

# INTRA-ARTICULAR REGENERATIVE INJECTION FOR MANAGEMENT OF PAINFUL IRREDUCIBLE TEMPOROMANDIBULAR DISC DISPLACEMENT

Mariam M. Bahgat <sup>1\*</sup> M. Sc, Nadia R. El-Helw <sup>2</sup> Ph.D, Ahmed M. Abdelhamid <sup>2</sup> Ph.D, Mohamed M. Fata<sup>3</sup> Ph.D, Medhat S. Ashour <sup>4</sup> Ph.D , Aly M. Atteya<sup>5</sup> Ph.D

## ABSTRACT

**INTRODUCTION:** Nearly all of non-dental related chronic orofacial pain problems are temporomandibular disorders (TMDs). TMDs are associated with joint pain, sounds and limitation of mandibular movements. Although TMDs are not life threatening conditions; nevertheless they negatively affect the patients' quality of life making the treatment necessary.

**OBJECTIVE:** To assess the effect of intra-articular injection of liquid phase concentrated growth factors (LPCGF), in patients with restricted mouth opening associated with irreducible disc displacement (DDwR).

**METHODOLOGY:** 12 patients with DDwR and limited mouth opening were enrolled in the study. Patients received an intra-articular injection of 2ml LPCGF with a 3D printed stabilization appliance (SA). The patients' symptoms were assessed clinically through Helkimo Anamnestic dysfunction index (Ai) and the maximum mouth opening (MMO) was measured at baseline as well as 1 week, 4 weeks, and 12 weeks post-treatment.

**RESULTS:** There was a significant relief in symptoms at the 4, and 12 weeks follow-up periods ( $p = 0.001$ ,  $p < 0.001$  respectively). The mean of MMO at the baseline was 31.75 mm, while 1 week after the injection it was significantly increased to 33.50 mm ( $p < 0.001$ ). Moreover, by 12 weeks, the MMO was significantly improved ( $p < 0.001$ ).

**Conclusion:** Intra-articular injection of LPCGF and SA could be considered a management protocol for patients suffering from DDwR as it relieved TMD symptoms and increased the MMO.

**KEYWORDS:** Temporomandibular disorders, Internal derangement, Growth Factors, Regenerative injection, Maximum mouth opening.

**RUNNING TITLE:** Regenerative injection for management of temporomandibular disc displacement.

1. Assistant Lecturer of Prosthodontics, Faculty of Dentistry, Alexandria University.
2. Professor of Prosthodontics, Faculty of Dentistry, Alexandria University.
3. Professor of Maxillofacial and Plastic Surgery, Faculty of Dentistry, Alexandria University.
4. Professor of Professor of Microbiology, High Institute of Public Health, Alexandria University.
5. Lecturer of Maxillofacial and Plastic Surgery, Faculty of Dentistry, Alexandria University.

**\*Corresponding author:**

[mariam.amin@alexu.edu.eg](mailto:mariam.amin@alexu.edu.eg)

## INTRODUCTION

Nearly all of non-dental related chronic orofacial pain problems are temporomandibular disorders (TMDs). TMDs comprise clinical disorders of temporomandibular joints (TMJ) and related musculature. TMDs are associated with joint sounds, pain and limitation of mandibular movements. Although TMDs are not life threatening conditions; nevertheless they negatively impact the patients' quality of life making the treatment mandatory. TMDs fall into three main categories; myofascial pain involving discomfort or pain in the muscles, joint internal derangement (ID) where the disc is displaced, and arthritis. ID is the major finding in TMD where the smooth joint functions are impaired (1).

Irreducible disc displacement (DDwR) is one of the subtypes of ID, where the disc is

displaced anterior to the condyle in the closed as well as the open-mouth positions resulting in interference in mandibular movements. TMJ pain as well limitation in mouth opening (MMO) is common signs and symptoms associated with DDwR (2).

Recognizing the signs and symptoms related to DDwR with its pathogenesis, the treatment of this disorder becomes essential. Several treatment approaches have been proposed from conservative modalities to surgical ones which proved their effectiveness in management of ID (3-9). However, conservative as well as minimally invasive treatment protocols as physical therapy, pharmacotherapy, occlusal appliances, intra-articular injections or combination of these treatments should be applied before any surgical interventions (6-9).

Among the various designs of occlusal appliances, hard stabilization appliance (SA) is proved to be effective (10-12) in treating joint pain associated with TMDs. Furthermore, several methods (13-18) have been suggested for the fabrication of SA including conventional methods to the use of computer aided designed and manufactured (CAD/CAM) ones.

The injection of autologous blood or its derivatives as platelet concentrates (PC) including platelet-rich plasma (PRP), platelet-rich fibrin (PRF), and plasma rich in growth factors has gained attention in the dental field. The theory of PC is related to the in situ release of growth factors which promote a revolution in regenerative medicine (19).

In 2021, Hamed et al. (20) published a systematic review and meta-analysis analyzing the available researches addressing the usefulness of PCs in pain reduction and MMO scores in patients with ID. They stated that PC reduces pain as well as increases MMO.

PC prepared through the centrifugation of a blood sample contains various growth factors with anti-inflammatory effects and healing enhancing properties; hence, stimulate cell proliferation and tissue repair (21-26).

The first generations of PC are PRP and plasma rich in growth factors (27, 28) which require chemical additives as calcium chloride and thrombin to be prepared. In 2000, Choukroun (29) introduced the next generation of PC, the PRF. PRF is produced by collecting a venous blood sample without adding anticoagulant in tubes then immediately centrifuged at a fixed speed for 10 minutes.

In 2006, Sacco (30) reported concentrated growth factor (CGF), a new generation of PC. CGF is produced through the centrifugation of blood with no additive and with alternating centrifugation speeds for 12 minutes resulting in a PC richer in growth factors than common PRF.

Several studies (21- 26) have described the intra-articular injection of PC for management of TMDs over years. However, limited studies investigated the effectiveness of the LPGCF, the latest generation of PC, introduced by Sacco. This purpose of our clinical trial is to assess the role of intra-articular injection of LPCGF in patients with limited mouth opening associated with DDwR.

## MATERIALS AND METHODS

### Ethical Considerations

This prospective clinical trial has received approval from the Research Ethics Committee, Faculty of Dentistry, Alexandria University, Egypt (international No.: IORG0008839, ethics committee number: 0128-04/2020). Signed consent were obtained prior to enrollment in this trial.

### Patients' Selection

This study was done at the Department of Prosthodontics, Faculty of Dentistry, Alexandria University. All patients enrolled had pain in the TMJ region. The criteria for inclusion were: (1) limited mouth opening (MMO <40mm); (2) irreducible disc displacement detected by MRI; (3) age between 20 and 40 years old; (4) presence of complete or nearly complete set of natural dentition; (5) Angle class I occlusion. Subjects were excluded if they had: (1) anterior disc displacement with reduction confirmed by MRI; (2) inability or unwillingness to undergo magnetic resonance imaging (MRI) (e.g. implanted electronic devices); (3) uncontrolled systemic disease, hematologic or neurologic disorders or inflammatory diseases; (4) ongoing anticoagulant drug therapy; (5) RCP greater than 2mm, and (6) open bite.

Patients were selected with the above mentioned strict selection criteria, and examined clinically through the Diagnostic Criteria for Temporomandibular Disorders (DC/TMDs) (31) criteria. Only 12 patients diagnosed as DC/TMDs Axis I group II.b indicating DDwR and confirmed by MRI were enrolled in this clinical trial. (Figure.1)

### Treatment protocol

Patients received an injection of 2 mL LPCGF in the superior joint space, under local anesthesia. In addition, the patients received a maxillary CAD/CAM hard clear SA (Figure.2) where they were instructed to wear the appliance only at night for the entire treatment period. The LPCGF was prepared from 10 ml the patient's venous blood drawn in plain vacutainers with no additives (Figure.3). Centrifugation of the tubes was done at alternating speeds for 12 minutes as was suggested by Sacco. (Figure.4)

### Intra-articular injection technique

After auriculotemporal nerve block was given; ultrasound- guided injection procedure was done using Murakami method (32). Using an 18- gauge needle in the superior joint space; the extracted 2mL of LPCGF was injected. (Figure.5)

### Assessments

#### Helkimo Anamnestic Index (Ai)

TMD symptoms were evaluated using Helkimo Anamnestic index (Ai) (33) before any treatment as well as after 1 week, 1month, and 3months from treatment.

#### Maximum Mouth Opening (MMO)

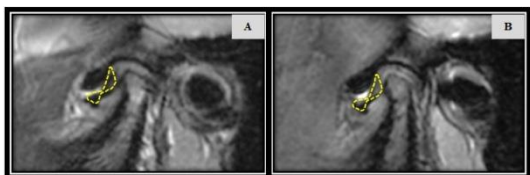
Assisted MMO was measured prior to any treatment as well as after 1 week, 1, 1month, and 3months from intervention. It was measured as follows: the tip of a ruler was placed against the mesio-distal center of the incisal edge of the mandibular left central incisor, and the distance to the mesio-distal center of the incisal edge of the maxillary left central incisor was read "unassisted

MMO” then the thumb and index fingers were placed in a scissors-position to open the mouth further if possible “assisted MMO”. The assisted MMO was then read and recorded. (31)

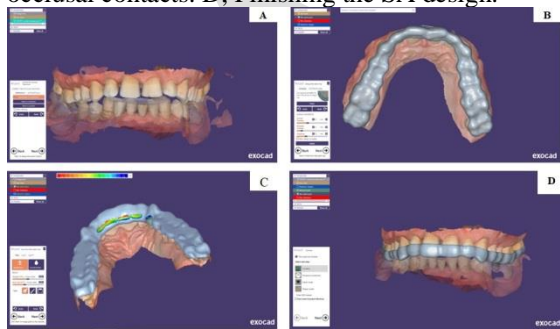
#### Statistical analysis

Collected data were analyzed statistically using SPSS software package version 20.0. (Armonk, NY: IBM Corp) (34). Qualitative data were represented using numbers and percentage (%). As for quantitative variables, mean  $\pm$  standard deviation were used. Verification of the normality of distribution of the variables was done using the Shapiro-Wilk test. For normally distributed quantitative data, ANOVA with repeated measures test was used, while for abnormally distributed quantitative variables, Friedman test was applied. Significant level was set at 0.05.

**Figure 1:** Oblique sagittal PD MRI sequence showing: A. anterior disc displacement in closed mouth position. B. in open mouth position where the articular disc is still anteriorly displaced confirming DDwR. (articular disc outlined in yellow).



**Figure 2:** Design of SA on software. A, Uploading jaw scan. B, Adjusting splint top. C, Adjusting occlusal contacts. D, Finishing the SA design.



**Figure 3:** Showing blood sample in vacutainer.



**Figure 4:** Showing collected blood sample in the centrifuge.



**Figure 5:** The injection of the prepared 2 ml of LPCGF in the superior joint space.



**Figure 6:** Change in Helkimo Anamnestic index (Ai) in through the follow-up periods.

## RESULTS

### Helkimo Anamnestic Index (Ai)

All patients at the baseline assessment were recorded as AiIII representing a severe condition. At the first follow-up period, after receiving SA in conjugation with LPCGF, there was an insignificant difference. However, at 1 month, and 3 months, there was a significant relief in TMD symptoms. Complete remission of TMD symptoms was manifested in 11 patients and graded as Ai0, while one patient was graded as AiI showing a mild condition. (Figure. 6)

### Maximum Mouth Opening (MMO)

The mean of MMO at the baseline was 31.75 mm, while 1 week after the injection it was significantly improved to be 33.50 mm. Furthermore, a significant positive effect was found by 1 month, and 3 months. (Table 1)

**Table 1:** Comparison between the different studied periods according to Maximum Mouth Opening (MMO)

MMO (mm)	Pre	1week	1month	3months	p
Min. - Max.	28.0 - 37.0	30.0 - 40.0	32.0 - 42.0	35.0 - 43.0	<0.001*
Mean ± SD.	31.75 ± 4.0	33.50 ± 3.78	35.50 ± 3.42	37.50 ± 2.54	
p <sub>0</sub>		<0.001*	<0.001*	<0.001*	
p <sub>1</sub>			<0.001*	<0.001*	
Sig. bet. periods			p <sub>2</sub> <0.001*		

F: F test (ANOVA) with repeated measures, Sig. bet. periods was done using Post Hoc Test (adjusted Bonferroni)

p: p value for comparing between the different studied periods

p<sub>0</sub>: p value for comparing between Pre and each other periods

p<sub>1</sub>: p value for comparing between 1week and each other periods

p<sub>2</sub>: p value for comparing between 1month and 3months

## DISCUSSION

TMDs encompass problems related to the TMJ and related musculoskeletal structures. The Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMDs) categorizes TMDs into 3 main categories which are muscle disorders, ID and osteoarthritis. (2)

Regarding ID, the most common type is the reducible disc displacement. However, DDwR presents a more challengeable disorder; specifically the type presented with limited mouth opening which negatively impacts the patients' quality of life. In DDwR, the disc has been displaced anterior to the condyle in the closed as well as the open-mouth positions which affects the mandibular range of motion (1, 2, 31).

The goals for treating patients with DDwR should not only be the relief of TMJ pain and dysfunction but also the prevention of disease aggravation.

Regenerative injection therapy is an injection of growth factors or an injection of a substance that induces the body to produce growth factors that initiate signaling cascades promoting the growth of normal cells and tissue repair (19).

As a little insight is found on the use of LPCGF as a form of regenerative injection for patients with DDwR, it was of essence to further investigate its effectiveness in the management of these patients. This clinical trial was designed to assess the effectiveness of LPCGF injection as a minimally invasive treatment modality for patients with limited mouth opening associated with painful DDwR.

For this purpose, 12 patients were selected from those who met the strictly identified selection criteria. All patients enrolled in this clinical trial had a painful TMJ locking with mouth opening less than 40 mm indicating DDwR. (1, 2, 31). Thorough diagnosis was done according to the DC/TMDs for its diagnostic reliability and validity (31).

Severity of the symptoms was assessed clinically at pre-intervention as well as 1 week, 4 weeks, and 12 weeks after the treatment using the Ai due to its simplicity and reliability (33).

Furthermore, MMO was noted at the same time intervals.

By assessing the data of Ai, a significant relief of TMD symptoms was noted. In addition, the patients reported pain-free mouth opening. These findings go in accordance with Yang et al. (35), Al-Delayme et al. (36), Torul et al. (37), and Giacomello et al. (38) who described similar effects of PC derivatives on TMD symptoms and MMO.

The improvement in the clinical parameters may be due to that intra-articular regenerative injection into the joint spaces improves the joint micro-environment leading to the relief of the TMD symptoms in a short period as well as prevention of further progression of the ID condition. Moreover, regenerative injections inhibit inflammatory biomarkers, produce more collagen fibrils, increase the joint space, and improve the joint mobility range owing to the in situ growth factors (19,35-38).

Furthermore, the increase in MMO could be attributed to the relief of pain, the regain of the elasticity within the articular disc that makes it foldable not interfering with the condylar translation besides the added positive effects of the SA in the treatment (39,40). Nevertheless, the actual rationale for the improvement remains unclear.

The current preliminary study demonstrated a novel treatment protocol for patients suffering from DDwR with the LPGCF and a CAD/CAM SA which proved to be useful in patients with limited MMO associated with DDwR. However, future studies are recommended with larger sample size and with comparison to other treatments.

## CONCLUSION

Intra-articular injection of LPCGF and SA could be considered a management protocol for patients suffering from DDwR as it relieved TMD symptoms and increased the MMO.

### CONFLICT OF INTEREST:

The authors of this research report no conflicts of interest.

## REFERENCES

1. De Leeuw R. Internal derangements of the temporomandibular joint. *Oral Maxillofac Surg Clin North Am.* 2008;20:159-68.
2. Schiffman E, Ohrbach R, Truelove E et al. Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for Clinical and Research Applications: recommendations of the International RDC/TMD Consortium Network and Orofacial Pain Special Interest Group. *J Oral Facial Pain Headache.* 2014;28:6-27.
3. Hosgor H, Bas B, Celenk C. A comparison of the outcomes of four minimally invasive treatment methods for anterior disc

- displacement of the temporomandibular joint. *Int J Oral Maxillofac Surg.* 2017;46:1403-10. doi: 10.1016/j.ijom.2017.05.010.
4. Bahgat MM, El-Helw NR, Abdelhamid AM, Emam MH. Botulinum Toxin Type-A...An Evolving Treatment Modality in The Management Of Temporomandibular Joint Disc Displacement. *Alex dent j.* 2018;43:57-61.
  5. Atteya AM, Warda MH, Fata MM, Medra AM, Gil FM. Prospective randomized study between arthrocentesis and operative arthroscopy in the management of temporomandibular joint internal derangement. *Alex dent j.* 2021 Apr 1;46:58-65.
  6. Han M, Markiewicz M, Miloro M, Wolford L, Pogrel MA. Surgery of the Temporomandibular Joint: Discectomy and Arthroplasty. In *Contemporary Management of Temporomandibular Disorders 2019* (pp. 107-127). Springer, Cham.
  7. Ângelo DF, Sanz D, Cardoso HJ. Unilateral temporomandibular joint discectomy without interpositional material in patients with disc perforation or fragmentation: A prospective study. *J Oral Maxillofac Surg Med Pathol.* 2022;34:375-80.
  8. Rodhen RM, de Holanda TA, Barbon FJ, de Oliveira da Rosa WL, Boscato N. Invasive surgical procedures for the management of internal derangement of the temporomandibular joint: A systematic review and meta-analysis regarding the effects on pain and jaw mobility. *Clin Oral Investig.* 2022 Mar 15:1-8.
  9. Murakami K. Current role of arthrocentesis, arthroscopy and open surgery for temporomandibular joint internal derangement with inflammatory/degenerative disease: pitfalls and pearls. *J Oral Maxillofac Surg Med Pathol.* 2022;34:1-1.
  10. Al-Moraissi EA, Farea R, Qasem KA, Al-Wadeai MS, Al-Sabahi ME, Al-Iryani GM. Effectiveness of occlusal splint therapy in the management of temporomandibular disorders: network meta-analysis of randomized controlled trials. *Int J Oral Maxillofac Surg.* 2020;49:1042-56.
  11. Liu MQ, Lei J, Han JH et al. Metrical analysis of disc-condyle relation with different splint treatment positions in patients with TMJ disc displacement. *J Appl Oral Sci.* 2017;25:483-9.
  12. Ok SM, Jeong SH, Ahn YW et al. Effect of stabilization splint therapy on glenoid fossa remodeling in temporomandibular joint osteoarthritis. *J Prosthodont Res.* 2016;60:301-7.
  13. Pho Duc JM, Huning SV, Grossi ML. Parallel Randomized Controlled Clinical Trial in Patients with Temporomandibular Disorders Treated with a CAD/CAM Versus a Conventional Stabilization Splint. *Int J Prosthodont.* 2016;29:340-50.
  14. Vasques MT, Mori M, Laganá DC. Three-dimensional printing of occlusal devices for temporomandibular disorders by using a free CAD software program: A technical report. *J Prosthet Dent.* 2020 Feb 1;123:232-5.
  15. Algabri RS, Alqutaibi AY, Abo-Alrejal H, Al Adashi O, Abdulrahman F, Amr Elkhadem A. Effect of computer-aided design/computer-assisted manufacture versus conventional occlusal splints on the management of temporomandibular disorders: a systematic review and meta-analysis. *Int Dent Med J Adv Res.* 2017;3:1-9.
  16. Alqutaibi AY, Algabri R, Ibrahim WI, Borzangy S. Does the facebow affect the outcome of CAD/CAM occlusal splint. Randomized clinical trial. *Saudi Dent J.* 2021;33:628-34.
  17. Berntsen C, Kleven M, Heian M et al. Clinical comparison of conventional and additive manufactured stabilization splints. *Acta Biomater Odontol Scand.* 2018;4:81-9.
  18. Gibreel M, Perea-Lowery L, Vallittu PK, Lassila L. Characterization of occlusal splint materials: CAD-CAM versus conventional resins. *J Mech Behav Biomed Mater.* 2021;124:104813.
  19. Chen J, Jiang H. A comprehensive review of concentrated growth factors and their novel applications in facial reconstructive and regenerative medicine. *Aesthetic Plast Surg.* 2020;44:1047-57.
  20. Al-Hamed FS, Hijazi A, Gao Q, Badran Z, Tamimi F. Platelet concentrate treatments for temporomandibular disorders: A systematic review and meta-analysis. *JDR Clin Trans Res.* 2021;6:174-83.
  21. Chen X, Wang J, Yu L, Zhou J, Zheng D, Zhang B. Effect of concentrated growth factor (CGF) on the promotion of osteogenesis in bone marrow stromal cells (BMSC) in vivo. *Sci Rep.* 2018;8:1-8.
  22. Lee HM, Shen EC, Shen JT, Fu E, Chiu HC, Hsia YJ. Tensile strength, growth factor content and proliferation activities for two platelet concentrates of platelet-rich fibrin and concentrated growth factor. *J Dent Sci.* 2020;15:141-6.
  23. Torul D, Cezairli B, Kahveci K. The efficacy of intra-articular injectable platelet-rich fibrin application in the management of Wilkes stage III temporomandibular joint internal derangement. *Int J Oral Maxillofac Surg.* 2021;50:1485-90.
  24. Haigler MC, Abdulrehman E, Siddappa S, Kishore R, Padilla M, Enciso R. Use of platelet-rich plasma, platelet-rich growth factor with arthrocentesis or arthroscopy to treat

- temporomandibular joint osteoarthritis: Systematic review with meta-analyses. *J Am Dent Assoc.* 2018;149:940-52.
25. Hançı M, Karamese M, Tosun Z, Aktan TM, Duman S, Savacı N. Intra-articular platelet-rich plasma injection for the treatment of temporomandibular disorders and a comparison with arthrocentesis. *J Craniomaxillofac Surg.* 2015;43:162-6.
  26. Lin SL, Tsai CC, Wu SL, Ko SY, Chiang WF, Yang JW. Effect of arthrocentesis plus platelet-rich plasma and platelet-rich plasma alone in the treatment of temporomandibular joint osteoarthritis: A retrospective matched cohort study (A STROBE-compliant article). *Medicine.* 2018;97:e0477.
  27. Marx RE, Carlson ER, Eichstaedt RM, Schimmele SR, Strauss JE, Georgeff KR. Platelet-rich plasma: Growth factor enhancement for bone grafts. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1998;85:638-46.
  28. Anitua E. The use of plasma-rich growth factors (PRGF) in oral surgery. *Pract Proced Aesthet Dent.* 2001;13:487-93
  29. Choukroun J, Adda F, Schoeffler C, Vervelle A. Une opportunit  en paro-implantologie: le PRF. *Implantodontie.* 2000;42:55-62.
  30. Sacco L. Lecture, International academy of implant prosthesis and osteoconnection, 2006;12:4.
  31. Ohrbach R, Gonzalez Y, List T et al. Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) Clinical Examination Protocol. 2014.
  32. Murakami K, Hosaka H, Moriya Y, Segami N, Iizuka T. Short-term treatment outcome study for the management of temporomandibular joint closed lock: a comparison of arthrocentesis to nonsurgical therapy and arthroscopic lysis and lavage. *Oral Surg Oral Med Oral Pathol Oral Radiol Endodontol.* 1995;80:253-7.
  33. Rodrigues AD, Kondo CA, Proc pio AS, Luz JG.. Helkimo and Craniomandibular Indices in the Classification of Temporomandibular Disorders. A Comparative Study. *Myopain.* 2016;23:94-9.
  34. Kirkpatrick LA, Feeney BC. *A Simple Guide to IBM SPSS Statistics for version 20.0.* wadsworth. Cengage Learning. 2012.
  35. Yang JW, Huang YC, Wu SL, Ko SY, Tsai CC. Clinical efficacy of a centric relation occlusal splint and intra-articular liquid phase concentrated growth factor injection for the treatment of temporomandibular disorders. *Medicine.* 2017;96:e6302.
  36. Al-Delayme RE, Alnuamy SH, Hamid FT et al. The efficacy of platelets rich plasma injection in the superior joint space of the tempromandibular joint guided by ultra sound in patients with non-reducing disk displacement. *J Maxillofac Oral Surg.* 2017;16:43-7.
  37. Torul D, Cezairli B, Kahveci K. The efficacy of intra-articular injectable platelet-rich fibrin application in the management of Wilkes stage III temporomandibular joint internal derangement. *Int J Oral Maxillofac Surg.* 2021;50:1485-90.
  38. Giacomello M, Giacomello A, Mortellaro C, Gallesio G, Mozzati M. Temporomandibular joint disorders treated with articular injection: the effectiveness of plasma rich in growth factors-Endoret. *J Craniofac Surg.* 2015;26:709-13.
  39. Altaweel AA, Ismail HA, Fayad MI. Effect of simultaneous application of arthrocentesis and occlusal splint versus splint in management of non-reducing TMJ disc displacement. *J Dent Sci.* 2021;16:732-7.
  40. Li Z, Zhou J, Yu L et al. Disc-condyle relationship alterations following stabilization splint therapy or arthrocentesis plus hyaluronic acid injection in patients with anterior disc displacement: a retrospective cohort study. *Oral Radiol.* 2022:1-9.