

BOTULINIUM TOXIN INJECTION, A POTENTIALLY EFFECTIVE METHOD FOR PREVENTING IMPLANT FAILURE IN PATIENTS WITH BRUXISM

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ABSTRACT

Purpose: Decreasing bone loss around implants is an important factor for implant durability. Pathological forces, such as bruxism, may result in bone loss and eventual implant failure. The aim of this study was to investigate the effect of botulinum toxin injection on biting forces, and its ultimate effect on peri-implant bone changes at different time intervals.

Materials and methods: A randomized clinical trial including 20 females (45-60 years old). All patients received an implant-supported partial denture. Patients were divided into 2 groups: 1. control group (CTR) (no injection), and 2. Botox group (BTX) (injected with botulinum toxin in their masseter muscle). T-scan was used for occlusal analysis (biting force), and was carried out at denture insertion after 2 weeks, 3 months and 6 months of insertion. CBCT was used to detect peri-implant bone changes, and was performed at insertion, 3 months, 6 months and 1 year after insertion. Results were analyzed via two-way (ANOVA) to compare between groups at different time periods, followed by Bonferroni's test post-hoc analysis.

Results: T-scan analysis and CBCT imaging showed that the biting force mean values and the mean crestal bone level changes in the BTX group were significantly lower than that of the control group.

Conclusions: Botox injection in the masseter muscle bilaterally for bruxer patients with edentulous areas would offer them a viable chance for implants as a treatment option.

KEYWORDS: Botulinum Toxin, Peri implant bone changes, Biting force, Bone loss.

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INTRODUCTION

Bruxism is a para-functional condition and causes several pathologic symptoms including inflamed stomatognathic system, tooth wear, myofacial pain, *Temporomandibular disorder (TMD)*, alveolar bone affection and tooth loss.^[1] Heavy occlusal loading caused by bruxism or other para-functional habits falls among the major contraindications for implant placement^[2].

Purified botulinum toxin was the first bacterial toxin used as a medicine. Since its introduction into clinical use, over 30 years ago, it has become a versatile drug in various fields of medicine. The clinical applications of botulinum toxin have been expanding and novel applications developed^[3].

Botox is a known neurotoxin that is derived from the bacterium *Clostridium botulinum*. Its therapeutic applications are variable and well documented^[4-7], alongside its cosmetic applications^[8,9]. There are seven known serotypes of Botox (A to G), however only two types; A and B, are available for medical and cosmetic uses^[10].

In Dentistry, the applications of Botox include treatment of TMJ disorders, Masseteric hypertrophy^[11], gummy smile^[12], mandibular spasm, to name a few. Its effectiveness in the treatment of bruxism and its symptoms including pain and muscle hypertrophy is well-established in many studies^[13,14]. However, Botox (BTX) is contraindicated in certain cases such as, pregnancy or lactation, neuromuscular disorders, allergy to any of the components of BTX-A or BTX-B, infections or inflammations of the injection sites and autoimmune diseases^[15].

Because of its action, partial muscle paralysis induced by BTX injection was related with not only reduced active loading but also an increase in the passive elastic modulus of muscle fiber bundles^[16]. BTX-A injection into masticatory muscles influences mastication by inducing muscle weakness and atrophy, having a direct effect on occlusal force distribution and balance^[17].

Bone healing and remodeling at an implant site is crucial within the first 3 months and if the conditions are favorable the rates of success are high^[18].

T-Scan is an occlusal analysis system used to collect and analyse several characters of the occlusal forces, such as the duration of biting and closing, the maximum occlusal force and distribution of occlusal force. Data is gathered by a special sensor in the system, and is subsequently visualized in special format, providing diagnostic imaging of the biting force distribution, balance and function of the masticatory muscles^[19].

The aim of this study was to evaluate the effect of bilateral botox injection in the masseter muscles, on the distribution of the biting forces in bruxer patients treated with implant-supported partial overdenture, and the subsequent effect on bone changes in peri-implant bone. The null hypothesis in this study was that botox injection would not affect the biting force percentage in bruxer patients, which would in turn would not decrease bone loss around the implants.

MATERIALS AND METHODS

Trial design:

This was a parallel-group, randomized, controlled clinical trial with a 1:1 allocation ratio. The trial was registered at ClinicalTrials.gov with an identifier number: NCT04940104.

Participants, eligibility criteria, and settings:

All steps of this study were approved by the Research Ethics Committee of the Faculty of Dentistry, The British University in Egypt (BUE), approval no. 20-001. All the patients who participated in this study were recruited from the Hospital of The British University in Egypt. Participants were informed about the detailed procedures and multiple radiation exposures; and they signed an informed consent.

The sample size was calculated using G*power 3.1.9.2 Software. Sample size calculation was based

on data obtained from a previous study [20]. The calculated sample size was 10 patients per group for a total of 20 patients. All the patients were females, ranging in age from 45 to 60 years .

The actual sample firstly comprised 24 patients. Four patients dropped out through the experiment. Hence, the number of the analyzed subjects was 10 in both groups. The inclusion and exclusion criteria for the participants were explained in Table 1.

TABLE (1): (original) Inclusion and exclusion criteria for participants

Inclusion criteria	Exclusion Criteria
Patients with partially edentulous mandible (for 1-3 years)	Presence of notable facial asymmetry
Patients with Kennedy Class I configuration who are indicated for rehabilitation with partial mandibular implant-supported overdenture prostheses	Dental pathologies or TMD
Complaining of Bruxism (mild to moderate)	Severe malocclusion
Female patients with the above criteria	Severe tooth wear
Patients ranging in age from 45 to 60	Pregnancy or possible pregnancy
	A history of any serious medical illness,
	A history of hypersensitivity to BTX-A
	Patients who had antispastic or muscle relaxant medication within 1 month of study entry
	Patients with normal biting habits (not bruxers)

Randomization

A computer random sequence table was generated using the random number generator at “random.org” by a person who was not involved in the clinical trial (S*B*). To insure 1:1 allocation ratio, the randomization was made in blocks. Randomized

allocation to BTX or CTR group had taken place before implant insertion to all the recruited patients.

Blinding

The Oral surgeon, outcome assessors (those who performed the T-scan and the CBCT analysis) and the statistician were totally blinded by the nature of the clinical trial. The outcome assessors were not told that half of the patients had received Botox injections.

Intervention

All patients have been partially edentulous for one to three years. A mandibular implant-supported removable partial denture was constructed for all patients using the same techniques of construction prior to implant placement.

Prosthetic procedures

Upper and lower alginate primary impressions (Alginmax, Major Prodotti, Dentari SPA, Moncalieri, Italy) followed by secondary impressions were taken using medium body rubber base (Swiss TEC, Coltene, Whaledent, Altstatten, Switzerland).

The partial overdenture design prescribed for all patients relied on lingual bar major connector, and RPA (mesial occlusal rest, distal proximal plate, Aker arm) clasp assemblies for retention and support.

Mounting of maxillary casts was done on semi-adjustable articulator (Dentatus type ARH, AB, Dentatus, Stockholm, Sweden) according to face bow records taken from each patient, (Dentatus face bow, Dentatus, Stockholm, Sweden) while Wax Wafer records taken at the proper vertical dimension were used to mount the lower casts. Setting up of artificial teeth was carried out in the edentulous mandibular region. The waxed up partial denture was tried in the patient’s mouth, and then flasked and processed into heat-cure acrylic resin (Lucitone 199, Dentsply, York, PA-USA). Laboratory remounting,

on the semi-adjustable articulator, was carried out before finishing the denture. Necessary adjustments were made to eliminate occlusal interferences and the denture was delivered to the patient.

Surgical Procedures

Each patient received two implants (Vitronex Elite, Italy) one on each side of the mandibular arch. The implants were placed parallel to each other and perpendicular to the occlusal plane, in order to facilitate impression taking. All implants were placed by the same oral surgeon, following single stage surgical protocol, using punch and drill.

After implant insertion, ball attachments (Vitronex Elite, Italy) were screwed onto the implants. The mandibular overdenture base was relieved to accommodate the newly inserted attachments and after blocking the attachments undercuts with temporary filling, direct pick-up technique was carried out to incorporate the ball housings into the denture base. Immediate loading protocol was carried out for all implants. All patients of both groups received overdentures following the aforementioned procedures.

Botox injection:

After receiving the overdentures, patients allocated to the two groups, control group (no injections) and BTX group who were injected with Botox (BoNT-A; Allergan®, Parsippany-Troy Hills, NJ) in predetermined 3 injection points in the masseter muscles bilaterally. Injection was done at the time of denture insertion. The front edge and deeper lying parts of the masseter muscles were not injected due to the proximity of the facial nerve, parotid gland, and zygomaticus major muscle.

Botox in the form of a freeze-dried powder was prepared at a concentration of 50 IU/mL (100 IU in 2 mL of sterile saline) and used immediately after preparation. The prepared Botox was injected into

each masseter muscle (bilaterally) at a dose of 30 IU per muscle using a 1-mL syringe with a 29G (1/2-inch) needle. Injections were performed at three points, 1 cm apart, at the center of the lower third of the masseter muscle; where each point was injected with 10U.

Bite force analysis

Both groups had their biting force distribution analyzed using the T-scan system on the day of denture insertion, after 2 weeks, 3 months and 6 months of denture insertion.

Computerized occlusal analysis was conducted using the T-scan system (T-scan® system, Tekscan, Boston, USA) to record and analyze the biting force of each patient. The system used a 100- μ m-thick recording sensor. All scanning procedures were carried out by the same clinician and at the same time of the day to avoid variability. The size of the sensor, large or small, was chosen to suit the patient's dental arch.

Prior to any occlusal acquisition sensitivity of the device was adjusted. The patient was asked to bite on the sensor, and a record for the maximum biting force was taken on the first molar region (key of occlusion). Percentage of force at maximum intercuspation of first molar region was recorded.

Assessment of crestal bone loss

Radiographic Cone Beam Computed Tomography (CBCT) evaluation was carried out for each patient in both groups, to assess bone level changes around implants

For standardization, (Buccal and lingual Crestal bone height) was measured apico-coronally as the vertical distance (in mm) between two reference points predetermined for each patient; the crest of the bone coronally, and the implant apex apically. For accurate measurement and follow-up, the examiner used the same points for measurement each time.

Bone height was measured buccal, lingual, mesial and distal to each implant, and a mean value taken of all readings for each implant. The procedure was repeated to monitor the changes in bone height around each implant at baseline, 3 months, 6 months and 12 months after denture insertion.

Statistical analysis

The data are expressed as the mean ± standard deviation (SD). The results were analyzed via two-way (ANOVA) to compare between groups at different time periods, followed by Bonferroni’s test post-hoc analysis. Unpaired t-test was used to compare between the two groups at the end of the study. All tests and figures were done by GraphPad Prism version 7.00 (GraphPad Software, San Diego, CA). P values < 0.05 were considered statistically significant.

RESULTS

Bite force analysis

Statistical analysis of the mean values of change in the percentage of biting force was done between the control group and BTX group at baseline, the results showed there was no significant difference between the control group and BTX group biting force with mean 42.98 ±5.3 and 42.39 ±5.72, respectively at the beginning of the study p=0.8345 using unpaired t-test.

The change in biting force was statistically evaluated between both groups at 2 weeks, 2 months and 6 months post BTX injection. The statistical analysis showed that the mean changes in the percentage of biting force maximum biting force at the first molarregion was significantly lower in the BTX group after 2 weeks and 3 months post botulinum toxin-A injection (p <0.0001). After 6 months, there was no statistically significant difference between the two groups (Table 2 & Fig.1).

TABLE (2): (original) Mean changes in the percentage of biting force at 2 weeks, 3 and 6 months

	Control (± SD)	BTX (± SD)	p-value
2 weeks	-0.063 (±0.17)	-4.7625 (±0.50)	< 0.0001*
3 months	-0.099 (±0.18)	-4.025 (±0.54)	< 0.0001*
6 months	0.225 (±0.16)	-0.975 (±0.46)	0.0862 ns

* Significant at p < 0.05 vs. control group at the same time interval using two- way ANOVA and Bonferroni’s post hoc analysis, SD; standard deviation. **ns; non-significant

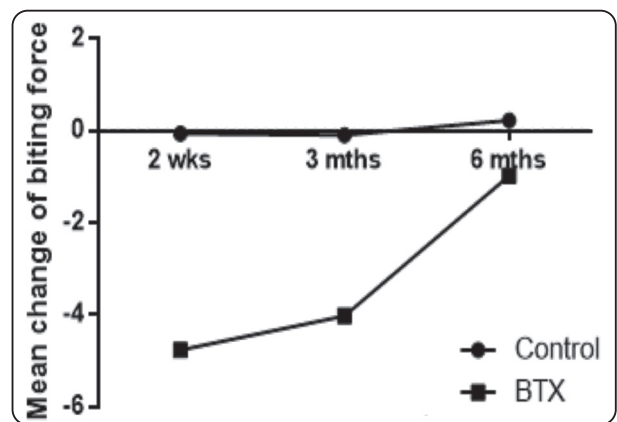


Fig. (1) The mean changes in the percentage of biting force (mean ± SD) in the control and BTX groups at different time intervals

Assessment of Bone level changes

Statistical analysis of crestal bone level changes were done in both control and BTX groups at baseline, 3 months, 6 months and 12 months after surgery, and the mean crestal bone level change was calculated for each group (Table 3).

The crestal bone level changes observed in BTX group were statistically significantly lower than those observed in the control group after three months, with a mean change of 0.379 (± 0.036) versus 0.478 (± 0.017), respectively (p< 0.0001) (Table 3 & Fig. 2).

At 6-month postoperatively, the crestal bone level changes were calculated from 3-6 months and results showed that BTX group had statistically significant lower bone changes than those observed in the control group, with a mean change of 0.370

± 0.034 versus 0.509 ±0.044 (p< 0.0001) (Table 2, Fig 2).

At 12 months, crestal bone level changes were calculated from 6-12 months for both groups. Statistical analysis showed that there was *no significant difference* in crestal bone changes between the BTX and the control group, with a mean change of 0.379 ± 0.043 versus 0.421 ±0.04 respectively (p= 0.763) (Table 3 & Fig. 2).

TABLE (3): (original) Mean values of crestal bone level changes at 3,6 and 12 months.

	Control (± SD)	BTX (± SD)	p-value
Baseline-3 months	0.478 mm (±0.017)	0.379 mm (±0.036)	< 0.0001*
3-6 months	0.509 mm (±0.044)	0.370 mm (±0.034)	< 0.0001*
6-12 months	0.421 mm (±0.04)	0.379 mm (±0.043)	0.0763

* Significant at p < 0.05 vs. control group at the same time interval using two- way ANOVA and Bonferroni's post hoc analysis, SD; standard deviation.

* p < 0.05 vs. control group at the same time interval. # p < 0.05 vs. respective group at different time intervals using two- way ANOVA and Bonferroni's post hoc analysis. Results are shown as mean ± SD, n=10 patient per group

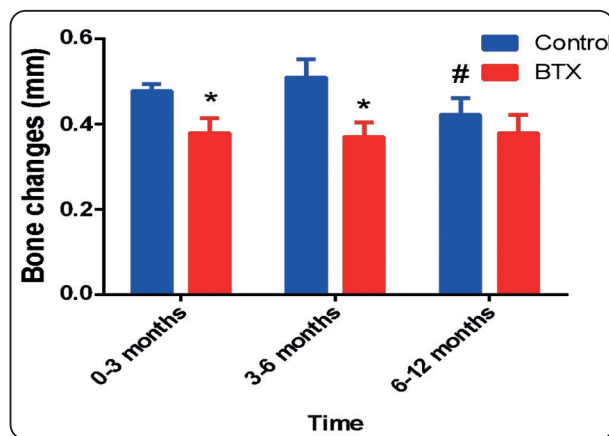


Fig. (2) Crestal bone changes (mm) in the control and BTX groups at 0-3, 3-6 and 6-12 month post-operatively.

DISCUSSION

This study investigated the effect of botulinum toxin injection on biting forces, and its ultimate effect on peri-implant bone changes in bruxism patients. Our results proved that the biting forces were decreased dramatically after botox injection leading to protection of peri-implant bone level and subsequently higher success rate for the implant prosthesis.

Bruxism is a motor activity of rhythmic teeth grinding that involves eccentric/lateral loads, which is supposed to have the potential for causing damage to the stomatognathic structures causing complications like masseter muscle hypertrophy and temporomandibular joint destruction [2,21,22]. It is also considered to be a risk factor for dental implants survival [22-25].

The applications of Botox in the dental field were proven to significantly reduce the masticatory function; and therefore, decrease the symptoms of bruxism (including masseter muscle hypertrophy [11] in multiple previous studies.[13,26-36]

Computerized occlusion analysis system (T-scan) was used for assessing the changes in biting force in this study as it is an objective clinical method that is both sensitive and accurate [19].

CBCT scan was used in this study for its well-proven diagnostic accuracy in assessing marginal bone loss and bone defects around implants, besides, its reliability, reproducibility and non-invasive nature that are verified to be superior to intraoral imaging. It also provides 3D evaluation compared to intraoral imaging, and less radiation dose compared to CT. [37-39]

The patients in this study were all chosen of the same gender (females), as the bite forces vary significantly between genders; male subjects generally have a larger bite force than female subjects [40].

Botulinum toxin type-A inhibits the exocytosis of acetylcholine on cholinergic nerve endings of motor nerves. The toxin binds to the nerve, is internalized within the nerve and inhibits the exocytosis of the neurotransmitter acetylcholine into the neuromuscular junction. This weakens the muscle for a period of three to four months^[41-43]. Injections of a small amount of this toxin into a muscle produces atrophy and weakness within 1-20 days and recovers over 2-4 months as new terminal axons sprout and restore transmission.^[44] The dosage of botox used in this study is the common generally applied dose of botulinum toxin A to inject the masseter muscle in several studies (25U -30 U).^[11,45-48]

In the current study, the effect of injection of BTX into the masseter bilaterally on the biting force at the first molar region was studied. The percentage of change in biting force was recorded via T-scan at 2, 3, and 6 months of injection with botox.

Changes in bite forces were evaluated at a specific region in the arch, which is the first molar region, as the magnitude of the forces varies between different areas in the mouth. It has been reported that the maximum bite force applied to a molar is several times stronger than that applied to an incisor^[49]. 17 (19) It was reported that the maximum bite force applied to the first molar ranged from 91 to 198 pounds (41.3 to 89.8 kg/cm²), whereas the maximum force applied to the central incisors ranged from 29 to 51 pounds (13.2 to 23.1 kg/cm²)^[49]. The first molar region was rather chosen in this study as it is the closer to the site of the applied implants; besides the strategic importance of the first molar in occlusion and occlusal forces^[50].

Results of the current study showed a significant difference in the changes in biting force between BTX group and control group at 2 and 3 months of injection, while the difference at 6-months was statistically insignificant between the two groups. This indicates that the biting force percentage at the

first molar region had decreased significantly in the BTX group two weeks after Botox injection, with a gradual recovery, almost returning to pre-injection level after 6 months. This was supported by previous studies, which claimed that the masticatory function drastically declined, by up to 20-40% after injecting the masseter muscle with Botox^[11,35,48]. Due to the reduction in the power of muscular voluntary contraction and masseteric function^[35,50].

The main effect of botulinum toxin type A is the temporary effect of muscle atrophy, followed by chemo denervation caused by an acetylcholine blockade at the neuromuscular junction by the toxin which blocks the release of calcium ions.^[43]

It was declared in some studies that when botulinum toxin was injected into the masticatory muscles, atrophy of muscle fibers began to appear between 1 and 3 days, and the most atrophy appeared in 1-4 weeks, and then it was followed by slowly recovering muscles to normal size after 3-4 months^[50]. Botox Doses from 25-50 U showed recovery within 12-24 weeks, while lower doses 15-50 U produced effects that lasted for 8-12 weeks, only one study injected 30 U in the masseter and lasted for 24 weeks.^[13]

The success of implant rehabilitation relies on the integration of the implants in hard and soft tissues. Marginal bone loss (MBL) is, therefore, a critical factor affecting the clinical outcome. Most studies proposed bone loss around an implant of less 1-1.5 mm in the first year of service, followed by 0.2 mm or less annually as criteria for implant success.^[39]

Results of the current study showed that the bone changes that occurred in the BTX study group were significantly less than the control group, particularly in the first 6 months. This proves that botox injection in the masseter muscles had a significant effect in decreasing bone loss around implants.^[43]

Based on the above argument, the mean bone changes revealed in this study by the BTX group at the first 6 months of implant placement (0.37 mm)

is considered a great success of the botox treatment, especially that the difference from the control group is statistically significant. This could be attributed to the decrease in biting forces as a direct result of injecting the masseter muscle with Botox.

Early implant loading disrupts the osteogenic ability of bone that could replace bone necrosis caused by surgical trauma, resulting in bone absorption at the time of wound healing particularly the oblique or horizontal forces from bruxism are more harmful than vertical loads. If the osseointegration was insufficient at this critical period, the implant is early lost even before the first prosthetic loading.^[18]

On the other hand, other studies failed to relate bruxism directly to implant complications or failure, and claimed that the process (i.e. implant failure) is rather multifactorial and depends on several combined with bruxism (e.g. surgical trauma, peri-implantitis, implant crest module, etc..). Therefore, many researchers consider bruxism as an exclusion criterion for the selection of their participants in clinical studies concerning treatment modalities with dental implants.^[2]

However, in the case of immediate loading implants, the use of botulinum toxin can be considered a method of controlling the potential occlusion load.

Several reports have found it to be safe and effective in the prophylactic reduction of masseter and temporalis muscle strength after implantation in immediate loading protocols in patients with bruxism.

The radiographic analysis of this current study showed that the bone changes that occurred in the BTX study group were significantly less than the control group, particularly in the first 6 months. This could be attributed to the decrease in biting forces as a direct result of injecting the masseter muscle with Botox. However, at 12 months after injection, there was no significant difference in crestal bone change

between the botox group and control group.

Botulinum toxin was proven to weaken the muscle; and hence, it improves postoperative recovery and healing.^[3] Wound healing was found to be improved if the muscles involved are injected with Botulinum toxin prior to surgery. The effect can provide some protective role on dental implant especially in patients with bruxism undergoing full-arch rehabilitation using immediately loaded dental implants^[22].

The effect of botox injection in the present study was temporary, where there was a gradual recovery in the bite force that reached the normal pre-injection level after 6 months of injection, and the changes in crestal bone levels after 1 year were insignificant compared to the control group.

Computerised occlusion analysis system is both sensitive and accurate, yet it still has some limitations. Clinical objective and subjective variables should be combined to comprehensively evaluate further the therapeutic efficacy of injection of BTX-A into the masseter muscle for patients with bruxism. Further studies and clinical studies with a longer follow-up period are required to determine the definitive duration period for masticatory forces to recover.

CONCLUSIONS

Within the limitations of this study, the following could be concluded

- 1- Injecting partially edentulous bruxer patients with Botulinum Toxin (Botox-A) has decreased the percentage of their biting force temporarily, and this resulted in a decrease in the overall bone changes around their placed implants, supporting partial overdentures.
- 2- Bilateral Botox (Botox-A) injection into masseter muscle (bilaterally), for bruxer patients with edentulous areas, would offer them a viable chance for implants as a treatment option.

REFERENCES

1. Mengatto CM, Coelho-de-Souza FH, de Souza Junior OB. Sleep bruxism: challenges and restorative solutions. *Clinical, cosmetic and investigational dentistry* 2016;8:71.
2. Lobbezoo F, Brouwers J, Cune MS, Naeije M. Dental implants in patients with bruxing habits. *Journal of oral rehabilitation* 2006;33(2):152–9.
3. Majid OW. Clinical use of botulinum toxins in oral and maxillofacial surgery. *International journal of oral and maxillofacial surgery* 2010;39(3):197–207.
4. Persaud R, Garas G, Silva S, Stamatoglou C, Chatrath P, Patel K. An evidence-based review of botulinum toxin (Botox) applications in non-cosmetic head and neck conditions. *JRSM short reports* 2013;4(2):1–9.
5. Kim S-Y, Kim Y-K, Yun P-Y, Bae J-H. Treatment of non-odontogenic orofacial pain using botulinum toxin-A: a retrospective case series study. *Maxillofacial plastic and reconstructive surgery* 2018;40(1):1–5.
6. Kwon K-H, Shin KS, Yeon SH, Kwon DG. Application of botulinum toxin in maxillofacial field: part I. Bruxism and square jaw. *Maxillofacial plastic and reconstructive surgery* 2019;41(1):1–13.
7. Watson NA, Siddiqui Z, Miller BJ, Karagama Y, Gibbins N. Non-aesthetic uses of botulinum toxin in the head and neck. *European Archives of Oto-Rhino-Laryngology* 2021;1–8.
8. Cavallini M, Cirillo P, Fundarò SP, Quartucci S, Sciuto C, Sito G, et al. Safety of botulinum toxin A in aesthetic treatments: a systematic review of clinical studies. *Dermatologic Surgery* 2014;40(5):525–36.
9. Satriyasa BK. Botulinum toxin (Botox) A for reducing the appearance of facial wrinkles: a literature review of clinical use and pharmacological aspect. *Clinical, cosmetic and investigational dermatology* 2019;12:223.
10. Raghavan R, Shajahan PA, Bos R. BOTOX AND ITS ROLE IN PROSTHODONTICS. *Guident* 2015;9(1).
11. Ahn KY, Kim ST. The change of maximum bite force after botulinum toxin type A injection for treating masseteric hypertrophy. *Plastic and Reconstructive Surgery* [Internet] 2007 [cited 2021 Nov 13];120(6):1662–6. Available from: https://journals.lww.com/plasreconsurg/Fulltext/2007/11000/The_Change_of_Maximum_Bite_Force_after_Botulinum.32.aspx
12. Mazzuco R, Hessel D. Gummy smile and botulinum toxin: a new approach based on the gingival exposure area. *Journal of the American Academy of Dermatology* 2010;63(6):1042–51.
13. Lee SJ, McCall Jr WD, Kim YK, Chung SC, Chung JW. Effect of botulinum toxin injection on nocturnal bruxism: a randomized controlled trial. *American journal of physical medicine & rehabilitation* 2010;89(1):16–23.
14. Fernández-Núñez T, Amghar-Maach S, Gay-Escoda C. Efficacy of botulinum toxin in the treatment of bruxism: Systematic review. *Medicina oral, patología oral y cirugía bucal* 2019;24(4):e416.
15. Witmanowski H, Błochowiak K. The whole truth about botulinum toxin—a review. *Advances in Dermatology and Allergology/Postępy Dermatologii i Alergologii* 2020;37(6):853.
16. Hong SW, Kang J-H. Decreased mandibular cortical bone quality after botulinum toxin injections in masticatory muscles in female adults. *Scientific reports* 2020;10(1):1–12.
17. Song JH, Cho ES, Kim ST, Ahn HJ. Change of distribution and timing of bite force after botulinum toxin type A injection evaluated by a computerized occlusion analysis system. *Yonsei medical journal* 2014;55(4):1123–9.
18. Irandoust S, Müftü S. The interplay between bone healing and remodeling around dental implants. *Scientific reports* 2020;10(1):1–10.
19. Zhang L, Liu Q, Zou D, Yu L. Occlusal force characteristics of masseteric muscles after intramuscular injection of botulinum toxin A (BTX-A) for treatment of temporomandibular disorder. *British Journal of Oral and Maxillofacial Surgery* 2016;54(7):736–40.
20. Lee H-J, Kim S-J, Lee K-J, Yu H-S, Baik H-S. Repeated injections of botulinum toxin into the masseter muscle induce bony changes in human adults: A longitudinal study. *The Korean Journal of Orthodontics* 2017;47(4):222–8.
21. Manfredini D, Lobbezoo F. Relationship between bruxism and temporomandibular disorders: a systematic review of literature from 1998 to 2008. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology* 2010;109(6):e26–50.
22. Mijiritsky E, Mortellaro C, Rudberg O, Fahn M, Basegmez C, Levin L. Botulinum Toxin Type A as Preoperative Treatment for Immediately Loaded Dental Implants Placed in Fresh Extraction Sockets for Full-Arch Restoration of Patients With Bruxism. *The Journal of craniofacial surgery* 2016;27(3):668–70.
23. Misch CE, Suzuki JB, Misch-Dietsh FM, Bidez MW. A positive correlation between occlusal trauma and peri-implant bone loss: literature support. *Implant dentistry* 2005;14(2):108–16.
24. Klineberg I, Kingston D, Murray G. The bases for using

- a particular occlusal design in tooth and implant-borne reconstructions and complete dentures. *Clinical oral implants research* 2007;18:151–67.
25. Gross MD. Occlusion in implant dentistry. A review of the literature of prosthetic determinants and current concepts. *Australian dental journal* 2008;53:S60–8.
 26. van Zandijcke M, Marchau M. Treatment of bruxism with botulinum toxin. *J Neurol Neurosurg Psychiatry* 1990; 53:530.
 27. Ivanhoe CB, Lai JM, Francisco GE. Bruxism after brain injury: successful treatment with botulinum toxin-A. *Archives of physical medicine and rehabilitation* 1997;78(11):1272–3.
 28. Watts MW, Tan E-K, Jankovic J. Bruxism and cranial-cervical dystonia: is there a relationship? *CRANIO®* 1999;17(3):196–201.
 29. Tan E-K, Jankovic J. Treating severe bruxism with botulinum toxin. *The Journal of the American Dental Association* 2000;131(2):211–6.
 30. Pidcock FS, Wise JM, Christensen JR. Treatment of severe post-traumatic bruxism with botulinum toxin-A: case report. *Journal of oral and maxillofacial surgery* 2002;60(1):115–7.
 31. See S, Tan E. Severe amphetamine-induced bruxism: treatment with botulinum toxin. *Acta neurologica scandinavica* 2003;107(2):161–3.
 32. Nash MC, Ferrell RB, Lombardo MA, Williams RB. Treatment of bruxism in Huntington's disease with botulinum toxin. *The Journal of neuropsychiatry and clinical neurosciences* 2004;16(3):381-a.
 33. Monroy PG, da Fonseca MA. The use of botulinum toxin-a in the treatment of severe bruxism in a patient with autism: a case report. *Special Care in Dentistry* 2006;26(1):37–9.
 34. Guarda-Nardini L, Manfredini D, Salamone M, Salmaso L, Tonello S, Ferronato G. Efficacy of botulinum toxin in treating myofascial pain in bruxers: a controlled placebo pilot study. *CRANIO®* 2008;26(2):126–35.
 35. Park HU, Kim BI, Kang SM, Kim ST, Choi JH, Ahn HJ. Changes in masticatory function after injection of botulinum toxin type A to masticatory muscles. *Journal of oral rehabilitation* 2013;40(12):916–22.
 36. Al-Wayli H. Treatment of chronic pain associated with nocturnal bruxism with botulinum toxin. A prospective and randomized clinical study. *Journal of clinical and experimental dentistry* 2017;9(1):e112.
 37. Naveau A, Shinmyozu K, Moore C, Avivi-Arber L, Jakerst J, Koka S. Etiology and measurement of peri-implant crestal bone loss (CBL). *Journal of clinical medicine* 2019;8(2):166.
 38. Nahai F, Lorenc ZP, Kenkel JM, Fagien S, Hirmand H, Nestor MS, et al. A review of onabotulinumtoxinA (Botox). *Aesthetic surgery journal* 2013;33(1_Supplement):9S-12S.
 39. Pour DG, Romozi E, Shayesteh YS. Accuracy of cone beam computed tomography for detection of bone loss. *Journal of Dentistry (Tehran, Iran)* 2015;12(7):513.
 40. Brekhuis PJ, Armstrong WD, Simon WJ. Stimulation of the muscles of mastication. *Journal of Dental Research* 1941;20(2):87–92.
 41. Aoki KR. Evidence for antinociceptive activity of botulinum toxin type A in pain management. *Headache: The Journal of Head and Face Pain* 2003;43:9–15.
 42. Nayyar P, Kumar P, Nayyar PV, Singh A. Botox: broadening the horizon of dentistry. *Journal of clinical and diagnostic research: JCDR* 2014;8(12):ZE25.
 43. Vigarniya MM, Rathee M. Therapeutic Application Of Botox For Treating Maxillofacial Disorders. *Guident* 2017;11(1).
 44. Dolly O. Synaptic transmission: inhibition of neurotransmitter release by botulinum toxins. *Headache: The Journal of Head and Face Pain* 2003;43:16–24.
 45. Mandel L, Tharakan M. Treatment of unilateral masseteric hypertrophy with botulinum toxin: case report. *Journal of oral and maxillofacial surgery* 1999;57(8):1017–9.
 46. To EWH, Ho WS, Wong WK, Pang PCW, Ahuja AT, Hui ACF, et al. A prospective study of the effect of botulinum toxin A on masseteric muscle hypertrophy with ultrasonographic and electromyographic measurement. *British journal of plastic surgery* 2001;54(3):197–200.
 47. von Lindern JJ, Niederhagen B, Appel T, Bergé S, Reich RH. Type A botulinum toxin for the treatment of hypertrophy of the masseter and temporal muscles: an alternative treatment. *Plastic and reconstructive surgery* 2001;107(2):327–32.
 48. Kwon K-H, Shin KS, Yeon SH, Kwon DG. Application of botulinum toxin in maxillofacial field: Part III. Ancillary treatment for maxillofacial surgery and summary. *Maxillofacial plastic and reconstructive surgery* 2019; 41(1):1–9.
 49. Howell AH, Manly RS. An electronic strain gauge for measuring oral forces. *Journal of dental research* 1948;27(6):705–12.
 50. Angle EH. Treatment of malocclusion of the teeth and fractures of the maxillae. *Angle's system* 1907; 21–4.