information. Pain is described as an unpleasant sensory or emotional experience, and in order to consciously experience pain, cognitive processing is necessary[2]. The pain pathway consists of transduction, transmission, modulation and perception [3].

Any rational anesthesia strategy should focus on intraoperative and postoperative pain control[4]. Adverse effects of opioids on the course of the early postoperative period are known. In addition to the traditional side effects of rats (depression of consciousness, excessive sedation, nausea, etc.), they have the ability to create opioid-induced hyperalgesia, immunosuppressive effects and reduce the effect of local anesthetics; In addition, opioid analgesia prevents accelerated postoperative rehabilitation of patients. The concept of multimodal analgesia allows refusing the use of opioid analgesics or reducing their dose to a minimum in the perioperative period. Multimodal analgesia involves the simultaneous administration of two or more drugs that affect different levels of acute pain syndrome formation[5].

The use of traditional methods of general anesthesia and postoperative analgesia with a combination of narcotic and non-narcotic analgesics is accompanied by an increase in hemodynamic parameters - both during the operation and during the four days of the postoperative period [6].

Management strategy, anesthetic choice and anesthetic doses must be adapted to the needs of the individual patient [7]

The aim of our study is to determine the correlations of acute postoperative pain with different types of anesthesia.

Methods

203 patients who underwent bariatric surgery were under our observation; 113 (55.67%) of them are women and 90 (44.33%) are men.

Standard anesthesia with opioids was administered to 49 (24.14%) patients - group I, multimodal + partial use of opioids - group II: 76 (37.44%), multimodal anesthesia - 78 (38.42%) - group III.

1 group

Propofol - potentiator of GABA A receptors, Fentanyl - opioid (narcotic analgesic), Sevoflurane - inhalation drug, Morphine - opioid (narcotic analgesic), Promedol - opioid (narcotic analgesic).

2 groups

Propofol - potentiator of GABA A receptors, Fentanyl - opioid (narcotic analgesic), Sevoflurane - inhalation drug,

Dexmedotomidine is a selective agonist of alpha 2 receptors, Locoregional analgesia (lidocaine, naropin, bupivacaine - sodium channel blockers).

3 groups

Propofol - potentiator of GABA A receptors, Sevoflurane - inhalation drug, Dexmedotomidine is a selective agonist, of alpha 2 receptors, Locoregional analgesia (lidocaine, naropin, bupivacaine - sodium channel blockers),

Dosing was done according to the individual characteristics of the patient.

Statistical Analysis

Categorical variables are expressed as frequencies and %. variables were compared with the use of the Fisher's Exact Test. Correlation analysis between categorical variables was performed by Spearman correlation analyses, p value <0.05 was considered as statistically significant. All statistical analyses were performed using SPSS version 23.

Results

The localization of pain after surgery is given in Table 1.

Table 1. Distribution of pain according to localization and type of anesthesia

Phases of postoperative care	localization of pain	Group I (With opioids) n=49		Group II (With partial use of multimodal opioids) n=76		Group III (multimodal) n=78		F	p
		n	%	n	%	n	%		
Phase I	in the operated area	47	95.92	43	56.58	14	17.95	58.12	<0.0001
	head	19	38.78	9	11.84	1	1.28	20.94	<0.0001
	throat	10	20.41	4	5.26	0	0.00	10.94	<0.0001
	waist	20	40.82	14	18.42	4	5.13	14.17	<0.0001
	muscles	25	51.02	15	19.74	2	2.56	26.98	<0.0001
Phase II	Pain in the lower back	9	18.37	3	3.95	0	0.00	10.38	0.0001
	Pain in the muscles	11	22.45	8	10.53	0	0.00	9.77	0.0001

Post-anesthetic pain after bariatric intervention in Phase I of post-anesthetic care was distributed as follows:

As we can see, pain in the operated area is the most common, while throat pain is the rarest.

During anesthesia with opioids, compared to the second and third groups, the pain in the operative area, as well as in the head, throat, waist and ears is significantly higher.

During multimodal anesthesia, pain is reliably less in all cases, and pain in the throat was not noted.

Correlations between type of anesthesia and pain during bariatric surgery are shown in table 2.

Table 2. Correlations between type of anesthesia and postoperative pain:

Factors		Anesthesia with opioids	With partial use of multimodal+opioids	Multimodal anesthesia
Pain in the operated area	r	0.504**	0.083	-0.526**
	p	<0.001	0.240	<0.001
Head pain	r	0.395**	-0.054	-0.294**
	p	<0.001	0.444	<0.001
Throat pain	r	0.301**	-0.050	-0.215**
	p	<0.001	0.480	0.002
Waist pain	r	0.320**	-0.006	-0.275**
	p	<0.001	0.933	<0.001
Muscles pain	r	0.422**	-0.018	-0.353**
	p	<0.001	0.797	<0.001
* - p<0.05,** - p<0.01				

Correlation analysis showed that opioid anesthesia was significantly correlated with postoperative pain, whereas multimodal anesthesia was significantly negatively correlated with all types of postoperative pain.

In the second phase, in the opioid anesthesia group, compared to the second group, there is significantly more pain in the lower back and muscles, and in the third group, there was no pain at all.

The distribution of patients according to the intensity of pain in phase II is given in diagram 1.

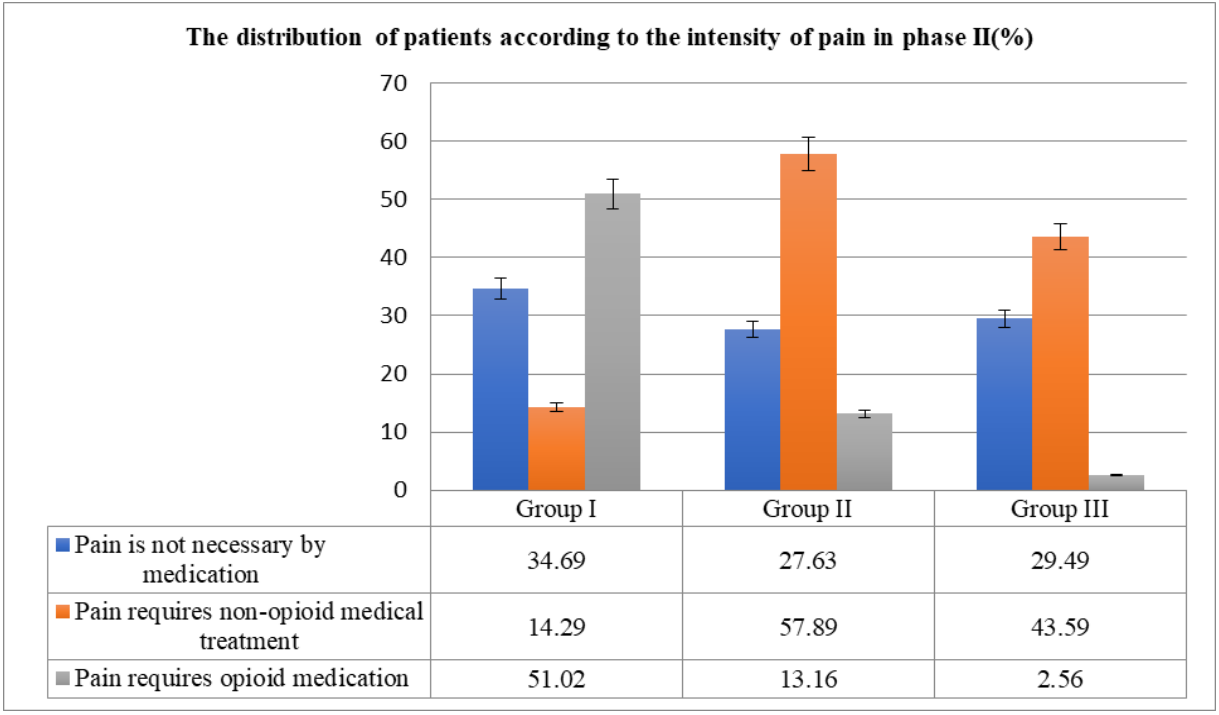

Diagram N1

No significant difference between the groups was observed in the frequency of patients who did not require medication for pain relief after surgery, the need for non-opioids was significantly higher in group II, and the need for opioids was significantly higher in group III.
The degree of pain in intra-hospital and post-hospital stages is given in Table 3.

Table 3. Assessment of pain quality at intrahospital and posthospital stages:

Post intensive stages	degree of pain	Group I (With opioids) n=49		Group II (With partial use of multimodal opioids) n=76		Group III (multimodal) n=78		F	P
		n	%	n	%	n	%		
Intrahospital stage	Pain (discomfort) is not necessary by medication	1	2.04	4	5.26	4	5.13	30.51	<0.0001
	Pain requires non-opioid medical treatment	28	57.14	25	32.89	2	2.56	20.78	<0.0001
	Pain requires opioid medication	20	40.82	19	25.00	0	0.00	30.51	<0.0001
Ambulatory stage	Pain (discomfort) does not require medical treatment	7	14.29	5	6.58	3	3.85	2.48	0.0865
	Pain requires non-opioid medical treatment	18	36.73	9	11.84	0	0.00	21.15	<0.0001

As can be seen from the table, the frequency of patients who did not require medical treatment during the intrahospital stage is not significantly different from each other, and the pain requiring non-opioid treatment is significantly less after multimodal anesthesia. No patient in this group required opioid treatment.
In the ambulatory stage, no patient in the multimodal anesthesia group needed medical treatment, and significantly fewer patients in group II needed non-opioid treatment.

Discussion

Multimodal anesthesia (MMA) refers to the use of additive or synergistic combinations of analgesics to achieve clinically necessary analgesia, with the goal of minimizing the significant side effects associated with higher doses of a single aquagenic medication, such as opioid analgesics[8], especially since a patient's first exposure to opioids often occurs in the perioperative setting, a vulnerable time when multimodal therapy can play a major role in reducing opioid exposure[9].
The importance of multimodal anesthesia is particularly emphasized in patients who may be prone to opioid-related side effects, such as patients with obstructive sleep apnea. Healthcare systems can also benefit from implementing effective MMA, as fewer opioid-related side effects can improve patient outcomes, lead to faster recovery, and rational use of resources [10].
Our study showed that there is a reduction in postoperative pain under multimodal anesthesia. Opioid-free anesthesia allows us to avoid their use in the perioperative period. According to our

study, the frequency of need for postoperative use of opioids is dramatically reduced in the multimodal anesthesia group.

Prevention of postoperative pain should begin immediately after planning the operative treatment. A multidisciplinary group of doctors, based on the conclusion made after assessing the patient's condition and risk factors, will draw up a perioperative plan for pain relief [12].

Conclusion: Multimodal anesthesia reduces perioperative pain and the need for perioperative opioid use.

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BOTOX COMPILATION

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ABSTRACT

Botulinum neurotoxin is a toxin produced by the anaerobic Clostridium botulinum bacteria. While Botox is used in many diseases thought to be caused by excessive contraction of striated and smooth muscles, it has also become popular with its use in the cosmetic field. When the toxin is injected into the muscles, it affects the nerve cells and creates partial and temporary paralysis, thus preventing the muscle from contracting too much. Botulinum toxin, which started to be applied in the perioral region for therapeutic purposes, is used in various areas such as temporomandibular joint disorders, bruxism, gummy smile, masseter hypertrophy, salivary gland problems. Although the therapeutic effect of Botox is temporary and relatively safe, it is essential to have knowledge of the relevant anatomy and the systemic and local side effects of drugs applied to the face.

Introductıon

Treatment options in dentistry are changing day by day, and non-conventional options like the use of botulinum toxin (Botox) are becoming increasingly popular. Botox (BTX) is a reversible, minimally invasive, and safe treatment option for numerous disorders in the maxillofacial region. Even though Botox has been known as an aesthetic treatment option used to eliminate facial wrinkles, it has long been used in medicine and dentistry in different treatment indications by blocking neuromuscular activity for a certain period (1).

Botulınum toxın

2.1. Mechanism of Action

Botox has eight serotypes (A, B, C1, C2, D, E, F, G), and all serotypes have a similar structure and molecular weight (2). When botulinum toxin is administered to muscles with high activity, paralysis occurs in the relevant muscles, and muscle activity decreases. Botulinum toxin shows its effect by inhibiting the release of acetylcholine (Ach), which provides conduction in all parasympathetic and cholinergic nerve endings (1-8). The toxin irreversibly binds to the presynaptic neuron, but it takes two weeks to complete its effect. The effect duration varies between 3-6 months. With repeated injections, the duration of the toxin's effect is prolonged.

2.2. Commercial Forms

The A, B, E, and F types of toxin are active in humans. Types A and B are used for therapeutic purposes. (4). The dosage of botulinum toxin (BTX) treatment varies with the brand of toxin used. The dose given for any toxin type is valid only for the specific preparation and cannot be added or transferred to the doses of other preparation unless it is the same toxin serotype. The toxin dose

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should be adjusted precisely because different preparations have varying effects on different body parts (5).
Some trade names and countries of origin of Botox are as follows:
Botox®: It is purified BTX-A isolated through the fermentation of C.botulinum. The Allergan company commercialized the purified BTX-A under the trade name Botox in 1991. Every vial of Botox provides 5 ng (nanograms) (100 U) of air-dried toxin. The vials also contain 500 µg of albumin and 900 µg of sterile vacuum-dried sodium chloride (without preservatives). There is FDA approval in many European countries, USA and Canada (6).

Dysport®: It contains 12.5 ng (500 U) of air-dried toxin, 125 µg of albumin, and 2.5 mg of lactose. Because Dysport comes from a different type A bacterial strain, its doses are not similar to those of Botox; they are higher and diffuse more compared to Botox (7).

Xeomin®: It is purified freeze-dried BTX-A that does not contain additional helper complex proteins (hemagglutinin and nonhemagglutinin). It is less immunogenic than other BTX-A products. Moreover, it is the only BTX form that can be stored at room temperature, whereas other forms should be kept in the refrigerator (8).

Myobloc®: It is made from Serotype B and is effective in treating movement disorders rather than cosmetic use. It can be used in cases of droopy eyelids, for some wrinkles, and as an alternative treatment for cosmetic neural blockade in patients resistant to BTX-A products. 1 U of Botox is approximately equivalent to 50-100 U of Myobloc. BTX-B is in an acidic solution which may result in painful injections (8).

2.3. Toxicity
The lethal dose for 50% of a human population (weighing approximately 70 kg) exposed to type A toxin is 90-150 ng intravenously, 700-900 ng by inhalation, and 70 µg orally. Since the dose usually used in dentistry is a maximum of 5 ng and is significantly smaller than the lethal dose, overdosing is nearly impossible (5-9).

2.4. Storage Conditions
The purified and powdered neurotoxin complex is packaged in vials containing 100 U of BTX-A. It is readied for use by diluting it with saline.
It is recommended to dilute the toxin by gently stirring the vial while not shaking it and avoiding foam formation; otherwise, the toxin will denature.
Botox® can be kept in the freezer at -5°C or below and in the refrigerator at 2-8°C for 6 months without diluting. The diluted Botox® should be used within 24 hours under the condition that it is stored in the refrigerator at 2-8°C. The literature has reported that it does not lose its activity up to 6 hours, loses 44% of activity by 12 hours, and 70% of activity within 1-2 weeks. When the diluted solution becomes frozen in the deep freezer, it becomes unusable since it will crystallize (10-11).

2.5. Resistance

Botulinum toxin is a protein capable of inducing potent neutralizing antibodies. Therefore, no more than 100 units should be administered in each treatment session, and intervals between treatments should not be shorter than one month to avoid antibody formation.

Other formulations can be used following resistance development because cross-reactions against other serotypes do not occur (12).

2.6. Contraindications

1) Muscular disorders (neuromuscular diseases such as Myasthenia Gravis and Eaton-Lambert Syndrome and motor neuron diseases)
2)Presence of infection at the injection site
3)Hypersensitivity to any known substance in the formulation
4)Patients receiving aminoglycosides or drugs inhibiting neuromuscular transmission
5)Pregnancy and lactation
6) Patients with unrealistic anticipations
7) Patients with psychological disorders (10)

2.7. Side effects

1. Pain during injection
2. Local edema, erythema, and ecchymosis due to injection
3. Temporary numbness and burning sensation at the administration site
4. Reversible muscular weakness
5. Flu-like syndrome
6. Diarrhea
7. Abdominal pain
8. Hypertension
9. Headache, dizziness (2)

3. Botox Applıcatıons İn Orthodontıc Practıce

3.1. Gummy Smile

Smiling has a significant role in expressing one's emotions and facial aesthetics. Therefore, patients anticipate not only dental aesthetics but also smiling aesthetics following orthodontic treatment (13).

In orthodontics, facial aesthetics are achieved by conventional measures such as leveling the dentition, correcting the profile, and improving the smile. A beautiful smile is created by harmonizing the teeth, lips, and gums with each other in appropriate proportions. The ideal situation is that the upper lip symmetrically exposes 2-3 mm of the gingiva, and the gum line follows the upper lip contour. A gummy smile is defined as excessive exposure of the gingiva during smiling (14).

Etiologic factors may be skeletal, dental, muscular, and iatrogenic. For example, muscular hypertrophy causing excessive lip movements may lead to a gummy smile. Therefore, the treatment approaches differ depending on the etiology. (15).

The muscles elevating and laterally retracting the upper lip while smiling are the levator labii superioris muscle, levator labii superioris aleque nasi muscle, levator anguli oris, zygomaticus major, zygomaticus minor, risorius and depressor septi nasi (16) (Figure 1).

While maxillary embedding is preferred if the gummy smile is of skeletal origin, alveoloplasty and/or gingivectomy is preferred for dentogingival origin, incisor intrusion for dental origin, myectomy is preferred in the presence of short upper lip, and Botox is preferred in the correction of the hyperactive upper lip (12).

Numerous surgical procedures have been described in the literature for the gummy smile. However, postoperative swelling, infection, postoperative pain, temporary or permanent nerve damage, and surgical and orthodontic relapse have led patients to alternative treatments.

Besides surgical approaches in muscle-related conditions leading to excessive lip mobility, Botox applications are also preferred since they offer painless and rapid solutions. In addition, Botox is an effective treatment, particularly in excessive gingival exposure due to excessive contraction of the lip muscles by blockade of the levator labii superioris alaeque nasi muscle and in limitation of upper lip movements (8).

A dose of 3 U is recommended for Botox injection at the injection point known as the "Yonsei point," located at the triangle's center formed by the levator labii superioris, levator labii superioris alaeque nasi, and zygomaticus minor muscles (8) (Figure 2). The advantage of the technique is that because it is a semi-permanent, minimally invasive, and painless procedure without postoperative morbidity, it is more acceptable for patients to undergo a radical change in appearance (17).

Polo (2005) treated cases with gummy smiles caused by excessive muscle contraction by injecting BTX-A into five patients and reported that the upper lip length increased by 124% and the gingival appearance decreased significantly. Likewise, in another study, Polo (2008) applied Botox to 30 gummy smile patients with a gingival exposure of 5.2+-1.4 mm. In the post-injection second week, the patients' average gingival exposure decreased to 0.09+-1.06 mm. The gingival exposure increased from the 2nd to the 24th week. However, it did not reach its initial values until the end of the 30-32nd week. Moreover, the application's other effect is a reduction of the nasolabial fold of (8).

Mazzuco and Hexsel (2010) identified four different gummy smile types and responsible muscles in 16 patients. They defined excessive gingival exposure as anterior if it was between canine and canine, posterior if it was in the premolar and molar regions, mixed if in both anterior and posterior regions, and asymmetric gummy smile if it was unilateral. In addition, the levator labii superior aleque nasi muscle was responsible in anterior cases, zygomaticus major and zygomaticus minor muscles in posterior cases, their combination in mixed cases, and unilateral levator labii superior aleque nasi, zygomaticus major and zygomaticus minor muscles in asymmetric gummy smile cases. To treat a gummy smile, they injected Botox into the muscles. The injection points were one cm lateral and inferior to the nasal area on the nasolabial fold for the levator labii superior aleque nasi muscle, and the most lateral point on the nasolabial fold and two cm lateral to this point at the level of the tragus for the zygomaticus major and minor muscles. The researchers treated gummy smiles in all patients and reported success rates of 96% for anterior, 61.06% for posterior, 90% for mixed, and 71.93% for asymmetric cases (18).

3.2. Masseter Hypertrophy

Masseter hypertrophy is a disorder characterized by either unilateral or bilateral enlargement of the masseter muscle. This condition can lead to malocclusion, bruxism, clenching and temporomandibular joint disorders. In its etiology, bruxism, psychosomatic factors, stress, parafunction, and trauma are involved (19).

The habits of unilateral chewing and clenching in patients may cause masseter hypertrophy resulting in facial asymmetry (2).
The results obtained with Botox injected into the masseter muscles in these cases seemed reliable and effective (20).
Smyth et al. (1994) performed the first botulinum toxin injection to the masseter muscle and stated that it was a less invasive method for shaping the lower face cosmetically (21).
After Botox administration, in most patients, a reduction in masseter hyperactivity was determined to result in a reduction in total muscle size over time (maximum reduction of 35.4%) (22).
Boris Bentsianov et al. (2004) demonstrated the injection sites in the masseter hypertrophy (20) (Figure 3).
To et al. (2001) evaluated the effect of Botox in masseter hypertrophy in five cases (4 cases - bilateral and one case - unilateral) using ultrasonography and EMG. They measured the volume changes with ultrasonography and the electrical activity with EMG. They received a positive response from all of their patients (23).
Baş et al. (2010) performed BTX-A injections in a patient with masseter hypertrophy developing due to unilateral chewing habits and in another with masseter hypertrophy whose etiology could not be determined. They reported atrophy of the masseter muscle and satisfactory facial appearance in both patients after three months (24).

3.3. Bruxism

Bruxism is defined as the parafunctional activity of the masticatory muscles occurring with repetitive mandibular movements and characterized by clenching or grinding of the teeth. In severe cases, bruxism might cause headaches and masseter hypertrophy. The prevalence of this condition, which is generally considered a clenching habit that occurs in response to stress and anxiety states, is 20% in the community (26). In addition, in bruxism, the excessive force exerted by the masticatory muscles on the dentition is a risk factor for tooth abrasion, muscle or joint pain, joint locking and sounds, and prosthetic restorations (25-26). The etiological factors are categorized as peripheral and central (27) (Table 1).
Contemporary bruxism treatments focus on reducing excessive muscular activity and protecting potentially affected structures such as teeth, masticatory muscles, and TMJ. Recent studies have shown that Botox application is effective in bruxism. The therapeutic efficacy of the toxin is achieved through the reduction of masticatory muscle contraction, including masseter, anterior temporalis, and in some cases, lateral pterygoid muscles (28).
In another study, BTX-A was injected into the masseter muscles of patients with a history of severe bruxism refractory to medical and dental procedures (mean dose: 61.7 U/side; range 25-100 U), and a mean therapeutic response time of 19 weeks was reported. Injecting Botox bilaterally into the masseter muscles was documented to significantly reduce the symptom severity for an average of 19±17 weeks (29). Botox treatment was effective on bruxism, and injections at a dose of <100 U were considered safe for healthy patients (30).

3.4. Temporomandibular Joint Disorders

Temporomandibular joint disorders (TMDs) are disorders affecting the temporomandibular joint (TMJ), masticatory muscles, and associated structures (31). Symptoms may include pain in the head, face, neck, and around the ear, noise from the joint, and restricted jaw movements (1).

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In most TMD cases, secondary muscle spasticity due to bruxism is an etiologic factor (32). The traditional treatment approaches in TMDs include physiotherapy and exercise, anti-inflammatory and analgesic drugs, muscle relaxants, oral splints, acupuncture, or their combination. Recently, Botox applications have also been proven effective in relieving pain and tenderness in TMD and have started to be practiced frequently (33). With BTX-A injection, attempts have been made to overcome pain in the joints and masticatory muscles, restriction in mouth opening, recurrent joint dislocations, and hyperactivity in the masticatory muscles. Even though there is no standard protocol for the use of Botox® for TMD, case reports have shown a reduction in pain, and improved function with 25 to 100 U of Botox® injected into the masseter and temporal muscles. Furthermore, Botox injection involving the lateral pterygoid muscles has also been reported as having a favorable therapeutic effect (34).

3.5.Oro-mandibular Dystonia

Oro-mandibular dystonia (OMD) is a movement disorder characterized by involuntary spasms and muscle contractions in the muscles around the TMJ and perioral muscles. OMD is considered a subgroup of TMD because of its affected muscles (35). As a result, trismus, bruxism, involuntary jaw opening-closing, and uncontrolled tongue movements are encountered (12). Most of the publications reported on OMD have been open-ended studies; however, they all have reported improvement with Botox injections. The most comprehensive and long-term study on this subject is the study conducted by Tan and Jankovic (1999) involving 162 patients with OMD. As a result of the injection of BTX-A into the masseter muscle and/or submental region, improvements in masticatory and speech functions were reported in 67.9% of patients, and the mean duration of clinical recovery was 16.4 ± 7.1 weeks (22-29-36).

3.6. Pathological clenching/teeth grinding (Trismus)

Trismus is a phenomenon causing chronic trauma to the gums and related tissues. Low Botox doses can potentially alleviate this disorder. Similarly, patients with a deep or cross bite undergoing orthodontic treatment encounter elevated chewing force due to prolonged masticatory muscle activity. With Botox, this unfavorable situation can be prevented; thus, the orthodontic treatment duration can be reduced, and patients can be provided with more comfortable eating, speaking, and swallowing functions (1-33).

3.7. Prevention of Post-Surgical Relapse

The utilization of Botox for paralysis of the geniohyoid muscle to prevent relapse in orthognathic surgical interventions in which the mandible was anteriorized has been reported (12).
Even though the perioperative use of Botox is not considered very often, it actually accelerates postoperative wound healing by reducing muscle strength in many fields. For example, in jaw fractures where rigid internal fixation is not suitable, Botox can be used to prevent muscle movement to reduce the displacing forces on the bone fragments and provide better stabilization (12).

4. Other uses of botox in dentistry

4.1. Trigeminal Neuralgia

Trigeminal neuralgia is a neurological condition causing acute severe pain and affecting the orofacial muscles, and mainly secondary to a blood vessel's trigeminal nerve compression. The pain is sudden and sharp, like a lightning flash (3).
Botox is used in trigeminal neuralgia in patients who are unresponsive to medical treatment, in patients in whom surgery cannot be performed, or in patients whose surgical treatment has failed (37).
Zhang et al. (2014) injected different doses of Botox or saline into trigger points in 84 patients with trigeminal neuralgia and achieved successful results independent of the dose in patients treated with Botox in their randomized controlled study. In Botox use for trigeminal neuralgia, rather than systemic side effects, local side effects such as edema at the injection site and facial asymmetry due to surrounding muscles' involvement were observed. (38).
BTX has been stated as a rapid, effective, and minimally invasive method for treating trigeminal neuralgia compared to other invasive treatments (39).

4.2. Sialorrhea and Salivary Secretion Disorders

Sialorrhea (excessive salivation) is a common condition arising from poor oral and facial muscle dominance (2). Since the salivary gland cells' secretions occur by cholinergic receptor activation, BTX depresses the glands' secretory activity. Sialorrhea is particularly common in cases with cerebral palsy, Parkinson's disease, Frey syndrome, amyotrophic lateral sclerosis, or motor neuron disease. Regarding the salivary gland, Botox is utilized in various conditions such as salivary fistulas, aspiration of saliva, dysphagia, idiopathic hypersalivation, sialocele, and chronic sialadenitis (40).
When the effects of Botox on salivary glands were analyzed, it was found that injections into the parotid and submandibular glands were effective in controlling hypersecretion (30). The salivary flow decreased significantly within four weeks after 30-70 U of Botox was injected into the parotid gland (41).

4.3. Mandibular Spasm

This muscle spasm originates from the spasm of all masticatory muscles and associated mandibular muscles (20). Botox treatment applied to the masticatory musculature effectively treats hyperfunctional or spastic muscles (42).

4.4. Combination with Dental Implant Applications

Overstrain of the masticatory muscles may interfere with osseointegration of implants and calli in jaw fractures. In this regard, injecting Botox into the masticatory muscles can provide a more stable environment and therapeutic benefit for the osseointegration of implants and fractures (43).

4.5. Facial nerve paralysis

For treatment of asymmetric appearance in cases of facial paralysis, a method that induces facial symmetry by intentionally creating partial facial paralysis by injecting Botox into the patient's normal (healthy) side of the face was proposed, and it was stated that visual symmetry of the patient could be achieved in this way (44).

4.6. Growth and Development Studies

Chemical denervation is achieved, muscle activities are reduced locally with Botox application, and muscle functions' contribution to craniofacial bone development can be identified (45).
In an animal study by Babuccu et al. (2009), a total of 4 groups were formed, including two groups in which Botox was injected into the right masseter and right temporalis muscles, a control group, and a group in which sterile saline was injected into the masseter and temporal muscles. Osteometric measurements revealed significant atrophy in the botox-injected groups' relevant muscles. The nasal bone, premaxilla, maxilla, and zygomatic arch dimensions were significantly reduced in the groups where Botox was injected into the right masseter and temporal muscles compared to the left-sided muscles. The masseter group showed no difference regarding skull dimensions and mandibular length compared to saline and control groups, whereas the decrease in skull dimensions was significant in the temporal group compared to the other groups. Therefore, it was stated that skeletal muscle denervation with Botox during the growth and development period negatively affected bone development. Researchers have even thought that with increasing utilization of BTX-A and comprehensive research that will be conducted on this subject, craniofacial development may be changed in the desired direction by manipulating muscle functions in craniofacial anomalies and deformities in the future (46).

Conclusion

Today, the use of Botox applications for aesthetic and therapeutic purposes in dental practice has become increasingly widespread. Even though more studies are needed about Botox applications in orthodontics, since its effect is reversible, it is a reliable and supportive treatment method. The correct indication and informing the patient are the issues that must be considered in practice.

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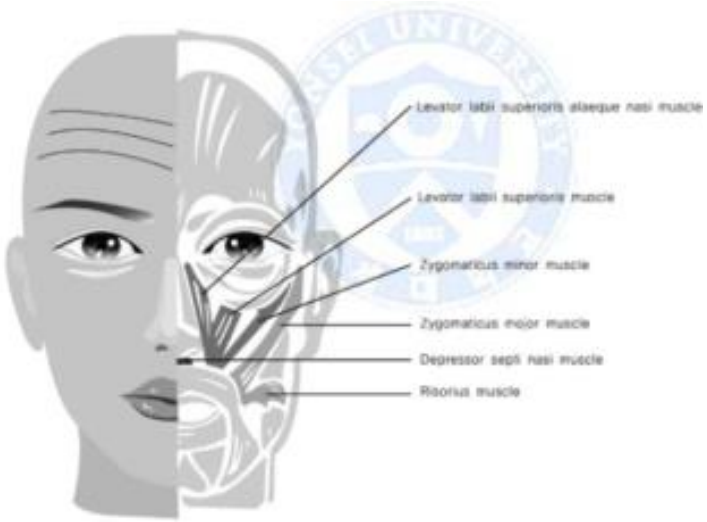

Figure 1. Muscles responsible for the gummy smile

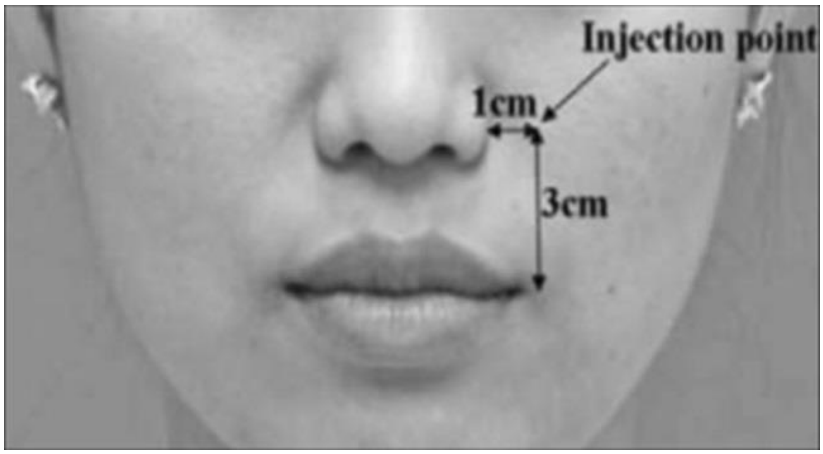

Figure 2. Yonsei point

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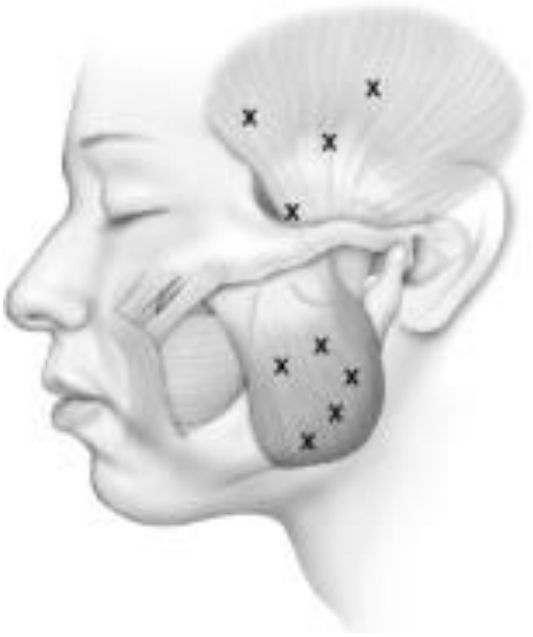

Figure 3. Injection sites

Table 1. Etiologic factors for bruxism.

Peripheral factors	Central factors	
	Pathophysiological	Psychosocial
Facial morphology	Sleep disorders	Stress
Condylar asymmetry	Alterations in brain chemistry	Anxiety
Dental arch's shape	Using various drugs	Fear
Malocclusion	Alcohol/coffee usage/smoking	Frustration
	Familial-genetic factors	Poor social support
Centric relationship-maximal intercuspidization unconformity	Nutritional deficiencies (calcium, magnesium, etc.)	Personality
Occlusal irregularities	Allergies	

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CERVİCAL THYMİC CYST: A RARE DİFFERENTİAL DİAGNOSİS İN LATERAL NECK MASSES

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ABSTRACT

A cervical thymic cyst (CTC) is a rare entity among lateral neck masses. They are usually diagnosed in early childhood and may be determined at any level of the descent of the thymus between the mandibular angle and superior mediastinum. CTC is commonly misdiagnosed as branchial cysts, lymphatic malformations, lymphadenitis, dermoid cysts, epidermoid cysts, or neoplastic masses. The exact diagnosis of cervical thymic cyst can be uncommonly made preoperatively, and histopathological examination of the surgical specimen is the only definitive diagnostic tool for most reported cases. We reported the clinical presentation and management of a cervical thymic cyst in a 9-year-old male to emphasize the importance of cervical thymic cyst in the differential diagnosis of lateral neck masses.
Keywords: Cervical thymic cyst, Lateral neck mass, Branchial cyst,

Introduction

A cervical thymic cyst is very rare, with only about 100 reported cases in the literature. (1) It is caused by the cessation of the regular embryologic migration of thymic primordium. Hsieh et al. reported that children's cervical thymic cysts accounted for 0.3 % of all congenital cervical cysts. (2) In 1901, Polloson and Piery made the first attempt at surgical cyst excision, but a total removal was succeeded in 1944. Clinical presentation and management of a cervical thymic cyst in a 9-year-old child have been reported in the literature review.

Clinical Report

A 9-year-old male presented to our department with a painless left-sided neck swelling of two months. His parents noticed the mass incidentally, increasing in size over time. The medical and family history was unremarkable. A painless, soft, semi-mobile about 9 x5 cm neck mass was palpated on physical examination. There were no overlying skin changes, weight loss, or pressure symptoms. All the hematological and biochemical tests and thyroid function tests were also normal. In the preoperative workup, ultrasonography was performed, and an isoechogenic mass with dense content on the left side of the neck was detected. Abscess or branchial cyst was taught as the primary diagnosis. Computerized tomography (C.T.) scan of the neck (Figure 1) showed a 90x40 mm fluid density hypodense lesion with septations, and the lesion was adjacent to the carotid artery and jugular vein. And Magnetic Resonance Imaging (M.R.) also had similar findings, and the primary diagnosis of the radiologists was lymphangioma (Figure 2).

Under general anesthesia, a transverse incision was taken over the cyst. It was under the sternocleidomastoid muscle adhering to the common carotid artery and jugular vein. After carefully separation from muscle and carotid sheath, the specimen was sent for histopathologic examination. The final histopathological investigation revealed multiloculated cysts lined by stratified squamous epithelium and thymic tissue in the cyst wall. Also, a parathyroid gland of about 5 mm was found in the periphery of the cyst. Six months following surgery, there was no recurrence or immunity problem.

Discussion

Thymic cysts are very rare lesions representing only about 1 % of cystic cervical masses. (3) Embryologically, the thymus is derived from the third pharyngeal pouch and descends into the mediastinum. The parathyroid gland may be found in the cyst wall, indicating the common embryonic origin from the third branchial pouch. (4) A parathyroid gland about 5 mm in size was also found in the wall of the excised cyst. Cervical thymic cysts are more common in males (males: females 3:2) and are usually present in the first decade of life. (5) Our patient was also male and nine years old. Cranially the ectopic thymic cyst passes posteromedial to the carotid sheath and ends near the pyriform sinus. Cranially and caudally, it may extend below the thyroid as far as the mediastinum. (6) Although the reported cysts vary, we found most of the cysts were about 4-5 cm in size. Craniocaudal length of our cyst was 9 cm, extending from the pyriform sinus to the upper mediastinum.

The differential diagnoses of cystic neck mass include second branchial cleft cyst, cystic hygroma/lymphangioma, thyroglossal cyst, ectopic thymic cyst, dermoid cyst, vallecular cyst, epidermoid cyst, necrotic lymphadenopathy, cystic nerve tumors, and cystic neuroblastoma. On ultrasonography, necrotic lymphadenopathy, cystic nerve tumor, or neuroblastoma have thick walls. A thin-walled cystic lesion can be due to a branchial cleft cyst, lymphangioma, thyroglossal cyst, and ectopic thymic cyst. While the thyroglossal cyst is usually in the midline, the others are in the lateral of the neck, as in our case. Exact radiological differential diagnoses of these lesions are not always obvious, but there may be some pointers. While branchial cleft cysts pass between the carotid bifurcation to end at the base of the tonsils, thymic cysts pass behind the carotid artery to terminate at the pyriform sinus. Also, thymic cysts extend more caudally, sometimes to the mediastinum; it is never seen in branchial cysts (6).

Making a preoperative diagnosis is important if it is the only functioning thymic tissue without the mediastinal thymus. Radiological techniques may provide a correct preoperative diagnosis and show the nature, extent, and relation with surrounding neurovascular structures. Preoperative CT should be obtained before surgery to confirm the normal or abnormal thymic tissue. Surgical removal of the CTC is the treatment of choice. The presence of normal thymic tissue in the cyst wall on histopathologic examination confirms the diagnosis. Removal of the lesion may leave the patient athymic. Although this is not a problem for adults, immunodeficiency problems may be seen in children. Possible complications include myasthenia gravis associated with ectopic thymic tissue or rarely developing a malignant thymoma. But there have been no reported immunodeficiency or myasthenia gravis after removing the cervical thymic cyst. Also, after six months following surgery, we have not seen any problem

Conclusion

A cervical thymic cyst is an infrequent differential diagnosis of a lateral neck mass. However, they should be considered in the investigation of cystic neck swellings. Imaging, surgical findings, and histopathological examination are essential in exact diagnosis. Our case emphasizes the need for considering cervical thymic cyst, although rare, as a differential diagnosis of a lateral neck mass.

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Figures

Figure 1. Axial CT scan showing the cyst, posterolateral to the left carotid artery and terminating at the pyriform sinüs.

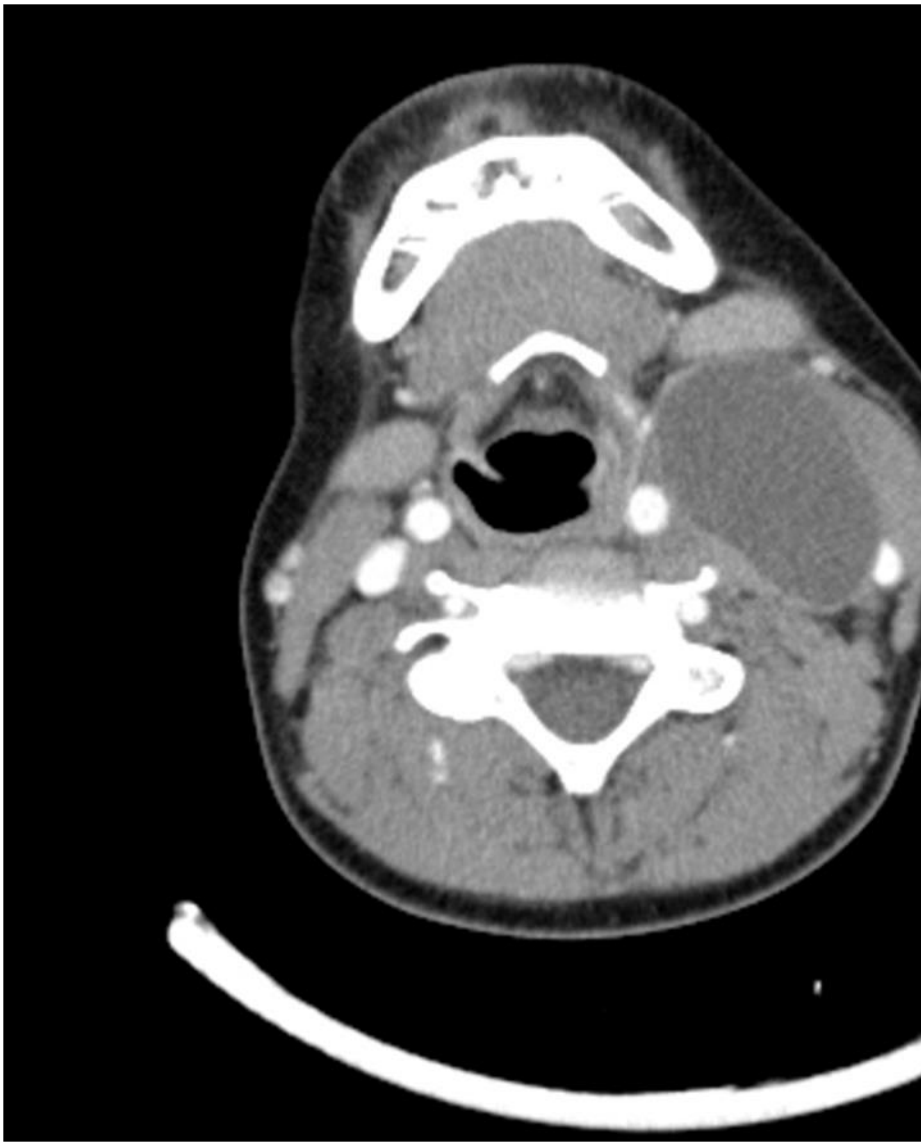

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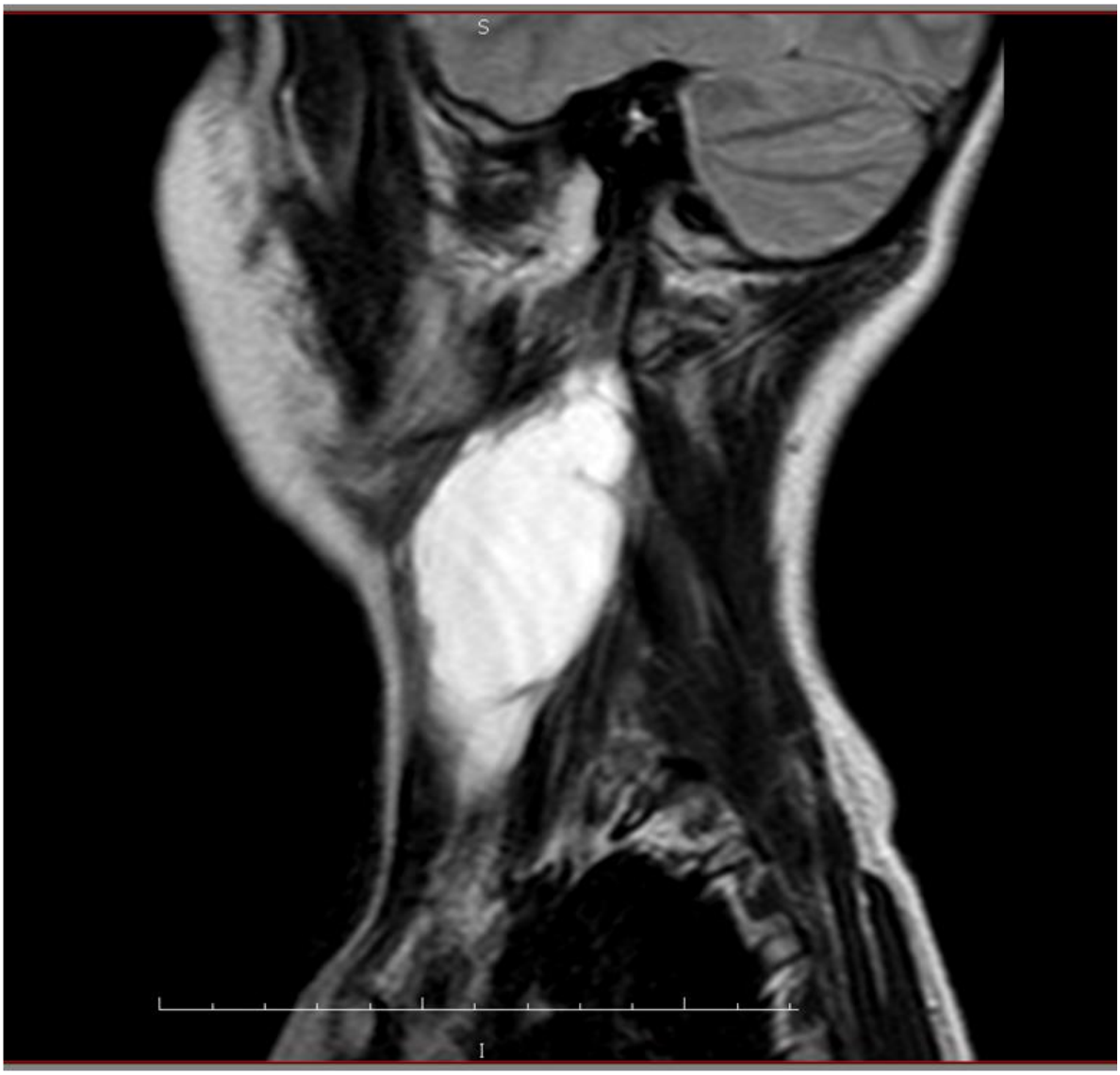
Figure 2. Sagittal MR image shows the cyst, 9 cm in length extending from pyriform sinus to upper mediastinum



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MODERN APPROACH TO THE CLINICAL VIEW, PATHOGENESIS AND TREATMENT METHODS OF ENDOMETRIOSIS

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Objective: Endometriosis is a progressive estrogendependent widely spread disease especially among women suffering of chronic pelvic pain (40-80%) and infertility (25-80%). Pathogenesis is multifactored, but ectopic dissemination of endometrial tissue with forming of endometrioid implants is doubtless. The role of stem cells in its pathogenesis is proved. The choice of therapeutic approaches is wide, however the unique approach has not been worked out yet. The management is determined with the aim of therapy (treatment of pelvic pain or infertility).
Results: Laparoscopic surgery and excision of en dometriomas are associated with decreasing pelvic pain. Therefore there is a number of patients for those surgery is the primary approach in endometriosis treatment. Bowel endometriosis is conjugated with severe pelvic pain and high risk of complicated surgery. Pharmacological agents (Gonadotrophin-Releasing Hormone analogs, progestagens, oral contraceptive pills, androgens, non-steroid anti-inflammatory drugs, etc.) are commonly applied ongoing for endometriosis of various location. They control pelvic pain syndrome effectively, but every of them has its advantages and disadvantages.
Conclusion: Elagolix treatment may become the basis of new strategy, which core is partial estrogen depression, therefore further research is required. Angiogenesis inhibition also represents a new line in endometriosis management. Sorafenib effects on stem cells proliferation, invasion and HIF-1 activation help to suppose new possibilities for its application. Anti-angiogenic drugs may show good result separate or being combined with hormone therapy and provide high efficacy of complex pharmacological approach.
Keywords: pelvic pain, endometriosis, infertility, stem cells, Gonadotrophin Releasing Hormone, oral contraceptive pills.

The relevance of the problem

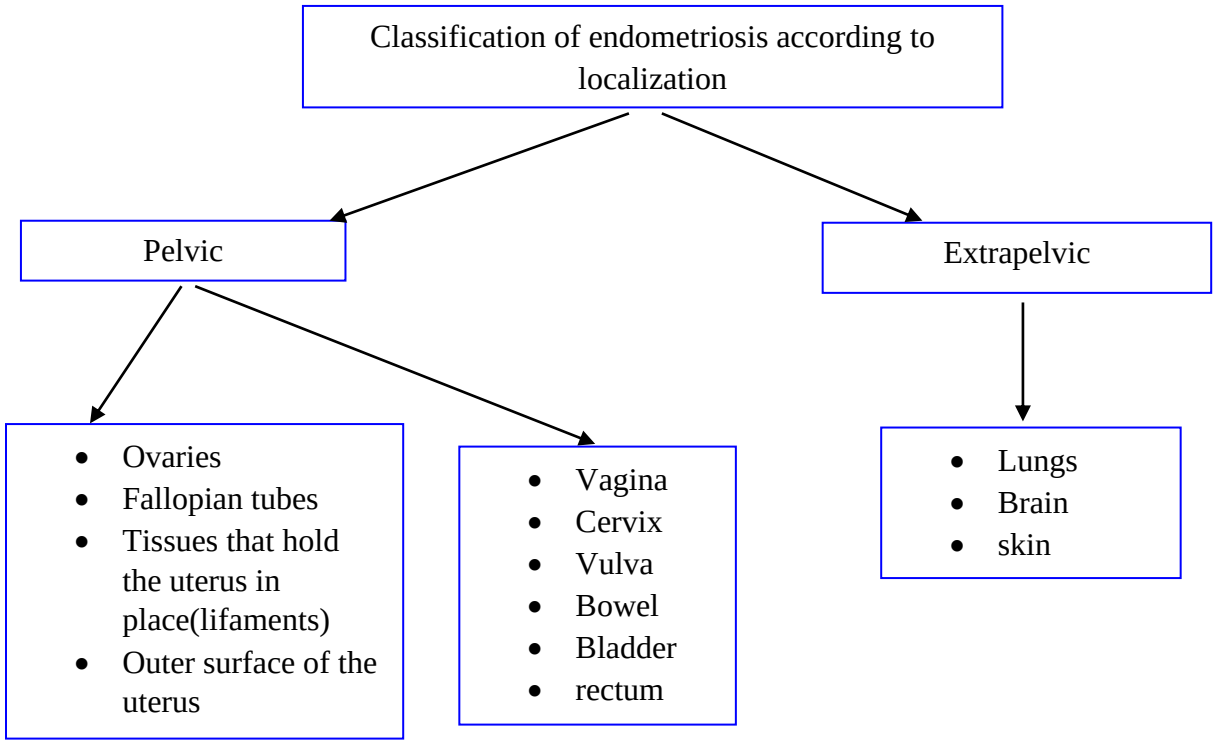
Endometriosis is an estrogen-dependent chronic progressive disease that is widespread in women with pelvic pain (40-80%) and infertility (25-80%). Although the pathogenesis of the disease is multifactorial, the spread of the endometrium to ectopic areas and the subsequent formation of endometrioid heterotopies are undeniable. The role of stem-shaped cells in this process has also been proven. Despite the wide range of treatment methods for endometriosis, a unified approach to them is not defined by specialists, and the choice of treatment method is determined individually by the goal (treatment of pelvic pain or infertility). Endometriosis remains an actual scientific and clinical problem, and its main controversial issues are: is endometriosis a disease; mechanisms of its formation and classification; genetic and immunological aspects; internal and external endometriosis and adenomyosis; diagnostic criteria, etc.

Terminology and classification

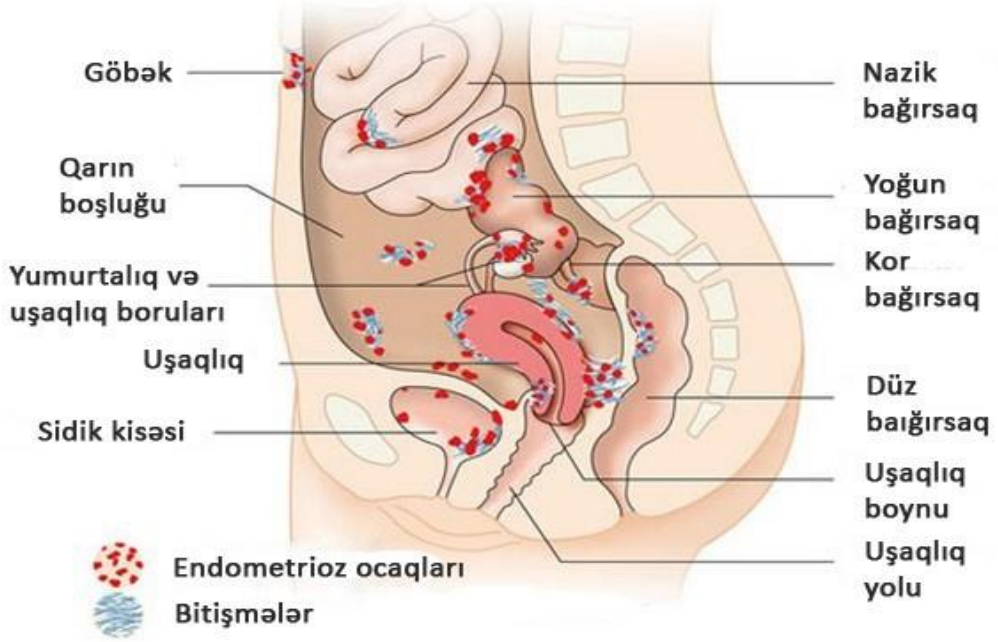
Endometriosis is a pathology characterized by the fact that endometrial tissue, normally found only in the inner lining of the uterus, is found in other membranes of this organ and other genital and extragenital organs outside the uterus. In most cases it is found in women of reproductive age

(20 to 40 years old), but it rarely occurs in postmenopausal women as well. Although it manifests itself in very frequent cases with pelvic pain and infertility, sometimes it can also be asymptomatic. It is usually found in the genitals and pelvic organs, but it can also appear in other areas. Since the endometrioid tissue contains receptors for hormones, the changes in the normal endometrium occur in that tissue and are manifested by bleeding once a month. There are several classifications of endometriosis. The most widespread classification is the one proposed by the American Veterinary Society (R-AFS) in 1979 and revised in 1985 and 1986. It is based on the calculation of the number of heterotopias expressed in points [I stage (minimal changes) - 1-5 points; II stage (moderate changes) – 6-15 points; III stage (acute changes) – 16-40 points; Stage IV (gross changes) – more than 40 points]. At the same time, clinical practice uses the classification of endometriosis based on its location. From this point of view, endometriosis is divided into two groups - genital and extragenital. Genital endometriosis can be located in the myometrium (adenomyosis), peritoneum, ovaries, cervix, uterus, and perineum. Extremal endometriosis, on the other hand, is not topographically related to the organs and tissues of the reproductive system, and mainly includes the organs of the abdominal cavity (appendix, rectum, small and large intestine), lungs and pleural cavity, skin (post-operative scars, extremities, lymphatic nodes).

Diagram 1



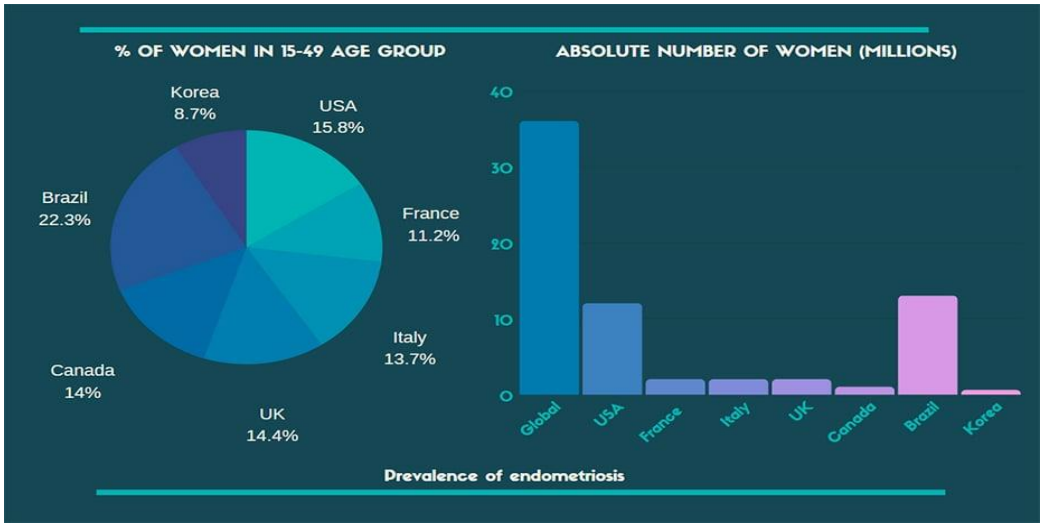
Picture 1



Epidemiology

Endometriosis ranks 3rd in prevalence after genital inflammatory diseases and uterine fibroids. It is observed in 7-50% of women. It occurs in 2-10% of women who apply for the first time, and in 30% of women who have undergone gynecological surgery. 20-50% of women suffering from infertility also have foci of endometriosis.

Picture 2. Prevalence of endometriosis in different countries



Pathogenetic factors

Hormonal disorders; immune system dysfunction and impaired biological response of endometrial cells to sex hormones; constitutional hereditary genetic predisposition; deficiency of the

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antioxidant system of the body; long-term tension of protective-adaptive reactions; prolonged use of intrauterine contraceptives; stressful situations.

Hormonal – the secretion and effect of progesterone is disturbed in patients. An elevated level of estrogens is noted, which stimulates the increased reproduction of endometrial cells. Most often, in such women, an increase in prolactin secretion and a violation of the function of the adrenal gland are observed.

Immunological – an imbalance in the growth and death of cells is characteristic. Intensified secretion of endothelial growth factor leads to the development of vessels and the spread of endometriosis foci. At the same time, the activity of killer cells decreases, apoptosis (genetically programmed death of cells) slows down. They investigated the inability of the immune system to cope with the cycle cell of retrograde mens fluid. If the immune system copes with endometriosis, then endometriosis is related to allergic and autoimmune pathologies. And the causality of this theory has not been fully investigated.

Retrograde theory (implantation theory) – it is the most widely accepted theory. It was first proposed by John Sampson. According to the theory, during menstruation, a part of the endometroid cells flows into the fallopian tubes, into the abdominal cavity, attaches to the peritoneal surface and develops there, but it appeared in women without mensis, in pre-pubescent girls (the theory did not justify itself), and endometriosis was also found in the lungs and brain, and this distanced us from this theory.
In addition, it is noted that endometroid cells differ from normal endometrial cells in their biochemistry, hormonal response and immunology. It is assumed that endometroid cells are a subset of endometrial cells.

Theory of endometrial formation – according to the theory, endometrial cells pass into the uterine wall during abortions, intrauterine diagnostic procedures, operations, that is, during manipulations accompanied by a violation of the integrity of the intrauterine mucous membrane. Moving to the muscle layer, endometrial cells begin to increase and multiply and create an endometriosis focus. This theory explains the appearance of foci of endometriosis in organs located far away by the proliferation of endometrial cells through blood vessels during operations on the uterus.

Other theories: stem-like cells; environment; müllerionosis (embryonic); coelomic metaplasia; autoimmune; oxidative stress theories. Although the exact cause of endometriosis is unknown, many theories have been presented to better understand and explain its development. These concepts do not necessarily exclude each other. The pathophysiology of endometriosis is most likely multifactorial and involves an interaction between several factors.

Symptoms of endometriosis
The course of endometriosis can be different: at the beginning the disease passes symptom-free and can be detected only as a result of preventive examinations. However, there are also acute symptoms of endometriosis. One of them is pelvic pain and is identified in about 16-24% of patients. The nature of the pain (mild, severe, spastic, stabbing pain), localization (lower back,

rectum, lower abdomen), the degree of pain does not depend on the degree and stage of proliferation of endometrioid tissue, the pain is associated with menstruation. It usually occurs 1 week before menstruation, during menstruation and 1 week after menstruation. If there is inflammation and adhesions, the pain is permanent and unrelated to menstruation, it becomes chronic. Pelvic pain has a significant negative impact on women's mental health and quality of life; especially in women suffering from pelvic pain, a high level of anxiety and depression, loss of working capacity, and restrictions on social activities are identified.

Dysmenorrhea — painful menstruation — it is found in 40-60% of patients. Most often it intensifies in the first 3 days of menstruation and is often due to bleeding into the cavity of the cyst and, as a result, its increased pressure; irritation of the peritoneum; and endometriosis bleeding from foci; are associated with compression of the blood vessels.

Dyspareunia (painful intercourse) – ain during defecation and urination. Discomfort and pain during sexual intercourse, which occurs when endometriosis is localized in the uterus, rectovaginal partition, oma-in the area of the uterine ligaments, and uterus-rectum cavity.

Menorrhagia — heavy and continuous menstruation — it is found in 2-16% of patients. It is often accompanied by adenomyosis and related diseases: uterine fibroids, ovarian polycystosis.
Infertility – it occurs in 25-40% of women with endometriosis. Gynecologists still do not know exactly what the mechanism of infertility in endometriosis is. It is assumed that inflammation and adhesions cause infertility. The main reason of infertility is the presence of adhesions in the pelvic organs, thereby the violation of normal anatomy.
Table 1. Main symptoms of localization of endometriosis.

Localization	**Symptoms**
Genital organs	Dysmenorrhea Pelvic pain Infertility Lumber-sacral pains Menstrual irregularity
Gastro-intestinal tract	Tenesmes and rectal bleeding Diarrhea, constipation
Urinary system	Hematuria (related to menstruation) Urethra obstruction
Scar area, umbilicus	Bleeding and pain associated with menstruation
Lung	Menstrual hemoptysis

Endometriosis and pregnancy
Endometriosis reduces the chances of pregnancy termination, so pregnant women with endometriosis should be constantly monitored. The probability of pregnancy after the first 6-14 months of endometriosis treatment is 15-56%. Main risks;; ectopic pregnancy; placental abruption

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- 1.5-6 times more common than other women; miscarriages; premature birth; preeclampsia according to recent evidence. In pregnant women with endometriosis, the prognosis is alleviated, the reason: an increase in progesterone level reduces the growth of endometric tissue; absence of menstruation; due to low levels of estrogen during lactation.

Diagnosis

To diagnose the disease, a gynecological examination is carried out. By means of colposcopy examination, the location and shape of the damage with endometriosis are clarified. The most valuable of radiological methods is spiral computed tomography. Because, by means of it, it is possible to accurately determine the nature of endometriosis, its localization, interaction with neighboring organs, as well as to clarify the state of the small pelvis cavity. One of the most informative research methods is magnetic resonance, which provides accurate visualization of small pelvic organs and their structure thanks to the high resolution of magnetic resonance imaging. Using this method, ovarian endometriosis is determined with an accuracy of 96%. One of the most accessible and widespread methods for diagnosing endometriosis is the ultrasound examination method. The method helps to clarify the location, dynamics, etc. of the focus under the influence of therapy.

Currently, one of the most accurate methods of diagnosing the disease is laparoscopy (puncture of the abdominal wall with the introduction of a special device - a laparoscope). For example, this method provides the diagnosis of ovarian endometriosis with an accuracy of 96%. Laparoscopy also assesses the degree of endometriosis; lesions may appear dark blue, powdery black, red, white, yellow, brown, or non-pigmented; detects the size of lesions; names endometriosis areas by various names, such as implants, lesions, or nodules. Larger lesions may appear inside the ovaries as endometriomas or "chocolate cysts", "chocolate", because they contain a thick brown liquid, mainly old blood.

The identification of various tumor markers in the blood serum is becoming increasingly important. Currently, most of the existing ones are the determination of CA-125, REA and SA 19-9 markers, as well as the RO-test (universal diagnostic test of tumor growth), carried out by the method of immunoenzyme analysis. It was determined that the concentrations of oncomarkers CA 125, CA 19-9 and REA in the blood serum of healthy people were on average 8.3, 13.3 degrees and 1.3 mg/ml, respectively. During endometriosis, these indicators are on average 27.2, 29.5 degrees and 4.3 mg/ml, respectively.

Treatment

In recent years, the treatment of endometriosis has been the most discussed aspect of the problem. The provision that is indisputable to this day — it is impossible to eliminate the anatomical substrate of endometriosis by means of any effect, except for surgical operation, at the same time, other procedures reduce the severity of disease symptoms in a limited number of patients and restore the functions of various parts of the reproductive system. The main goal of treatment — hormonal treatment aimed at preventing the growth of endometrioid cells and slowing down the progression of the process; treatment of infertility; surgical operation aimed at eliminating the hearth.

The most common variants of surgical intervention during pathology: destruction of foci in the cervix and uterus with laser, cold or electric current; removal of the uterus with or without increments; ablation (endoscopic resection) of endometriosis foci; laparoscopic removal of foci in

the ovaries and peritoneum. Most often, hormonal treatment is prescribed before and after surgery. Hormonal therapy is also prescribed at times when there are contraindications to surgery. The goal of treatment is inhibition of ovulation, lowering of estrogen level, stopping of menstrual bleeding. All this leads to the atrophy of the endometrium and the reduction of the size of endometrioid foci.

However, surgical treatment is not always appropriate or acceptable to the patient. Alternatively, it can be considered a method of treating minimal and moderate endometriosis (without diagnostic testing), or rather, symptoms that are likely to be the cause of this disease. This therapy can be accepted only after a thorough examination of the patient, provided that there are no possible causes of other (non-gynecological) symptoms, with the exception of volumetric formations in the abdominal cavity, and only by a doctor who has extensive experience in the treatment of endometriosis.

The most commonly used drugs for the treatment of endometriosis are: progestagens; estrogen-gestagenic preparations; agonists of gonadotropin-releasing hormone; antigestagens.

Symptomatic treatment of endometriosis includes the following group of drugs: non-steroidal anti-inflammatory agents: spasmolytic drugs; iron preparations for the correction of anemia.

A socially significant complication of endometriosis is infertility. For its treatment, in vitro fertilization is widely used (IVF). IVF is effective during endometriosis only in 10-20% of cases. It is most commonly indicated in women over 35 years of age, for severe disseminated forms of the disease, in severe lesions of the fallopian tubes.

Prevention

Avoid excessive physical stress during childhood and youth; taking combined oral contraceptives; reducing abortions and other intrauterine manipulations; avoiding contact between healthy and damaged tissues during surgical treatment of endometriosis.

Prognosis

Endometriosis tends to recur. During the last year's 5 years of treatment, this disease occurs in 40% of women, and in the next 5 years-in 75%. When menopause begins, the probability of recurrence of the disease decreases. In the case of radical removal of the organ damaged by the disease, the process does not progress.

Conclusion

Thus, for endometriosis, paradoxical aspects of etiopathogenesis and their clinical contrasts, the cause of which has not yet been found, are characteristic. In fact, in the benign nature of the disease, local invasion, an aggressive course with wide spread of foci is possible; minimal endometriosis is often accompanied by severe pelvic pain, large endometrioid cysts are asymptomatic; the cyclic effect of hormones causes the development of endometriosis, while continuous use stops the development of the disease. Such enigmas stimulates further deepening and expansion of fundamental and clinical research in all areas of the problem of endometriosis.

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THE IMPORTANCE OF STUDYING THE CHANGES IN BONE METABOLISM PARAMETERS IN PRE- AND POSTMENOPAUSAL WOMEN WITH DIABETES

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ABSTRACT

Determine the directionality of changes in serum bone remodeling markers and bone mineral density in pre- and postmenopausal women with this disease. The analysis included 142 women with diabetes as a case group and 43 women, as a control group. The results show that a distinctive feature in the group of patients with type 1 diabetes is a deeper violation of mineral metabolism and bone resorption accelerating with a decrease in the concentration of magnesium and calcium in the blood serum. Changes in bone metabolism in the majority of examining subjects with DM2 are associated with inhibition of bone formation and, to a much lesser extent, bone resorption accelerating during the late pre-menopause and continuing at similar rates in the early years of post-menopause with a decrease in the intensity of bone mass loss in old age. A special feature of bone metabolism in diabetes mellitus against elevated values of the parathyroid hormone is the high activity of bone remodeling with a predominance of bone resorption, as evidenced by the positive correlation between the level of the parathyroid hormone and the biochemical bone resorption marker.
Keywords: diabetes mellitus, postmenopause, bone turnover

Abbreviations:

ALP	alkaline phosphatase
b-CTx	C-terminal telopeptide of type I collagen
BMI	body mass index
BMD	bone mineral density
Ca^{2+}	ionized calcium
CT	calcitonin
DM	diabetes mellitus
DM1	type 1 diabetes mellitus
DM2	type 2 diabetes mellitus
DXA	dual-energy X-ray Absorptiometry
ELISA	enzyme-linked immunosorbent assay
FPG	fasting plasma glucose
GFR	Glomerular filtration rate
HOMA-IR	homeostatic model assessment of insulin resistance
HbA1c	glycosylated hemoglobin
K^{+}	potassium
Mg^{2+}	magnesium
Na^{+}	sodium
P^{+}	inorganic phosphorus
PINP	aminoterminal pro-peptide of procollagen type I
PTH	Parathyroid hormone

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tCa	total calcium
T-score (L1-L4)	lumbar spine area T-score
T-score (Prox.)	proximal femur areaT-score
T-score (FN)	femoral neck areaT-score
25 (OH) D	vitamin D

Introduction

Diabetes mellitus (DM) is a chronic metabolic disease that has an important impact on overall health [1,2]. Diabetes affects over 425 million adults worldwide and is projected to reach 629 million by 2045 [3]. Until recently, the list of target organs affected by diabetes did not include bone tissue. The presence of this disease in anamnesis increases the probability of fractures, predisposing to a higher incidence of falls and decreasing bone mineral density [4]. Postmenopausal remodeling of bone tissue in the older age group of patients is induced or aggravated by diabetes mellitus (DM) leading to an increased risk of femoral neck fracture with DM1 by 12 times and in patients with DM2 up to 2.5 times even those without diabetes [1]. The aim of the study was to determine metabolic bone changes associated with diabetes mellitus in pre- and postmenopausal women. Determination directionality of changes in serum bone remodeling markers and bone mineral density in the pre- and postmenopausal periods in this disease.

Materials and Method

The research was provided according to the principles of the Helsinki Declaration and was approved by the Health Research Ethics Committee of Azerbaijan Medical University. After an explanation of the aim of the study, written informed consent from each participant was received.

A cross-sectional study included 57 women with DM1 and 85 women with DM2 in the pre- and post-menopause who had previously not been diagnosed with osteoporosis. The age of surveyed women is from 40 to 68 years (56.3 ± 0.9 and 57.6 ± 6.2 years). Duration of diabetes: 17.08 ± 0.8 and 8.15 ± 4.6 years, the mean value of HbA1c was 57 ± 0.2 and 58 ± 1.6 mmol/mol, neuropathy and retinopathy were detected in 42% and 88% of patients. The control group comprised of 43 women (55.4 ± 1.2 years) without a history of diabetes.

Exclusion criteria: women who had been treated for osteoporosis or had a history of fracture, and patients with diseases of the endocrine system, liver, and kidneys of the non-diabetic nature, diabetic nephropathy of the 4-5 stage in the anamnesis.

Some subjects' characteristics were prospectively collected: BMI in kg / m2 (25.8 ± 0.3 and 30.2 ± 3.83 kg / m2) was calculated; menopausal status of surveyed women was assessed using the Cooperman index (duration of menopause averaged 13.4 ± 0.8 and 10.7 ± 0.6 years).

Blood samples were drawn before 10-hour a.m.; they were put into heparin for subsequent centrifugation, stored at -70°C, and thawed immediately before serum biomarker and hormonal analyses. Biochemistry panel, including HbA1c, sodium, potassium, magnesium (Mg^{2+}), total calcium (tCa), ionized calcium (Ca^{2+}), phosphate (P^{+}), creatinine, albumin, alkaline phosphatase (ALP), aminoterminal pro-peptide of procollagen type I (PINP), C-terminal telopeptide of type I collagen (beta-CTx) in serum, was measured using on an automatic electro-chemiluminescence analyzer (COBAS C, Roche Diagnostics GmbH Mannheim, Germany). Glomerular filtration rate (GFR) was calculated by CKD-EPI equation: (=141 x min (SCr(mg/dl)/k,1)a x max (SCr/k,1)-1,209 x 0.993 age (x1.018 if female) (in ml/min/1,73 m^2). Commercially available human ELISA

assays of insulin, parathyroid hormone (PTH), calcitonin (CT) and vitamin D (25 (OH) D) were performed according to manufacturer's instructions. Insulin sensitivity was assessed by homeostasis model assessment of insulin resistance (HOMA-IR) using the following equation: (fasting insulin (μU/ml) × fasting glucose (mmol/l) / 22.5).

All subjects underwent DXA on a densitometer (DXA HOLOGIC, Discovery QDR 4500A, USA) for the lumbar spine (L1-L4), proximal femur (Prox.) and femoral neck (FN) areas. WHO criteria for diagnosis of osteoporosis by BMD (T-score ≤ 2.5SD), osteopenia (T-score from -1 to -2.5 SD), and normal (T-score > -1).

The statistical analysis was carried out using STATISTICA 10 program. Data were presented as mean (M) and confidence interval (95% CI) unless specified otherwise. Statistical analysis was done using unpaired parametric data analyzed by Mann—Whitney U test. Spearman's rank correlation was calculated to assess the power of connection between the parameters. A value of p <0.05 was considered statistically significant.

Results

A total of 142 pre- and postmenopausal women with diabetes as a case group and 43 women, without diabetes mellitus, as a control group was recruited in this case-control study. According to the results of the study, in the women's group with DM1 and DM2, the mean value of tCa level with some tendency to lower in comparison with the control group did not significant differences (p >0.05) and corresponded to the age reference range, with the tendency to decrease in postmenopause. Values of Ca^{2+} in the DM1 and DM2 group of patients were significantly lower than the control values (p <0.05); the maximum decrease of Ca^{2+} concentration was observed in the postmenopausal subgroup of patients with DM1 and DM2 (p <0.05). In the control group, the mean P values in the serum in postmenopausal women were significantly lower than in patients with DM1 and DM2 (p <0.05). Clinical parameters of the study groups are illustrated in Table 1.

Table 1. Comparison of the parameters of bone metabolism and the T-score of the DXA with DM1 and DM2 in pre- and postmenopause in comparison with the control group

Groups / Characteristics	T1DM, n=57		T2DM, n=85		Non-DM Controls, n=43	
	T1DM premenop., n=12	T1DM postmenop., n=45	T2DM premenop., n=14	T2DM postmenop., n=71	Controls premenop., n=15	Controls postmenop., n=28
tCa, mg/dL	9,4±0,08 (9,2-9,5)		9,4±0,05 (9,3-9,5)		9,4±0,07 (9,2-9,5)	
	9,4±0,19	9,3±0,08	9,6±0,09	9,4±0,06	9,5±0,16	9,3±0,08
Ca^{2+}, mmol/L	1,06±0,01 (1,03-1,08) [a]		1,06±0,01 (1,03-1,09) [a]		1,1±0,01 (1,07-1,12)	
	1,09±0,02	1,05±0,01[a]	1,07±0,04	1,06±0,01 [b]	1,12±0,02	1,09±0,01
P, mg/dL	5,3±0,14 (5,1-5,6)		4,9±0,10 (4,7-5,1)		5,04±0,13 (4,7-5,3)	
	5,6±0,34	5,3±0,15 [a]	5,1±0,20	4,9±0,12	5,3±0,21	4,8±0,14
PTH, pg/dL	53,99±2,21 (49,5-58,48)		50,18±1,71 (46,74-53,61)		48,3±3,13 (41,8-54,79)	
	42,49±6,24	56,29±2,16 [b]	44,41±2,54	51,31±1,95	42,15±6,69	50,83±3,41
вит. D_3, ng/mL	21,85±1,6 (18,59-25,1) [a]		24,11±1,31 (21,48-26,73)		27,56±2,48 (22,45-32,66)	
	25,34±4,06	20,68±1,64	29,35±5,18	23,17±1,23	29,71±5,06	26,48±2,81
CT, pg/mL	12,54±1,43 (9,61-15,47) [a3]		10,65±0,88 (8,88-12,43) [a]		6,88±0,93 (4,94-8,83)	
	6,1±2,09	14,35±1,57 [ab]	4,9±0,87	11,83±0,94[ab] 2	3,36±1,65	8,43±0,92[b2]

ALP, IU/L	112,5±5,08 (102,35-122,71)		121,0±3,78 (113,5-128,6)		115,6±6,67 (102,1-129,03)	
	109,5±10,62	113,3±5,83	112,5±7,95	122,7±4,24	110,4±9,16	118.3±9,06
PINP, ng/mL	36,69±2,03 (32,61-40,77) [a4]		42,03±1,32 (39,41-44,65) [a]		49,72±3,14 (43,39-56,03)	
	43,59±7,12	34,85±1,71 [a2]	47,1±4,32	41,03±1,31[ab]	53,55±5,44	47,67±3,85
b-CTx, ng/mL	0,563±0,04 (0,477-0,650)		0,511±0,02 (0,460-0,563)		0,483±0,03 (0,420-0,547)	
	0,510±0,09	0,578±0,04	0,457±0,06	0,522±0,02	0,437±0,05	0,508±0,03
T-score (L1-L4)	-2,48±0,2 (-2,8; -2,1) [a3]		-1,26±0,16 (-1,5; -0,9)		-1,37±0,26 (-1,9; -0,8)	
	-2,01±0,39 [a]	-2,61±0,23 [ab2]	-0,80±0,35	-1,35±0,19	-0,81±0,3	-1,67±0,36
T-score (Prox.)	-1,87±0,18 (-2,2; -1,5) [a4]		-1,03±0,16 (-1,3; -0,7)		-0,69±0,21 (-1,1; -0,2)	
	-1,28±0,34	-1,99±0,2 [a3b]	-0,80±0,18	-1,07±0,19	-0,34±0,28	-0,86±0,27
T-score (FN)	-2,01±0,19 [a3] (-2,4; -1,6)		-1,27±0,15 (-1,5; -0,9) [a]		-0,83±0,23 (-1,3; -0,3)	
	-1,52±0,41	-2,11±0,22 [a2]	-0,94±0,28	-1,32±0,17 [a]	-0,53±0,38	-0,99±0,29

[a] - $p<0,05$; [a2] - $p<0,01$; [a3] - $p<0,005$; [a4] - $p<0,001$ compared with the control group data;
[b] - $p<0,05$; [b2] - $p<0,01$ compared with subgroup premenopausal patients;

In the control group, the mean PTH index was lower in comparison with the diabetes group, but did not significantly difference (p <0.05) and in both groups showed a rise in post-menopause. In women with long-term diabetes, the level of PTH was statistically significantly different from that in women with diabetes duration of less than 10 years (p <0.05). There was significant negative correlation between PTH levels and P1NP (r = -0.532, p = 0.001) and also a positive correlation between bone resorption marker b-CTx (r = 0.413, p = 0.002). As a result of the study of patients with DM1 and DM2, a decrease was observed below the reference mean value of vitamin D, statistically significant in comparison with the control group (p <0.05), with a decreasing trend in postmenopause in both groups. In addition, patients in the case group had correlation of Ca2+ level and vitamin D with serum levels of PTH concentration: r = -0.378, p = 0.01 and r = -0.461, p = 0.001. In a control group of postmenopausal women, the serum CT level was statistically significantly lower than in patients with diabetes (p <0.05).

The data obtained as a result of the study show an increase in serum PTH and CT levels along with a decrease in the calcium concentration allows one to assert that there is a violation of the secretion of calcium-regulating hormones and their connection with pathological bone remodeling in type 1 and type 2 diabetes mellitus. It should be noted that with the increase in the disease's duration and in the stage of decompensation, the severity of these changes is increasing.

Patients with DM1 and DM2 showed a decreasing trend in serum bone formation marker PINP levels in 35.5% and 18.3%, with sufficient statistical significance and an increase in the bone resorption marker of b-CTx in 16.6% and 5.8% of patients. At the same time, the values of the bone resorption marker b-CTx did not statistically significantly differ from the values of the subjects from the control group. In the postmenopausal subgroup of patients with DM1 and DM2, the mean b-CTx was slightly higher than in premenopausal women. However, according to the age norm, it did not go beyond the reference values. A part of women with diabetes (20%) showed a decrease in the bone formation marker PINP, against the background of unchanged bone resorption. Data from several authors in studies evaluating bone remodeling indices in diabetes also indicate a decrease in mainly bone formation markers, while bone resorption markers in most studies did not differ statistically from control ones [6].

The P1NP level was negatively correlated with HbA1c (DM1: r = -0.328, p = 0.03; DM2: r = -0.301, p = 0.02). The analysis of the data showed a statistically significant relationship between the duration of DM and the level of b-CTx (DM1: r = 0.349, p = 0.08; DM2: r = 0.214; p = 0.04),

apparently due to hyperglycemia-induced inhibition of osteoblastic function [7]. Also, the dependence of PTH and b-CTx changes in the group of patients with DM1 and DM2 were determined ($r = 0.413$, $p = 0.002$ and $r = 0.507$, $p = 0.001$).

In women with DM1 and DM2, premenopause tended to lower values of b-CTX and P1NP, reflecting a slowdown in bone remodeling compared to the control group women, regardless of age and duration of the disease. In subgroups of postmenopausal women with DM1 and DM2, compared with the control subgroup, predominant decrease in bone formation was observed, indicating that there is an inconsistency observed between bone remodeling processes.

In DM, the number of cases of reduction of BMD in the vertebrae (L1-L4) in women was 75%, in the proximal femur and femoral neck area - 39%. In 83 out of 142 women with diabetes, changes in the T-score were found only in lumbar spine area, in 32 females only in the femur. In 24 cases, a combination of changes in the two regions was determined. Thus, a part of women ($n = 115$) who have detected changes in only one of the studied areas the risk of misdiagnosis rises substantially if only one zone was measured.

In the control group, the number of cases of osteoporosis in the vertebrae (L1-L4) was 14%, in the proximal femur and in the femoral neck areas - 2.3% and 7%. Osteopenia in vertebrae was detected in 23% of women. In the proximal femur area, osteopenia in the control group of women was found in 26%, and in the femoral neck area in 28% of cases.

A negative correlation was observed between T-score of L1-L4 Lumbar spine and duration of diabetes (DM1: $r = -0.568$, $p = 0.001$; DM2: $r = -0.267$, $p = 0.04$). In women with diabetes in postmenopausal women, the decrease in BMD in this area is corresponding to an increase in the disease's duration with concomitant age-related changes. The mean negative correlation was also noted in the subgroup of postmenopausal women (DM1: $r = -0.515$, $p = 0.01$ and DM2: $r = -0.416$, $p = 0.04$). A statistically significant correlation was observed between the T-score of L1-L4 region and b-CTx level (DM1: $r = -0.452$, $p = 0.002$; DM2: $r = -0.357$; $p = 0.09$). This suggests that the presence of diabetes in the history of exacerbation of bone marrow homeostasis, thereby contributing to the development of osteoporosis in the later postmenopausal period.

Discussion

Analysis of data on markers of bone tissue metabolism in women showed a statistically significant relationship between the duration of DM with the level of b-CTx and the T-score measured in the lumbar spine region. This indicates that both bone metabolism markers and DXA are independent factors indicative of changes in bone tissue, which can be of great importance for early diagnosis and evaluation of the effectiveness of the therapy [7,8]. In general, the processes of bone formation and resorption are closely related, and formation markers and resorption markers tend to change in a coordinated manner. The dissociation of these processes observed with diabetes, when the formation markers are reduced, while the resorption markers do not change, may show that the markers of bone metabolism may indicate very specific changes in bone remodeling processes associated with a disruption in the metabolism of carbohydrates in diabetes. It is possible that glucose changes the concentration of markers circulating in the blood, affecting bone metabolism [6,9], which can clinically increase the bone tissue fragility in patients with diabetes.

The study showed that in most patients, altered bone metabolism is associated with inhibition of bone formation and, to a lesser extent, with bone resorption. Osteoporosis is less common in postmenopausal women with diabetes type 2 compared to non-diabetic patients. So, patients with

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type 2 diabetes had lower b-CTx values and relatively higher levels of P1NP, reflecting less pronounced bone metabolism changes compared with patients with type 1 diabetes, regardless of age and duration of the disease. In type 2 DM, a less pronounced increase in the activity of bone resorption biochemical marker was determined than in type 1 DM, while the formation marker did not differ from the values of the control group. In case of type 1 DM, according to the results of biochemical markers of bone remodeling, on the contrary, the inhibition of bone formation processes were determined and the processes of bone tissue resorption were enhanced. This indicates the different directions of the pathogenetic mechanisms of the development of diabetic osteopathy in the early stages of type 1 and type 2 diabetes. This process more pronounced in the late perimenopause and is still high during the early postmenopause with a decreased intensity of bone loss n the late postmenopausal period compared with the healthy women group.

Conclusions

The results of this study indicate that changes in bone metabolism in most of the examined patients are associated with inhibition of osteogenesis and, to a much lesser extent, with bone resorption. The processes of bone resorption accelerate in the late premenopausal period and continue at the same pace in the first years of menopause. However, in the future in postmenopause, there is a decrease in the intensity of bone loss.

This processes are associated with the duration of diabetes, as indicated by the level of b-CTx and T-score of the lumbar spine. The bone resorption marker in patients with type 2 diabetes is lower than in the case of type 1 diabetes.

Disclosures

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$$f(x) = a_0 + \sum_{n=1}^{\infty} \left(a_n \cos \frac{n\pi x}{L} + b_n \sin \frac{n\pi x}{L} \right) \qquad (1)$$

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	Times New Roman, 16 pt, Bold, centred	Times New Roman, 11 pt, Bold, Left aligned	Times New Roman, 10 pt, Bold, Left aligned	Times New Roman, 8 pt, Justified	Garamond, 11 pt, Justified
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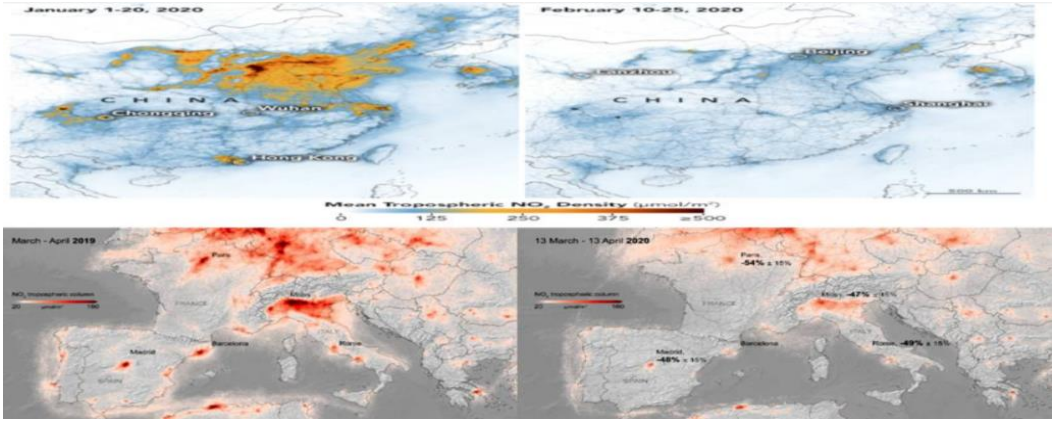

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1. W. S. Author, "Title of paper," Name of Journal in italic, vol. x, no. x, pp. xxx-xxx, Abbrev. Month, year. https://doi.org/10.21467/ajgr
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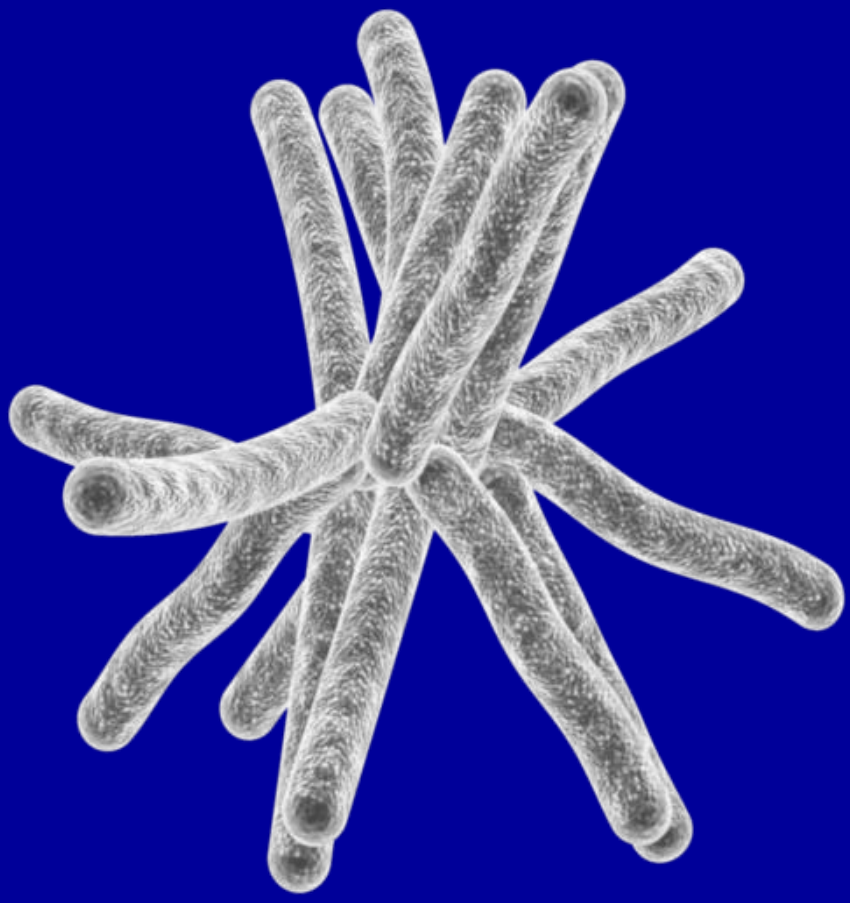

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