

Could Silent Inflammation Originating in Jawbone Cavitations Play a Role in Activating the CCL5/CCR5 Axis in Female Breast Cancer? A Diagnostic and Therapeutic Gap in Osteoimmunological Interactions

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Introduction: Breast cancer (BC) is one of the leading causes of cancer mortality worldwide. The chemokine CCL5 and its receptor CCR5 have been demonstrated to be associated with tumour progression, immune evasion, and metastasis.

Objective: Recent evidence indicates that chronic inflammatory conditions in the jawbone, specifically fatty degenerative osteonecrosis of the jaw (FDOJ), may serve as a continuous source of CCL5 overexpression, potentially influencing BC development.

Methods: This multicentre study, conducted in Germany, Portugal and Slovenia, investigated the correlation between FDOJ-related CCL5 expression and BC. Patients undergoing surgical removal of FDOJ areas were examined using advanced imaging (trans alveolar ultrasonography) and multiplex cytokine analysis to detect bone marrow defects and measure CCL5 levels.

Results: The results demonstrated a marked increase in CCL5 expression in FDOJ samples in comparison to healthy jawbone tissue.

Discussion: Statistical analysis revealed a strong correlation between FDOJ and elevated CCL5, thereby supporting the hypothesis that jawbone inflammation may activate the CCL5/CCR5 axis in BC patients. This finding suggests that FDOJ may represent an underrecognized inflammatory comorbidity that contributes to BC progression.

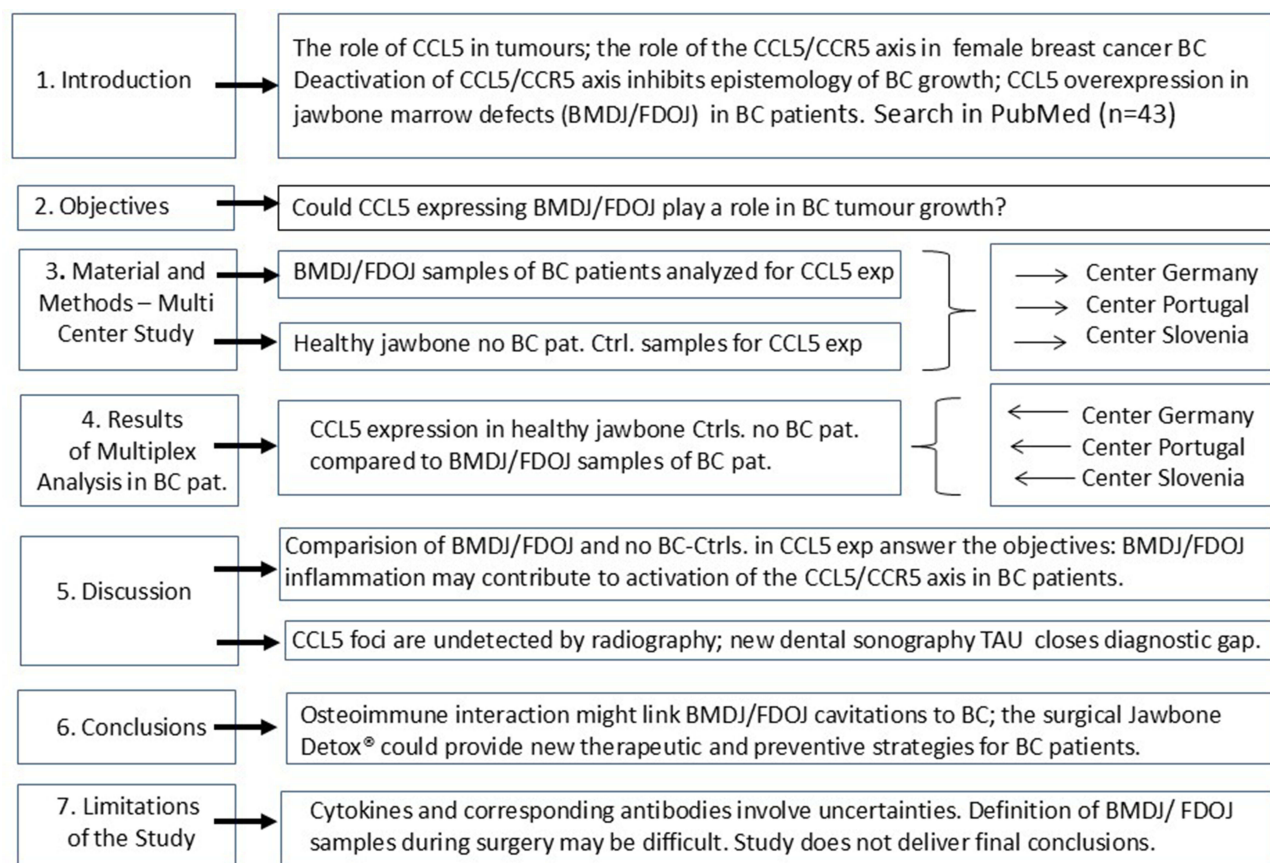
Conclusion: The study under discussion highlights a hitherto unidentified osteoimmune mechanism that links inflammation of the jawbone to cancer pathways. It also emphasizes the potential benefit of targeted surgical interventions such as “Jawbone Detox[®]” in reducing chronic CCL5 levels. Such approaches have the potential to offer novel preventive and therapeutic options for patients diagnosed with BC. Further clinical studies are required to confirm the effects of FDOJ treatment on immune function and BC outcomes.

Keywords: breast cancer, CCL5, CCR5, FDOJ, trans alveolar ultrasonography, TAU

Introduction

The link between inflammation and cancer is now well established and represents a new paradigm: Our immune response is not necessarily just to protect us from infection and cancer. Chemokines, cytokines and exosomes help tumors to shape the inflammatory microenvironment. Overall, tumor-induced inflammation is an important factor in tumor progression.¹ Extensive studies explain tumor epistemology in the context of a complex and dynamic tumor microenvironment consisting of cells, blood vessels, extracellular matrix (ECM), cytokines and chemokines.² Inflammatory processes mediated by the tumor microenvironment have been highlighted in breast cancer (BC) progression.³ BC is a leading cause of death in women worldwide. BC caused 670000 deaths globally in 2022.⁴ Despite advances in the treatment of the

Graphical Abstract



disease, 20–30% of patients with early BC will relapse with distant metastases.⁵ These figures underscore the importance of early detection and effective treatment strategies in the fight against BC.

The Role of CCL5 in Tumors

Chemokines regulate the infiltration of different subsets of immune cells into the tumor, so these molecules influence tumor immunity and therapeutic outcomes in patients.

Chemokines also target tumor and stromal cells and regulate angiogenesis, stem cells, proliferation and tumor survival.⁶ In addition, the chemokine CCL5 was closely associated with immune checkpoint molecules in 8 tumor types.⁷ Elevated CCL5 levels are a marker of poor outcome in patients with melanoma, breast, cervical, prostate, gastric or pancreatic cancer.⁷ Data support the involvement of CCL5 in the pathogenesis of colorectal cancer (CRC) and indicate its potential value as a therapeutic target.⁸

Especially one cytokine is intensively discussed in the epistemology of cancer, and this is CCL5: CCL5 expression is high in advanced disease (stages II and III), particularly in triple- negative BC,⁹ and low in benign breast disease.¹⁰ Serum CCL5 levels are higher in BC patients than in healthy individuals.¹¹ Studies substantiate that CCL5 levels are elevated in primary and metastatic breast tumors.¹² CCL5 secreted by hematopoietic cells is involved in the progression of BC.¹² CCL5 may be a prognostic biomarker and may be associated with immunotherapeutic efficiency in cancer. In summary, CCL5 has been tentatively identified as a biomarker of immune response and prognosis in cancer patients.⁷ Furthermore, it is possible that in patients diagnosed with benign breast disease, CCL5 expression may indicate an

ongoing, but as yet undetected, malignant process.¹³ BC cells responsible for cancer recurrence are characterized by a pro-inflammatory gene expression program, which includes CCL5.¹⁴

The Role of the CCL5/CCR5 Axis in Tumors of the Female Breast

There is compelling evidence that the CCL5/CCR5 axis is involved in the invasive and metastatic behavior of many cancers.¹⁵ Overall, current evidence suggests that the CCL5/CCR5 axis is a potential therapeutic target in various cancers.¹⁵ The interactions of chemokines with their receptors regulate immune and inflammatory responses.¹⁵ The interaction between CCL5 and CCR5 plays an active role in the recruitment of leukocytes to target sites.¹⁰ Researchers have identified the CCL5/CCR5 axis as a key player in tumor progression.¹⁶ Human BC cell lines found to express CCR5 exhibit functional response to CCL5 and tended to be higher in advanced stages of the disease.¹⁷ Increased expression of CCL5 and CCR5 is associated with BC, and CCL5/CCR5 expression levels differ in different genetic subtypes of BC.¹⁷

Following the CCL5/CCR5 axis has been extensively studied in the context of tumorigenesis. The CCL5/CCR5 axis always aims to create a more favorable microenvironment for tumor cell survival, as tumor cells can “hijack” chemokine networks to support tumor progression.¹⁸ In this context, the CCL5/CCR5 axis is gaining increasing attention, as abnormal expression and activity of CCL5 and its receptor CCR5 have been reported in tumors.¹⁸ CCR5 expression has been found to be preferentially expressed on regulatory T cells (Tregs). Intra tumoral injection of CCL5 led to an increase in tumor infiltrating Tregs.¹⁹ Elevated levels of CCL5 and its receptor CCR5 were found in more than 58% of patients with basal BC.²⁰

Deactivation of CCL5/CCR5 Axis Inhibits Epistemology of BC Tumor Growth

If we consider CCL5/CCR5 as a contributor and potential trigger in the development of BC, the impact of anti-CCL5/CCR5 treatments on the immune integrity of the patient should also be evaluated. The optimal therapeutic modalities would need to address two conflicting needs: the need to prevent the deleterious involvement of CCL5 and activated CCR5 in BC, and the need to protect their potentially beneficial activities in immunity, including anti-cancer immune responses.²¹ CCL5/CCR5 also recruits Tregs, MDSCs and TAM to induce immunosuppression of the tumor.²¹ Research suggests that CCR5 antagonists could be used as adjuvant therapy to reduce the risk of metastasis in patients with basal BC.²² In addition, CCR5 secreted by the tumor microenvironment is highly sensitive to drug blockade, particularly in BC.²³ Due to the interactions between CCR5 signaling and immune checkpoint function, research into blocking the CCL5/CCR5 axis in tumor therapy has gained a broad application perspective.^{23–26} Attenuation of tumor promoting inflammation in tumor tissue and objective tumor responses were observed.²⁶ Studies therefore suggest that the myeloid CCL5-CCR5 axis is an excellent target for cancer immunotherapy.²⁷ CCR5 promotes the invasiveness and metastatic potential of BC, while CCR5 inhibition abolishes them.

Therefore, CCR5 antagonists may represent an alternative therapeutic approach for patients with metastatic basal BC.²⁸ BC cells stimulate de novo secretion of the chemokine CCL5/RANTES from mesenchymal stem cells, which then acts in a paracrine manner on cancer cells to promote their motility, invasion and metastasis.²⁹ This enhanced metastatic ability is reversible and depends on CCL5 signaling via the chemokine receptor CCR5.³⁰ In summary, specific therapies that inhibit the CCL5/CCR5 axis not only prevent tumor progression but can also significantly delay tumor growth. Specific therapies to inhibit the CCL5/CCR5 axis and potential blockers of CCR5 activity include:

- A. Leronlimab is a humanized IgG4, kappa monoclonal antibody that blocks the expression of CCR5 with a long safety record treating patients with HIV.³¹ Leronlimab has been shown to bind to CCR5 in several BC cell lines. Binding of leronlimab to CCR5 reduced ligand-induced Ca²⁺ signaling.^{31,32}
- B. As a CCR5 antagonist, maraviroc directly competes with CCL5 to bind to CCR5, blocks CCR5 internalization and inhibits T-cell chemotaxis.³³ Maraviroc may inhibit the recruitment of mesenchymal stem cells (MSCs), monocytes and some growth factors by tumor cells, which could reduce cancer progression. The autocrine CCL5-CCR5 axis reprograms immunosuppressive myeloid cells and enhances anti-tumor immunity.³⁴

- A. Anibamine is the first natural CCR5 antagonist that inhibits CCR5/CCL5 interactions. It reduced the proliferation rate of most prostate cancer cell lines. At the same time, anibamine was able to significantly alter the morphology, metastasis and adhesiveness of cancer cells, making it a favorable therapeutic agent for the treatment of prostate and ovarian cancer due to its high affinity for CCR5 and inhibited proliferation rate of cancer cells. As CCR5 antagonists, anibamine and their analogues significantly suppressed CCL5-induced intracellular Ca(2+) flux.^{34,35}

CCL5 Overexpression in Jawbone Marrow Defects (BMDJ/FDOJ) in Breast Cancer Patients

The death of local bone marrow cells due to chronic stimulation by insults such as jawbone inflammation can lead to chronic osteoimmune dysregulation. In previous publications, this chronic inflammatory process was defined in bone marrow defects of the jaw (BMDJ) as fatty degenerative osteonecrosis of the jaw (FDOJ) associated with chronic overexpression of the proinflammatory cytokine CCL5 (also called RANTES = Regulated And Normal T cell Expressed and Secreted).^{36,37} BMDJ/FDOJ, also called as “Cavitations”, is also primarily defined in the literature as “bone marrow oedema”,^{38,39} or silent or subclinical inflammation without the typical signs of acute inflammation.^{38,39} Clinical experience with the notable fatty degenerative morphology of BMDJ/FDOJ (see section 1.1.3) led us to investigate cytokine expression in tissue samples easily excised from such defects. We investigated 128 BMDJ/FDOJ samples in 128 patients with a cytokine panel of FGF-2, IL-1ra, IL-8, IL-6, IL-10, MCP-1, TNF- α and CCL5.^{39,40} Results are shown in Table 1 and Figure 1.

Summary of the Role of CCL5 in Tumors and Potential Therapeutic Implications

- CCL5 plays a crucial role in tumor biology by influencing the infiltration of various immune cells. Elevated CCL5 levels are a marker of poor prognosis in melanoma, breast, cervical, prostate, gastric and pancreatic cancer.^{7–14}
- The CCL5/CCR5 axis is critical for the invasiveness and metastasis of many cancers. In particular, CCL5 expressions are high in advanced BC, whereas it remains low in benign breast lesions. Overexpression of CCR5 on regulatory T cells (Tregs) has been observed in several tumor types and promotes tumor progression.^{15–20}
- As a therapeutic approach, deactivation of the CCL5/CCR5 axis inhibits tumor growth, with the most promising CCR5 antagonists leronlimab and maraviroc.^{21–34}
- Chronic inflammation in BMDJ/FDOJ also lead to excessive expression of CCL5, which may play a role in tumour progression.^{39–42}

Objectives

This study investigates whether chronic CCL5 overexpression in BMDJ/FDOJ tissues contributes to CCL5/CCR5 axis activation in breast cancer (BC).^{4,5} It aims to quantify CCL5 levels in these often-overlooked jawbone defects in BC patients in a multicenter research.

Materials and Methods

Multicentre Study on the Expression of CCL5 in BMDJ/FDOJ of Patients with BC

To confirm the CCL5 overexpression in the BMDJ/FDOJ,^{39–42} a further international multicentre study was performed to confirm the earlier results of Lechner and co-authors.^{43,44} The BMDJ/FDOJ clinical specimens were provided by patients undergoing surgical debridement of the pathologic bone marrow tissue in BC patients at each of the authors’ clinics in

Table 1 In Contrast to the Expressions of FGF-2, IL-1ra, IL-6, IL-8, MCP-1 and TNF- α , CCL5/RANTES Shows a Singular 35-Fold Overexpression Compared to Healthy Jawbone Marrow

pg/mL	FGF-2	IL-1ra	IL-6	IL-8	MCP-1	TNF- α	RANTES
MV BMDJ/FDOJ (n=128)	781,5	731	5,5	3,5	121,1	5,2	5.188
MV Ctrl (n=19)	27,6	195,5	101,0	7,5	20,3	11	149,9
P-value	0,001	<0,001	<0,001	<0,001	0,001	<0,001	0,19
StDev	$\pm 717,1$	$\pm 979,6$	$\pm 11,5$	$\pm 48,9$	$\pm 118,8$	$\pm 10,1$	$\pm 3.004,7$

Notes: Bold numerical value of 5.188 shows singular overexpression of RANTES/CCL5.

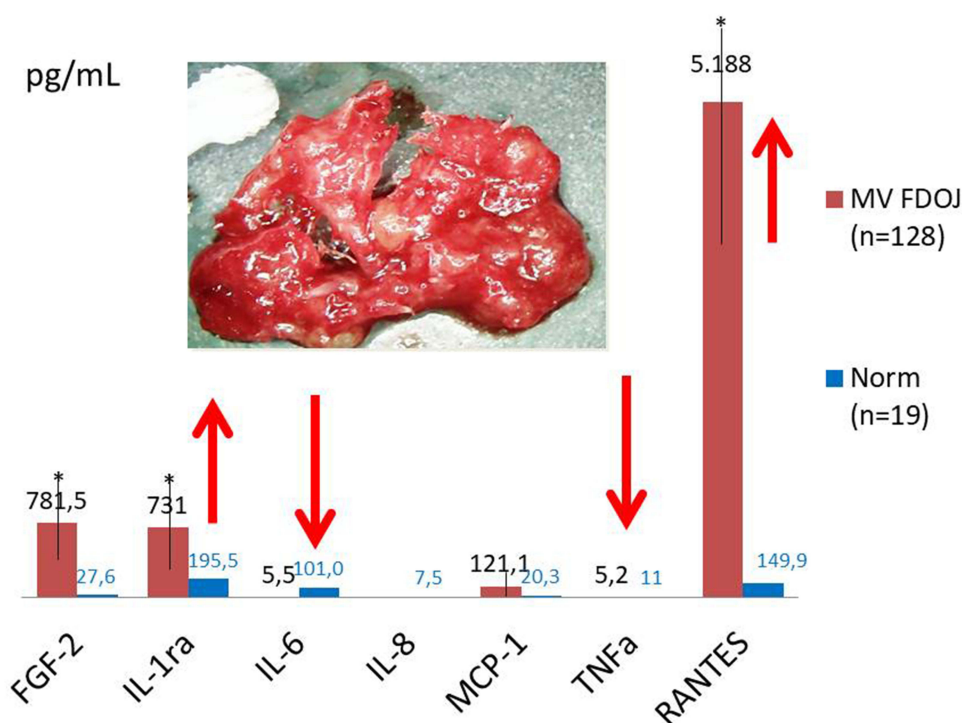


Figure 1 Cytokine expression in 128 BMDJ/FDOJ samples with a cytokine panel of FGF-2, IL-1ra, IL-8, IL-6, IL-10, MCP-1, TNF-α and CCL5.

Notes: Columns in red (MV) represent the mean value of the respective cytokine for 128 BMDJ/FDOJ samples; columns in blue (Norm) represent the mean value of each cytokine in 19 healthy jawbone samples. The distribution of multiplex analysis of 128 BMDJ/FDOJ samples shows marked singular over expression of CCL5, mild over expression of IL-1ra and downregulated TNF-α and IL-6 expression.^{41,42} It is clinically noteworthy that, with the exception of cases of atypical facial pain and trigeminal neuralgia, BMDJ/FDOJ does not elicit a pain response in most patients. The absence of a painful inflammatory response may be explained by the reduced expression of TNF-α and IL-6, with TNF-α expression reduced by a third and IL-6 expression reduced by only a tenth compared to expression levels in 19 samples of healthy bone marrow. Thus, levels of these acute inflammatory mediators are insufficient to drive acute and painful inflammation in most cases of BMDJ/FDOJ.⁴⁰ Red arrows indicate extreme deviations above or below the healthy control values. *Indicates the upper end of the StDev.

Germany, Portugal and Slovenia. The detailed description below was carried out using the same methodological steps in diagnostics and BMDJ/FDOJ adjustment in all three clinics. (Exception: Portugal: No TAU for preoperative findings).

Each patient expressed an interest in determining whether chronic inflammation was present in the jawbone. The present patient centered study was conducted as a retrospective case-control study and was classified as such by the Institute for Medical Diagnostics, Nikolaistr. 22, D-12247 Berlin (IMD-Berlin), according to DIN EN 15198/DIN EN 17025 and received an exemption. All patients provided their written informed consent to participate in this study.

The samples and data were obtained during routine clinical practice and evaluated retrospectively. Normal medical care of the patients was performed. Institutional approval was not required to publish the case details. Patients taking medications for symptoms relief were not required to discontinue these medications except for those affecting bone metabolism as an exclusion criterion. All patient details were deidentified. This study was conducted in accordance with the Declaration of Helsinki.

Medication used to alleviate any sensitivities was not stopped. The use of medications to treat systemic diseases was not considered an exclusion criterion. The exclusion criteria included the use of cortisone and bisphosphonates due to their effects on bone metabolism. The samples analyzed were collected during the normal procedures of an oral surgery performed at each dental clinic of the authors. The healthy jawbone samples were collected during the drill procedure for implant placement and with the patient consent. In all of the authors' clinics the BC patients diagnosed from FDOJ/BMDJ had surgery in the affected part of the jaw after local anesthesia and folding off a mucoperiosteal flap. The cortical layer was removed. All patients showed osteolytic spongy areas and degenerative fatty tissue as described in chapter 3.1 and in Figure 2. In all cases, surgery was done in edentulous jaw areas in the range of former wisdom teeth and the adjacent retromolar areas. The presence of BMDJ/FDOJ was evaluated preoperatively for each patient through an OPG (orthopantomography), cone-beam computed tomography/Digital volume tomography (CBCT/DVT) and trans alveolar ultrasound device (TAU) (except research Portugal).

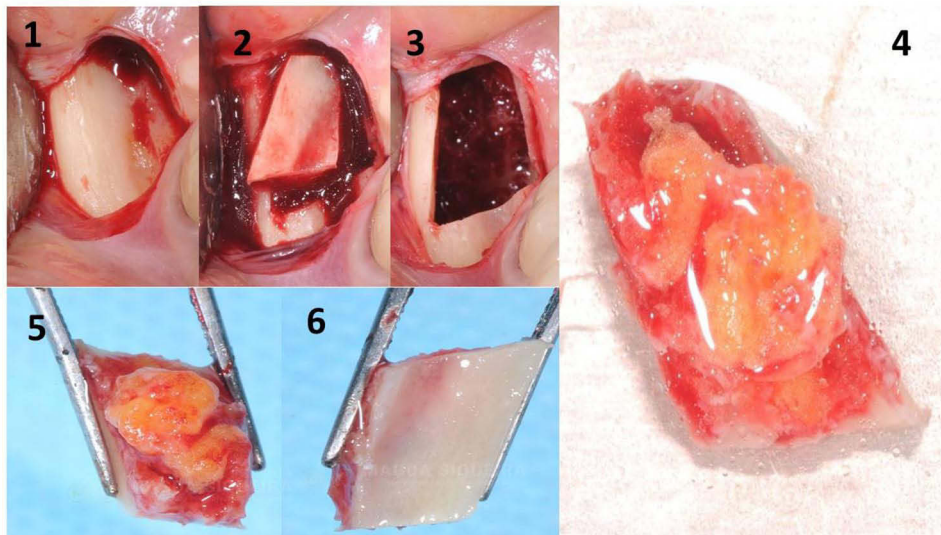


Figure 2 Surgical procedure of BMDJ/FDOJ sample collection (“Jawbone Detox[®]”); one of the tissue samples taken during surgery.
Notes: Upper panels 1 through 2 show the oral surgical procedure to get access to the bone marrow defect. Panel #3 shows the medullary jawbone cavity in retromolar area after curettage of the softened bone marrow defect of BMDJ/FDOJ. Right panel #4 shows the fatty degenerated osteonecrosis (FDO) within the bone marrow defect (BMDJ) with the typical yellowish staining characteristic of fatty degeneration of the jawbone (FDOJ). Lower panels 5 and 6 show the extent of the BMDJ/FDOJ specimen and the cortical lid, removed in panel #2 (Courtesy by: Prof. Dr. José Scarso Filho, Sao Paulo and Dra. Magda Siqueira).

Morphology of Bone Marrow Defects of the Jaw (BMDJ/FDOJ) and Collection of Tissue Samples

Figure 2 shows the oral surgical procedure of sample collection (“Jawbone Detox[®]”) and one of the tissue samples taken during surgery for a bone marrow defect in the jaw.

Statistical Analyses

Descriptive statistical analyses of the measurements of the BMDJ/FDOJ specimen and control groups were performed. Assessment of whether non-parametric or parametric testing would be more appropriate for the analysis was performed through analysis of data distribution, means, and medians. Student’s *t*-test or Spearman’s Rho was used to determine the differences between cohorts. A value of *p* = 0.05 was set for significance.

Results

The results of the multicenter evaluation of CCL5 expression in BMDJ/FDOJ samples of BC patients analyzed for CCL5/RANTES expression and healthy control samples are shown in Table 2. The number of healthy controls and of BMDJ/FDOJ is also shown in Table 2. Specific results of Munich, Germany, are shown in Figure 3. Specific results of Lisboa, Portugal, are shown in Figure 4. Specific results of Ljubljana, Slovenia, are shown in Figure 5.

Table 2 The Number of Healthy Control Samples and of BMDJ/FDOJ Samples of BC Patients Analyzed for CCL5/RANTES Expression

Munich, Germany		Lisbon, Portugal		Ljubljana, Slovenia	
Ctrl Healthy RANTES/CCL5	BMDJ/FDOJ RANTES/CCL5	Ctrl Healthy RANTES/CCL5	BMDJ/FDOJ RANTES/CCL5	Ctrl Healthy RANTES/CCL5	BMDJ/FDOJ RANTES/CCL5
448	4,876	557	1,602	312	2,562
720	2,2	1,108	13,348	613	1,762
583	4,8	880	1,543	338	8,862

(Continued)

Table 2 (Continued).

Munich, Germany		Lisbon, Portugal		Ljubljana, Slovenia	
Ctrl Healthy RANTES/CCL5	BMDJ/FDOJ RANTES/CCL5	Ctrl Healthy RANTES/CCL5	BMDJ/FDOJ RANTES/CCL5	Ctrl Healthy RANTES/CCL5	BMDJ/FDOJ RANTES/CCL5
810	4,845	848.3	1,038	570	6,737
640	5,025	± 276.8	9,339	640.2	518
530.8	2,487		3,011	± 158.5	5,475
± 210.6	5,886		1,933		3,725
	2,162		4,544.8		5,825
	7,225		$\pm 4,823.9$		4,037
	526				1,086
	5,867				4,058.9
	3,887				$\pm 2,674.3$
	4,148.9				
	$\pm 1,938.5$				

Notes: Figures in GREEN are CCL5/RANTES expressions of control specimen and in RED are CCL5/RANTES expressions of BMDJ/FDOJ specimen (in pg/mL). Munich, Germany BMDJ/FDOJ RANTES/CCL5: In BC patients: Germany = 12; Ctrl healthy RANTES/CCL5: No BC patients: Germany = 5. Lisbon, Portugal BMDJ/FDOJ RANTES/CCL5: In BC patients: Portugal = 7; Ctrl healthy RANTES/CCL5: No BC patients: Portugal = 3. Ljubljana, Slovenia BMDJ/FDOJ RANTES/CCL5: In BC patients: Slovenia = 10; Ctrl healthy RANTES/CCL5: No BC patients: Slovenia = 4.

Summary Results Multicenter Study

- Comparison of BMDJ/FDOJ multicentre evaluation of CCL5/RANTES expression levels in BC patients: Germany = 12, Slovenia = 10, Portugal = 7 (Figure 6).
- Comparison of healthy jawbone multicentre evaluation of CCL5/RANTES expression levels from patients with no BC: Germany = 5, Slovenia = 4, Portugal = 3 (Figure 7).
- Comparison of healthy jawbone multicenter evaluation of CCL5/RANTES summary of all healthy jawbone evaluations (no BC) and all BMDJ/FDOJ evaluations of CCL5/RANTES in BC patients (Figure 8).

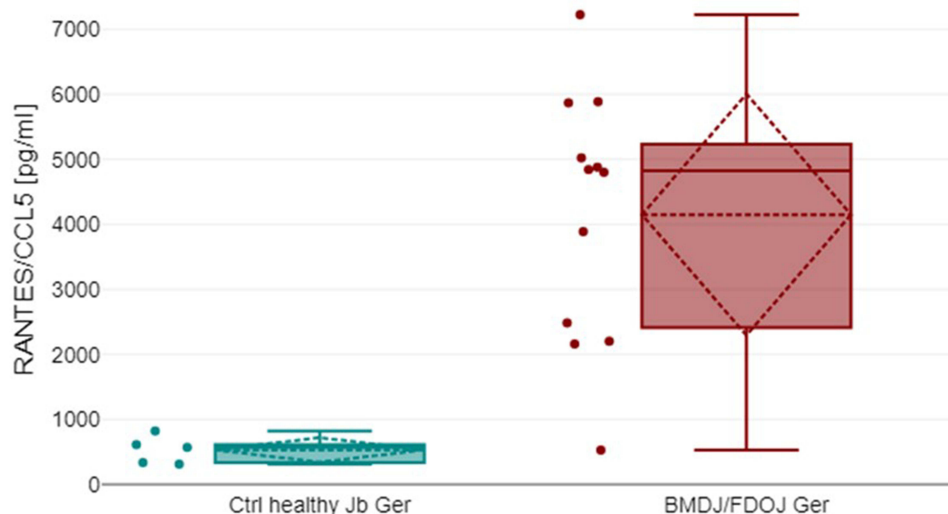


Figure 3 CCL5/RANTES expression in BMDJ/FDOJ samples of BC patients and healthy control samples. Specific results of Munich, Germany.

Notes: RANTES/CCL5 ctrl. healthy jawbone versus BMDJ/FDOJ Germany: *t*-test for independent samples (assuming unequal variances) revealed that the difference was statistically significant with regard to the dependent (variable, $t(11.61) = -6.38$, $p = <0.001$, 95% confidence interval $[-4859.54, -2376.65]$). Thus, the null hypothesis that there is no difference in the mean between the two groups was rejected. The Cohen's *d* of 3.39 indicates a large effect. 95% confidence interval of the difference. The mean age of BC patients Germany was 52.6 (± 12.35) years.

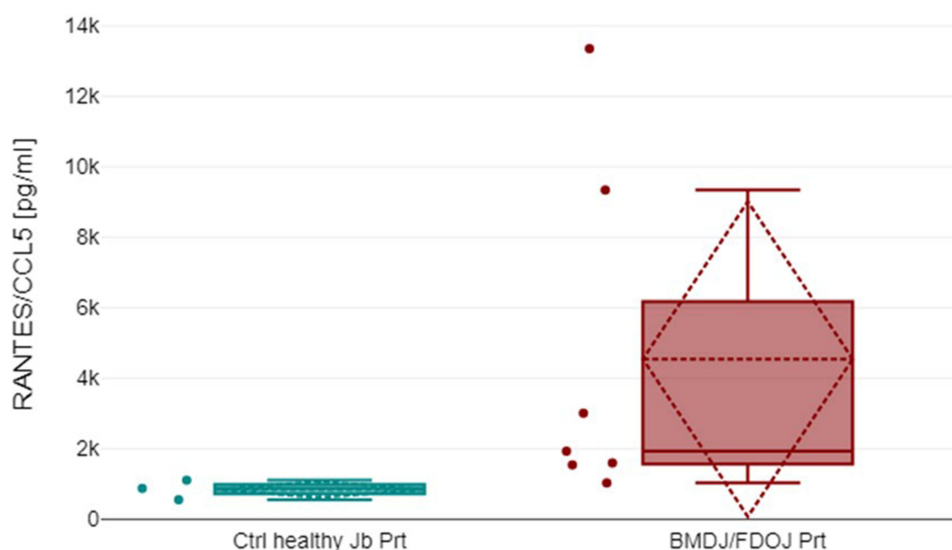


Figure 4 CCL5/RANTES expression in BMDJ/FDOJ samples of BC patients and healthy control samples. Specific results of Lisboa, Portugal.

Notes: RANTES/CCL5 ctrl. healthy jawbone versus BMDJ/FDOJ Portugal: An independent samples t-test (assuming unequal variances) indicated that the difference was not statistically significant with respect to the dependent variable ant, $t(6.09) = -2.02$, $p = 0.089$, 95% confidence interval $[-8161.48, 768.43]$. Thus, the null hypothesis that there is no difference in the mean between the two groups was not rejected. The Cohen's d of 1.39 indicates a large effect. 95% confidence interval of the difference. The mean age of BC patients Portugal was 50.4 (± 9.84) years.

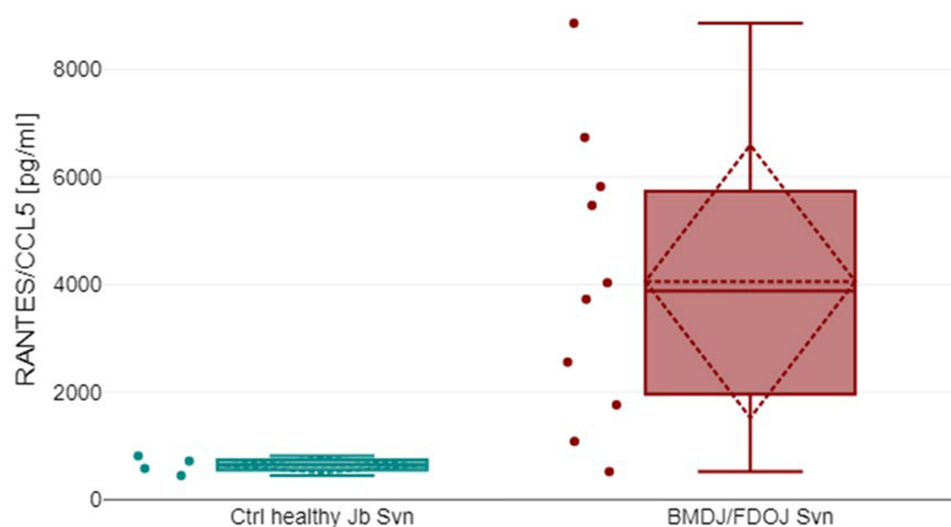


Figure 5 CCL5/RANTES expression in BMDJ/FDOJ samples of BC patients and healthy control samples. Specific results of Ljubljana, Slovenia.

Notes: RANTES/CCL5 ctrl. healthy jawbone versus BMDJ/FDOJ Slovenia: An Independent samples t-test (assuming unequal variances) indicated that the difference was statistically significant for the dependent variable, $t(9.16) = -4.02$, $p = 0.003$, 95% confidence interval $[-5335.52, -1501.78]$. Thus, the null hypothesis that there is no difference in the mean between the two groups was rejected. The Cohen's d of 2.38 indicates a large effect. 95% confidence interval of the difference. The mean age of BC patients Slovenia was 48.5 (± 6.86) years.

Discussion

The findings suggest that ischemic BMDJ/FDOJ may be an overlooked comorbidity in breast cancer, with chronic CCL5/CCR5 signaling potentially originating from these jawbone lesions.⁴⁵

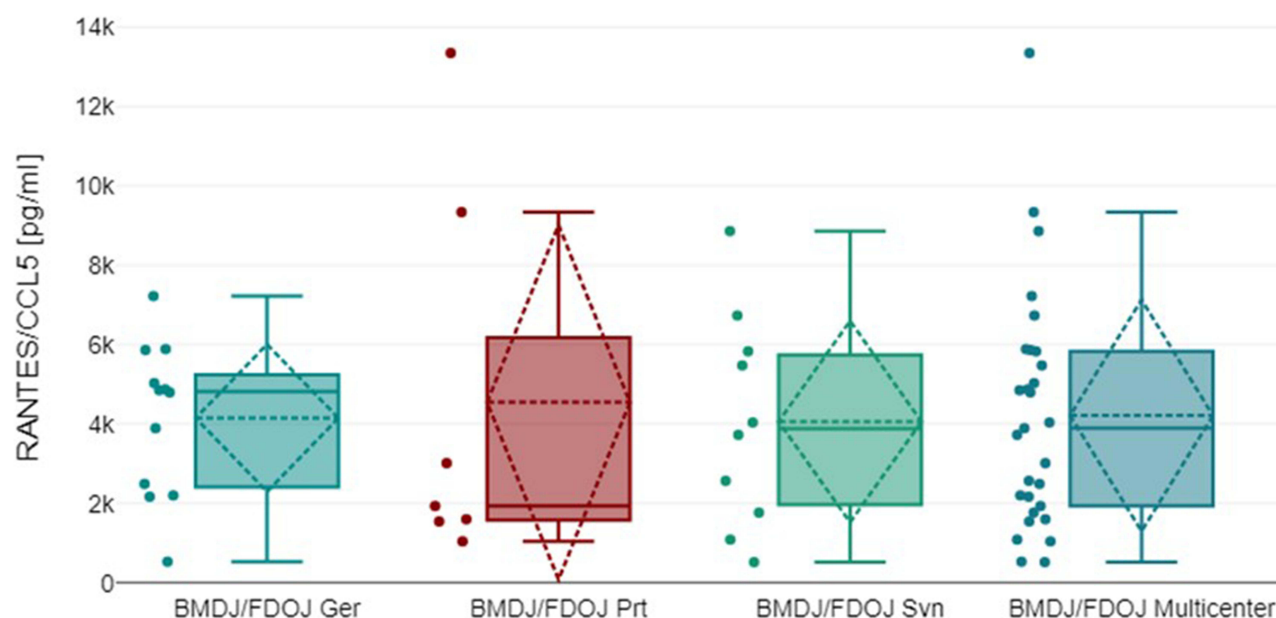


Figure 6 Comparison of BMDJ/FDOJ multicentre evaluation of CCL5/RANTES expression levels in BC patients.

Notes: Comparison of BMDJ/FDOJ multicentre evaluation of CCL5/RANTES in pg/mL; number of BMDJ/FDOJ samples: Germany: n = 12; Portugal: n = 7; Slovenia: n = 10; right column is MV of all.

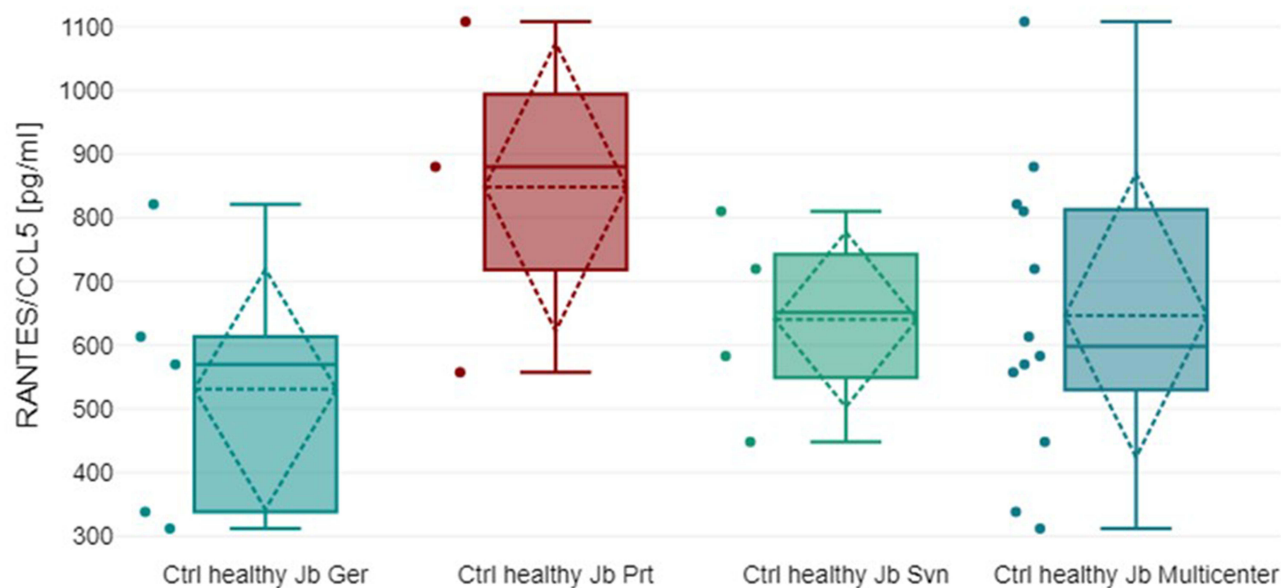


Figure 7 Comparison of healthy jawbone multicentre evaluation of CCL5/RANTES expression levels from patients with no BC.

Notes: Comparison of healthy jawbone multicenter evaluation of CCL5/RANTES in pg/mL; number of healthy jawbone samples: Germany: n = 5; Portugal: n = 3; Slovenia: n = 4; right column is MV of all.

Working Hypothesis: Possible Interactions Between the CCL5/CCR5 Axis of Mesenchymal Stem Cells and BMDJ/FDOJ CCL5 Signaling

Disruption of the CCL5/CCR5 axis with CCL5 inhibitors, in turn, has a positive effect on the tumor. CCR5 inhibitors appear to be suitable for attenuating the tumorigenic BC process. Based on this, our working hypothesis is that reducing CCL5 expression in bone marrow defects may contribute to tumor therapy or prevention (see Chapter 3) in a comparable process:^{10–13}

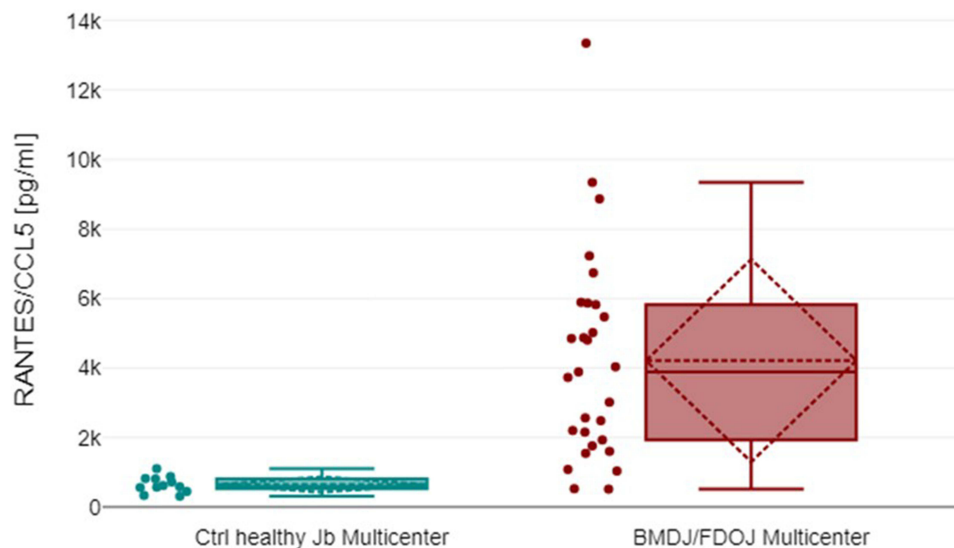


Figure 8 Comparison of healthy jawbone multicenter evaluation of CCL5/RANTES summary of all healthy jawbone evaluations (no BC) and all BMDJ/FDOJ evaluations of CCL5/RANTES in BC patients.

Notes: All RANTES/CCL5 ctrl. healthy jawbone versus BMDJ/FDOJ in multicenter study: An independent samples t-test (assuming unequal variances) indicated that the difference between *Ctrl healthy Jb multicenter* and *BMDJ/FDOJ multicenter* was statistically significant for the dependent variable ant, $t(28.82) = -6.43$, $p = <0.001$, 95% confidence interval $[-4701.9, -2431.65]$. Thus, the null hypothesis that there is no difference in the mean between the two groups was rejected. The Cohen's d of 2.21 indicates a large effect. 95% confidence interval of the difference.

a. Consistent with findings suggesting a tumor enhancing role of CCR5 ligands in cancer, CCL5 secretion by mesenchymal stem cells increased the metastatic potential of BC.^{9,10,12}

b) Direct inhibition of CCL5 signaling from cancer cells to endothelial cells may represent a novel strategy to block angiogenesis, tumor growth and spread in BC.^{13,24,32}

c) At the same time, studies of CCL5/RANTES expression in pathologically altered BMDJ/FDOJ areas exhibit years of CCL5 overexpression, usually unnoticed by the patient^{38–42,45} and simultaneously difficult or impossible for the dentist to detect.^{42,46}

Of particular interest in this context is a study published in Nature on the metastasis of BC cells:²⁹ The key message of this publication for our local dental view on the association of BMDJ/FDOJ expressed CCL5 signaling effects on BC is that “this enhanced metastatic ability is reversible and is dependent on CCL5 signaling through the chemokine receptor CCR5.”²⁹ This possible regression of metastatic tendency by interruption of the CCL5/RANTES signaling pathway cited here³⁰ could be understood as a hypothetical therapeutic approach for BC metastasis prevention by diminishing BMDJ/FDOJ signaling:

If CCL5 overexpression promotes tumor formation and blockade of the corresponding receptor CCR5 has a beneficial therapeutic effect by inhibiting tumor growth, then reducing chronic CCL5 signaling induction from BMDJ/FDOJ areas could act in the same sense as pharmacological blockade of CCR5. Then minimally invasive dental surgery to remove chronic CCL5 expression from BMDJ/FDOJ areas prior to tumor development might have a desirable preventive and possibly positive therapeutic effect.^{38–42}

Why is This Hypothesis New to Integrative Medicine and Dentistry?

Although prior literature adequately documents the connection between the CCL5/CCR5 axis and BC pathophysiology, our study is the first attempt to propose a novel, multicenter-based hypothesis suggesting a potential chronic and subclinical activation of the CCL5/CCR5 axis in BC patients. This hypothesis raises a critical question: How might impaired wound healing in jawbone cavitations⁴⁵—specifically BMDJ/FDOJ lesions with elevated CCL5 expression—be linked to the established role of the CCL5/CCR5 axis in BC progression?^{43,44,47,48} While a direct biophysical connection

between these two processes has not yet been conclusively demonstrated in either scientific or clinical contexts, we propose two plausible mechanisms that support our working hypothesis (see Figure 9):

1. Systemic Dissemination Hypothesis: Elevated peripheral CCL5 levels originating from chronically inflamed or incompletely healed jawbone tissue may circulate systemically and contribute to the inflammatory microenvironment associated with tumorigenesis in BC.
2. Immune Cell Trafficking Hypothesis: Specific immune cell subsets may be primed or activated within the distinct microenvironment of the jawbone lesion, potentially co-expressing CCL5 or responding to its presence. These cells may subsequently home to breast tissue, where they modulate immune responses or promote tumor-supportive conditions.

These proposed pathways—though speculative at this stage—form the conceptual framework for future experimental validation and represent a compelling new direction in the investigation of tumor–bone marrow axis dynamics.

Areas of BMDJ/FDOJ Not Detected by Radiographic Methods

The presence of BMDJ/FDOJ is largely neglected today in mainstream dentistry today because of the limited ability of conventional radiographic techniques to diagnose the location and extent of BMDJ/FDOJ. We have previously highlighted the difficulties in diagnosing BMDJ/FDOJ using conventional methods in a previous publication.^{49,50} A clinical example is documented in Figure 10 which shows the clinical situation of a 47-year-old female patient who presented with an adenocarcinoma of BC, where conventional radiographs showed no BMDJ/FDOJ. During the surgical debridement of the BMDJ/FDOJ tissue, characteristic BMDJ/FDOJ was found in the lower left edentulous wisdom tooth area. Pathological examination of this FDOJ specimen revealed features of osteonecrotic metastases of an adenocarcinoma of BC. In parallel with histopathology, multiplex cytokine analysis (Luminex Corporation, Austin, TX, USA) was performed on the BMDJ/

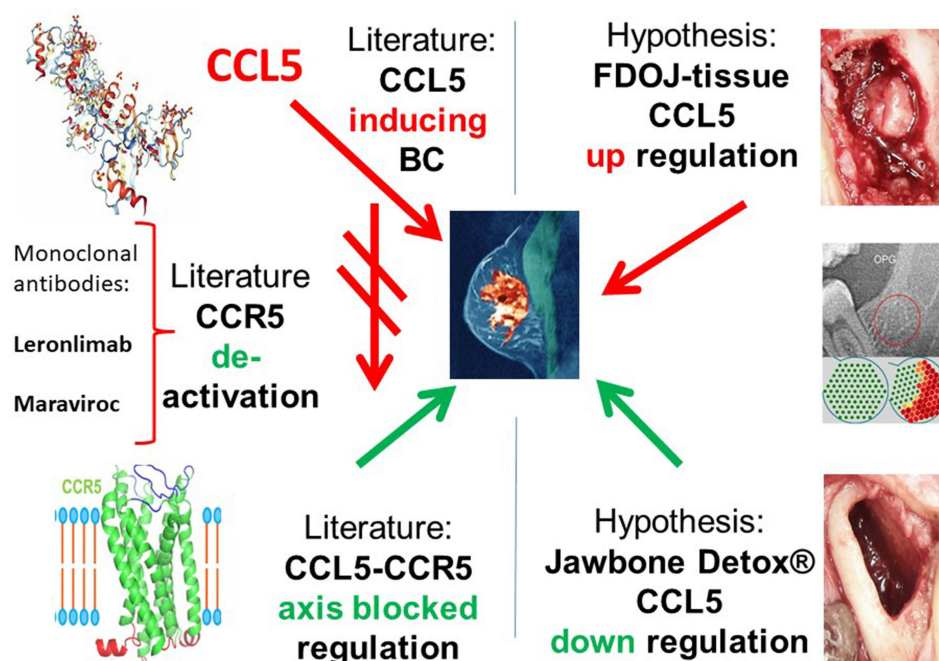


Figure 9 Two plausible mechanisms how impaired wound healing in jawbone cavitations might be linked to the established role of the CCL5/CCR5 axis in BC progression. **Notes:** The left part of Figure 9 shows the links of the CCL5-CCR5 axis to BC as described in detail in the literature, even with therapeutic deactivation of the CCL5 receptor. The right part shows the hypothesis of potential links of CCL5 expressions from BMDJ/FDOJ areas (upper picture) to BC including their diagnostic radiographic failure opposite to ultrasonography display (middle picture). The green arrows show the suspected therapeutic down-regulation of CCL5 expression after surgical removal of the CCL5 sources in the affected BMDJ/FDOJ areas (bottom row of pictures). The red arrows show the suspected damaging up-regulation of CCL5 expression in the affected BMDJ/FDOJ areas (upper row of pictures).

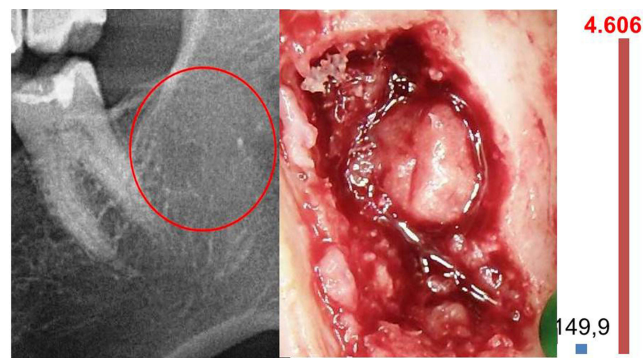


Figure 10 BMDJ/FDOJ situation of a BC patient, conventional radiographs (left window) showing no BMDJ/FDOJ, cytokine assay of osteonecrotic area showing high CCL5/RANTES expression of 4,606 pg/mL (right window, red column).

Notes: Left window: OPG radiography with completely unremarkable presentation of the bony structures in the area of 38/39. Middle window: Bone marrow defect in area 38/39 with tumor-related BMDJ/FDOJ osteonecrosis; through manifestation of a highly differentiated, tubular adenocarcinoma of the breast. Right window: Multiplex analysis of BMDJ/FDOJ sample from this medullary pathology reveals high CCL5 overexpression of 4,606 pg/mL (red column) compared to 149,9 pg/mL in healthy jawbone (blue column).⁴⁴ The red circled area shows the radiographically unremarkable BMDJ/FDOJ area.

FDOJ of the tissue sample in area 38/39 - similar tissue morphology to that shown in Figure 2. The most striking result of this analysis is the high CCL5/RANTES expression of 4,606 pg/mL (red column) of this osteonecrotic area in the cytokine assay shown in Figure 10. The left window exhibits the opposite inconspicuous radiograph of the retromolar area and the even contrary CCL5 expression of 149,9 pg/mL in healthy jawbone (blue column, right window, Figure 10).^{43,44}

New Trans Alveolar Ultrasound (TAU) Imaging of CCL5 Expression Foci

To assist the clinician in diagnosing these debilitating effects of FDOJ/BMDJ defects and to fill the connected diagnostic gap as shown in section 6.1, a computer-assisted through-transmission alveolar ultrasound (TAU) device has been developed (see Figure 11).^{48,49} In hundreds of comparable findings such as displayed in Figure 10, same inconspicuous findings on the two-dimensional orthopantomogram (2D-OPG) and three-dimensional cone beam (3D-digital volume tomogram/CBCT/DVT) can be confirmed using a TAU measurement in the authors' clinics. The availability of a TAU imaging system, which allows for the measurement of bone density in the area of a presumed BMDJ/FDOJ, is a significant step forward in the detection of occult CCL5 expression foci in the jawbone (see Figure 11).^{48,49}

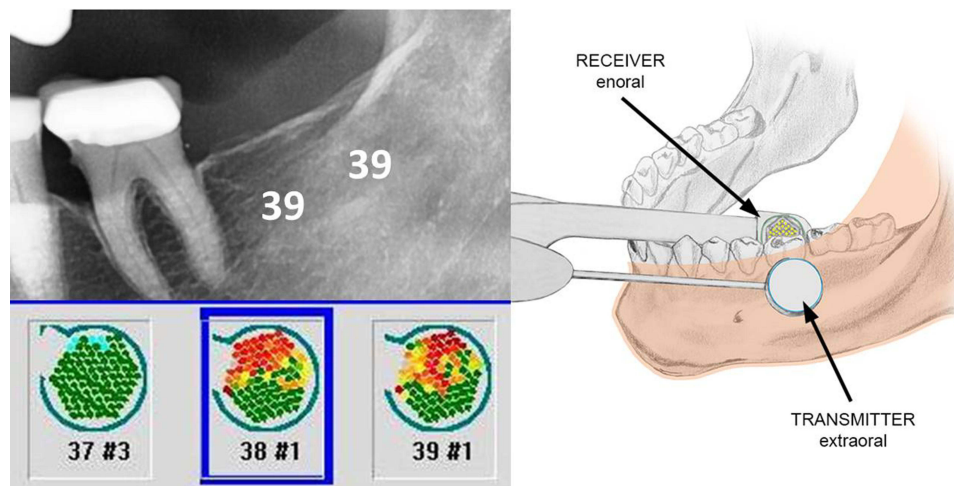


Figure 11 Comparison of radiographic and of through-transmission alveolar ultrasound (TAU) imaging of BMDJ/FDOJ areas (left windows). Principle of TAU imaging system (right window).

Notes: Upper left panel: OPG radiography with inconspicuous bone structures in retromolar areas 38/39. Lower left panel: The TAU-n device displays high and healthy bone density in green (tooth area #37) and reduced bone density in BMDJ/FDOJ areas in red (edentulous area #38 and retromolar area #39). Right panel: Schematic diagram of trans alveolar sonography in the TAU-n device: Extraoral transmitter and intraoral receiver that converts the attenuation of passing ultrasound waves into images with 91 piezoelectric receiver pixels (see lower part of left panel) indicating decreasing jawbone density in green, yellow, orange and red.^{48,49}

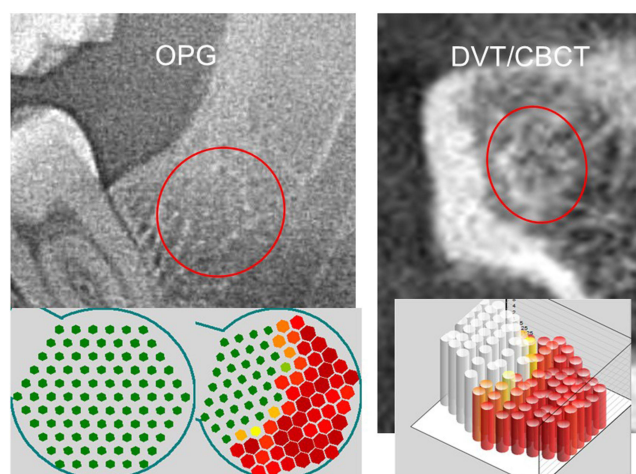


Figure 12 Comparison of radiographic findings on OPG and DVT/CBCT of a BMDJ/FDOJ area with the TAU findings in 2D and 3D.

Notes: Left upper window OPG of areas #37 and #38: No osteonecrotic changes in the medullary space; no indication for surgical intervention. Lower left window: Two-dimensional (2D) TAU image of area #37 and #38: Apical area of molar in green indicates healthy jawbone; retromolar area in red indicates osteonecrotic medullary space, as shown in middle window of Figure 10 which is a clear evidence of pathological change of medullary bone tissue. Upper right window: Unremarkable DVT/CBCT comparable to OPG findings. Bottom right window: Three-dimensional (3D) TAU-n imaging of areas #37 and #38: Intense staining in red indicates osteonecrotic lesions in this jawbone area, which coincidentally indicates chronic CCL5 overexpression.^{44,46,48,50,51} The red circled area shows the radiographically unremarkable BMDJ/FDOJ area.

Figure 12 shows a comparison of the unremarkable radiographic findings on OPG and DVT/CBCT of a retromolar jaw area with the completely opposite TAU-n findings in 2D and 3D, showing clear osteonecrosis. Figures 10, 11 and 12 show the diagnostic gap in radiographic imaging of BMDJ/FDOJ areas. TAU accurately images and identifies “cavitation” porosity in BMDJ/FDOJ. Studies show that in 84% of cases, BMDJ/FDOJ lesions in TAU images were more obvious and easier to identify on TAU images than on radiographs of the same site.⁴⁶ TAU imaging was found to be significantly superior to radiology in the detection of microscopically confirmed BMDJ/FDOJ. Because of these diagnostic difficulties with radiographic methods, BMDJ/FDOJ is often underdiagnosed by dentists.^{42,46,50,51} A newly developed ultrasound device, TAU, is able to detect and localize BMDJ/FDOJ, making TAU a useful tool to promote cooperation between professionals in the assessment or treatment of osteoimmunological diseases and to link such diseases to the immune system and BC. Our hypothesis lies at the interface of morphology and immunology of chronic osteolytic changes in the jawbone. TAU is a novel imaging modality in dentistry and offers the possibility to non-invasively assess occult BMDJ/FDOJ in the human jawbone (see Figure 12).^{44,46,48,50,51}

Limitations and Challenges of the Study

Although a standardized diagnostic routine involving OPG, DVT/CBCT, and TAU (with the exception of Portugal) was employed across the participating clinics to differentiate between BMDJ/FDOJ and healthy jawbone areas, certain limitations affect the comparability of results in this multicenter study. Variability in intraoperative sampling—due to bleeding, anatomical differences among patients, and operator technique—contributes to uncertainty. Furthermore, working with cytokines and their corresponding antibodies introduces additional challenges. Antibodies targeting the same cytokine can differ in binding affinity, specificity, and sensitivity. These discrepancies may arise not only between different manufacturers but also between production batches from the same source. The nature of the sampled BMDJ/FDOJ tissue—ranging from fatty to partially liquefied—can also influence cytokine measurement outcomes. The instability of certain cytokines may further impact results by affecting antibody binding or signal intensity.⁵² As a result, this study places greater emphasis on the relative changes in cytokine levels compared to a control group, rather than on absolute numerical values.⁵³ These values should be interpreted as indicative rather than definitive, especially when comparing results across different studies. Caution is advised in extrapolating direct quantitative comparisons.

Conclusion

The multi-centric study concludes that:

- All the samples analyzed showed a high content of the inflammatory cytokines CCL5 compared to the control samples. These results confirm that BMDJ/FDOJ lesions are important sources of CCL5 which, according to the literature, might act as a trigger in the onset, progression and/or recurrence of BC.
- Surgical cleaning of these lesions could contribute to relieving and regulating the patient's entire immune system, possibly contributing to a better prognosis of the disease.
- However, the diagnosis of this type of lesion is difficult and insufficient using conventional radiographic methods (OPG and CBCT), so trans alveolar ultrasound (TAU) is available as an alternative for a more accurate diagnosis.
- There is a need to inform doctors and dentists about the importance of diagnosing and treating BMDJ/FDOJ as a measure of prevention and promotion of overall health, especially in more compromised patients.

Data Sharing Statement

The authors declare that all relevant data supporting the findings of this review are included in this article. For further requests, the corresponding author should be contacted.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Dr. J. Lechner is the holder of two patents used in the TAU apparatus CaviTAU[®] PCT/EP2018/084199 and PCT/EP2020/058962. The authors report no other conflicts of interest in this work.

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