



Research article

The production and materials of mouthguards: Conventional vs additive manufacturing - A systematic review

Victor Paes Dias Gonçalves^a, Carlos Maurício Fontes Vieira^a, Henry Alonso Colorado Lopera^{a,b,*}

^a State University of the Northern Rio de Janeiro - UENF, Advanced Materials Laboratory - LAMAV, Av. Alberto Lamego, 2000, 28013-602 Campos dos Goytacazes, RJ, Brazil

^b CCOMposites Laboratory, Universidad de Antioquia (UdeA), Calle 70 No. 52-21, Medellin, Colombia

ARTICLE INFO

Keywords:

Mouthguard

Sport

Additive manufacturing

Polymers

Materials

ABSTRACT

This investigation presents a critical analysis of mouthguard production, focusing on the evaluation of conventional vs additive manufacturing methods, the materials involved, and aspects such as their failure and prevention. It also summarizes the current trends, perspectives, and the main limitations. It is shown that some of the shortcomings can be solved by implementing additive manufacturing technologies, which are systematically reviewed in this research. Due to the specific materials used to produce mouthguards, there are certain additive manufacturing technologies that dominate and a wide variety of raw materials. The costs vary depending on the technology.

1. Introduction

Mouthguards (MTs) are devices used in many sporting activities to protect participants from injuries such as tooth and jaw damage, among other issues [1–7]. The literature emphasizes how the functions of mouthguards benefit the athletes who use them [8–10], mainly by preventing dental trauma, such as enamel fracture (Fig. 1a), enamel-dentin fracture (see Fig. 1b), crown fracture with exposure of pulp tissue (see Fig. 1c), and root fracture (Fig. 1d). There is considerable debate about how the use of mouthguards affects an athlete's performance [11–14]. Some research that includes clinical studies and meta-analyses shows that personalized MTs do not negatively affect the athlete's performance, and in some cases their performance even improves [15–26]. However, other authors have reported on athletes who have stopped using MTs due to discomfort when wearing them, and who have experienced difficulties in breathing, speaking, and drinking [27–29].

There is not much data regarding the discomfort of using MT made with additive manufacturing. However, there are challenges reported to solve from traditional MT, which include: a) Poorly fitted dental guard side effect that can cause pain [95–96]; b) Uncomfortable to use because of its thickness (necessary to reduce the impact force of an injury) when placed in the oral cavity [97]; c) Lack of retention can discourage its use [98]. From these possible limitations, a) and c) are directly related to a good design and precise fabrication of this, guaranteeing a good fit and ensuring a good device retention. Additive manufacturing (AM) data regarding the solution of these problems is still under development, however AM can contribute with a more personalized and precise MT, which

* Corresponding author. State University of the Northern Rio de Janeiro - UENF, Advanced Materials Laboratory - LAMAV, Av. Alberto Lamego, 2000, 28013-602 Campos dos Goytacazes, RJ, Brazil.

E-mail address: henry.colorado@udea.edu.co (H.A. Colorado Lopera).

<https://doi.org/10.1016/j.heliyon.2024.e34294>

Received 28 December 2023; Received in revised form 8 July 2024; Accepted 8 July 2024

Available online 8 July 2024

2405-8440/© 2024 Published by Elsevier Ltd.

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certainly can limit the discomfort. Only a few works have addressed this topic, such as Li et al. [65], who gave a comparison of conventional and 3D protectors. These authors discussed, through a randomized clinical trial, the improvement in satisfaction, mainly related to comfort and retention when using a MT by additive manufacturing via FDM.

The conventional method for making a mouthguard consists of two steps: first, information is obtained about the dental arch, and second, the device is made [30–33].

In the conventional method, there is a high possibility of failure in both stages, resulting in a device with imperfections. This makes it difficult for athletes to accept the mouthguard [34–42]. The individualized mouthguard technique consists of making a mold of the patient's mouth, creating a plaster model, cutting out the model and delimiting the entire work area. This method involves all teeth, except for the third molars [43]. It is therefore necessary to create relief in the area of the labial frenulum, a soft tissue structure that lies between the central incisors. The prepared plaster model is placed on the machine platform, the vinyl sheet is then heated, and the metal support that holds the sheet is lowered until it meets the model. The model is finally removed from the vinyl sheet, and when it is cold enough, cutting can begin around the delimitation of the work area [43,44]. Finally, finishing and polishing processes must be carried out to guarantee the mouthguard fits correctly on the patient and, if necessary, adjustments can be made by trial and error to create a customized (see Fig. 2) or multi-laminated MT (see Fig. 3).

In an attempt to solve conventional manufacturing problems, dentistry has moved into Industrial Revolution 4.0, aiming to improve the efficiency and productivity of its processes [45–48]. The digital age has become increasingly more significant in the dental sector, and with the advent of innovative technologies, there are many new areas and technological possibilities that could provide solutions to overcome the current limitations [49–51]. As a first step towards innovation and modernization, sports dentistry has extensively incorporated the use of intraoral scanning to obtain digital models [51]. This has improved speed [52], efficiency [53], and in many cases cost-benefits due to factors such as time savings [54,55], good acceptance in terms of patient comfort [56,57], distortion reduction [58,59], 3D previews [60,61], and data storage and transfer by digital means [62–64]. The ASTM defines Additive manufacturing as the “process of joining materials to make objects from 3D models data, usually layer upon layer, as opposed to subtractive methodologies, such as traditional machining” [99]. The process started with the name of Rapid prototyping in the 80's, but quickly was transformed into a wider technology beyond the prototyping to 3D printing (3DP) in the 90's [100]. Additive manufacturing (AM) became popular in the 2000's, and now the terms AM and 3DP are almost everywhere used as synonyms [101, 102]. Li et al. [65] and Sousa et al. [31] agree that the possibility of reducing material waste, costs, and the need for consultations, and improving precision, make this technology attractive. There have been numerous studies comparing traditional processes with additive manufacturing, including comparisons with traditional machining [66], supply chains [67], polymer manufacturing [68], ceramics [69], food [70], and many other areas. In general, the main advantages of additive manufacturing are the production of more complex shapes (some of which would be impossible using traditional manufacturing) [71,72], the development of a new era of design without limits [73], the possibility of more sustainable processes [74,75], and a method that is more adaptable method to customer needs [76,77], thereby making the technology available everywhere [78]. This review uses a systematic approach to find the trends, advantages, limitations, and different perspectives on mouthguards, with special emphasis on additive manufacturing as a possible solution to some of the current MT limitations.

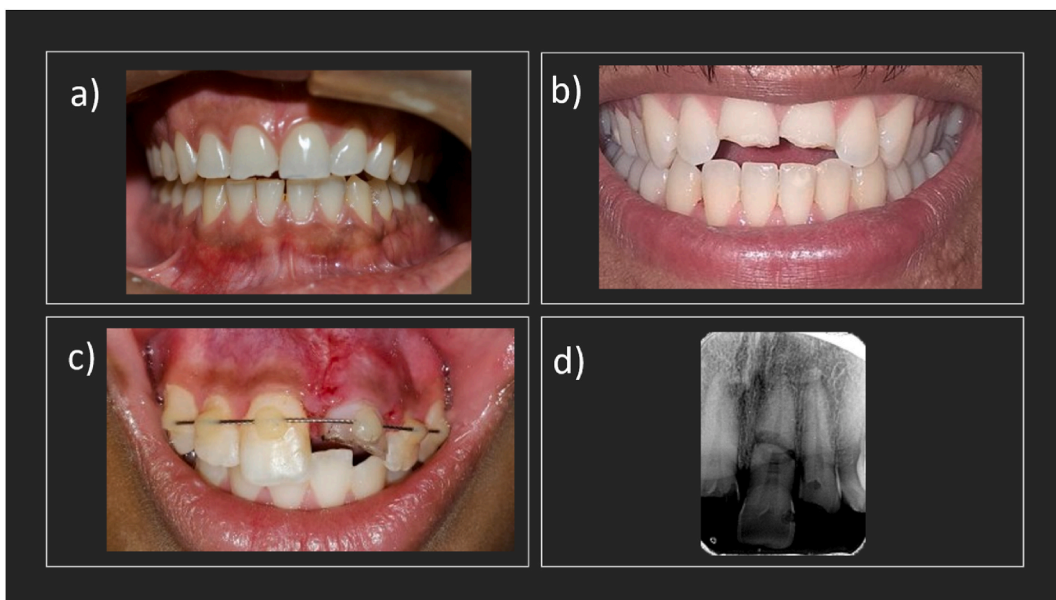


Fig. 1. Types of dental trauma.
Source: Author.



Fig. 2. Mouthguard custom.
Source: Author.



Fig. 3. Mouthguard multilaminare.
Source: Author.

2. Materials and methods

This systematic review was carried out in accordance with the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines [79]. The inclusion criteria, according to the population, interventions, comparisons, and outcomes (PICOS), were carried out as follows: Population (P): Mouthguard; Intervention (I): Clothing/Manufacturing; Comparison (C): Conventional Manufacturing vs Additive Manufacturing; Result (O): Materials Used, Advantages and Technical Limitations; Study Design(S): Randomized clinical trial; Crossover randomized clinical trial.

2.1. Search strategy

A systematic search for information was conducted in March 2024 using the Scopus, Pub Med, Web of Science, Latino-americana, and Literatura Caribenha em Ciências da Saúde (LILACS) databases, which provided a wide variety of sources on the subject. Eligible studies were found using the keywords “mouthguard”, “manufactured”, and ‘Additive Manufacturing’, looking at articles published from 2015 to March 2024.

2.2. Focused question

To answer the following focused question, “is it possible to manufacture MTs via additive manufacturing?”, this review uses a systematic search to find: i) trends in the materials used, and ii) the advantages and limitations of the manufacturing technologies involved.

2.3. Eligibility criteria

The inclusion criteria selected for the current study were as follows: studies on mouthguards produced by additive manufacturing and studies on the mechanical and finite elements of mouthguards. The exclusion criteria selected were: book chapter, systematic review, or meta-analysis with incomplete data.

2.4. Study selection and data extraction

All articles identified electronically were scanned by title and abstract. Articles that appeared in more than one database search were considered only once. Two assessors (CMFV and VPDG) carried out the research process independently. In cases of any discrepancy, the decision was made by consensus with a third author (HACL). Full texts were obtained for all articles identified and considered potentially relevant. Titles and abstracts of identified articles were assessed independently by two researchers who decided whether they met the inclusion criteria for the review. The electronic search was complemented with a detailed search from the reference list of the researched articles.

2.5. Quality assessment and risk of bias

Two review authors independently undertook the risk of bias assessment for the study. Disagreements were solved by discussion with a third review author until a consensus was reached. The assessment was carried out according to the criteria described in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions [80]. The following dimensions were considered: random sequence generation, allocation concealment, participant blinding, professional blinding, blinding of outcome evaluators, incomplete outcomes, selective outcome reporting, and sample calculation. The risk was assessed using pre-specified criteria for study suitability. The overall risk of bias of the included studies was categorized and reported according to the following: low risk of bias (plausible bias unlikely to seriously alter the results) if all key domains were assessed as a low risk of bias; unclear risk of bias (plausible bias that raises some doubt about the results) if one or more key domains were assessed as an unclear risk of bias; or high risk of bias (plausible bias that seriously weakens confidence in the results) if one or more key domains were assessed as a high risk of bias.

3. Results

3.1. Synthesis and study characteristics

The search performed in the databases with the keywords is shown in the block diagram of Fig. 4. After the database had been sorted and the duplicates removed, a total of 16 studies were found, while 6 were excluded because they involved traditional thermoplastics processes.

The results of the eligible studies in the systematic review were described in Table 1, including the type of intervention (test used and technical standard), type of study, material used, country, published journal of the authors, and conclusion. Due to the variety of interventions and heterogeneity of studies, combining all included studies in a meta-analysis was not statistically appropriate.

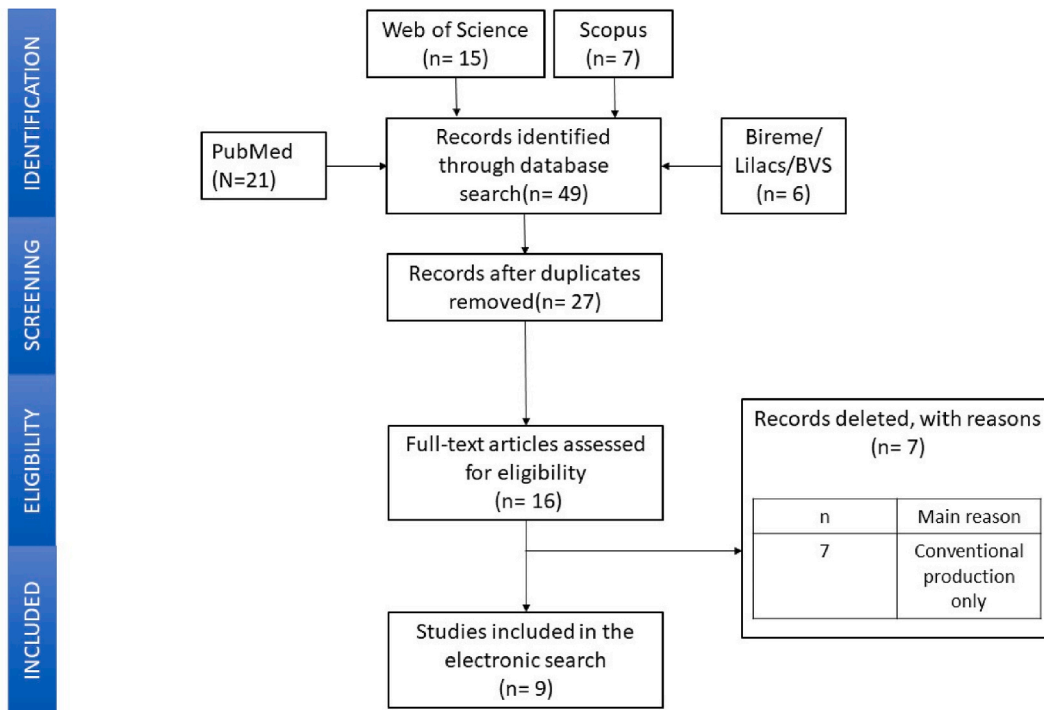


Fig. 4. Research flowchart. Source: Author.

Table 1 shows that there are 2 articles from 2020, 4 from 2021, 2 from 2022, to 1 from 2023. The distribution of articles included in the systematic review by country of study demonstrates a high concentration of studies from Europe: Szarek & Paszta [81]; Sousa, Pinho, and Piedade [82]; Pinho and Piedade [83]; Saunders et al. [84]; Schewe et al. [85]; Moreira et al. [86]; and Trzaskowski et al. [87]. Only the study by Li et al. [65] was carried out in China.

3.1.1. Materials studied

- EVA: used in multiple studies (Li et al., Szarek & Paszta, Saunders et al.), often compared with other materials such as PEEK, Neoprene rubber, and ID Arnitel 2045.
- PEEK: examined in combination with EVA for comfort and adaptation (Li et al.).
- Neoprene rubber (Polychloroprene): evaluated for impact absorption (Szarek & Paszta).
- Agilus 30 and Rigor: studied aiming clinical adaptation but found not biocompatible (Unkovskiy et al.).
- ABS, HIPS, PMMA, TPU: various combinations tested for mechanical properties and durability (Sousa, Pinho, Piedade; Pinho & Piedade).
- ID Arnitel 2045: considered viable for 3D printed mouthguards (Saunders et al.).

Table 1

Details of main articles.

Reference	Country	Journal	Material	Type of study	Tests	Technical standard	Conclusion
Li et al. [65]	China	Digital Dental Technologies	EVA PEEK	Concept Test	Occlusal stability AND feeling questionnaire	Not used	Material with greater comfort and adaptation
Szarek & Paszta [81]	Poland	FIBRES & TEXTILES in Eastern Europe	EVA Neoprene rubber (polychloroprene)	finite element	1-Punch to the chin, impact force: 1000 N, velocity: 15 m/s, Mooney-Rivlin. 2-Direct Punch, impact force: 500 N	Not Used	Material capable of absorbing impact.
Unkovskiy et al. [88]	Switzerland	Int. J. Environ	Agilus 30 e Rigor	Concept Test	Clinical Evaluation Adaptation	Not used	Ideal material is not biocompatible
Sousa, Pinho, Piedade [82]	Portugal	Materials and Design	Poli(acrilonitrila-butadieno-estireno) – ABS HIPS, PMMA, TPU, EVA	Mechanical Test	chemical, thermal, surface, and mechanical	ASTM D790	No conclusion on an ideal material. Suggested filament combination strategy
Pinho & Piedade [83]	Portugal	Polymers	ABS-TPU-ABS HIPS-TPU-HIPS PMMA-TPU-PMMA	Mechanical Test	1-Three-point bending tests (3 MT) 2- Transverse impact 3- Aging in artificial saliva	ASTM D790; SO 179	The multimaterial with the best results was ABS-TPU-ABS.
Saunders et al. [84]	England	Scientific Reports	ID Arnitel 2045 EVA	Mechanical Test	Low-strain rate testing setup - Instron 8854_e High-strain rate testing setup via Te Split Hopkinson Pressure bar (SHMT).	ASTM D2240	Results indicate that 3D printed mouthguards are a viable option
Schewe et al. [85]	Germany	Materials	Ethylenvinylacet and Agilus 30	Mechanical Test	A ball-drop test—based on the descriptions of Chowdhury et al. steel ball (524 g).	Not Used	A rubber-like additively processed polymer does not appear to provide the same load damping effect as conventional thermoformed materials
Moreira et al. [86]	Portugal	Frattura ed Integrità Strutturale	PETG+1 mm TPU (ERKOLOC) RESIN Orto- IBT	Mechanical Test	drop-weight	Not Used	Inadequate ERKOLOC due to associated damage and inadequate IBT due to the material having low elastic energy.
Trzaskowski et al. [87]	Poland	Polymers	Four tips resin IBT	Mechanical Test	Tensile strength, flexural strength, notch strength, shore hardness, sorption, and solubility tests	ASTM D570; ISO 27:1998; PN-68/C-89028	The most favorable properties, due to the high notch-toughness and tensile strength as well as low Shore hardness and sorption, were found in the Keyortho IBT

- > Ethylene-vinyl-acetate and Agilus 30: compared for load damping effect, with conventional materials being more effective (Schewe et al.).
- > PETG+1 mm TPU (ERKOLOC), RESIN Orto-IBT: tested for structural integrity and found inadequate (Moreira et al.).
- > Four tips resin IBT: exhibited favorable mechanical properties (Trzaskowski et al.).

3.1.2. Types of studies

- Conceptual tests: evaluated occlusal stability, feeling questionnaire, and clinical adaptation.
- Finite element analysis: assessed impact absorption capabilities.
- Mechanical tests: included tests like three-point bending, transverse impact, aging in artificial saliva, low and high strain rate testing, and ball-drop tests.

3.1.3. Technical standards

- Not used in several studies (Li et al., Szarek & Paszta, Unkovskiy et al., Schewe et al., Moreira et al.).
- ASTM and ISO standards employed in mechanical testing (Sousa, Pinho, Piedade; Pinho & Piedade; Saunders et al.; Trzaskowski et al.).

3.1.4. Carrot2 workbench

After analyzing Table 1, a search was used using the words ‘Materials of Mouthguards AND additive manufacturing’ to check areas of interest using Carrot2 Workbench, see Fig. 5, where 63 documents were found. The articles found are dispersed in 20 clusters, with the main in the following order by the number of documents: mouthguard, dental, Present Status in Polymeric Mouthguards, Impact Behaviour of 3D Printed Cellular Structures, and Multi-Material. The number of documents demonstrated an opportunity in this topic for innovation and for producing more research. Table 2

3.1.5. Citation mapping

The articles demonstrate powerful integrated citation mapping, indicating that prominent academic scholars have read them and have cited them in their research papers. Google citation mapping clearly exhibits one piece of seminal research. The full list is shown in Table 3 and is demonstrated in Fig. 6 [92].

Research conducted by Rabbit [92] developed an AI-powered tool designed for academic publication discovery. Its visualization maps enable users to uncover connections between publications or authors that might otherwise go unnoticed. For instance, by browsing authors, users can discover research teams they were previously unaware of. The network view feature enables users to visualize interconnected posts. In the context of citation mapping, this tool illuminates how articles interact with one another, highlighting points where one article cites another. Green dots represent papers from the current research, while blue dots represent papers referenced by the articles outlined in Table 1. The articles by Sousa et al. [82], Pinho & Piedade [83], and Moreira et al. [86]

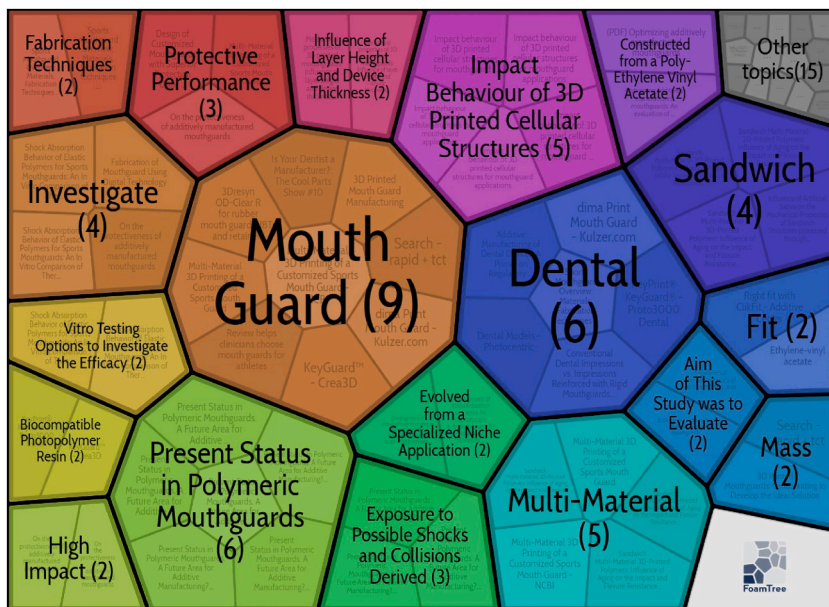


Fig. 5. Carrot2 workbench database search. Source: Author.

Table 2
Assessment of risk of bias and study quality.

Reference	Random Sequence Generation,	Allocation Concealment	Participant Blinding	Professional Blinding	Blinding Of Outcome Evaluators	Incomplete Outcomes	Selective Outcome Reporting	Sample Calculation
Li et al. [65]	High	High	High	High	High	Low	Low	High
Szarek & Paszta [81]	High	High	High	High	High	Low	Low	High
Unkovskiy et al. [88]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Sousa, Pinho, Piedade [82]	Low	Low	Low	Low	Low	Low	Low	Low
Pinho & Piedade [83]	Low	Low	Low	Low	Low	Low	Low	Low
Saunders et al. [84]	Low	Low	Low	Low	Low	Low	Low	Low
Schewe et al. [85]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Moreira et al. [86]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Trzaskowski et al. [87]	Low	Low	Low	Low	Low	Low	Low	Low

Table 3
Citations of each article by Google.

Reference	2020	20,221	2022	2023	2024	Total
Li et al. [65]	6	3	3	12	1	27
Szarek & Paszta [81]	0	0	4	7	2	13
Unkovskiy et al. [88]	0	1	0	1	0	2
Sousa, Pinho, Piedade [82]	0	3	10	12	4	29
Pinho & Piedade [83]	0	0	7	7	2	15
Saunders et al. [84]	0	0	1	6	1	8
Schewe et al. [85]	0	0	0	4	1	5
Moreira et al. [86]	0	0	0	5	1	6
Trzaskowski et al. [87]	0	0	0	6	1	7
Total	6	7	25	60	13	112

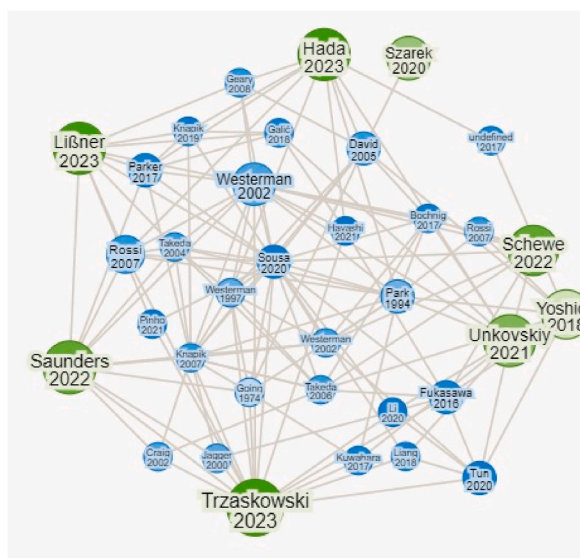


Fig. 6. Citation mapping.
Source: Author.

belong to a collaborative group, are published sequentially, and use literature already published as a basis.

3.2. Outcome of quality assessment and study outcomes

The assessment of the risk of bias of the selected studies is shown in. In assessing the risk of bias, Random Sequence Generation, Allocation Concealment, Participant Blinding, Professional Blinding, Blinding of Outcome Evaluators, and Sample Calculation sessions were considered high risk for articles that did not follow technical standards and that only used a relationship between a control group and a group of test materials. On the other hand, studies that used technical standards and had more than one test variable presented a low risk of bias. For the Incomplete Outcomes and Selective Outcome Reporting session, all articles were low risk as they presented results in a direct and clear way.

4. Discussion

In the literature, there is currently a shortage of studies about the production of mouthguards using additive manufacturing and an ideal material has not yet been found. Therefore, different production methods and materials should be investigated to achieve a better solution. A typical mouthguard is made with a copolymer of EVA, a material that has all the characteristics necessary to provide protection, is non-toxic, easy to shape and handle, and has biocompatibility, low cost, and primarily the ability to absorb and dissipate stresses during impact with a rigid object [89–91]. However, additive manufacturing of this material is still very limited.

The studies presented in Table 2 mostly show a low risk of bias. Articles comparing a single material, such as those by Li et al. [65] and Unkovskiy et al. [88], generate a greater risk of bias as they did not use a randomized sequence and did not blind participants and professionals. In some articles, these details were not given, such as in Szarek & Paszta [81], Schewe et al. [85] and Moreira et al. [86].

Sousa et al. [82] highlighted that additive manufacturing (AM) has been proposed for the production of personalized mouthguards but there are few studies reported in the literature for the manufacture of mouthguards using this technology. The additive manufacturing approach would provide mouthguards with higher precision, a better design details, and trying to look for materials that can optimize and perhaps reduce in the future the thickness, all aspects to improve towards a better conform.

Saunders et al. [84] and Schewe et al. [85] compared the conventional production method using EVA against AM using filaments with the extrusion method, showing that EVA is superior in deformation and mechanical damping properties.

The studies of Szarek & Paszta [81] and Li et al. [65] are optimistic about materials that need to be evaluated. They obtained positive results and made interesting observations of the process. Szarek & Paszta [81] reported on the production of MTs with light polyurethane foam using a computer numerical control (CNC) machine. They simulated a punch to the chin via Finite Element Analysis (FEA) and showed that the material had positive mechanical properties.

Li et al. [85] used a randomized clinical trial (with blinding) and a questionnaire to assess participant perception of using conventional MTs (Erkoflex 4 mm under vacuum) and digital MTs with poliéter-éter-cetona (PEEK), and the corresponding degree of satisfaction (retention, appearance, occlusal comfort and lip comfort). They evaluated occlusal stability through occlusal analysis of the T-scan III. According to the questionnaire responses, the digital MT was superior in appearance, occlusal comfort, and lip comfort. Also, 88.9 % of participants chose digital mouthguards for future use and the results presented in the occlusal analysis showed that digital mouthguards had stable and balanced bilateral contact with the lower teeth when compared with conventional mouthguards. The data must be on sides with a smaller thickness used, having less impact on the lateral profile of the participants. However, the authors retracted that the benefits are due to significantly simplifying the production process and also reducing errors in the printing and plaster transfer process. Huang et al. [93] and Zhou [94] highlight the need for a thin and soft material that maintains the mechanical properties and work by Li et al. [85] follows this principle through manufacturing via FDM.

Pinho & Piedade [83] obtained positive results using the ABS-TPU-ABS sandwich structure due to the higher resilience value of all combinations of materials and because of their good bending properties. The TPU had a stabilizing effect in relation to artificial saliva and deformation prevention, while the TPU Core dissipated the impact energy. It was found that teeth, bone structure, and joints were protected, but these were not assessed in relation to the shape of the mouthguard.

Moreira et al. [86] aimed to evaluate the impact response of different materials, including 3D printing materials (4 mm IBT resin) with EVA-based composition. Five different materials were subjected to impact tests with energies of 1.72 J, 2.85 J and 4.40 J. Low velocity impact tests were performed using a drop weight testing machine. A 10 mm diameter impact with a mass of 3.4 kg was used and the tests were conducted on specimens with a circular section of 55 mm. The impact blows were aimed at the center of the specimens which were supported centrally. Ortho IBT resin, a monomer based on acrylic esters, was selected because its Shore hardness is like EVA (A 85). It was the material that absorbed the highest energy of all the tests, and thus, the material with the lowest stored energy (elastic energy). This material has a poor damping capacity, and cohesive fracture of the sheet (fractured) was observed.

Trzaskowski et al. [87], evaluated the mechanical properties of four flexible polymeric resin materials produced using SLA to find the ideal material for making MTs. The authors performed tensile strength, flexural strength, notch strength, Shore hardness, and solubility tests. The Keyortho IBT resin (EnvisionTEC) showed the best results due to its high notch toughness and tensile strength, as well as low Shore hardness. However, the authors report that the study was limited because no comparisons were made with EVA, which is the gold standard material for manufacturing. Although all authors concluded that 3D printed materials give a degree of protection, there is still no printed material that has behavior similar to the EVA produced by conventional techniques, i.e. that can absorb and dissipate impacts while maintaining dimensional stability [88]. This is therefore an opportunity for further research and development in this area.

The creation of a MT through a digital drawing has not yet been discussed in the literature. The AM dental software itself does not

have a specific configuration for creating a MT, meaning that features such as the occlusal plates and surgical guides must be adapted to develop the MT design.

There are several advantages to producing MTs using AM. For example, as the MT can be reproduced accurately, it can be conveniently replaced in cases of wear or loss (as long as there is no change in the athlete's dental arch). Furthermore, there is greater manufacturing fidelity, simple workflow, reduction in material waste, device standardization, a uniform thickness throughout the entire arch, and an increased acceptance by athletes regarding the use of the device. Moreover, since the literature does not provide any clear option as to a suitable material, it would seem pertinent to explore a material with greater strength and durability than that used in the conventional manufacturing method.

This work was limited by the fact that it was not possible to use meta-analysis due to the non-standardization of the studies analyzed and the lack of complete results. In the literature, greater standardization of the tests is needed. Most of the articles focus only on the final product, and do not study the characterization of materials using technical standards or any further characterization in materials science. Only some research, such as that by Sousa, Pinho, Piedade [82], Pinho & Piedade [83], Saunders et al. [84] and Trzaskowski et al. [87], carried out this type of characterization.

Mouthguards are currently classified into five types: Type I (stock), II (prefabricated) and types III, IV and V, custom-made (made to measure). Type IV is the multilaminar variety and type V is the sports optimizer variety. Confirming and standardizing a material could add a new classification of mouthguards to the literature, i.e. those that are produced by digital flow.

5. Conclusion

Additive manufacturing is a promising and feasible method that can be used to produce sports mouthguards that provide advantages to both dentistry and to the sports world. When compared with traditional manufacturing, AM can produce mouthguards in a faster and more simplified way. Currently, the field is quite open to research and development. While the number of studies on the subject is growing in the literature, there are clear gaps in knowledge in terms of materials, sustainable methods, and properties such as durability and stability, all of which are needed for MT optimization. These limitations are opportunities for research and development and for the commercial sector as well.

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Victor Paes Dias Gonçalves: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Carlos Maurício Fontes Vieira:** Validation, Supervision, Project administration. **Henry Alonso Colorado Lopera:** Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Henry A Colorado reports a relationship with Elsevier that includes: board membership. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors wish to thank the Brazilian agencies, CNPq, process number 302976/2022-1, and FAPERJ, process number E-26/200.847/2021.

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