

XENOGENEIC COLLAGEN MATRIX VERSUS CONNECTIVE TISSUE GRAFT FOR SOFT TISSUE AUGMENTATION AT IMPLANT SITE. A RANDOMIZED, CONTROLLED CLINICAL TRIAL

MATRICE XENOGENICA IN COLLAGENE VERSUS INNESTO DI TESSUTO CONNETTIVO PER L'INCREMENTO DEI TESSUTI MOLLI PERI-IMPLANTARI: STUDIO CLINICO CONTROLLATO RANDOMIZZATO

Lorenzo Landini¹, Chiara Gori¹, Tommaso Giuntoli¹, Giulia Bertini¹, Luigi Barbato¹, Michele Nieri¹, Francesco Cairo¹,

¹Section of Periodontology, Department of Surgery and Translational Medicine, A.O.U. Careggi, University of Florence, Florence, Italy

Key words:

Collagen matrix, connective tissue graft, keratinized tissue, soft tissue augmentation, randomized clinical trial, dental implants.

Running title:

Soft tissue augmentation at implants

Abstract

Background: The purpose of the present randomized clinical trial (RCT) is to compare Xenogeneic Collagen Matrix (XCM) versus Connective Tissue Graft (CTG) for soft tissue augmentation at implant site.

Material and methods: Soft tissue augmentation procedure with XCM (test) or CTG (control) was performed at 60 implants in 60 patients at the time of implant uncovering. Measurements were performed by a blind and calibrated examiner. Outcome measures included soft tissue thickness (GT), apico-coronal Keratinized Tissue (KT), peri-implant bone levels (BLs), chair time and post-operative discomfort. Visual Analogue Scale (VAS) was used to evaluate patient satisfaction.

Results: After 6 months, CTG yielded to significantly higher GT increase than XCM (0.3 mm; $p=0.0001$). Both procedures resulted also in a significant KT width increase compared with baseline with no significant difference between treatments. XCM was associated with significant less chair-time ($p<0.0001$), less post-operative pain ($p<0.0001$), painkillers intake ($p<0.0001$) and higher final satisfaction than CTG ($p=0.0195$). There was no significant difference for final BLs.

Conclusions: Both procedures increased amount of KT compared with baseline. CTG was more effective than XCM to increase peri-implant soft tissue thickness.

Clinical Relevance

Scientific rationale for the study

The effect of XCM or CTG for soft tissue augmentation at implant site is poorly investigated in RCTs.

Principal findings

CTG resulted in higher soft tissue thickness than XCM. Both procedures yielded similar apico-coronal KT compared with baseline. XCM was associated with significant better patient-reported outcomes including less post-operative pain and higher final satisfaction than CTG.

Practical implications

CTG should be preferred when increase in thickness is the primary treatment goal, while XCM is a viable alternative when the increase in apico-coronal KT and the reduction of patient morbidity is the primary target of therapy.

Background

Emerging evidence suggested that keratinized tissue (KT) around dental implant might be critical to prevent plaque accumulation, mucosal recession and peri-implant inflammation (Lin et al. 2013, Gobbato et al. 2013, Brito et al. 2014). An adequate volume of peri-implant soft tissue seems to be also critical in preventing crestal bone resorption that may occur when thin peri-implant mucosa is detectable (Linkevicius et al. 2010). Therefore, the careful management of soft tissue around implants is considered a key factor in order to obtain aesthetic outcomes and to support long-term maintenance in implant dentistry (Cairo et al. 2008). Different surgical strategies may be used to improve the amount of KT around dental implants, including the use of pedicle flaps and soft tissue grafts (Cairo et al. 2008, Thoma et al. 2014).

Xenogeneic Collagen Matrix (XCM), a two-layer product of porcine origin favoring blood vessels ingrowth, was recently introduced. Clinical studies showed that XCM may be a viable alternative for gingival augmentation purpose (Sanz et al 2009), for improving root coverage outcomes (Jepsen et al. 2013) and may represent a possible alternative to CTG for limiting morbidity due to harvest procedure (Cairo et al. 2014).

The aim of this RCT is to compare Xenogeneic Collagen Matrix versus Connective Tissue Graft for soft tissue augmentation at implant site.

Material and methods

Participants

The present study is a parallel, randomized single-center clinical trial according to the CONSORT statement (<http://www.consort-statement.org/>). Two different treatment modalities for obtaining soft tissue augmentation at the time of implant uncovering were compared: Xenogenic Collagen

Matrix (XCM) (Test group) and Connective Tissue Graft (CTG) (control group). The flowchart of the study is presented in figure 1.

The study protocol was approved by the Ethical Board (Ref. Prot.12/P CESM del 17.06.2013). Informed consent was obtained from all subjects included in the study. Experimental procedures were conducted according to the principles outlined in the Declaration of Helsinki on study involving human subjects, as revised in 2004. Experimental procedures were performed from July 2013 until March 2016.

Participants satisfying the following entry criteria were recruited:

- Age ≥ 18 years
- No systemic diseases or pregnancy.
- Self reported smoking ≤ 10 cigarettes/day.
- No probing depths ≥ 5 mm
- Full-mouth plaque score (FMPS) and full-mouth bleeding score (FMBS) $\leq 15\%$ (measured at four sites per tooth).
- Single dental implant treatment with a scheduled second stage surgery for implant uncovering at both upper and lower jaw
- Need of soft tissue augmentation for aesthetic purpose and/or functional reasons.
- No previous soft tissue augmentation procedure at experimental site.

Exclusion criteria were:

- Disease affecting connective tissue metabolism
- Diabetes
- Allergy to the collagen
- Pregnant or lactating women
- Participation in an investigational device, drug or biologic study within the last 6 months prior to the study start
- Untreated periodontal disease
- Dental implants previously uncovered or applied with a single-stage procedure
- No residual keratinized tissue (KT) at experimental area.

Interventions/Operator/Investigators

All surgical procedures were performed by a single expert periodontist (F.C.) with more than 10 years of experience in periodontal plastic surgery and implant dentistry. The examiner, blinded with respect to the surgical procedures, assessed all the clinical outcomes of treatments and attended a preliminary calibration session reporting intra-class correlation coefficient of 0.87 (CI 95% 0.82; 0.91).

Clinical measurements before surgery (T0)

After data collection regarding age, gender, medications, smoking habits, number of cigarettes/day, the following measurements were taken at baseline (before implant uncovering) for each treated implant by a blind examiner, using a periodontal probe (PCP UNC 15, Hu-Friedy):

- KT 0: Baseline buccal Keratinized Tissue at baseline measured as the distance between mucogingival junction (MGJ) to the most coronal point of the ridge using a periodontal probe (PCP UNC 15, Hu-Friedy)
- GT 0: Buccal Gingival thickness at baseline measured 1,0 mm coronal to the MGJ using an injection needle, perpendicular to the tissue surface, with a silicon stop over the gingival surface. The silicon disk stop was then placed in tight contact with the soft tissue surface and fixed with a drop of cyanoacrylic adhesive. After needle removal, the distance between needle tip and the silicon stop was measured using a digital caliper with 0.01mm of accuracy (Cairo et al. 2016a).

All variations in the soft tissue were monitored considering the position of the gingival margin (GM) and MGJ at further follow-ups.

Intra-operative measurements

The following measurement was taken immediately after the end of surgical procedure at each experimental implant.

- KT1: the amount of KT immediately after the end of surgery evaluated as the distance between MGJ and the most coronal point of KT stabilized at the healing abutment
- Bone levels: distance in mm between bone levels at mesial (mBL) and distal (dBL) site of the experimental implant using the first thread as reference point. This measurement was obtained after the application of healing abutment using an intra-oral x-ray obtained with parallel technique. The measurements were rated positive when the bone crest (BC) was placed coronal to the first implant thread and negative when BC was below the reference point.

When patient was allocated in the control group (CTG), the type of harvesting procedure was described in the charting. Chair-time of the surgical procedure was also measured from the end of local anaesthesia until the completion of the last suture. In addition, data regarding patient-reported outcomes measures (PROMs) regarding hardship perception of procedure and pain during surgery were measured by Visual Analogue Scale-VAS from 0 to 100 after surgery.

Clinical measurements to monitor early healing

The amount of buccal KT was evaluated at 7 (time for suture removal) and 14-days. In addition, data on possible soft tissue complications (necrosis, edema, bleeding) were also collected. General discomfort and pain using VAS were also registered at the 7-days follow-up. A further evaluation of KT amount was performed at 1-month follow-up.

Clinical measures at the 3 (T1) and 6-months (T2) follow-ups

- KT: Buccal Keratinized Tissue measured as the distance between mucogingival junction (MGJ) and the gingival margin.
- GT: Buccal Gingival thickness measured 1,0 mm coronal to the MGJ using the same method reported above.
- Rec: Recession depth at 6 points for implant
- PD: Probing depth at 6 points for implant
- Bop: Bleeding on probing as yes/no in 6 points/implant
- PI: Plaque as yes/no in 6 points/implant

At the 6-month follow-up only (T2), data regarding final bone levels (BLs 6m) were collected using the same procedure reported above. In addition, patient outcomes regarding aesthetic and overall satisfaction with VAS scale was collected. In case of drop out, the related reason was registered.

Treatment procedures

Before surgery, a careful evaluation of residual buccal, crestal ad lingual KT was performed. After local anaesthesia, a crestal or slightly lingual horizontal incision was performed. Care was taken to preserve an adequate amount of lingual KT. A split-thickness buccal flap was gently raised-up beyond the MGJ. Implant screw was then removed and healing abutment was applied. The randomization sealed and opaque envelope was then opened and patient allocated to test or control group. In the test group a double layer of XCM (Mucograft®, Geistlich Pharma AG, Wolhusen, Switzerland) was applied. The first layer was applied and secured over supra-periosteal tissue while the second one was gently applied over the first one. Both layers were carefully sutured at supra-periosteal buccal tissue with resorbable sutures. In the control group a CTG was harvest at palatal side using trap door approach or de-epithelialized free gingival graft procedure. A standard 1-mm thick CTG was sutured at buccal supra-periosteal tissue. The flap was then carefully sutured to completely cover XCM or CTG. Complete clinical cases regarding test and control group were presented in Fig. 2 and 3.

Post-surgical instructions and Prosthetic treatments

Patients were instructed to avoid mechanical trauma and tooth brushing for 2 weeks and to intermittently apply an ice bag for the first 4 hours. Patients received ibuprofen 600 mg at the end of the surgical procedure and were instructed to take another tablet 6 hours later; they were also instructed to take additional doses if needed. Chlorhexidine mouthrinsings (0.12%) were prescribed twice daily for 1min. Smokers were reminded to quit smoking in the first 2 weeks after surgery. Seven days after surgery, sutures were removed. Two weeks after surgery, patients were instructed to resume mechanical tooth-cleaning. Prosthetic treatment including the application of a temporary crown and the final rehabilitation was performed according to the specific treatment plan. The prosthodontist was blind in respect to the type of soft tissue augmentation procedure performed. Professional oral hygiene procedures were performed at 3- and 6- months follow-up

Sample size

The sample dimension was calculated using difference in GT, $\alpha = 0.05$, power of 80%, and standard deviation 0.63mm (Wiesner et al. 2010). The minimum clinically significant difference in GT (δ) was 0.5mm.

On the basis of these data, the needed number of patient to be enrolled to conduct this study has been calculated as 26 for the test group (XCM) and 26 for the control group (CTG). In order to compensate for 10% of potential dropouts, the final sample was 30 patients for each group.

Randomization/Allocation concealment/Masking of examiners

Each experimental subject was randomly assigned to one of the two treatment regimens. A blocked randomization in order to obtain the same number of patients in each arm was used. Treatment assignment was noted in the registration and treatment assignment form that was kept by the study registrar (M.N., statistician). Allocation concealment was performed by opaque sealed envelopes, sequentially numbered. The statistician generated the allocation sequence by means of a computer-generated random list and instructed a different subject to assign a sealed envelope containing the treatments (XCM and CTG). The opaque envelope was opened after flap elevation and treatment assignment communicated to the operator. Blinding of examiners was maintained throughout all experimental procedures.

Statistical analysis

Descriptive statistics were performed using mean \pm standard deviation for quantitative variables and frequency and percentage for qualitative variables. The statistical unit was the patient. Primary outcomes variable was soft tissue thickness (GT) difference, considered as the difference between thickness at T0 (GT T0) and thickness at 6 months follow-up (GT 6m). An analysis of covariance was performed for this outcome variable using treatment as explicative variable and GT T0 as a covariate. The interaction term Treatment and GT T0 was added to the model if significant.

The analysis of covariance was also performed for difference in apico-coronal KT amount and bone levels difference comparing baseline and 6 months of follow-up; t-tests were performed for chair time, number of postoperative painkillers, number of days with discomfort, PD, Rec, number of BoP sites, VAS regarding final aesthetic and overall satisfaction. Fisher exact tests were performed for complications and the presence of postoperative oedema. This analysis was defined a priori. Intention to treat analysis was applied. Statistical analysis was performed with JMP 11.0 SAS Institute Inc.

Results

Experimental population, patients and defects characteristics at baseline

An original sample of 68 patients satisfying the entry criteria was identified; 8 of 68 declined to participate into the experimental procedures. A total of 60 patients were enrolled in the study; 30 patients were allocated to XCM treatment (test group) and 30 to CTG (control group). In the test group, 27 (90%) Straumann Bone levels implants and 3 (10%) Astra Tech dental implants were used, while in the control group 22 (73%) Straumann Bone levels and 8 (27%) Astra Tech dental implants.

In XCM group, twenty out of 30 were females (67%), and the mean age was 50.3 ± 12.4 years [Minimum: 21; Maximum: 73]. Nine patients were smokers (30%). A total of 17 implant at upper jaw and 13 at the lower jaw were treated. The baseline mean width of KT (KT 0) was 3.1 ± 1.2 mm while the mean baseline GT (GT 0) was 2.1 ± 0.63 mm. In CTG group, twenty-four out of 30 were females (24%), and the mean age was 48.3 ± 11.8 years [Minimum: 22; Maximum: 69]. Six patients were smokers (20%). A total of 27 implant at upper jaw and 3 at the lower jaw were treated. The baseline mean width of KT (KT 0) was 3.5 ± 1.1 mm while the mean baseline GT (GT 0) was 2.1 ± 0.59 mm. Regarding the harvesting procedure, in 23 cases was used the trap door approach, in 4 the single incision technique, in 2 the de-epithelized graft and 1 from maxillary tuberosity. There was no clinical difference at baseline between the two groups.

Evaluation of the surgical procedure and post-operative period (1, 2, 4 weeks)

Immediately after surgery the apico-coronal amount of KT was 4.7 ± 1.2 mm for XCM and 5.0 ± 1.6 mm for CTG. At this time BLs were 0.7 ± 0.2 mm for test group and 0.8 ± 0.3 mm for control group. The mean duration of the surgical procedure was 35.5 ± 9.4 minutes for the test group and 51.7 ± 7.0 minutes for the control group (difference: -16.2 min; 95%CI from -20.5 to -11.9; $p < 0.0001$). Hardship perception of the procedure in term of VAS value was 17 ± 13 in the test group and 35 ± 23 in the control group (difference: -18; 95%CI from -28 to -8; $p = 0.0008$). No significant difference was reported for perceived pain (difference: -4; 95%CI from -8 to 1; $p = 0.0940$). After 7 days, patients from the XCM group reported an intake of 2.2 ± 0.8 anti-inflammatory tablets compared with 3.9 ± 0.7 for the CTG group (difference -1.7; 95%CI from -2.1 to -1.3; $p < 0.0001$). Patients allocated in the test group experienced also significantly lower intensity of post-surgical pain than the control group (13.0 ± 10 vs 37.0 ± 15 VAS values, difference -24; 95%CI from -31 to -17; $p < 0.0001$) and lower number of unconformable days (1.2 ± 0.7 vs 2.4 ± 0.7 ; difference -1.2 days, 95%CI from -0.9 to -1.6, $p < 0.0001$). At 2 weeks, the only significant difference was the higher number of sites with edema (20 vs 7 sites) in the control group (relative risk 0.35; 95%CI from 0.17 to 0.70; $p = 0.0016$). No other significant difference was detected in the post-operative period.

Clinical outcomes

Descriptive statistics of peri-implant soft tissue for test and control group is presented in table 1. Furthermore, KT changes at each interval are presented in fig. 4.

At the final follow-up, two dropouts in the test group were registered. Both patients did not comply with the recall visits for the distance from their house after the 4 weeks visits, but successfully completed prosthetic treatment at the referral dentist office. All remaining 58 patients attended to all follow-up visits and no significant complication was reported. No implant failure was registered. At the final visit all patients were highly satisfied, with 95 ± 5 mean VAS value in the test group and 91 ± 9 in the control group. The difference was significant (difference 4; 95%CI from 1 to 8; $p = 0.0195$). Furthermore, patients were also satisfied in term of aesthetic outcomes with no difference between groups (90 ± 8 for test group vs 90 ± 9 for control group, difference 0.1; 95%CI from -4 to 5; $p = 0.9715$).

At the 6-month follow-up visit, both procedures resulted in a significant increase in KT width compared with baseline ($p < 0.0001$). In the XCM group the final KT was 4.3 ± 1.2 mm while the CTG group was 4.4 ± 1.5 mm. There was no significant difference between treatments (difference 0.1 mm 95%CI from -0.3 to 0.5; $p = 0.4754$). In addition, both procedures yielded to a significant increase of gingival thickness (GT) compared with baseline ($p < 0.0001$). The final soft tissue thickness was 3.0 ± 0.7 in the XCM group and 3.4 ± 0.6 mm in the CTG group. The increase in KT thickness was significantly lower in the test group (difference -0.3 mm; 95%CI from -0.5 to -0.2; $p = 0.0001$). After 6 months, only a single case of 1-mm soft tissue recession was identified in the

test group. No significant difference was also reported in term of mean bone levels at the last follow-up (difference 0.1 mm; 95%CI from -0.1 to 0.3; p=0.3022). Inferential statistics comparing test and control group is presented in table 2.

Discussion

Recent information supports the importance of KT around implant to improve aesthetic outcomes, soft tissue stability and to prevent peri-implant inflammation (Tonetti et al. 2014). The present RCT was performed to test XCM versus CTG for soft tissue augmentation at implant site. A total of 60 dental implants on 60 patients were treated at the time of second stage surgery.

The outcomes of the study showed that CTG was more effective than XCM for improving soft tissue thickness at implant site, leading to a mean 0.3 mm higher increase in soft tissue thickness. Modern clinical research in implant dentistry suggest that gingival thickness may play a significant role in preventing bone resorption, showing that less bone loss may occur at thick mucosal tissue compared with thin soft tissue (Puisys & Linkevicius 2015). A possible explanation may be related to the higher capability of thick soft tissue in counteracting the inflammation process related to infection at microgap level, limiting its widespread at bone level (Ericsson et al. 1995, Herman et al. 2000). In addition, when minimal amount of soft tissue is coronal to the bone crest, a bone resorption occurs for allowing the formation of biological dimension around implant (Berglundh & Lindhe 1996). A recent SR suggests also that thick peri-implant soft tissue is associated with 0.8 mm less bone loss than thin tissue in the short term (Suarez-Lopez Del Amo 2016). In the present RCT, both procedures resulted in a significant improvement of soft tissue thickness compared with baseline (1.2mm for CTG and 0.9mm for XCM); interestingly, 79% of XCM-treated sites and 93% of CTG-treated sites achieved final soft tissue thickness ≥ 2.5 mm. The magnitude of thickness increase was similar for that obtained with CTG (Weisner et al. 2010) or XCM (Froum et al. 2015) in pilot studies testing soft tissue increase at implant site. Furthermore, in another pilot RCT a similar effect in soft tissue augmentation was described comparing CTG to a stable collagen matrix prototype (Thoma et a. 2016).

In the present RCT a significant increase in apico-coronal KT dimension was reported for both techniques, with no significant difference between procedures. The importance of KT dimension was pointed out in an early experimental study in the animal model demonstrating that minimal amount of KT was associated with higher gingival recession/bone loss under experimental peri-implantitis conditions (Warrer et al. 1995). More recently, clinical studies applying modern implant systems showed significant benefits in preserving KT at dental implants, reporting that higher amount of KT prevented plaque accumulation, mucosal recession and peri-implant inflammation (Lin et al. 2013, Gobbato et al. 2013, Brito et al. 2014). In the present study, both procedures were associated with ~ 1 mm increase of final KT compared with baseline. This finding is similar to that reported in another RCT where CTG and XCM were used for pure gingival augmentation proposal at implant site and sutured over the recipient bed without flap coverage (Lorenzo et al. 2012). In

the present study both XCM and CTG were completely submerged under a split-thickness buccal flap in order to maximize the blood supply that has shown to be the critical factor during healing process (Guhia 2001). Furthermore, the increased amount of KT is in accordance to that observed when using CTG (Cairo et al. 2012, Cairo et al. 2016a) or XCM (Jepsen et al. 2013) under coronally advanced flap for root coverage purpose. Interestingly, specific time-frame change in buccal KT amount was described in this RCT for both techniques (fig. 4). In fact, after a visible tissue augmentation due to the inflammatory phase at 1-week, a tissue shrinkage trend due to the resolution of the inflammation was detectable in the 2th/4th week. Between the 1- and 3-month follow-ups a significant KT increase was shown; this finding was probably due to augmented amount of well-organized collagen fibers originating from the grafted connective tissue (Nobuto et al. 1988). It can be speculated that this may be similar when applying a collagen matrix under the split-thickness flap: after the blood clot stability, an ingrowth of blood vessel into the matrix occurred leading to a subsequent collagen fibers maturation (Thoma et al. 2011). This may explain the final increase in KT detectable after the application of XCM.

The present study confirms that the use of CTG is associated with longer chair-time and greater morbidity (Cortellini et al. 2009; Cairo et al. 2012) than XCM. Surgical-time was 16 minutes longer than XCM ($p < 0.0001$) and patients experienced significantly higher post-surgical discomfort ($p < 0.0001$) and reported greater anti-inflammatory tablets consumption ($p = 0.0001$). All treated patients were highly satisfied in terms of final aesthetic outcomes after both treatments with no significant difference between groups, thus confirming that soft tissue reconstruction is associated with high patient satisfaction at the final follow-up (Cairo et al. 2016b). Interestingly, when assessing overall final patient satisfaction, higher VAS values was reported for XCM treated than controls, thus supporting the detrimental effect of harvesting procedure on patient opinion (McGuire et al. 2003).

Within the limits of this study, the following conclusions can be drawn:

- CTG was more effective than XCM for improving soft tissue thickness at implant site.
- XCM and CTG obtained similar amount of apico-coronal KT after 6 months.
- XCM is associated with shorter surgical time, lower post-operative morbidity, less anti-inflammatory tablets consumption and higher final patient satisfaction than CTG.

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Table 1: Descriptive statistics at baseline, 1, 3 and 6 months regarding peri-implant soft tissue conditions.

Variable	XCM (baseline) N=30	CTG (baseline) N=30	XCM (1 month) N=29	CTG (1 month) N=30	XCM (3 months) N=28	CTG (3 months) N=30	XCM (6 months) N=28	CTG (6 months) N=30
KT (mm)	3.1 (±1.2)	3.5 (±1.7)	4.5 (±1.2)	4.7 (±1.7)	3.7 (±1.1)	4.0 (±1.7)	4.3 (±1.2)	4.4 (±1.5)
GT (mm)	2.1(±0.6)	2.1 (±0.6)	-	-	2.8 (±0.7)	3.1 (±0.5)	3.0 (±0.7)	3.4 (±0.6)

Legend:

KT = width of keratinized tissue; GT = Gingival Thickness; XCM= Xenogenic Collagen Matrix; CTG= Connective Tissue Graft.

Table 2: Inferential statistics comparing clinical outcomes for test and control group at 1(1m), 3 (3m), and 6 (6m) months.

Variable	XCM	CTG	Difference	95% CI	p-value
KT 6m (mm)	4.3 (±1.2)	4.4 (±1.5)	0.1	-0.3; 0.5	p=0.4754
KT 6m-KT 0 (mm)	1.1 (±0.8)	0.9 (±0.8)	0.1	-0.3; 0.5	p=0.4754
GT 6m (mm)	3.0 (± 0.7)	3.4 (± 0.6)	-0.3	-0.5;-0.2	p<0.0001
GT 6m –GT 0 (mm)	0.9 (± 0.2)	1.2 (± 0.3)	-0.3	-0.5;-0.2	p<0.0001
Bone Levels 6 m (mm)	-0.2 (±0.4)	-0.2 (±0.4)	0.1	-0.1; 0.3	p=0.3022
PD 6 m (mm)	2.8 (± 0.2)	2.9 (± 0.3)	-0.1	-0.2;0.01	p=0.0705
Rec 6 m(mm)	0.04 (± 0.2)	0.0 (± 0.0)	0.04	-0.04;0.1	p=0.3262
Bop (n)	0.1 (± 0.4)	0.3 (± 0.5)	-0.2	-0.4;0.1	p=0.2016
VAS Est 6m (0-100)	90 (±8)	90 (±9)	0.1	-4; 5	p=0.9715
VAS Sat 6m (0-100)	95 (±5)	91 (±9)	4	1; 8	p=0.0195

Legend:

KT = width of keratinized tissue; GT = Gingival Thickness; XCM= Xenogenic Collagen Matrix; CTG= Connective Tissue Graft; PD= mean Probing depth; Bop= Bleeding on Probing; VAS Est 6m= Visual Analogue Scale for Aesthetic satisfaction at 6 months; VAS Sat 6m= Visual Analogue Scale for overall satisfaction at 6 months

Figure 1: CONSORT flowchart of the study

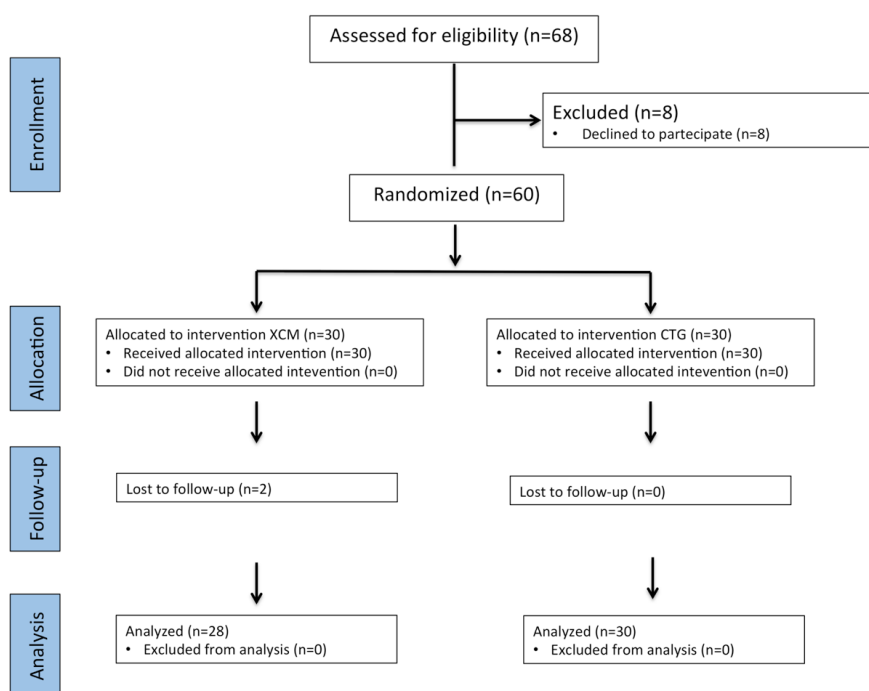


Figure 2

2 a: baseline conditions; 2b: fixture application; 2c: guided bone regeneration; 2d: baseline of experimental procedures, 6 months after implant application; 2e: clinical case allocated to XCM; 2f: final soft tissue healing at the last follow-up; 2g: final x-ray

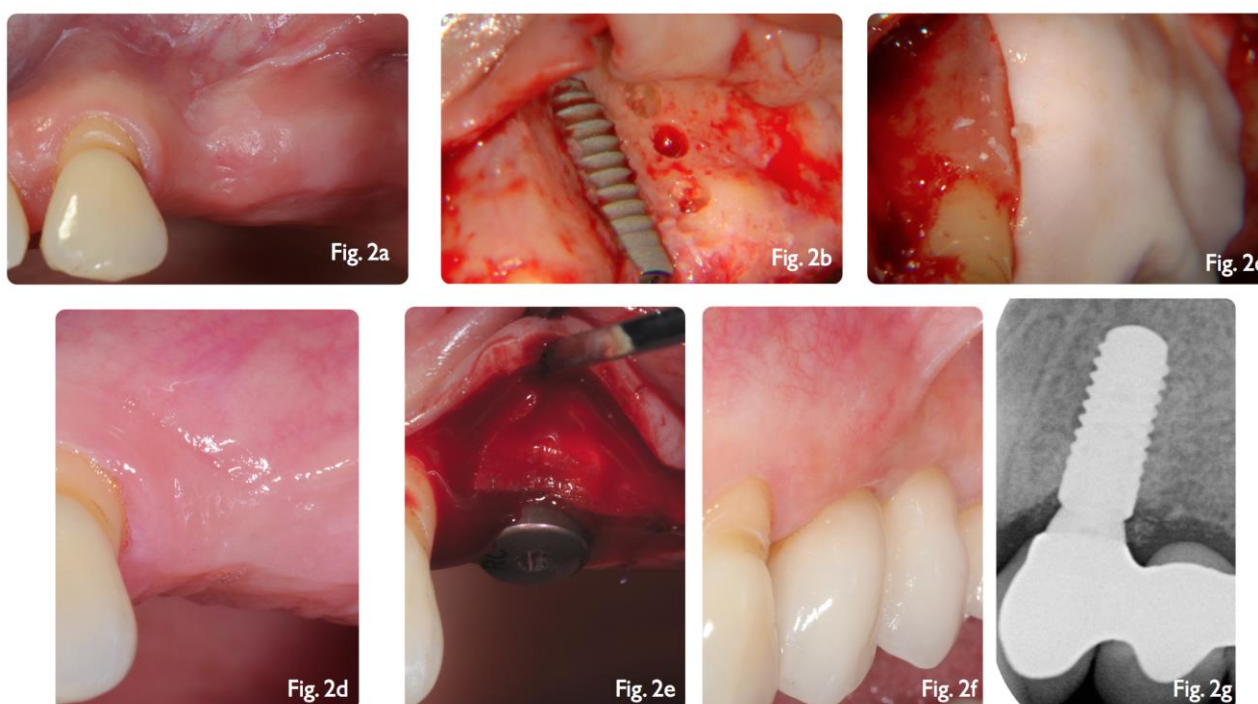


Figure 3

3 a: baseline conditions, tooth 2.1 was scheduled for extraction due to root fracture; 3b: fixture application; 3c: guided bone regeneration; 3d: baseline of experimental procedures, 6 months after implant application; 3e: clinical case allocated to CTG; 3f: final soft tissue healing at the last follow-up; 3g: final x-ray

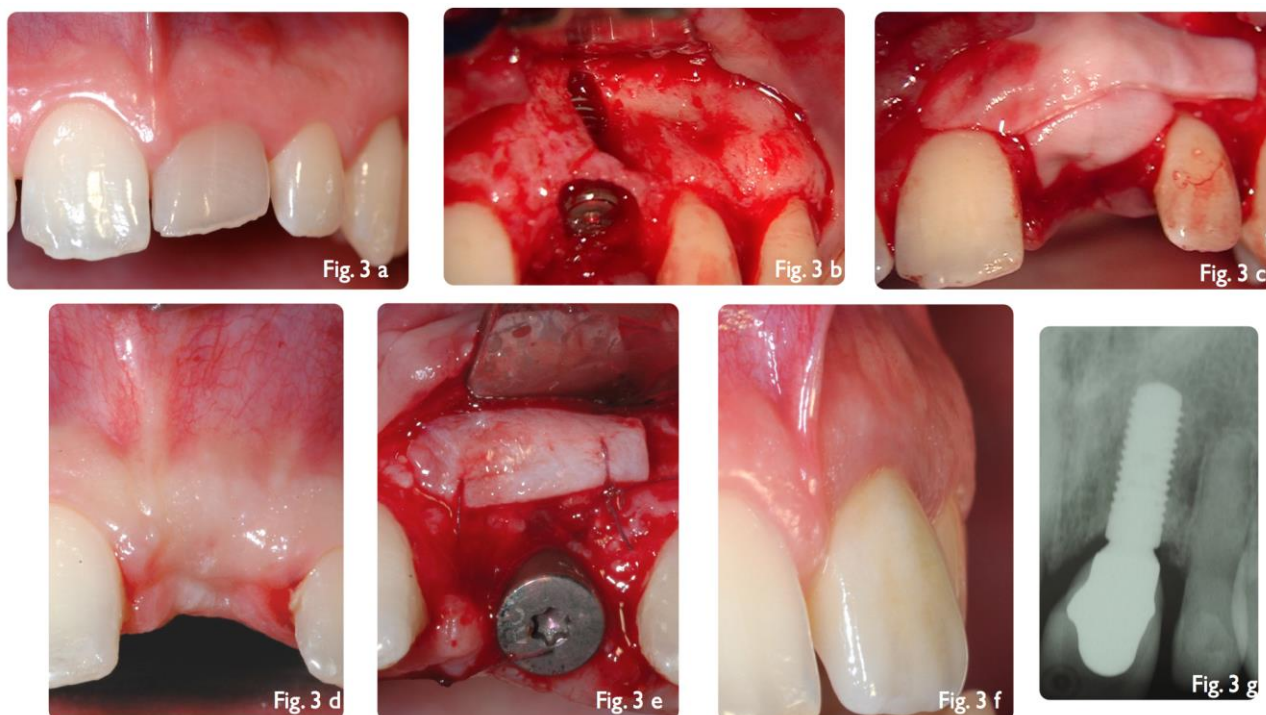
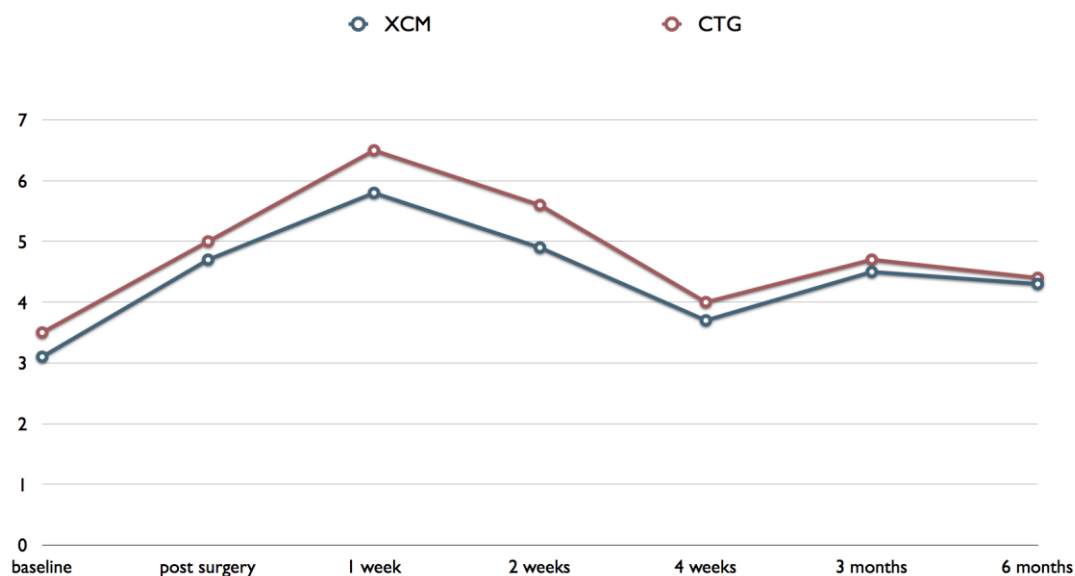


Figure 4

KT changes at each interval (XCM, Xenogenic Collagen Matrix; CTG, Connective Tissue Graft)



Correspondence to:

Dr. Francesco Cairo, E-mail: cairofrancesco@virgilio.it

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