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Wound Fluid Cytokine Profile Following Bone Regeneration Procedures

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Clinical parameters available to evaluate early healing phases of bone regeneration procedures are limited. This study explores wound fluid (WF) content for molecular markers to differentiate wound healing responses in the early postoperative period after bone graft placement. Fifteen patients (50 ± 5 years old; 8 men) scheduled to receive tooth extraction and bone graft placement at maxillary nonmolar single-tooth sites were recruited. Primary wound closure was not intended at time of surgery. Gingival crevicular fluid from adjacent teeth or WF from surgical wound edges were collected (30 seconds) at baseline, at 3, 6, and 9 days, and at 1 and 4 months. Multiplex protein assay was used to determine concentration of various wound healing mediators. Immediately after surgery, 87% of surgical sites exhibited open wound. At day 9, mean wound exposure was 4.8 ± 0.4 mm. At 1 month, all wounds were clinically closed. The WF tripled in volume at day 3 and day 6 ($P \leq .05$), compared with baseline gingival crevicular fluid, and gradually decreased as wounds closed. The WF concentrations of interleukin (IL)-6, placental growth factor, plasminogen activator inhibitor 1, insulin-like growth factor binding protein 1, and soluble cluster determinant 40 ligand were increased during early healing days, generally with peak concentration at day 6 ($P \leq .004$). Conversely, WF concentrations of IL-18 and epidermal growth factor were decreased after surgery, generally not reaching baseline values until wound closure ($P \leq .008$). In general, WF cytokine expression kinetics were concordant with wound closure dynamics ($P \leq .04$). These results suggest that WF molecular markers such as IL-6, and to a lesser extent placental growth factor and IL-18, might help differentiate wound healing responses after bone regeneration procedures.

Key Words: bone regeneration, cytokines, gingiva, gingival crevicular fluid, inflammation, wound healing

INTRODUCTION

Guided bone regeneration (GBR) is a surgical procedure applied to augment alveolar bone ridge dimensions, often in preparation for future implant placement. The GBR procedure was developed through modifications to the guided tissue regeneration procedure, whereby a barrier membrane is used to prevent epithelial cell migration and allow undifferentiated mesenchymal cells to proliferate, differentiate, and migrate to effectively regenerate the periodontal ligament apparatus around periodontally involved teeth.[1] Although similar biomaterials are used in both procedures, the main barrier membrane function at an edentulous site is to contain the bone graft and provide wound stabilization.[2] Clinical parameters, such as presence or absence of edema, necrosis, bleeding, suppuration, physical opening of the wound, and mobility of the bone graft and/or barrier membrane, have typically been used to evaluate the early postsurgical healing of GBR.[3] Although often used, this approach has major limitations, including subjectivity and difficulty in obtaining repeated measurements. Furthermore, it is still debatable whether an open early wound negatively affects GBR outcomes.[4,5] Given the long timeframe required for complete GBR healing and implant placement, better diagnostic tools, preferably objective and minimally invasive, are needed to evaluate early phases of wound healing and determine the quality of regenerating tissues after GBR and before implant placement.

The interaction between hard and soft tissues makes pre- and post-implant wound healing a complex process and, consequently, bone regeneration procedures commonly result in limited bone gain and significant resorption.[6] Soft tissue thickness and blood supply from flap to underlying biomaterials are considered important determinants affecting bone

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regeneration outcomes.[7,8] Similarly, as wound healing is regulated by host mediators such as pro- and anti-inflammatory cytokines, regulation of local inflammation appears important for the outcome of wound healing.[9,10] It is well known that the role of macrophages in osseous wound healing, especially where residual bone graft materials remain, depends on environmental conditions.[11] It has been speculated that under prevailing pro-inflammatory conditions, macrophages produce tumor necrosis factor-alpha (TNF-α) and lose their ability to synthesize bone morphogenetic protein-2; in a more suitable healing environment, wound healing macrophages produce pro-osteogenic factors, including bone morphogenetic protein, to promote bone formation.[12] However, evidence linking the GBR wound inflammatory state to tissue perfusion and bone-healing outcomes is scarce.[13] Similarly, objective and minimally invasive approaches that would provide information on soft tissue/wound inflammation and blood perfusion recovery are very limited. Therefore, this study aims to explore wound fluid (WF) content for wound healing–related molecular markers following GBR procedures. The WF cytokine expression kinetics are reported in this article as a complement to our previous study on flap blood perfusion recovery after surgeries performed to augment postextraction alveolar ridge bone dimensions.[13]

Materials and Methods

Patient selection and study design

The study was a prospective observational clinical study. Adult, systemically healthy nonsmokers with stable periodontium who were seeking tooth extraction and/or bone graft procedure (socket preservation or GBR) for a single maxillary nonmolar site, bounded on either side by natural teeth, were recruited. Collected data on clinical healing, flap blood perfusion recovery (assessed by Laser Doppler flowmetry [LDF]), and bone augmentation outcomes (evaluated by cone beam computerized tomography) were previously reported.[13] Briefly, clinical examination and sample collection were conducted before surgery and at 3, 6, 9 days, 1 month, and 4 months after surgery. Wound healing was observed by using standard clinical parameters and by determining WF (collected from wound edges) volume and content. Clinical measurements and fluid sampling were performed by a single trained examiner (L.A.). The study protocol (#2014H0150) was approved by The Ohio State University (OSU) Institutional Review Board. The approval met the current WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. All participants provided written informed consent.

Surgical procedures

All surgical procedures were performed by OSU periodontal residents under direct faculty supervision, as previously reported.[13] Briefly, routine surgical protocols, including atraumatic extraction, were applied. After tooth extraction, the buccal flap was elevated to assess buccal plate integrity. When socket walls were intact (4-wall residual defect), socket preservation was performed using allograft bone material (FDBA, Straumann, Andover, Mass) and collagen wound dressing (Collagen Plug, Zimmer Biomet, Carlsbad, Calif) to seal the socket entrance. When buccal ridge deficiency was noted, GBR was performed using the same allograft and collagen membrane (Biomend Extend, Zimmer Biomet) placed under the flap, covering the buccal bony defect and sealing the socket. Flaps were approximated with absorbable sutures (coated Vicryl [poly(lactic-co-glycolic acid)], Ethicon LLC, Cincinnati, Ohio) without any effort to obtain primary closure. Patients received prescriptions for antibiotics, analgesics, and antimicrobial rinse (0.12% chlorhexidine gluconate; 3 times daily for 2 weeks) per standard clinical protocol.

Crevicular/wound fluid sampling and multiplex assays

Gingival crevicular fluid (GCF) samples were obtained from adjacent teeth at baseline and after wound closure. The WF samples were obtained from wound area edges at each postoperative visit until clinical wound closure. A total of 6 samples (30-second sampling time/sterile paper strip [Periopaper, Oraflow Inc, Hewlett, NY]) were collected at each time point. The GCF and WF volume was immediately determined using a calibrated electronic volume quantification unit (Periotron 8000, Oraflow Inc). Samples were then stored (–20°C, sterile vials) until further processing. Fluid elution was performed as previously detailed.[14] A commercially available panel (Bio-Plex ProHuman Cancer Biomarker panel 2, Bio-Rad Life Sciences, Hercules, Calif) for multiplex assays was used to determine molecular markers, including urokinase type plasminogen activator (uPA), Insulin-like growth factor binding protein 1, interleukin (IL)-18, soluble FAS ligand (sFASL), plasminogen activator inhibitor (PAI-1), soluble CD40 ligand (sCD40L), endoglin, placental growth factor (PlGF), IL-6, epidermal growth factor (EGF), heparin-binding EGF-like growth factor (HB-EGF), and transforming growth factor alpha (TGF-α). Molecular marker levels are reported as concentrations per WF unit volume.

Data management and statistical analysis

Descriptive statistics were expressed as mean $\pm$ standard error. Sample size was determined using a priori test, to detect 2-fold difference between 2 time points for well-known GCF cytokine concentration (eg, IL-6) at the $P = .05$ level.[14,15] Data were analyzed using statistical software (GraphPad Prism 5, GraphPad Software, Inc, La Jolla, Calif, and Statistical Analysis Software [SAS PROC GENMOD], version 9.3, SAS Institute Inc, Cary, NC). Repeated measures mixed model with Bonferroni adjustments was used to compare time-dependent differences for changes in GCF/WF amount and content (statistical significance at $P \leq .01$). Sandwich estimator was used to control the correlation due to dependence of the observations among repeated measurements. Generalized linear mixed model was used for analyzing repeated measured categorical wound healing parameters. Spearman correlation coefficients were calculated to reveal the association between various parameters for the data obtained from days 3, 6, and 9 (specifically focusing on WF content; statistically significant correlations at $P \leq .05$ with $r \geq 0.5$ classified as strong, $0.3 > r < 0.5$ classified as moderate, and $r \leq$

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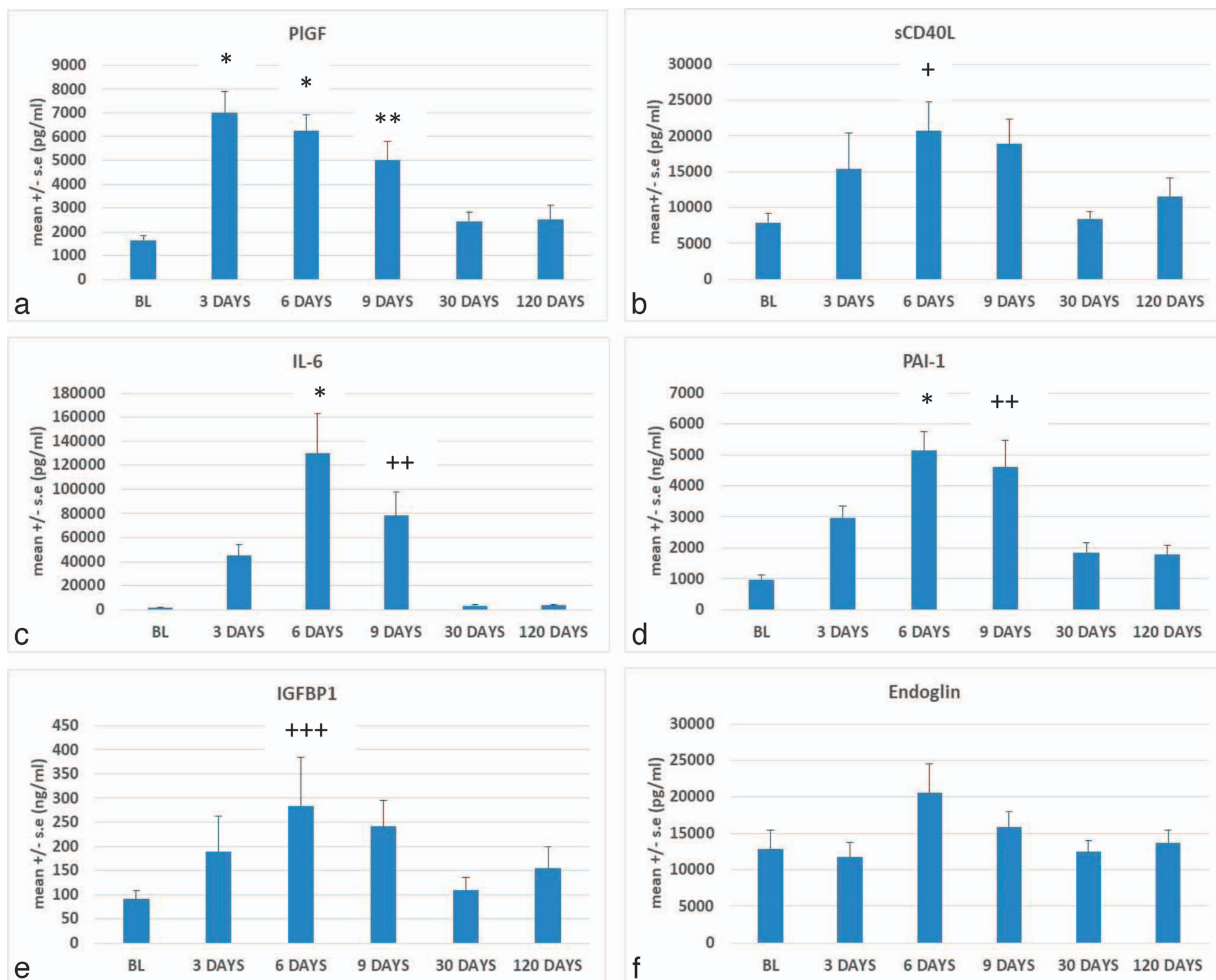

Figure 1. Mediators with increasing concentrations during early wound healing. Statistically significant differences compared with baseline. $^{+}P = .004$; $^{++}P = .0005$; $^{+++}P = .005$; $^{*}P < .0001$; $^{**}P = .001$.

0.3 classified as weak correlation). Statistical analysis was performed by an independent statistician (V.O.Y).

Results

Study population and clinical findings

Data related to clinical healing parameters and cone beam computerized tomography outcomes were previously published.[13] Briefly, clinical wound healing was uneventful with minimal changes in bone volume between the immediate postsurgical and the 4-month assessments.[13]

Molecular marker changes

Figure 1 presents the kinetics for wound healing mediators expressed at high concentrations in WF during early phases of wound healing. The PlGF WF concentration significantly increased 5-fold by day 3 (7002 ± 912 pg/mL) compared with GCF baseline (1659 ± 175 pg/mL; $P < .0001$) and decreased back to baseline levels (2442 ± 367 pg/mL) by day 30 (Figure 1a). The sCD40L baseline GCF concentration was 7939 ± 1,189 pg/mL. It increased almost 3-fold by day 6 (20 672 ± 4139 pg/mL; $P = .004$) and decreased back to baseline levels by day 30 (8410 ± 1055 pg/mL; Figure 1b). The IL-6 WF concentration reached a significant 84-fold increase at day 6 (130 140 ± 32 954 pg/mL; $P = .0001$), compared with baseline GCF (1554 ± 507 pg/mL), with a sharp return to baseline levels (3125 ± 1036 pg/mL) by day 30 (Figure 1c). The PAI-1 baseline concentration was 960 ± 156 ng/mL. It increased 5-fold by day 6 and 9 (5138 ± 612 ng/mL, $P < .0001$; 4598 ± 880 ng/mL, $P = .001$; respectively) (Figure 1d). The IGFBP1 also increased at day 6 postoperatively (284 ± 101 ng/mL versus 91 ± 18 ng/mL at baseline; $P = .005$; Figure 1e). Endoglin levels showed nonsignificant increases in the early postoperative healing period ($P > .01$; Figure 1f). The uPA GCF concentration before surgery was 196 ± 33 ng/mL. A nonsignificant increase in WF uPA concentration was noted by day 6 ($P > .01$) with an initiation of a decline by day 9 (data not shown). Similarly, local

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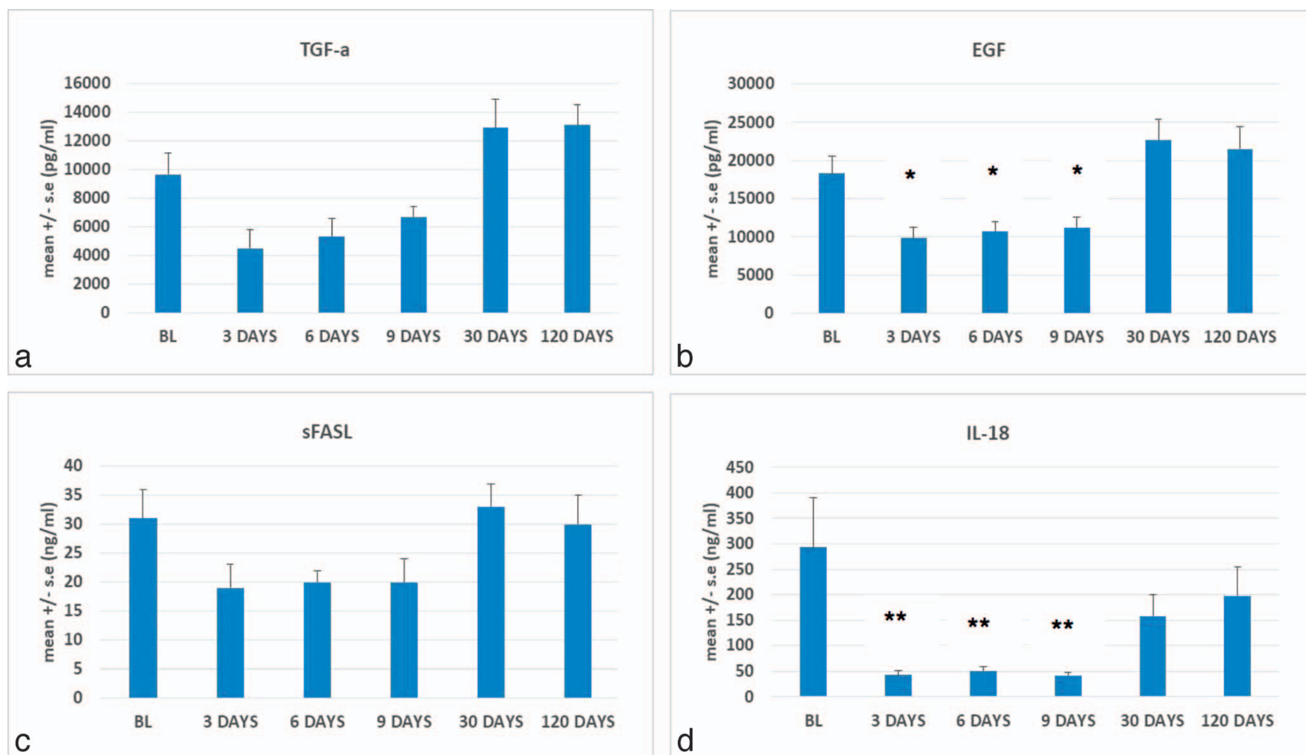

Figure 2. Mediators with decreasing concentrations during early healing. Statistically significant differences compared with baseline: $^*P \leq .008$; $^{**}P \leq .0001$.

HB-EGF concentration was nonsignificantly increased after surgical intervention ($P > .01$; data not shown).

Figure 2 presents the kinetics for molecular markers expressed at low concentrations in WF during early phases of healing. The TGF-α levels remained largely unchanged ($P > .05$; Figure 2a). The EGF levels significantly decreased from baseline (18 314 ± 2237 pg/mL) at the early postoperative days (day 3: 9804 ± 1506 pg/mL; day 9: 10 190 ± 1380; $P = .002$ and $P = .008$, respectively) and returned to baseline levels (22 664 ± 2769 pg/mL) by day 30 (Figure 2b). Local sFASL concentration was nonsignificantly decreased after surgical intervention (31 ± 5 ng/mL at baseline, 20 ± 2 ng/mL at day 6 and day 9, 33 ± 4 ng/mL by day 30; $P > .01$; Figure 2c). The IL-18 baseline levels were high (293 ± 98 ng/mL), decreased approximately 6-fold at day 3 (43 ± 9 ng/mL; $P = .0001$) and stayed at low levels during early days of healing (up to day 9; $P < .0001$). An increase back to baseline levels in IL-18 concentration was noted by day 30 (158 ± 42 ng/mL; Figure 2d).

Correlations between molecular and clinical parameters

Tables 1 and 2 present possible correlations among flap blood perfusion recovery rate, clinical healing parameters, and molecular wound healing mediators. The previously reported[13] LDF readings from the healing flaps were tested for possible correlation with WF volume and content changes. There was no significant correlation between LDF readings and postoperative WF volume measurements ($r = 0.108$, $P = .3$). However, the percent LDF change from baseline was correlated with WF PlGF and IL-6 concentrations (positive, weak correlation; $r = 0.294$, $P = .005$ and $r = 0.226$, $P = .03$ respectively; Table 1).

When possible correlations among molecular marker levels were explored, IL-18 was correlated with PlGF (weak negative), IL-6 (moderate negative), sFASL (strong positive), and TGF-α (strong positive) (Table 1). In addition, EGF was correlated with sFASL (strong positive), TGFα (weak positive), sCD40L (strong positive), PAI-1 (moderate positive), and IL-6 (moderate negative; Table 1). Finally, TGF-α was correlated with sFASL (moderate positive), IL-6 (moderate negative), and PlGF (moderate negative; Table 1).

Clinical parameters used to evaluate wound healing were compared with molecular marker levels for possible correlations (Table 2). The findings revealed that IL-6 was strongly negatively correlated with wound closure and positively correlated with wound exposure dimensions (both mesiodistal and buccolingual dimensions) (Table 2). Similarly, IL-18, PlGF, and PAI-1 were strongly negatively correlated with wound closure and mostly moderately positively correlated with wound exposure dimensions (Table 2). Similar in direction but less strong correlations were found between sCD40L and wound closure/exposure (Table 2). There was a moderate positive correlation between wound closure and either TGFα or EGF, consistent with the moderate negative correlations between wound exposure dimensions and these mediators (Table 2). The correlation between hydrogen peroxide test positivity and concentrations of molecular markers were positive for IL-6, IL-18, PlGF, and PAI-1 and negative for TGFα, EGF, and sFASL (Table 2), mirroring the results for wound exposure dimensions. Erythema was also correlated with IL-6, IL-18, PlGF, and PAI-1 (moderate positive correlation; Table 2) as well as with TGFα and EGF (moderate negative correlation;

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Table 1

Correlations between flap blood perfusion and wound fluid cytokine concentrations (correlation coefficients greater than 0.5 are in bold)*

	IL-6	IL-18	PlGF	TGF-α	EGF
%ΔLDF	r = 0.226; P = .03§	NR	r = 0.294; P = .005§	NR	NR
IL-6		r = −0.411; P ≤ .001‡	**r = 0.837; P < .001**†	r = −0.367; P < .001‡	r = −0.329; P = .002‡
IL-18	r = −0.411; P ≤ .001‡		r = −0.291; P = .006†	**r = 0.504; P < .001**†	NR
PlGF	**r = 0.837; P < .001**†	r = −0.291; P = .006†		r = −0.346; P < .001‡	NR
TGF-α	r = −0.367; P < .001‡	**r = 0.504; P < .001**†	r = −0.346; P < .001‡		r = 0.261; P = .01§
sFASL	NR	**r = 0.603; P < .001**†	NR	r = 0.327; P = .002‡	**r = 0.670;** P < .001†
sCD40L	**r = 0.666; P < .001**†	NR	**r = 0.746; P < .001**†	NR	**r = 0.800; P < .001**†
PAI-1	**r = 0.749; P < .001**†	NR	**r = 0.707; P < .001**†	NR	r = 0.463; P < .001‡

*EGF indicates epidermal growth factor; IL, interleukin; %ΔLDF, percentage difference in laser Doppler flowmetry from baseline; NR, statistically nonsignificant correlations are not reported; PAI-1, plasminogen activator inhibitor 1; PlGF, placental growth factor; sCD40L, soluble cluster determinant 40 ligand; sFASL, soluble FAS ligand.

†Strong correlations: at $P \leq .05$ level with $r \geq 0.5$.

‡Moderate correlations: at $P \leq .05$ level with $0.3 > r < 0.5$.

§Weak correlations: at $P \leq .05$ level with $r \leq 0.3$.

Table 2). Bleeding was correlated with IL-6 and PlGF (moderate positive correlation; Table 2) and with EGF and sFASL (moderate negative correlation; Table 2).

Discussion

This study aimed to explore WF content for relevant molecular markers after GBR surgeries and to correlate their levels with conventional clinical parameters used to evaluate early phases of wound healing. The novel findings of this study indicate that WF molecular marker levels exhibit significant dynamic changes during early healing and correlate strongly with clinical parameters typically used to assess postoperative wound healing. In particular, IL-6 and PlGF levels increased significantly during early healing and consistently positively correlated with clinically assessed wound healing parameters that indicate incomplete wound closure, such as wound exposure dimensions, positive H_2O_2 test, and bleeding. Among the various markers analyzed, IL-6 was the most strongly correlated with clinical parameters. To the best of our knowledge, the present study, which is complementary to our previous study[13] is the first to correlate levels of specific WF molecular markers with wound healing clinical parameters, including gingival flap blood perfusion (as assessed by LDF).

Soft tissue wound healing after conventional flap surgery is generally completed within 5 weeks (35 days).[16,17] Consistent with this evidence, complete wound closure was observed by 1 month (30 days) in the present study. This occurred despite the lack of primary closure at surgery completion and the presence of biomaterials (bone graft and barrier membrane) underneath the flap.

The observed WF molecular marker responses can be broadly grouped into 3 categories, based on their relative levels before (as measured in adjacent tooth GCF) and after surgery. First, markers whose levels were significantly increased after surgery, including IL-6, PlGF, PAI-1, and sCD40L; second, markers with levels that significantly decreased after surgery,

Table 2

Correlations between clinical parameters of wound healing and wound fluid cytokine concentrations (correlation coefficients greater than 0.5 are in bold)*

	Erythema	Bleeding	Wound Closure	H_2O_2 Positive Test	Wound MD Exposure (mm)	Wound BL Exposure (mm)
IL-6	r = 0.410; P = .0003‡	r = 0.365; P = .002‡	**r = −0.727**; P < .0001†	r = 0.432; P = .0001‡	**r = 0.612**; P < .0001†	**r = 0.653**; P < .0001†
IL-18	r = 0.329; P = .004‡	NR	**r = −0.520**; P < .0001†	r = 0.332; P = .004‡	r = 0.436; P = .0001‡	r = 0.465; P < .0001‡
PlGF	r = 0.348; P = .002‡	r = 0.342; P = .003‡	**r = −0.590**; P < .0001†	r = 0.429; P = .0001‡	r = 0.494; P < .0001‡	**r = 0.551**; P < .0001†
TGFα	r = −0.360; P = .002‡	NR	r = 0.473; P < .0001‡	r = −0.467; P < .0001‡	r = −0.396; P = .0006‡	r = −0.431; P = .0002‡
EGF	r = −0.321; P = .005‡	r = −0.402; r = 0.0004‡	r = 0.378; P = .0009‡	r = −0.458; P < .0001‡	r = −0.396; P = .0006‡	r = −0.396; P = .0006‡
PAI-1	r = 0.317; P = .006‡	r = 0.235; P = .04§	**r = −0.506**; P < .0001†	r = 0.303; P = .009‡	r = 0.403; P = .0004‡	r = 0.457; P < .0001‡
sFASL	NR	r = −0.337; P = .003‡	r = 0.256; P = .03§	r = −0.353; P = .002‡	r = −0.345; P = .003‡	r = −0.318; P = .006‡
sCD40L	NR	NR	r = −0.387; P = .0007‡	NR	NR	r = 0.272; P = .02§
Endoglin	NR	NR	NR	NR	NR	NR
IGFBP-1	NR	NR	r = −0.234; P = .04§	NR	NR	NR

*BL indicates buccolingual; EGF, epidermal growth factor; IGFBP-1, insulin-like growth factor binding protein 1; IL, interleukin; MD, mesiodistal; NR, statistically nonsignificant correlations are not reported; PAI-1, plasminogen activator inhibitor 1; PlGF, placental growth factor; sCD40L, soluble cluster determinant 40 ligand; sFASL, soluble FAS ligand.

†Strong correlations: at $P \leq .05$ level with $r \geq 0.5$.

‡Moderate correlations: at $P \leq .05$ level with $0.3 > r < 0.5$.

§Weak correlations: at $P \leq .05$ level with $r \leq 0.3$.

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including IL-18 and EGF; and third, markers whose levels remained unchanged or exhibited nonsignificant changes (endoglin, TGF-α, uPA, HB-EGF, and sFASL). Among the WF markers that showed significant concentration changes, IL-6 and IL-18 had the greatest relative changes from baseline, with 84-fold increase and 6-fold decrease, respectively.

The WF molecular marker level changes exhibited strong, moderate, weak, or no correlation with clinical healing parameters. It was apparent that markers that exhibited significant correlations with clinical parameters could be generally grouped into 1 of 2 categories. The first category included markers (eg, IL-6 and PlGF) that exhibited a strong positive association with parameter values relating to negative healing outcomes, such as greater wound exposure dimensions, incomplete wound epithelialization (positive H_2O_2 test), and bleeding. The second included markers (eg, TGFα and EGF) that demonstrated a strong positive association with parameter values relating to positive healing outcomes, such as greater wound closure.

Previously, we have shown that IL-6 dramatically increases in WF after implant or periodontal surgery,[14] and this cytokine was the WF molecular marker that most strongly correlated with clinical parameters. The higher the WF IL-6 levels, the more likely the residual open wound dimensions were greater and less likely that the wound was closed. These findings suggest that detection of IL-6 levels merits further investigation in oral fluids, including saliva, as an objective and noninvasive tool to assess oral wound healing progress. A similar relationship, albeit less strong, was observed between clinical parameters and either PlGF or IL-18. Previously, PlGF has been detected in GCF,[18–20], in surgical drain fluid after oral surgery,[21] and human skin WF after experimental blisters.[22] The latter study did not report on possible correlations between biomarker levels and clinical healing parameters; however, skin WF PlGF levels were lower in conditions potentially associated with improved wound healing.[22] Both IL-6 and PlGF were the 2 molecular markers that also showed a statistically significant, albeit weak, correlation with flap perfusion changes. Local IL-18 levels, which were strongly correlated with both IL-6 and PlGF levels in the present study, have been previously reported to be elevated in GCF from periodontitis patients,[23,24] and shown to increase in anatomical or pathological fluids after orthopedic,[25,26] neurologic,[27,28] or lung[29] injury. Levels of IL-8 have not been hitherto examined in relation to surgical wound healing. Overall, the significance of these novel findings is 2-fold: First, these results provide evidence of differential inflammatory response by using a minimally invasive tool after GBR surgery. Second, the results suggest an alternative, objective, and noninvasive approach to evaluate early phases of wound healing after GBR surgery, complementing or potentially even bypassing the conventional, mostly subjective, clinical parameters.

As with all clinical studies, the present one is not without limitations. It was conducted as a prospective observational clinical study in a training center, and included a particular population consisting of 15 subjects (9 women) with a mean age of 50 years. It is well documented that age and gender can negatively affect oral wound healing.[30] Individuals over 65 years old were excluded from this study, and gender distribution was even. Standard surgical protocols were not modified for the study. Thus, indications for extraction included hopeless teeth due to fracture, caries, or severe periodontal attachment loss. Primary wound closure was obtained when possible, without performing extended flap elevation or vertical releasing incisions, to prevent additional trauma and compromised blood supply.[31] In addition, surgeries were conducted by several clinicians with various experience levels. Each of these factors might have affected particular clinical wound healing outcomes or specific molecular responses. However, it is unlikely that all of these factors have negatively affected the reported consistent strong association between molecular markers and clinical parameters. The present study also has certain strengths. The restricted clinical wound size and anatomical location, intentionally limited to a single tooth site with intact mesial and distal teeth within maxillary anterior sextant, made it possible to control surgical trauma magnitude and to minimize the effect of such parameter on outcomes. It is likely that this study design aspect made possible the identification of WF molecular markers, such as IL-6, that exhibit strong association with soft tissue clinical healing responses. An additional strength of the study is the concurrent use/analysis of multiple clinical parameters and molecular markers. The consistency of the reported trends and associations validates this approach. However, the present study results need to be validated by further research in different populations and settings and on more challenging wounds (ie, of greater size) to firmly establish the possible association between specific WF marker levels and the postoperative course of surgical wound healing.

Conclusions

This study correlates for the first time oral wound healing clinical parameters with particular WF molecular markers. Specifically, IL-6 and PlGF appear to be strongly correlated with various clinical parameters such as wound exposure dimensions. Additional studies are needed to develop minimally invasive diagnostic tools to evaluate early wound healing outcomes of GBR procedures to better follow, predict, and control healing outcomes.

Abbreviations

EGF: epidermal growth factor
GBR: guided bone regeneration
GCF: gingival crevicular fluid
HB-EGF: heparin-binding EGF-like growth factor
IGFBP-1: insulin like growth factor binding protein-1
IL: interleukin
LDF: laser Doppler flowmetry
OSU: The Ohio State University
PAI-1: plasminogen activator inhibitor 1
PlGF: placental growth factor
sCD40L: soluble cluster determinant 40 ligand
sFASL: soluble FAS ligand
TGF-α: transforming growth factor alpha
TNF-α: tumor necrosis factor alpha

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uPA: urokinase type plasminogen activator
WF: wound fluid

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Note

The authors declare no conflicts of interest with this study.

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