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Review

Patient-specific, printed titanium implants for reconstruction of mandibular continuity defects: A systematic review of the evidence

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1. Introduction

Three dimensional (3D) planning/computer-aided-design (CAD) and virtual surgery has evolved to the point that it improves efficiency, accuracy, creativity and reproducibility in cranio-maxillofacial (CMF) surgery (Steinbacher, 2015). The process of CAD (following analysis of 3D imaging data) provides the means to rapid-prototype a stereolithigraphic resin model/mould upon which a titanium implant can be flexed, pressed or moulded pre-operatively (and most importantly, checked against the stereolithigraphic model) for subsequent intraoperative use. This technique has become standard practise in maxillofacial centres worldwide. We know that when compared to traditional intra-operative shaping techniques, it improves accuracy and efficiency in mandibular reconstruction; notably eliminating the time taken during surgery to bend the plate by eye that would otherwise be required using the traditional approach, yet allowing as much time as needed by the technician preoperatively to achieve the best 'handmade' result possible (Gil et al., 2015). With the advent of additively-manufactured, '3D-printed' titanium (more specifically selective laser melting; SLM), it has been proposed by one author group that SLM ('printed') mandibular reconstruction plates further reduce the duration of surgery and frequency of complications, as well as producing a more accurate reconstruction due to the elimination of human error in the final stages of fabrication (in contrast to a plate bent to a stereolithigraphic model preoperatively) (Tarsitano et al., 2016a). Printing titanium plates/implants enables a seamless, automated transition from CAD to computer aided manufacture (CAM), further reducing the introduction of human error in the fabrication stage.

2. Objectives

The purpose of this systematic review was to evaluate the quality and volume of available evidence relating to the benefits and limitations of 'three-dimensionally-printed' titanium patient-specific implants (PSIs) in mandibular reconstruction. In particular, the study sought to evaluate reported benefits and limitations (including complications) of printed titanium and to categorise them into themes, in order to contextualise the current vogue for this approach to mandibular reconstruction.

3. Materials and methods

3.1. Search technique

A systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Liberati et al., 2009).

Records were identified by the lead author through searches of two medical databases: PubMed and Scopus. These two were selected for reasons of optimal coverage and utility (Falagas et al., 2008).

Article screening was performed as follows: where title and abstract appeared to meet the inclusion criteria (or if impossible to ascertain this from title and abstract alone), the full-text versions of the articles were obtained.

3.2. Search terms

In order to identify articles relating specifically to mandibular reconstruction by various surgical approaches, including those

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involving bony free flaps (with the aid of printed titanium), a selection of both general and focussed terms was used. The first search term was designed to be as non-specific as possible and to yield a high number of articles ("reconstruction" AND "plate" AND "mandible").

In addition, a focussed search to identify studies which included specific related surgical techniques was performed by using a set of specific terms. These were compiled by using a "primary" PLUS "secondary" stem: *e.g. "3D printing" + " jaw"*. In all possible combinations, a further 36 focussed search terms were used (Table 1).

3.3. Inclusion/Exclusion Criteria

All articles, (clinical, animal and laboratory/benchtop studies) were included providing the content directly related to three key conditions of the reconstructive implant: (1) Printed (additively manufactured) (2) Titanium for (3) Mandibular Reconstruction.

Articles were excluded from analysis if they: related to dental implants (rather than mandibular) or subtractively-manufactured (i.e. milled) PSIs, discussed CAD/CAM mandibular implants but with ambiguity over the specific technique of fabrication, were conference papers (not published in peer-reviewed journals) or were written in any language other than English.

3.4. Data collection

For each selected paper, authors, geographical location (by primary author), time from submission to acceptance to publication (in initial and final form), type of study/level of evidence according to the 2009 Oxford Centre for Evidence-based Medicine (CEBM) Levels of Evidence (Phillips et al., 2009), number of clinical cases (involving printed titanium), duration of follow-up, type of surgery, complications and study findings were recorded.

All articles were critically appraised by the lead author (AG) with flaws in the study design/methodology/analysis noted. Direct clinical studies of patients were objectively assessed for bias using a methodological quality rating system (Table 2), as described by Starch-Jensen et al. (2018).

Articles were grouped according to positive and negative themes pertaining to the rationale for and against the use of printed titanium for mandibular reconstruction.

4. Results

4.1. Literature search

Searches using the PubMed and Scopus databases revealed a total of 3046 records (titles and abstracts). Seventy-four records meeting the inclusion criteria were downloaded as full-text articles. Following full-text evaluation, 22 articles were excluded for the following reasons: conference papers, ambiguity/inconsistency over plate/implant fabrication method and dental (rather than mandibular) implant reconstructions. The remaining 52 articles were included in the final data analysis.

Table 1
Primary and secondary stems for 36 focussed search terms.

Primary stems	Secondary stems
"3D printing"	"DCIA"
"Additive manufacturing"	"Fibula"
"Electron beam melting"	"Flap"
"Laser sintered"	"Jaw"
"Laser sintering"	"Mandible"
"Selective laser melting"	"Scapula"

Table 2
Methodological quality rating system as described by Starch-Jensen et al., (2018).

Classification of the potential risk of bias:
1 Random selection in the population (yes/no)
2 Definition of inclusion and exclusion criteria (yes/no)
3 Report of losses to follow-up (yes/no)
4 Validated measurements (yes/no)
5 Statistical analysis (yes/no)

The included studies were categorized as follows:
- Low risk of bias (plausible bias unlikely to seriously alter the results) if all the quality criteria described above were met
- Moderate risk of bias (plausible bias that weakens confidence in the results) if one of these criteria was not met
- High risk of bias (plausible bias that seriously weakens confidence in the results) if two or more criteria were not met

4.2. Study time and place

Selected papers were published between 1st November 2009 and 1st March 2018. The mode and median year for publication in their final form (online or print) was 2016, with 15 of the 52 articles published that year.

Italy was the commonest source of submitted studies (12 articles), representing more than twice the output of any other country. Europe was the most prolific geographical region for research output overall (Fig. 1).

4.3. Quality of submitted articles

Both clinical and non-clinical study types were reported. From 31 clinical studies, 139 patients received printed titanium mandibular implants. Thirteen percent of these clinical studies (n = 4) were from the 2009 CEBM level 2 evidence group (cohort-type studies) and 23% (n = 7) level 4 (case series). Sixty-five percent (n = 20) were case reports which are not included in the 2009 CEBM levels of evidence and therefore constituted 'non-evidence'. The remaining 21 studies fell into the level 5 (n = 19) and 3 (n = 2) evidence groups. No randomised controlled trials or other studies from the CEBM group 1 were identified (Table 3).

Risk of bias, according to methodological quality rating system described by Starch-Jensen et al. was evaluated in the 31 clinical studies involving patients (Starch-Jensen et al., 2018). Ninety-four percent (29/31) were deemed to have to be 'high-risk' of bias (20 case reports, 7 case series and 2 cohort-type studies). Two 'moderate-risk' cohort studies were identified. No studies were identified as 'low-risk'. With regards to the individual bias risk criteria scored, all 20 case reports (by their nature) failed all 5 criteria. From the 11 remaining clinical studies (7 case series and 4 cohort-type

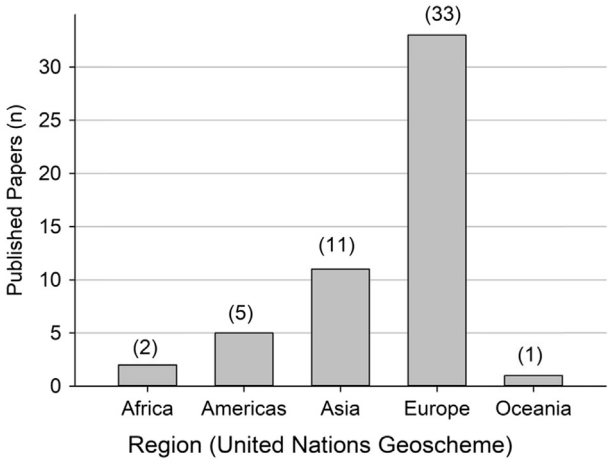

Fig. 1. Geographical distribution of studies by location of primary author.

Table 3
Types of study evaluated.

CEBM level of evidence group	Overall frequency	Details of study methodologies	Number of articles
1	Nil	-	0
2	7.7%	Cohort studies	4
3	3.8%	Systematic reviews (of 3b and better studies)	2
4	13.5%	Case series	7
5	36.5%	'First principles' animal-based studies	2
		Cadaveric/Bench/Virtual surgery lab studies	13
		Opinion articles	2
		Review articles	2
'Non-evidence'	38.5%	Case reports	20

studies), none involved a "random selection in the population", 6 clearly "identified inclusion and exclusion criteria", 4 reported the state of "losses to follow-up", 6 used "validated measurements" and 3 used "statistical analysis".

Data relating to the time for an article to be accepted was obtained from 71% (37/52) articles and was a median of 100 days (mean 146, range 7–277). Revisions to original submissions were reported in 12 articles, of which one article was revised more than once (with four revisions) (Nasr et al., 2017).

Time from acceptance to first publication (be it in online or print form) was obtained in 77% (40/52) of articles, with a median of 18.5 days (mean 49.9, range 0–347) and time from acceptance to publication in final form was a median of 95 days (mean 114.8, range 0–379).

4.4. Clinical studies

Duration of follow up was reported in 74% (23/31) and ranged from 2 weeks to 72 months (median 6 months, mean 12 months).

Printed titanium implants were used predominantly for reconstruction following mandibular resection, although numerous other indications were described (Table 4).

Table 4
Types of surgery performed.

Category of surgery	Number of cases
Lateral mandibulectomy reconstruction	48
Hemi/Subtotal mandibulectomy reconstruction (including condyle)	27
Subtotal mandibulectomy reconstruction (excluding condyle)	23
Anterior mandibulectomy reconstruction	21
Aesthetic lower border reconstruction	13
Acute comminuted trauma	2
Total mandibular reconstruction	1
Orthognathic (post traumatic) reconstruction	1
Temporomandibular Joint Reconstruction	1
Unspecified	2

Complications were reported in 7/31 clinical studies and occurred in 12% (17/139) of patients overall (Table 5).

4.5. Themes

Study findings and conclusions were grouped into themes, pertaining to benefits (Table 6) and limitations (Table 7) of additively manufactured (printed) titanium implants in mandibular reconstruction.

5. Discussion

5.1. Studies reviewed

A variety of search terms were used in order to retrieve as many relevant papers as possible. A non-specific search term ("reconstruction plate mandible") revealed a large number of articles of which the vast majority were irrelevant. More specific remaining search terms composed of 6 primary and 6 secondary stems (Table 1) revealed a considerably smaller number of papers with a greater degree of relevance to the topic.

The concept of 'printing' a titanium plate or implant for mandibular reconstruction has evolved internationally over the last decade but most research activity in this field has taken place within the last two years. Geographically, central Europe appears to be the driving force for research in this field, producing three times the research output of Asia; the closest rival (Fig. 1). Authors from Italy and Germany were the greatest individual contributors, followed by Finland, Sweden and China. Interestingly, the Americas (including the USA) made a relatively small contribution to the overall research output despite the USA's current strong presence internationally in biomedical research overall (Conte et al., 2017). The relatively differing research output of these geographical locations may reflect a difference in overall clinical use of printed titanium for mandibular reconstruction. Analysis of international market sales would be needed to confirm or refute this.

Table 5
Reported complications.

Study	Number of patients in study with a printed implant	Number of complications in cases of printed implants	Details
Huo et al. (2015)	1	1	Failure/fracture of plate carrying bone graft to bridge segmental defect.
Qin et al. (2015)	11	1	Plate failure/fracture in a patient with right mandible ameloblastoma.
Thor et al. (2016)	1	1	Fibrous tissue at plate-bone interface at anterior end of plate (but with no detrimental non-union clinically).
Mommaerts, 2016a	12	3	Patients 1&2: intraoral wound dehiscence and infection. Patient 3: Rotation of implant around single fixation screw (required revision under LA).
Tarsitano et al. (2017b)	7	2	Patient 1: Limited mouth opening. Patient 2: Anterior displacement of the neo-condyle.
Rana et al. (2017)	22	8	Wound dehiscence in 8 patients (4 had plate exposure clinically).
Jo et al., 2018	1	1	Exposure of plate submentally 1 month postoperatively, required a local flap for coverage.

Table 6
Positive themes for printed titanium patient-specific implants and plates.

Positive Themes	Advantages of printed titanium implants/plates	
Biomechanical	Finite element analysis (FEA); biomechanical tailoring of implant, virtual simulation of biomechanics and prediction/ prevention of failure	Xu et al., (2017), Suska et al., (2016), Huo et al., (2015), Qin et al., (2015), Narra et al., (2014), Jahadakbar et al., (2016), Tuomi et al., (2017), Nasr et al., (2017), Al-Ahmari et al., (2015), Moiduddin et al., (2017), Bertol et al., (2009), Luo et al., (2017), Andani et al., (2014)
	Biomechanical superiority to plate-only reconstructions	Tarsitano et al. (2017a)
Dimensional	Accuracy of reconstruction	Tarsitano et al., (2017a), Lee et al., (2016), Hatamleh et al., (2016), Derand et al., (2012), Ciocca et al., (2015), Tarsitano et al., (2016b), Fantini et al., (2013)
Surgical technique	Reduced duration of surgery	Ciocca et al., (2012a), Fernandes et al., (2016), Ma et al., (2017), Ciocca et al., (2012c), Qassemyar et al., (2017), Rana et al., (2017), Tarsitano et al., (2016a)
	Novel designs	Xu et al., (2017), Markwardt et al., (2014a), Goodson et al., (2017), Tarsitano et al., (2017a), Leiser et al., (2016)
	Complex designs	Xu et al. (2017)
	Enhanced/novel surgical techniques and options, collaborative/ multidisciplinary approach	Goodson et al., (2017), Salman et al., (2017), Leiser et al., (2016), Ma et al., (2017), hatamleh et al., 2016, Probst et al., (2016), Tuomi et al., (2014), Tarsitano et al., (2015)
	Alternative to/avoiding free-flap reconstruction	Markwardt et al., (2014a), Fernandes et al., (2016), Tarsitano et al., (2017a), Suska et al., (2016), Rachmiel et al., (2017), Bedogni et al., (2014), Lee et al., (2016), Jo et al., 2018, Nickels (2012), Qassemyar et al., (2017), Qin et al., (2015), Reitemeier et al., (2016), Markwardt et al., (2014b), Kontio (2014), Choi and Kim, 2015
	Amenable to combining with tissue engineered materials	Markwardt et al., (2014a), Kontio (2014)
Appearance & Social Function	Reproduction of 'ideal' morphology using mirroring techniques rather than basing morphology on preoperative diseased mandible	Ciocca et al., (2012a), Ciocca et al., (2012c)
	Aesthetics/lower border contour	Goodson et al., (2017), Tarsitano et al., (2017a), Watson et al., (2014), Mommaerts (2016a), Mommaerts (2016b), Fantini et al., (2013)
	Improved quality of life	Fantini et al. (2013)
Mastication & Dental	Planning for/simulation of functional movement in articulation/ mastication	Ciocca et al., (2012a), Leiser et al., (2016)
	Optimised reproduction of dental occlusion	Ciocca et al., (2012a), Ciocca et al., (2012c), Fantini et al., (2013)
	Augmented dental implant rehabilitation	Salman et al., (2017), Rachmiel et al., (2017), Ciocca et al., (2012c)
	Condylar/temporomandibular joint reconstruction	Ciocca et al., (2012b), Ackland et al., (2017), Tarsitano et al., (2017b), Ciocca et al., (2016)
Safety & Complications	Optimised/improved osseointegration and biological safety (non-cytotoxicity)	Suska et al., (2016), Lee et al., (2016), Thor et al., (2016), Tuomi et al., (2017)
	Reduction in specific complications/recovery time	Ackland et al., (2017), Qassemyar et al., (2017), Rana et al., (2017), Tarsitano et al., (2016a), Probst et al., (2016)
Logistics	Improved accessibility to design and planning software improves accessibility to printed implants	Derand et al. (2012)
	Speed of implant production	Leiser et al., (2016), Qassemyar et al., (2017), Goodson et al., (2017)
	Economics	Tarsitano et al. (2016a)
	Planning and design can now be performed without the need for ionising radiation/CT	Eijnatten et al. (2016)

Table 7
Negative themes for printed titanium patient-specific implants and plates.

Negative Themes	Disadvantages of printed titanium implants/plates	
Logistics	Economics	Ciocca et al., (2012a), Tarsitano et al., (2017a), Ma et al., (2017)
	Duration of planning, design and fabrication	Ma et al., (2017), Rana et al., (2017)
	Complexity of planning, design and fabrication	Bertol et al., 2009
Surgical technique	Lack of flexibility to surgical plan	Ciocca et al. (2012a)
Mastication & Dental	Limited dental rehabilitation with implant-only reconstructions	Tarsitano et al. (2017a)
Safety & Complications	Limitations in condylar reconstructions	Lee et al. (2016)

Bearing in mind that CAD and additively manufactured (printed) titanium implants seems to be a rapidly evolving field of CMF surgery, we sought to evaluate the article submission-to-publication timelines, thus evaluating how timely evidence was at the point of publication. Publication timeline data was available in just over two-thirds of the articles. The duration from submission to publication (in any form) was comparable, if not better than other reported timelines in MEDLINE-indexed journals (Li and Xu, 2018; Wallach et al., 2018). However, the revision rate was considerable; required in a third of cases and might imply that even though the published articles were relevant and timely, the quality of original submissions in this field could be improved upon.

Only three-fifths (31/52) of the studies in this systematic review were clinical studies that reported specifically on the use of printed titanium implants in individual patients/groups, of which two-thirds (20/31) were case-reports and therefore were classified as

'non-evidence' and inherently biased. All of the remaining clinical studies were rated as either 'high-risk' (7 case series and 2 cohort studies) or 'moderate-risk' (2 cohort studies) of bias, with no studies considered to be 'low-risk'. However, it should be borne in mind that by virtue of the fact that each treatment is unique, the use of PSIs will continue to be reported on a case-by-case basis and the relative abundance of case reports and short series is somewhat unavoidable. Nevertheless, there are few prospective clinical studies comparing printed titanium PSIs with conventional treatments and no randomised controlled trials at all. Amongst all possible clinical applications for printed titanium implants in mandibular reconstructive surgery, the commonest indication was post-resection in 86% (121/139) of cases (e.g. for treatment of malignancy, osteoradionecrosis or ameloblastoma) (Table 4).

Two-fifths of all articles evaluated (21/52) were either CEBM level 5 evidence (19 articles) and did not study patient groups (e.g. bench studies, opinion articles etc.) or could be defined as 'systematic reviews' of sorts but failed to report in sufficient detail those patients with additively manufactured implants (2 articles). There is a wealth of laboratory based 'first-principles' bioengineering studies, looking at the biomechanical performance of mandibular implants using computerised virtual surgical implantation and known biomechanical properties of the implants (as planned for the additive manufacturing process). Although the findings were interesting and purport biomechanical advantages of printed titanium PSIs, evidence from well-designed prospective clinical studies to back these theoretical claims is lacking. Like most research questions surrounding the benefits of surgical therapies, there is a great need for prospective comparative studies (observational or interventional). One systematic review reported that "3D printed titanium fixation plates were recently tried and have been shown to be very useful for the ideal reconstruction of the mandible" but failed to cite the relevant study or number of patients involved (Choi and Kim, 2015). Another systematic review on CAD-CAM mandibular reconstruction reported studies of printed plates but did not specify what proportion of the total 178 patients received additively manufactured implants (as opposed to other CAD-CAM approaches using milled or implants 'pre-bent' to a stereolithigraphic CAD surgical model for example) (Tarsitano et al., 2015). Our review differs by focussing specifically on the role of 3D printed titanium, rather than other implant manufacturing techniques or CAD-CAM mandibular reconstruction as a whole.

5.2. Complication rates

One of the key aims of this systematic review was to evaluate the safety profile of printed titanium PSIs. In conventional free-flap reconstruction of the mandible (with stock reconstruction plates bent into shape by the surgeon), rates of plate-related complications requiring plate removal vary between centres. Wood et al. in their series of 307 patients over a 12 year period reported a plate removal rate of 35% amongst patients who underwent mandibular reconstruction with a traditional titanium plate plus fibular free flap, 21% of those with a osteocutaneous radial forearm free flap and 11% of those with a scapular free flap (Wood et al., 2018). Amongst the 139 patients in this systematic review, the reported complication rate for all types of surgery (post oncological resection and otherwise) was 12% which is comparable with figures reported by Wood et al (Table 5). However, some of the complications identified might not even have required plate/implant removal, such as the otherwise clinically inconsequential fibrous tissue formation at the plate-bone interface at 33 months post operatively reported by Thor et al. (2016). Furthermore when focussing on reconstructions of resectional mandibular defects specifically, is slightly lower (i.e. excluding the 13 'aesthetic' and 7 other non-resectional PSI surgeries, which includes the 3 complications reported by Mommaerts in their series of 12 patients with aesthetic lower border reconstruction) (Mommaerts, 2016a). The complication rate identified in this study should be interpreted cautiously as duration of follow up was reported in just under three quarters of the patient group and where it was reported, was highly variable; in some cases follow up may not have been adequate enough to pick up complications that might present 'late'. Furthermore, this study relies on authors' integrity and correct interpretation of what actually constitutes a "complication". Nevertheless, this systematic review is the largest to date and the reported 12% plate-related complication rate identified is the best estimate available.

5.3. Positive themes/benefits

One of the most frequently reported benefits of a printing titanium PSIs in mandibular reconstruction is the biomechanical advantage over conventional plating techniques (Table 7). Bending of a stock titanium osseosynthesis plate introduces new stresses in a relatively random fashion within the substance of the plate, meaning its biomechanical performance and the risk of failure with cyclical loading is unpredictable but ever-present (Tuomi et al., 2017). Additively manufactured PSIs are fabricated according to a digitally-planned structure. With the benefit of finite element analysis (FEA) of the digital design, many authors purport that failure of the PSI can be predicted, thus designs can be modified prospectively (before additively manufacturing the plate) to account for and avoid such problems. In their canine model, Xu et al. manipulated the tetrahedral porous structure of the condylar implant to mimic the Young's modulus of bone, thus avoiding an overly stiff implant and with the addition of a customised inlay rod combined with an onlay plate, the transfer of force between implant and bone was reportedly optimised (Xu et al., 2017). Other studies similarly reported the ability to use FEA to determine the alloy composition, micro-structure (e.g. porosity/tetrahedral structure) and macro-structure (e.g. tailored positioning of screw holes, implant fillet radius at the transition between implant and bone) of the implant. These factors influence its stiffness (Young's modulus) to better match the adjoining native bone; minimising implant failure or loosening of screws (through stress shielding) under physiological loading (Suska et al., 2016; Qin et al., 2015; Narra et al., 2014; Jahadakbar et al., 2016; Nasr et al., 2017; Al-Ahmari et al., 2015; Moiduddin et al., 2017; Luo et al., 2017; Andani et al., 2014). Huo et al. retrospectively demonstrated the value of FEA in planning the design of an additively manufactured PSI. Their FEA study of a fractured printed titanium PSI in a patient with a segmental mandibular defect confirmed that FEA would have been able to predict the exact site of the actual physical plate fracture and therefore can be incorporated into the design of similar additively manufactured PSIs in the future, thus minimising if not preventing 'predictable' plate failures (Huo et al., 2015). In addition, Tarsitano et al. also propose that the biomechanical advantages of CAD additively manufactured PSIs make a "customised bridging mandibular prosthesis" a suitable and biomechanically superior alternative to stock plate-only reconstructions (Tarsitano et al., 2017a). Furthermore, from a more simplistic point of view, porosity can also be planned into the design to optimise the weight of the implant/plate for physiological mandibular movements (Bertol et al., 2009).

Dimensional accuracy is commonly pushed as a key 'selling point' for printed titanium PSIs in mandibular reconstruction. Seven articles commented on the high reproducibility of the actual mandibular reconstruction in relation to the computerised plan. In a cohort study of 30 post-resection mandibular microvascular reconstructions with printed titanium PSIs versus a separate group

undertaken with pre-bent stock reconstruction plates, Tarsitano et al. demonstrated a statistically significant superiority of printed plates when trying to conform to the presurgical planned position of bony landmarks such as the gonial angle, bigonial diameter and chin protrusion (Tarsitano et al., 2016b). The same author group reported in another case, an error of 0–0.4 mm at the condyle, 0–0.8 mm at the angle and a mean error of 1.3 mm at the coronoid in a subtotal mandibular implant-only reconstruction (Tarsitano et al., 2017a). The clinical impact of the dimensional accuracy of additively manufactured implants was exemplified in two studies where both a segmental and a hemimandibular defect were reconstructed simultaneously with corresponding maxillary osteotomies in both cases, with good occlusal outcomes in both (Lee et al., 2016; Hatamleh et al., 2016). Ciocca et al. compared 5 mandibular reconstructions using printed titanium PSIs (plates) alongside fibular free flaps versus 5 cases performed with pre-bent stock reconstruction plates with fibular free flaps. Even though they identified a superior accuracy of fibula positioning in the printed plate group, they were unable to demonstrate a statistically significant difference and the study therefore may have benefitted from greater numbers to confirm/refute their findings. Nevertheless, they and other authors support the notion that printed titanium PSIs produce a reconstructed mandible that more precisely replicates the presurgical computerised plan than conventional surgical techniques (Ciocca et al., 2015; Derand et al., 2012; Fantini et al., 2013).

Twenty-eight articles discussed the positive impact of additively manufactured plates and implants on surgical technique. Ciocca et al. describe the reconstructive phase (flap fixation and insetting) with this technique as taking only 1 h and a time-cost saving of 618 Euros compared to bending a stock plate intraoperatively (Ciocca et al., 2012a). Similarly Tarsitano et al. identified an average time saving of 33 min in 20 patients with printed plates versus 40 patients with intraoperatively bent plates (Tarsitano et al., 2016a). However, we know that similarly, a mandibular reconstruction plate 'pre-bent' to a stereolithigraphic resin model prior to surgery also saves time (Gil et al., 2015). It is therefore difficult to attribute Ciocca's and Tarsitano's findings as a unique property of printed PSIs. A 'shorter' duration of surgery (relative to conventional plating techniques) was frequently cited in other studies as an advantage but unfortunately these claims were rarely supported by prospectively collected data (Fernandes et al., 2016; Ma et al., 2017; Ciocca et al., 2012c). Qassmyar et al. cited a reduction in surgical time because 3-dimensional custom-made mandibular prostheses (without autologous bone) inherently saved time as a bona fide alternative to free-flap reconstructions, with total surgical time for segmental mandibulectomies for ameloblastoma and osteoradionecrosis taking 140 and 110 min respectively (Qassemyar et al., 2017). From their experience of 22 patients with printed titanium PSIs, Rana et al. suggested that printed PSIs can reduce the ischaemia time by reducing the time needed to fit the bony free-flap into the mandibular defect when compared to hand-bent plates; reporting a median of 45.5 ± 7.0 min (Rana et al., 2017).

It is apparent from the literature that novelty and complexity in implant design can be a desirable benefit of printed titanium PSIs, in some cases leading to alternative surgical approaches altogether. The canine model by Xu et al. highlights how the bone-implant interface can be better adapted to minimise stress shielding by combining a tailored inlay rod with an onlay plate (Xu et al., 2017). Markwardt et al. demonstrated a customised tubular implant combined with bone substitute core to regenerate bone in a Göttingen minipig model, effectively using a novel implant design as a 'carrier' to potentiate tissue engineering in segmental mandibular reconstruction (Markwardt et al., 2014a). Kontio's 2014 "update on mandibular reconstruction" similarly supports the role of CAD-CAM PSIs in combination with bone substitutes to avoid the donor site morbidity of free-flap harvesting (Kontio, 2014). Following on from their previous study, Markwardt et al. also developed a modified 2-part implant which further improved the implant's primary stability (Markwardt et al., 2014b). In 2017, Goodson et al. demonstrated how a customised fibular 'cradle plate' can optimise superior positioning of the fibula segment whilst reconstructing the lower border contour in segmental mandibular defects, avoiding the need for a double-barrelled fibular flap, thus increasing pedicle length for microvascular anastomosis (Goodson et al., 2017). Tarsitano et al. report from their 2015 systematic review that the CAD-CAM approach with additively manufactured plates improves the practicality of using a higher number of flap osteotomies, achieving a more anatomical mandibular form (Tarsitano et al., 2015). Two separate author groups describe the effective treatment of severely comminuted mandibular fractures by using load-bearing mandibular PSIs incorporating a gutter-like component to carry comminuted bony segments; something that would be difficult to replicate with a stock reconstruction plate (Leiser et al., 2016; Ma et al., 2017). Other reported design novelties of printed titanium PSIs include the incorporation of designated suture anchoring holes (for resuspension of masticator muscle insertions) and minimising the risk of plate exposure by using a well-fitting lingually applied PSI (implying that bending a plate manually would have been considerably more challenging) (Tarsitano et al., 2017a; Probst et al., 2016). Tuomi et al. make the point that additively manufactured PSIs make surgery (and surgical planning) a more collaborative, multidisciplinary approach (Tuomi et al., 2014). It is perceivable that although a multidisciplinary approach may add extra work when creating and vetting the surgical plan pre-operatively, it may produce better-audited, slicker and safer surgeries overall.

One of the most commonly cited benefits of printed titanium PSIs was the ability to use an implant-only reconstruction "as a whole", as an alternative to free-flap mandibular reconstruction (Choi and Kim, 2015), avoiding all of the associated risks of the latter surgical approach altogether (long duration of surgery, donor site morbidity, flap failure and non-union for example). This was proposed by Reitemeier et al. in their animal cadaveric feasibility study of tubular "contour identical implants" suggesting PSIs as a "promising approach to bridge continuity defects of the mandible whenever an immediate reconstruction with autologous bone is not possible" and supported in a similar study by Markwardt et al (Reitemeier et al., 2016; Markwardt et al., 2014b). A series of 11 cases of implant-only mandibular reconstruction by Qin et al. reported only 1 complication of plate failure in a patient with segmental resection for ameloblastoma. In their series, the authors developed a better understanding of the technique and proposed specific refinements to optimise the design and biomechanical performance of implant-only reconstructions (Qin et al., 2015). PSIs were used in this manner (as an alternative to free-flap reconstruction) by many authors, both for segmental reconstructions (Tarsitano et al., 2017a; Suska et al., 2016; Rachmiel et al., 2017; Bedogni et al., 2014) and for those involving replacement of the mandibular condyle (Fernandes et al., 2016; Lee et al., 2016; Nickels, 2012; Qin et al., 2015), for both benign and malignant disease. One case with segmental resection for osteoradionecrosis required ongoing radiotherapy on the background of previous squamous cell carcinoma. The authors did not report any complications in the 12 month postoperative period for that patient (Qassemyar et al., 2017).

Traditional pre-plating techniques with pre-bent stock reconstruction plates often focus on restoring the mandible to the presurgical morphology. However, in the presence of disease, this might not be the 'ideal'. Printed titanium PSIs can incorporate CAD

assisted by 'mirroring' techniques in order to produce a symmetrical mandible, using the 'healthy' side to virtually reconstruct the diseased side before proceeding to implant fabrication (Ciocca et al., 2012a, 2012c). An improved and predictable three-dimensional hard-tissue aesthetic is a well-recognised feature of PSIs in comparison to pre-bent reconstruction plates (Tarsitano et al., 2017a), especially when focus is placed upon reconstruction of the mandibular lower border morphology specifically (Goodson et al., 2017; Watson et al., 2014; Mommaerts, 2016a, 2016b). Along with other functional outcomes such as mastication, these benefits are purported to provide an overall improvement in quality of life outcomes (Fantini et al., 2013). However, as demonstrated by the evidence-level profile of this systematic review, such claims are frequently based upon authors' opinions and not on prospectively collected data using validated qualitative outcome measures. This claim needs to be better supported with well-designed observational and interventional studies wherever feasible.

With regards to augmenting dental/masticatory function, a key benefit of a CAD-CAM implant such as a printed titanium PSI is that with a known/planned shape and structure, the prosthetic and contralateral native condylar movements and masticatory forces on the implant can be evaluated virtually before committing to fabrication and insertion of the implant itself (Fantini et al., 2013). This principle was adopted in two reports, reporting centric occlusion with good masticatory function, and good mandibular articulation as the outcomes (Ciocca et al., 2012a; Leiser et al., 2016). However, such outcomes are crudely subjective and a more quantitative measure of occlusion and mandibular excursion (pre and post-operatively) from prospective studies is warranted to qualify this suggested benefit. Ciocca et al. in their 2015 cohort study also eluded that a printed PSI provides superior dental occlusion. They compared fibular flaps fitted with 5 printed PSIs versus 5 pre-bent stock plates and identified a mean difference in accuracy of the planned position of fibula segments (for subsequent dental rehabilitation) but failed to show a statistically significant difference. In their study, a total of 10 patients were assessed and a slightly different measuring technique was used in each treatment group (comparing the pre-bent plate outcomes to the presurgical mandibular form whereas the printed plate outcomes were compared to the 'ideal' virtual surgical plan) (Ciocca et al., 2015).

The capacity for dental implant rehabilitation is cited as another benefit of PSIs in reconstruction of resectional mandibular defects (Ciocca et al., 2012c). Salman et al. suggested that the accuracy of bony flap reconstruction combined with a printed titanium PSI enabled the successful incorporation of an immediate 5-tooth definitive endosseous dental implant restoration during the single mandibular procedure (thus avoiding second-stage surgical or early restorative procedures). Unfortunately their article included follow-up for only 2 weeks so the ultimate success of those implants would require further confirmation. Nevertheless, their report eludes to an impact of precise bony reconstruction on dental rehabilitation (Salman et al., 2017). A study involving pre and post-operative bite registrations of dental occlusion would be a suitable method to quantitatively assess occlusal outcomes in mandibular reconstruction. Unfortunately, none of the published studies reviewed did this. Rachmiel et al. demonstrated the technical feasibility of using a printed titanium PSI with integrated dental implant abutments following resection of an ameloblastoma, negating the need for a bony free-flap. Their PSI incorporated a mesh carrier for particulate bone graft surrounding the implant abutments. They reported stable occlusal and aesthetic (symmetry) outcomes 1 year postoperatively but the viability of the surrounding particular graft collar was not reported upon (Rachmiel et al., 2017).

On the matter of restoring condylar function, numerous advocate the incorporation of a patient-specific anatomical condylar head incorporated into the PSI (condyle-only temporomandibular joint reconstruction) following oncological resection of the mandibular ramus condyle unit (Ciocca et al., 2012b, 2016; Tarsitano et al., 2017b). It is reasonable to state that amongst the surgical community, there is considerable concern over the use of condyle-only temporomandibular joint reconstructions following the adverse outcomes of glenoid fossa erosion and heterotopic bone formation with stock implants identified by Lindqvist et al., in 1992 (Lindqvist et al., 1992). Consequently, the current vogue is to use a condylar and glenoid fossa component in combination wherever possible (Westermark et al., 2006). However, in a series of 9 patients with printed PSIs including condyle-only joint replacements, short-term outcomes were encouraging. In that study the follow-up was limited and wide-ranging between patients (2–72 months) and the authors proposed a larger study to confirm their preliminary findings (Tarsitano et al., 2017b). In a similar earlier 2016 study of 5 patients, none of the patients encountered clinical complications and quantified changes in anatomical dimensions of the glenoid fossa were small (thickness increased in one patient by 0.48 mm and reduced in another by 0.11 mm) at 5 years follow-up. The authors postulating that creation of a patient-specific anatomical condyle "conserved the physiology of the articular surfaces" (Ciocca et al., 2016). In addition to partial temporomandibular joint (TMJ) arthroplasty, additively manufactured PSIs have been developed for total joint replacements (including both a condyle and fossa component). Ackland et al. used printed titanium to produce their "Melbourne prosthetic TMJ". With the incorporation of FEA into their PSI design, they were able to produce an implant with superior biomechanical properties (and masticatory forces) with lower screw stresses than a commercially available stock prosthesis (Ackland et al., 2017). This serves as a promising approach to design of patient-specific TMJ replacements hereon.

As with any novel treatment, safety and minimising complications is the primary concern. In terms of biocompatibility, there is considerable opinion that additively manufactured titanium/alloy PSIs are safe and in some cases, the design and fabrication technique actually improves osseointegration through selective porosity and tailored biomechanical properties (Suska et al., 2016; Lee et al., 2016). A safe cytotoxicity profile was confirmed scientifically by Tuomi et al. using in-vitro techniques (Tuomi et al., 2017) and osseointegrative capacity by Thor et al. following removal of a printed titanium PSI from a patient using analytical techniques such as microcomputed tomography, backscattered-scanning electron microscopy, histology, and quantitative-polymerase chain reaction (Thor et al., 2016). Minimisation of complications principally relates to the aforementioned benefits (e.g. reducing predictable biomechanical failure, minimising dimensional inaccuracy, reducing duration of surgery and avoiding the risks of microvascular reconstruction) but some additional specifics are mentioned by a few authors, for example: reduced risk of nerve injury (from screw/implant placement) (Ackland et al., 2017; Probst et al., 2016), reduced free-flap ischaemia time due to speed of fitting the bone flap into the defect (Rana et al., 2017) and reduced duration of hospital stay with associated net economic benefits (Tarsitano et al., 2016a).

Positive themes relating to the logistics of using printed titanium PSIs were mentioned, suggesting that this approach to mandibular reconstruction is becoming increasingly accessible (with development of designated commercial software in particular) (Derand et al., 2012) and feasible to the average surgeon with acceptable design and fabrication times (Leiser et al., 2016; Qassemyar et al., 2017). In 2017 we reported a turnaround time

from acquisition of presurgical CT scan data to insertion of the sterile PSI of 7 days. The requirement for presurgical CT scanning is not a commonly reported problem for patients requiring mandibular reconstruction since the scan is commonly indicated for other clinical reasons anyway. Nevertheless, Eijnatten et al. report in their study of cadaveric mandibles the ability to accurately use ultrashort echo time MRI sequences for assessment and planning of printed titanium PSIs, avoiding ionising radiation altogether (Eijnatten et al., 2016). This advancement opens another avenue for the application of additively manufactured PSIs in other patient cohorts, such as paediatric and benign pathologies where ionising radiation may be relatively contraindicated.

5.4. Negative themes/limitations

There is considerable contradiction in the literature regarding the healthcare economics of printed titanium PSIs. Despite the fact that one author group have cited cost savings from reduced duration of surgery and hospital stay (Tarsitano et al., 2016a; Ciocca et al., 2012a), the same group acknowledge that the cost of designing and fabricating the implants is a disadvantage (Ciocca et al., 2012a; Tarsitano et al., 2017a), as do others (Ma et al., 2017) (Table 7). To address this, there clearly is a need for an economic evaluation of printed titanium PSIs in direct comparison with conventional and comparable surgical techniques, for example comparing with pre-bent stock reconstruction plates in free-flap reconstruction of mandibular resection defects. Other negative logistical pre-surgical issues include the duration and complexity in the design and fabrication process, which are seen as a significant limitation by some authors, despite the positive opinions of others aforementioned (Ma et al., 2017; Rana et al., 2017; Bertol et al., 2009).

One of the most seemingly obvious but least-mentioned limitations of PSIs, regardless of fabrication technique is the limited ability (or inability) to adapt the implant to changes in the surgical plan intraoperatively (Ciocca et al., 2012a). For example change in extent of mandibular resection due to tumour growth, equipment (saw) failure or technical error by the surgeon might render the implant useless. In this situation, the fall-back would be more traditional techniques such as intraoperative bending of stock reconstruction plates. Therefore, it is imperative that any surgeon wishing to use printed titanium PSIs is well-versed in both techniques.

There are some specific indications for printed titanium PSIs that authors exercise caution. Tarsitano et al. acknowledge that dental rehabilitation with osseointegrated dental implants in PSI/plate-only segmental reconstructions (i.e. without autologous bone) is impossible (Tarsitano et al., 2017a). Presumably they did not consider PSI-integrated dental abutments as per Rachmiel et al. (2017) or they did not feel that this approach was a viable/safe option. It might be unfavourable to integrate dental abutments into the structure of a mandibular PSI for two reasons: i) limited biological width/barrier of mucosa between the contaminated oral environment and the mandibular PSI with subsequent risk of catastrophic metalwork infection, and ii) risk of difficulty in removing the abutments in the event of infection/failure (whereas an osseointegrated dental implant will naturally loosen or can be otherwise unscrewed from bone). Integration of dental abutments into the mandibular PSI may therefore present an unnecessary risk. If using PSI-only (non-osseous) mandibular reconstructions, mucosa-borne prostheses could be tried with caution, or perhaps more safely, no dental prosthesis in the affected region at all. On the specific matter of condylar/total TMJ reconstruction, there is differing legislation internationally over the safety profile of using additively manufactured implants for reconstruction of articular joints. In some countries such as the United Kingdom, use of a PSI in this context is 'off-licence' and requires the formal written acknowledgement of this by the operating surgeon before implantation. In the report by Lee et al., the Korean Ministry of Food and Drug Safety would not Permit reconstruction of the TMJ with an additively manufactured PSI. Consequently the authors had to use a stock joint replacement connected to the printed PSI to overcome this (Lee et al., 2016). The lack of high-level clinical evidence for or against the use of printed titanium in TMJ reconstruction (and the resulting uncertain safety profile) means that at present, its application in this setting is limited.

6. Conclusions

Over the last decade, additive manufacture and the use of printed titanium PSIs for mandibular reconstruction has boomed in central Europe, and to a slightly lesser extent worldwide. Complication rates with this novel approach appear to be in keeping with existing/traditional techniques. The reported benefits of this approach are numerous but with only a few key limitations. However, the overall scientific quality of the evidence available is average at best, with clinical evidence predominantly low-level and at moderate-to-high risk of bias. In order to confirm or refute the positive and negative themes identified in this review, well-designed prospective clinical studies are needed, comparing 3D-printed titanium PSIs side-by-side with other customised and traditional approaches (such as milled, pre-bent or intraoperatively-bent reconstruction plates for the management of resectional defects for example). Nevertheless, the trends in their use and reported benefits seemingly outweighing reported limitations suggests that 3D-printed titanium PSIs have an increasingly valuable role in mandibular reconstruction.

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Conflicts of interest

None to declare.

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