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Model-free digital workflow and immediate functional loading of implant-supported monolithic glass-ceramic crowns: A case series

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A R T I C L E I N F O

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A B S T R A C T

Objectives: The aim of this study was to evaluate surgical and prosthetic outcomes of immediate functional loading of implants with glass-ceramic screw-retained single crowns.

Methods: A total of 22 implants were placed. Within 24 h, functional full-contour glass ceramic crowns were delivered to patients. The amount of attached gingiva, Simplified Oral Hygiene Index Score, bleeding on probing, time after extraction, bone type, implant size, soft tissue thickness, primary stability, a general fit of the restoration, occlusal and proximal contacts were recorded. Restorations were followed-up at 1, 3, and 6 months tracking marginal bone loss (MBL), noting changes in occlusal and interproximal contacts, checking other possible complications.

Results: One implant failed and was removed after 4 weeks (95.5% survival rate). The rest of the implants and crowns functioned with no complications during the follow-up period of 6 months. Factors such as time after extraction, bone type, implant size, soft tissue thickness, and primary stability recorded in Ncm and implant stability quotient (ISQ) values, were not associated with MBL ($p<0.05$). Mean MBL was found to be 0.3 mm (standard deviation = 0.42) mesially and 0.4 mm (standard deviation = 0.66) distally. One distal and one mesial proximal contact were found to be missing at the 6-month check-up appointment.

Conclusions: Within the limits of this study, fully digital workflow without a 3D printed model could be successfully employed for immediate functional loading with single-unit implant-supported crowns. Further studies are needed to obtain long-term results with a larger sample of patients.

Clinical significance: Model-free digital workflow and immediate functional loading of implant-supported monolithic glass-ceramic crown might be viable option to restore a single tooth defect.

1. Introduction

Various protocols for immediate dental implant loading have been in use for more than 30 years [1]. According to the literature, the survival rate may vary from 86 to 100% [2]. while success rates have been reported to range from 95 to 100% [1]. “Implant survival”, according to the literature, means that the implant is present in the mouth at the time of the examination regardless of the state of the prosthetic component or the patient’s satisfaction. “Implant success”, on the other hand, means that the implant functions with no biological changes or with acceptable biological changes around the implant and that the patient is satisfied with the treatment [3]. Marginal bone loss (MBL) could be seen as one of

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the most important factors when judging implant success. An immediate loading protocol should be considered when there is a favorable biologic situation, a need to preserve soft tissue contour or to increase time- and cost-efficiency of the treatment [4,5].

Immediate functional loading is considered when the restoration is delivered immediately after the surgery and has functional occlusal contacts. On the other hand, immediate non-functional loading (immediate restoration) is considered when the restoration is delivered immediately after implantation but has no occlusal contacts (static or dynamic) [6]. Unfortunately, some studies do not indicate the type of immediate loading properly [5,7], and details about the condition of occlusion are often missing.

It is well documented, that placing an immediate restoration without occlusal contacts is a highly successful protocol to restore single tooth defects [8–10]. Moreover, with adequate primary stability, an implant can withstand the immediate functional loading [4,5,11–16]. Bone type, defect size, implant size, macro-design, and surface characteristics - all play important roles [1,17,18]. Various implant insertion torque and implant stability quotient (ISQ) values are recommended for immediate loading with different prosthetic options [4,19]. As remodeling takes place, secondary stability should compensate for the loss of primary stability.

Digital dentistry has certainly changed implant dentistry significantly in recent years. Fully digital workflow for implant restorations is becoming standard in everyday practice [20–22]. Furthermore, if the full contour restoration is selected for restoration, there is a possibility to follow not only the fully digital, but also the model-free approach, when the restoration is finalized without having the master model [23–25]. Significant interest in these kinds of procedures is observed for numerous reasons. Simplification of the manufacturing process, time saving are just a few of the advantages [22,25–27]. It is also important to note that digital workflow is preferred by the patients as well [28,29]. One of the limitations of these kinds of model-free reconstruction is the lack of individualization options. Studies have demonstrated, that, even though, patients prefer digital workflow, conventional layered restoration produces more favorable esthetics compared to monolithic restorations [30]. Also, it should be taken into consideration that these kinds of pre-sintered materials might decrease an average life of burs and machine itself.

There is very limited data on the clinical outcomes of immediately loaded implants with full-contour ceramic restorations produced using a model-free digital workflow. Also, there is a lack of information about the stability of occlusal and proximal contacts after immediate functional loading of single crowns. Surgical, prosthetic, and other factors possibly associated with treatment outcomes should be investigated more in detail.

This case series study aimed to evaluate the clinical acceptance of immediately functionally loaded single glass-ceramic restoration on implant made utilizing model-free fully digital by checking general fit, occlusal and interproximal contacts. Furthermore, to follow up reconstructions and evaluate biological and prosthetic outcomes after 1, 3, and 6 months checking marginal bone, occlusal and interproximal contact changes. The null hypotheses were, that the factors investigated have no association with the biologic and prosthetic outcomes of immediately loaded single implants with glass-ceramic screw-retained crowns and that the number of occlusal and proximal contacts will not change significantly during the observation period.

2. Materials and methods

2.1. Patient sample, inclusion, and exclusion criteria

Patients were enrolled in this case series study at two private clinics in Lithuania. Permission from the Ethics Committee for Biomedical Research was obtained (No 158 200–16–861–370). Nineteen subjects who required a single tooth implant-supported crown in the healed after extraction, posterior region of the mandible were included following inclusion and exclusion criteria (Table 1). Nine males and thirteen females (mean age – 34.4 (standard deviation = 11.6) years) participated in this study.

Bone Level Tapered SLActive® (Institut Straumann AG, Basel, Switzerland) implants were used in the study. The selection of implant size was based on bone dimensions measured in the cone beam computerized tomography (CBCT) (iCAT, Hatfield, Pa, USA) images. Implant placement was performed only in healed, post extraction sites. The width of the bone crest had to allow a minimum of 1.5 mm of bone on both lingual and buccal sides after implant placement. Professional hygiene procedures were done not less than 2 weeks before the surgical appointment.

2.2. Surgical procedures

Before the initiation of surgical procedures, the shade of the adjacent teeth was taken using a Vita 3D Master or Vita Classic® (Vita, Bad Säckingen, Germany) shade guide and digital photography. Following local anesthesia, a crestal incision was made at the edentulous area. Full-thickness flap was elevated to expose the alveolar ridge. Measurement of the vertical thickness of soft tissues was made on the lingual aspect of the flap before the

The surgical procedure for implant placement was carried out according to the recommendations of the manufacturer. A profile drill was used at the coronal third part only in bone type 2 situations. The taping step was omitted to achieve good primary stability. For selected cases, where marginal bone impeded scan post seating, a bone profiler set was used. All cases included in the study had an implant insertion torque of more than 40 Ncm and an ISQ value of no less than 70. The maximum insertion torque allowed was 60 Ncm and implant insertion speed was 15 rpm. Implants were placed approximately 1 mm subcrestally considering implant platform position on the buccal side. Amoxicillin 500 mg 3 times a day for 5 days and chlorhexidine gluconate 0.12% solution mouth rinse before the surgery and for one week after the surgery was administered to all patients. Sutures were removed after one week.

2.3. Prosthetic procedures

All fully functional crowns were delivered within 24 h after implant

Table 1
Inclusion and exclusion criteria were used in the study. *Bilateral cases were treated in two stages, one side first, then the other side two months later.

Inclusion	Exclusion
19–65 years old	Severe parafunctional habits (bruxers or clenchers, nail-biting, etc.). Presence of *linea alba* or tooth impressions on the tongue
Mandible	
Missing molars or premolars unilaterally*	
Single implant-supported crowns	Smoking: more than 10 cigarettes per day
Max. 3 missing posterior teeth	Canine or group guidance absent, occlusal interferences on posterior teeth
Minimum 7 mm ridge width in the molar region, allowing an implant size of at least 4.1 × 10mm	Diabetes, radiation treatment, chemotherapy, bisphosphonates, osteoporosis, rheumatoid arthritis
Minimum 6 mm ridge width in premolar region, allowing an implant size of at least 3.3 × 10mm	Active periodontal disease or history of aggressive periodontitis
No need for bone augmentation	OHI-S less than 0.5
Healed implant site (at least 3 months after extraction)	
Antagonists present (natural or restored)	
Professional oral hygiene performed no more than 3 months earlier	

placement. Following implant installation, a Cerec® (Dentsply Sirona, York, PA, USA) two-piece scanbody was used to transfer the dimensional location of the implant. Sirona scanpost was screwed onto implant with torque wrench according to manufacturer's recommendation. Then Sirona scanbody was fixed onto scanpost. Omnicam® (Dentsply Sirona) intraoral scanner (IOS) (CEREC AC software 4.3) was used to take the full-arch digital impressions and bite registration according to the recommendations of the manufacturer with natural lighting conditions. Standard recommended occlusal-buccal-oral surface scanning strategy was utilized. Calibration was performed before every scanning procedure. The intraoral scanner data and shade information were sent to the laboratory. CAD/CAM specialist and technician with more that 20 years of experience designed fully functional final restorations using inLab CAD (Dentsply Sirona) software and were milled from n!ce® (Institut Straumann AG) glass-ceramic (lithium aluminosilicate ceramic reinforced with lithium disilicate) A14L type LT (low translucency) blocks using a Cerec MC XL (Dentsply Sirona) milling unit. All restorations were milled with the Cerec® IPS e.max® CAD fine milling strategy. After successful milling, all restorations were polished manually for approximately 5 min, as no crystallization firing is required for the material. Then, the crowns were stained with VITA AKZENT® Plus (VITA Zahnfabrik) stain and cemented to the titanium (Ti) bases (Variobase® C, Institut Straumann AG) using Multi-link cement (Ivoclar Vivadent, Schaan, Lichtenstein) according to the recommendations of the manufacturer. The cementation procedure was done freehand and without 3D printed master models (Fig. 1). To manufacture a single crown on implant using pre-sintered ceramics it took on average: 15 min to design a restoration in a CAD system, 40 min to mill the crown, 90 min to stain and glaze it.

2.4. Outcome variables

Clinical and radiological data were collected before and during surgery, at restoration delivery, after 1 week, and 1, 3, and 6 months later. Surgery variables were the following: attached gingiva, implant length, implant diameter, bone type, implant position according to bone crest. Clinical examinations included a general evaluation of restoration fit, recording the amount of attached gingiva, Simplified Oral Hygiene Index (OHI-S), bleeding on probing (BOP), occlusal and proximal contacts.

Occlusal and proximal contacts were achieved on final restorations with control of 8-μ shim-stock foil (Hanel, Coltene, Altstätten, Switzerland). No contacts were left during eccentric movements. Also, occlusal contacts were marked with a 12-μ occlusion foil (Hanel) and photographs were taken. Waxed dental floss (Oral-B, The Procter & Gamble Company, Cincinnati, Ohio, USA) was used for the evaluation of proximal contacts at delivery and during the follow-up period.

Intraoral radiographs were obtained using an intraoral parallel dental radiography technique with a standard holder at delivery (baseline) and after 1, 3, and 6 months (Fig. 2).

Measurements of the MBL (the distance between the abutment/fixture junction and the first visible contact of the bone to implant surface) were made at the mesial and distal aspects using Romexis software (Planmeca, Helsinki, Finland) after the image calibration procedure. Calibration of periapical radiographs was done according to implant neck diameter. MBL was estimated as the difference in marginal bone level between the baseline and follow-up radiographs. Two investigators (JP and MK) were responsible for determining bone level in periapical radiographs. Calibration between investigators was done using a random selection of non-study periapical implant radiographs. If measurements were different between investigators, a brief discussion was made to increase the reliability of measurements. To determine intraclass correlation coefficient between two investigators, 20 non-study radiographs were measured for statistical analysis.

Fig. 1. Glass-ceramic crown cemented to the titanium base before delivery.

2.5. Statistical analysis

Descriptive statistics such as frequency tables for qualitative and quantitative variables were used to describe patient-related information, anatomical and implant features, surgical and prosthetic interventions, biological and prosthetic outcomes for general knowledge. Mean and standard deviation were calculated for quantitative variable (marginal bone changes in mm) to assess the radiographic bone-level parameters. The univariate logistic regression model was used to evaluate the potential risk factors for biological and prosthetic outcomes. The Shrout–Fleiss reliability score was calculated for the evaluation of the quantitative intraclass correlation coefficient between two investigators, JP and MK comparing randomly selected 20 randomly selected non-study single implant periapical radiographs [31]. Interobserver kappa values were >0.75, meaning excellent. A two-tailed p-value (< 0.05) was considered statistically significant. Statistical analysis was performed using SAS version 9.2 (SAS Institute Inc., NC, USA).

3. Results

3.1. Patients sample

Twenty-two bone-level tapered implants were placed in 19 patients in this clinical study. The mean age of patients was 34.3 years (standard deviation = 11.65). Meant time after extraction was 80.9 months (standard deviation = 112) and ranged between 4 and 360 months. Nineteen implants were inserted in molar sites and 3 in the premolar region in the mandible. Other characteristics of the cases are presented in Table 2.

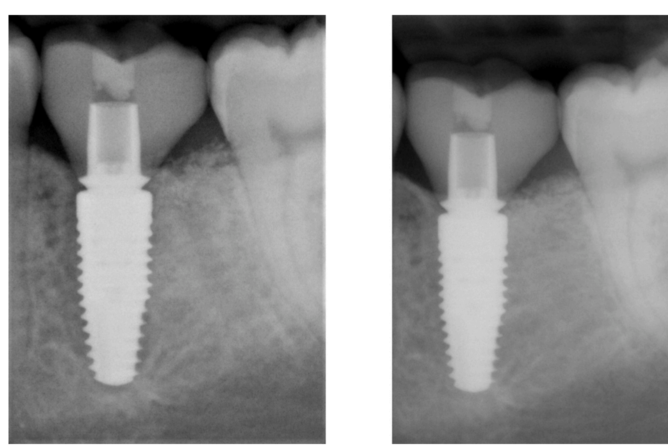

Fig. 2. Intraoral radiographs taken at the insertion (left) and 6 months later (right).

Table 2
Summary of biological, surgical, and prosthetic parameters of the cases included in the study.

Characteristic	
Attached gingiva (mm)	4.7 +/−1 mm
Implant length	12 mm: 11, 10 mm: 11
Implant diameter (molar region) $n = 19$	4.1 mm: 17, 4.8 mm: 2
Implant diameter (premolar region) $n = 3$	3.3 mm: 2, 4.1 mm: 1
Bone type	Type II: 14, Type III: 8
Cases with subcrestal positioning of 1 mm (%)	68%
Cases with subcrestal positioning of 2 mm (%)	32%
Vertical thickness of soft tissues (mm)	2 mm and more
Cases, when bone profiler set, was needed (%)	27%
No adjustments needed	4%
Minor adjustments needed (done chairside)	92%
Major adjustments needed (sent back to the dental technician)	4%

3.2. Prosthetic outcomes

All delivered crowns matched the esthetic demands of the patients. All crowns (except one for the removed implant) functioned with no technical/mechanical complications after 6 months. The need for adjustments of restoration contours at the time of delivery is presented in Table 2. According to C. Mangano et al. classification [32] Minor adjustments were needed for most cases. For one case notable adjustments of occlusal and proximal surfaces were needed (no new crown had to be produced, as chair-side adjustment and polishing was sufficient). No major adjustments needed. All complications were technical, meaning 18 of 22 crowns had occlusal contact holding shim-stock foil. All 22 crowns had contacts that were marked with 12µ occlusion foil. Two distal and one mesial proximal contact surfaces were missing during a delivery appointment, but at the end of the follow-up period, only 1 proximal contact was missing mesially and distally (Fig. 3). No technical or mechanical complications noted in follow-up period according to G. Salvi et al. classification [33].

No statistically significant relationship between implant size, time after extraction, bone type, soft tissue thickness, primary stability (Ncm or ISQ values), and MBL was found. No significant changes in the number of occlusal and proximal contacts were identified during the follow-up.

3.3. Biological outcomes

Good primary stability was achieved with a mean insertion torque of 48 Ncm (standard deviation = 4.2) and a mean ISQ value of 76 (standard deviation = 4.33). The healing of the implantation sites was uneventful. One implant failed and was removed after 4 weeks. It should be mentioned that this patient has had a medical record of complicated implant healing and loss in another site. In this case, a lack of bleeding was observed at the site of the osteotomy. The OHI-S index at the 6-month follow-up was 0.3 (standard deviation = 0.18). Mean MBL was 0.3 mm mesially (standard deviation = 0.42) and 0.4 mm (standard deviation = 0.66) distally (Figs. 4, 5).

4. Discussion

Both null hypotheses were accepted. The factors investigated have no association with the biologic and prosthetic outcomes of immediately loaded single implants with glass-ceramic screw-retained crowns and the number of occlusal and proximal contacts will not change significantly during the observation period.

This study has shown that immediate loading with the final crown on an implant can be regarded as a viable treatment option that reduces treatment time and provides satisfactory outcomes. Although the 6-month results demonstrate positive outcomes, it is important to mention that careful patient selection and treatment planning are of crucial importance, as one implant was lost in a patient having a previous history of complicated healing. Certain factors are important when we consider the result of this study. Implant properties (type, dimensions, neck design), implant-abutment connection, fit of the prosthesis, occlusion factors, implant site properties, and other factors can cause the variation of results [34,35]. It is unknown if immediate

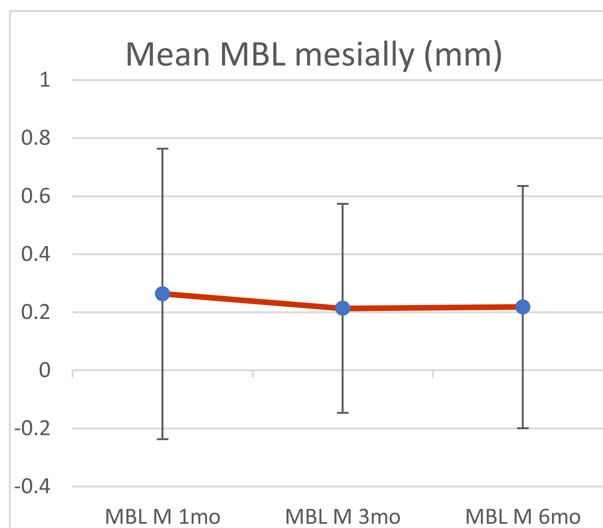

Fig. 4. MBL changes during 6 month follow-up period at mesial sites of implants on periapical radiograph. (Mean with standard deviation).

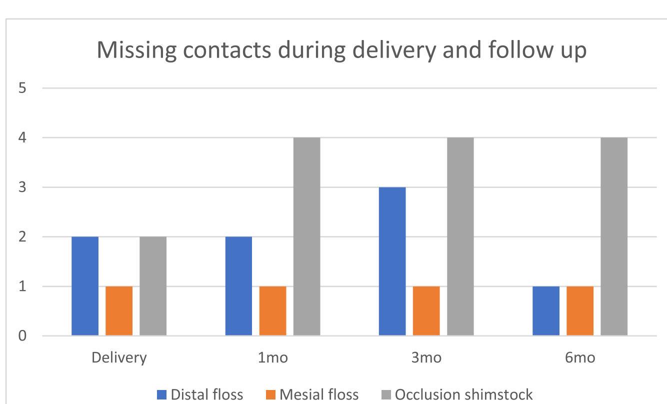

Fig. 3. Stability of occlusal and proximal contacts during the follow-up period (delivery, 1, 3 and 6 months).

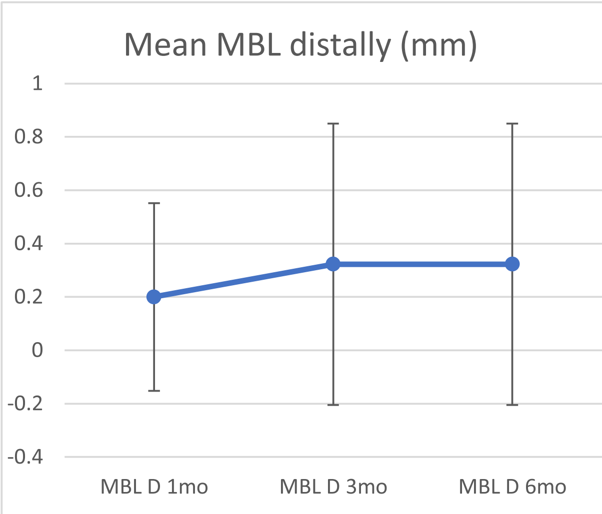

Fig. 5. MBL changes during the 6 month follow-up period at distal sites of implants on periapical radiograph. (Mean plus standard deviation).

implant loading protocols can be applied safely in patients who have parafunctional activities, suffer from diabetes or osteoporosis, smoke, or have some other systemic risk factors [1]. For this reason, patients with certain conditions were excluded from the study [36].

The primary stability of implants might not be so crucial when multiple implants are rigidly connected, because implants are splinted and forces are distributed to all implants [37,38]. With short span and particularly with single-unit restorations, the primary stability should not be compromised.

Functional loading of a single unit crown carries the challenge of maintaining implant stability under occlusal loading without the option of implant splinting. It has been suggested that micromovements exceeding 150 microns lead to implant encapsulation rather than osteointegration [39]. Therefore, implant insertion torque of 32, 35, and 40 Ncm and higher have been suggested as a prerequisite for immediate loading [1]. Since single implants were functionally loaded in this study, insertion torque of 40–60 Ncm was chosen. However, some studies may suggest that higher insertion torques could be associated with the risk of decreased secondary stability due to more intense bone remodeling [40]. Moreover, a meta-analysis by Li et al. revealed that there are no statistically significant differences between high insertion torque and conventional insertion torque in terms of effects on marginal bone resorption [41].

An apically tapered implant with a rough surface was selected for the study, as these features were found to help achieve better primary stability and were considered suitable for immediate loading [39,42,43]. According to the literature, some surface treatments could further promote secondary stability [18,44]. Morse taper connection, as used in this study, minimizes microleakage and micromovement and helps avoid disturbing peri-implant tissue formation around a newly inserted crown [45,46].

Immediate implant loading has traditionally been achieved with a temporary restoration. Temporary restorations have certain disadvantages related to the possible negative effects of poly-methyl methacrylate or composite materials used subgingivally, inferior connection stability due to lower insertion torque, risk of documentation from the abutment, etc. Moreover, repeated disconnections of prosthetic components at later restorative stages are inevitable and may negatively influence bone stability [36]. It has been shown that the 'one abutment one time' or 'definite abutment' concept could provide better soft and hard tissue response around implants [47]. In these cases, however, an additional prosthetic procedure is needed to fabricate the final restoration that is cemented to the custom abutment. Recent advances in digital technologies allow the fabrication of final restorations in a much faster way [25]. According to the literature, digital implant impressions with IOS for multiple-implant situations could still lack accuracy, but for single-unit screw-retained restorations, it could be considered clinically acceptable [25,48,49]. Therefore, based on reported high success rates with immediately loaded implants and the advantages of the early introduction of a final restorative component, the immediate delivery of a final restoration after implantation could be a rational solution. Moreover, fewer appointments and less treatment time can contribute to patient satisfaction [50].

Especially for single-unit restorations, digital workflows are becoming more backed by scientific research [21,22,24] and adopted by more practitioners. A completely digital workflow for veneered restorations would require 3D printed master models. They still lack validation for application with fixed partial dentures [51,52]. 3D printed models can be omitted when full-contour restorations are produced [23]. Also, the production of monolithic restorations is more cost-effective [25,27,52,53]. First choice material for monolithic posterior implant crowns is zirconia due to its biocompatibility and good mechanical properties for such restorations [54]. Besides zirconia as a monolithic restoration material for single-unit restorations, lithium disilicate–based ceramics are also used very widely, even though some authors suggest that zirconia has better mechanical properties and biocompatibility than lithium disilicate [55]. On the other hand, unlike zirconia, lithium-disilicate based ceramics do have a wear pattern more similar to enamel [55]. Some of lithium disilicate ceramics do not require sintering, so treatment time can be shortened further even though these kinds of materials might decrease the average lifetime of milling machines or burs. This is because materials in the green state are much softer than those pre-sintered. Studies show that polished zirconia is a very biocompatible material [56–58]. Similarly, a favorable peri-implant soft tissue outcome was reported with lithium disilicate–based materials [35,59]. To increase the efficiency of the workflow, glass-ceramic material (lithium aluminosilicate ceramic reinforced with lithium disilicate), which does not require crystallization treatment and can be used as a full-contour material with a model-free digital workflow, was chosen. Using the milling blocks with a prefabricated interface for the Titanium base (A14 blocks) allowed to avoid milling of the complex geometric form. Due to this, the consistency of the workflow became better and production time was shortened. The results of this study have shown that a model-free digital workflow can provide clinically acceptable results.

MBL data after the 6-month follow-up period in this study suggests, that the results are similar to other studies, showing less than 1.5 mm of MBL in the first year. Two implants had MBL higher than 1.5 mm after 6 months, which cannot comply with implant success criteria [60,61]. However, it was reported, that with longer observation periods marginal bone gain can be expected [62].

Mean MBL after 3 months was 0.3 mm in this study compared to 0.75 mm loss reported by other authors [63]. Similarly, as in other studies, no statistically significant associations between soft tissue thickness, implant positioning level subcrestally, bone profiling, and MBL were found [64,65].

All deviations in the selected workflow can result in less than optimal occlusal contacts. This can be regarded as a significant risk factor, considering that functional immediate loading treatment was implemented with single-unit crowns. In this study, a meticulous occlusal check to eliminate eccentric forces was implemented during the delivery of the restoration and follow-up visits [39]. However, the parafunctional activity could not be diagnosed objectively and, therefore, remained a risk factor.

Implants placed and loaded conventionally tend to lose proximal contacts during a 5–15 year period, as observed by Papageorigious et al. [66]. this is explained by the continuous migration of neighboring teeth, with a tendency for the crown to lose its mesial contact point. In vivo animal studies were used to show that immediately loaded implants can adapt their position better during the healing phase than ones with delayed loading [67]. Therefore, occlusal and proximal contacts hypothetically might be less stable with immediate implant loading. Data on the dynamics of the occlusal and proximal contact surface of immediately loaded implant-supported restorations are scarce [5,7]. The results of this study showed stable proximal and occlusal contacts during this relatively short follow-up period.

This study has some limitations. Firstly, follow-up time is quite short. Further follow-ups are planned every year with an update of scientific publications. Secondly, the number of implants placed could be higher, but because of strict exclusion criteria, the number of implants placed is acceptable. Further studies should be carried out with a large number of participants. Moreover, a control group of implants reconstructed conventionally could be introduced in a similar study to make a comparison between groups. Lastly, different results might be expected with different equipment and software that was used in the current study. Development of immediate loading protocols, clinical trials with a focus on single visit final restorations are very important. This kind of procedure, when everything is done in a single visit, economical and time effectiveness, patients' comfort, minimal invasiveness is becoming more important in dentistry. Backed by clinical research, definite immediate single unit restorations on implants might be a reasonable and widely used algorithm to reconstruct such defects when cases are carefully selected.

5. Conclusions

Within the limitations of the current study, the following conclusions can be made:

1 Digital workflow with a model-free approach can be safely used in combination with immediate loading;
2 Immediate functional loading with a single-unit implant-supported crown fabricated from glass ceramics provided clinically acceptable biological and prosthetic outcomes;
3 Marginal bone loss was not significantly associated with any factors investigated (the amount of attached gingiva, Simplified Oral Hygiene Index Score (OHI-S), bleeding on probing (BOP), time after extraction, bone type, implant size, soft tissue thickness, primary stability, occlusal and proximal contacts) and was similar as reported in other studies;
4 Occlusal and proximal contacts were stable throughout the follow-up period;
5 Further studies with a larger number of patients should be made to confirm the outcomes of the present investigation

CRediT authorship contribution statement

Justinas Pletkus: Methodology, Data curation, Writing – original draft, Writing – review & editing. **Vygandas Rutkūnas:** Conceptualization, Methodology, Validation, Writing – original draft, Visualization, Supervision. **Ieva Gendvilienė:** Investigation, Visualization. **Rokas Borusevičius:** Investigation, Visualization. **Agnė Gedrimienė:** Software, Writing – review & editing. **Adomas Auškalnis:** Conceptualization, Methodology, Visualization, Supervision. **Marius Kubilius:** Methodology, Investigation, Writing – review & editing. **Jotautas Kaktys:** Software, Validation, Data curation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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