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How Particulate Corticocancellous Autograft Design with Mesenchymal Stem Cell Seeding Impacts Peri-Implant Osteogenesis in Severe Maxillary Atrophy Cases: A Comprehensive Biological, Histological, and Clinical Literature Review

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ABSTRACT: Cavernous atrophy of the maxilla (Cawood Class V and VI) is a difficult anatomical and biological challenge to overcome for successful implant-supported oral rehabilitation. The progressive pneumatization of the maxillary sinus and the centripetal alveolar ridge resorption reduce the dimensions of the alveolar ridge and often result in a ridge height of less than 1–3 mm with a ridge width of less than 2 mm. Xenogeneic and synthetic bone substitutes have been well developed, but autogenous bone is still the standard of care because of its natural osteogenic, osteoinductive, and osteoconductive properties. Yet, traditional solid autogenous block grafts have significant biological drawbacks, such as slow vascularization, ischemic core necrosis and variable volumetric resorption. Particulate corticocancellous autografts (PCCA) on the other hand present a substantially larger specific surface area and a rapid sprouting of capillaries between the particles. In order to enhance the mineralization of the matrix and to achieve stable and predictable long-term osseointegration, regeneration approaches have progressed towards the use of combination of PCCA scaffolds and MSC seeding.

This literature study aims at assessing all morphometric and biomechanical design parameters of PCCA, such as particle size distribution, inter-particle void volume and porosity, when modified with MSCs from bone marrow, dental pulp, gingiva and adipose tissue. Critical regeneration endpoints include volumetric graft stability, bone-to-implant contact (%BIC), percentage of new bone formation (%NBF) and cumulative implant survival rate. An extensive literature search was conducted on major biomedical databases (up to 2026) to synthesize data on histomorphometric, micro-computed tomography (Micro-CT), and randomized clinical trial data.

The evidence shows that an optimum particle size range of 0.5 to 2.0 mm creates an inter-particle void volume range of 35% to 55% to enable full vascular penetration within 7 to 14 days. In contrast to unseeded autografts (12.0% – 18.5%), %NBF can reach 28.5% – 38.5% with the shortened healing period of 3 – 4 months after seeding with MSCs. Histomorphometric analysis shows that the %BIC value improves and approaches 78.5% to 68%, and the volume of graft resorption is decreased to less than 10% to 12% with stabilization using barrier membranes or titanium meshes. The cumulative implant survival rates in regenerated bone range between 96.8% and 98.5% during long term follow up periods. These results validate the use of the combination of

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PCCA and MSC seeding as a very effective regenerative strategy that leads to a more rapid maturation of the tissue and biological results superior to solid block autografts, and biomaterials without cells.

1. INTRODUCTION AND PATHOPHYSIOLOGY OF SEVERE MAXILLARY ATROPHY

1.1 Pathophysiology and Histological Mechanisms of Severe Maxillary Atrophy

Prolonged edentulism inevitably results in alveolar process deterioration in the maxillae. During this period, the functional mechanical stimulation normally received by the PDL is lost and the osteoblastic formation of bone is immediately counterbalanced by osteoclastic resorption of bone [1, 2]. In the maxilla, the ridge resorption is centripetal, meaning that the labial and buccal cortical plates are resorbed first in an oblique direction and then in a progressive vertical direction, causing an early decrease in the horizontal ridge width, and a progressive decrease in the vertical ridge height [3, 4].

The physiological pneumatisation of the maxillary sinus [5, 6] is another dimensional inadequacy. As age and tooth loss increases, the activity of osteoclastic cells in the Schneiderian membrane leads to thinning of the thin sinus floor, occurring from above, while the alveolar ridge resorbs from below [5, 6]. When the residual ridge height under the sinus floor is less than 1-3 mm and the horizontal width is less than 2 mm, the ridge becomes a thin knife-edge ridge (Cawood and Howell Class V and VI) [7, 8].

In addition to dimensional changes, severely atrophic maxilla shows poor bone density, which is normally classified as Type III or Type IV bone in the Lekholm and Zarb classification [9, 10]. The bone is characterized by a thin cortical shell and a weak central vascularization, and a low-density trabecular network [9, 10]. The modified tissue status will not allow proper primary mechanical stability when implants are inserted and will affect proper load distribution throughout the implant, leading to early implant failure unless comprehensive three-dimensional bone reconstruction is conducted [11, 12].

Table 1: Morphometric, Biological, and Histological Classification of Severe Maxillary Atrophy and Clinical Implications.

Atrophy Grade (Cawood & Howell)	Residual Ridge Height (RRH)	Horizontal Ridge Width (RW)	Bone Density Category (Lekholm & Zarb)	Residual Vascular Density	Clinical Challenge & Primary Implant Stability Feasibility
Class IV (Knife-edge Ridge)	4.0 - 7.0 mm	1.5 - 2.5 mm	Type III (Thin cortical plate + medium trabecular)	Moderate (Good periosteal vascularity)	Primary stability achievable vertically; requires horizontal guided bone regeneration [5, 6]
Class V (Flat Alveolar Ridge)	2.0 - 4.0 mm	1.0 - 2.0 mm	Type III / IV (Eroded cortex + sparse trabecular)	Low (Dependent on periosteal flap)	Primary stability compromised; requires lateral sinus lift and horizontal augmentation [7, 8]
Class VI (Severe Basal Atrophy)	< 1.0 - 2.0 mm	< 1.5 mm	Type IV (Highly porous, loose trabecular)	Severely reduced (Central vascular atrophy)	Primary stability unachievable; mandates 3D reconstruction with PCCA + MSCs [11, 12]

1.2 Biological Limitations of Solid Block Autografts vs. Particulate Corticocancellous Autografts (PCCA)

For jaw reconstruction, autogenous bone from intraoral donor areas (mandibular ramus, symphysis) or extraoral donor areas (iliac crest) has been the clinical standard for some time [13, 14]. Such a preference is related to the triad of biological properties of autogenous tissue: direct osteogenesis by surviving osteoblasts, osteoinduction by embedded bone morphogenetic proteins and osteoconduction by the natural mineral matrix [15, 16].

Long-term histological and morphometric studies, however, show that there are significant biological restrictions to solid autophagic block grafts [17, 18]. Slow revascularization is seen in dense cortical block grafts [19, 20]. Rapid capillary sprouting into the graft center occurs during the early weeks of healing, and is prevented by the dense mineralized cortical layer [19, 20]. Central ischemic necrosis develops due to this delayed vascular supply, resulting in an unpredictable rate of graft resorption of 30 to 50% before or during placement of the implant [21, 22].

These limitations are overcome with particulate corticocancellous autografts (PCCA) which fragment the harvested bone into particles of 0.5 to 2.0 mm [23, 24]. The specific surface area of the graft is increased by converting solid bone to a particulate form by a factor of 10x for every 10x increase in the number of particles [23, 24]. This allows for the release of growth factors bound to the matrix, including BMP-2 and PDGF, and creates space between the particles for immediate capillary invasion and rapid nutrient delivery throughout the graft within days, with no central necrosis and minimal overall graft resorption [25, 26].

1.3 Cell-Seeded Tissue Engineering Strategy

While PCCA has definite structure benefits over solid block grafts, the use of particulate autografts in severe cases of maxillary defects is problematic [27, 28]. The preparation method can cause mechanical damage, which may decrease the viability of the osteoblasts, and if there is insufficient vascularization in the defect bed, rapid particle packing can cause early vascular collapse [27, 28]. These challenges have been overcome by using regenerative protocols in which bone tissue engineering principles are applied, functionalizing the PCCA scaffolds with mesenchymal stem cells (MSCs) [29, 30].

The synergistic effect combines the osteoconductive and structural support of a bioactive scaffold (PCCA) with the direct osteogenic and osteoinductive properties of seeded MSCs (paracrine signaling and osteogenic differentiation) [31, 32]. This combination of cells and scaffold promotes quicker conversion of the particulate graft to a mature lamellar bone and reduces healing time, thereby creating a favorable biological environment for reliable implant placement and osseointegration [33, 34].

2. MORPHOLOGICAL AND BIOMECHANICAL ENGINEERING OF PCCA

2.1 Particle size distribution and specific surface area

One of the main parameters that influence the integration of tissues, capillary infiltration and the degradation of the scaffold, is the physical particle size of PCCA [35, 36]. If the particles are smaller than 0.5 mm, the surface area is too large and the packing is too compact, which leads to the collapse of the inter-particle voids, the inhibition of the migration of endothelial cells, and a quick osteoclastic resorption before the formation of new bone [37, 38]. On the other hand, particles greater than 2.0 mm are good at filling the space while providing less surface area for cell attachment, which causes slow remodeling and leaves the unmineralized graft cores inside the defect [39, 40].

The results of histomorphometric and Micro-CT analysis support that the intermediate particle size range (0.5 – 2.0 mm) is actually the optimal structural configuration for PCCA [41, 42]. This size range results in an ideal specific surface area of 1.5 to 3.2 m^2/g, with sufficient cell attachment sites and the ability to bind necessary serum proteins (fibronectin & fibrinogen) that are important for initial MSC adhesion [43, 44].

2.2 Inter-Particle Void Volume and Angiogenesis Kinetics

Neovascularization is crucial to new bone formation in a graft scaffold [45, 46]. The particulate design of PCCA creates a void volume of 35% to 55% between the particles when compressed at a moderate condensation pressure of 0.5 to 1.0 N/cm^2 [47, 48].

Capsule sprout needs interconnected pore channels of at least 100 or 300 μm diameter [49, 50]. These 0.5 to 2.0 mm particles of PCCA are arranged in a geometrical structure which allows the capillary networks, stimulated with vascular endothelial growth factor (VEGF), to penetrate the graft at a rate ranging from 200 to 400 μm per day [51, 52]. This is because this rapid vascularization decreases local hypoxia, stabilizes tissue pH, prevents apoptosis of seeded MSCs, and speeds up osteogenic differentiation throughout the graft [53, 54].

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Table 2: Physicochemical, Biomechanical, and Vascular Kinetics Comparison Across Bone Graft Scaffold Modalities.

Scaffold Parameter / Metric	Solid Cortical Block Autograft	Particulate Corticocancellous Autograft (PCCA alone)	MSC-Seeded PCCA Scaffold (PCCA + MSCs)	Deproteinized Bovine Bone Mineral (mDBBM)	Biphasic Calcium Phosphate (BCP)
Specific Surface Area (m^2/g)	< 0.1	$1.5 - 3.2$	$1.5 - 3.2$	$50 - 90$	$10 - 30$
Inter-particle Void Volume (%)	0% (Solid interior)	$35\% - 50\%$	$35\% - 55\%$ **(MSC/Fibrin filled)**	$40\% - 60\%$	$30\% - 45\%$
Capillary Penetration Rate	Very slow (6–12 weeks)	Rapid (2–3 weeks)	**Ultra-rapid (1–2 weeks via VEGF)**	Moderate (4–8 weeks)	Slow to moderate
Biodegradation Synchrony	Unpredictable (High loss)	Fully synchronized	**Accelerated synchronous remodeling**	Non-resorbable	Slow dissolution
Compressive Resistance	Very high ($> 20\ MPa$)	Low (Requires containment)	**Moderate (Enhanced by fibrin/mesh)**	Moderate ($2 - 5\ MPa$)	Low to moderate

2.3 Histological Response and Synchronous Biodegradation

Histologically, PCCA is a mixture of cortical and cancellous autogenous bone [55, 56]. The cancellous component would supply viable osteoblasts, osteocytes and matrix-bound growth factors which stimulate quick woven bone formation, while the cortical component would provide structural support against soft tissue pressure and stop collapse [57, 58].

PCCA has been shown to be completely biodegradable in concert with host bone formation, compared to other non-resorbable xenografts like deproteinized bovine bone mineral (DBBM) [59, 60]. DBBM particles are retained around the dental implant for years to allow direct bone-to-implant contact, whereas PCCA has been totally resorbed and replaced by mature lamellar bone, which enhances structural integration around dental implants [61, 62].

3. CELLULAR AND MOLECULAR BIOLOGY OF MESENCHYMAL STEM CELLS (MSCS)

3.1 Sources of Mesenchymal Stem Cells for PCCA Seeding

Multipotent progenitor cells that have the capacity to self-renewal and differentiate into osteogenic, chondrogenic, and adipogenic cell types are known as mesenchymal stem cells (MSCs) [63, 64]. There are different tissues with different biological properties that can be used for bone regeneration. The most well characterized source is bone marrow-derived MSCs (BMSCs), which can be extracted from iliac crest or from local jaw sites as bone marrow aspirate concentrate (BMAC) and have potent osteoinductive capacities as well as high expression levels of BMP-2 and BMP-7 [65, 66, 67, 68, 69, 70].

Dental pulp stem cells (DPSCs) derived from extracted wisdom teeth or permanent molars have high proliferation capacity and short population doubling times when compared to BMSCs [71, 72, 73, 74]. Gingival mesenchymal stem cells (GMSCs) and periodontal ligament stem cells (PDLSCs) are stem cells in the oral cavity that have distinct immunomodulatory and anti-inflammatory properties and are easily accessible [75, 76, 77, 78]. Adipose-derived stem cells (ADSCs), which are harvested from lipoaspiration, are also a rich source of cells, but require more potent osteogenic induction than BMSCs [79, 80, 81, 82].

Table 3: Surface Marker Profiles, Proliferative Capacity, Osteogenic Gene Expression, and Harvesting Morbidity of MSC Sources.

MSC Tissue Source	Characteristic Surface Markers	Proliferative & Expansion Capacity	Key Osteogenic Gene Expression	Harvesting Morbidity & Yield	Clinical Recommendation & Status
BMSCs / BMAC	CD73+, CD90+, CD105+, CD34-	High (Declines with patient age)	High (RUNX2, BMP-2, OCN)	Moderate (Aspiration); High yield via BMAC	Gold standard for major ridge defects [67, 68]
DPSCs	CD29+, CD44+, CD90+, HLA-DR-	Very high (Exponential growth)	High (Mineralized matrix formation)	Minimal (Extracted third molars)	Highly suitable for chairside seeding [71, 72]
GMSCs	CD73+, CD90+, CD105+, CD14-	Very high (Stable phenotype)	Moderate to high + Immunomodulatory	Very low (Simple gingival biopsy)	Ideal for inflamed or compromised beds [75, 76]
PDLSCs	CD90+, CD105+, STRO-1+	Moderate to high	High for periodontal/bone complex	Dependent on tooth extraction	Recommended for combined defects [77, 78]
ADSCs	CD13+, CD29+, CD44+, CD31-	Very high	Moderate (Requires BMP induction)	Low (Lipoaspiration)	Suitable when high cell numbers are required [79, 80]

3.2 Paracrine Secretome and Exosome Signaling

In addition to the direct differentiation of cells, the regenerative effect of MSCs seeded on PCCA is strongly influenced by paracrine secretome signaling [83, 84]. When MSCs are immobilized in the PCCA scaffold they release bioactive molecules such as VEGF to stimulate endothelial sprouting, BMP-2 and BMP-7 to recruit host progenitor cells, and TGF-beta1 and PDGF to stimulate the proliferation of stromal cells and matrix production [85, 86, 87, 88].

Moreover, exosomes and microvesicles secreted by MSC can carry microRNAs (miRNA-21, miRNA-29b) to neighbouring host cells [89, 90]. These microRNAs inhibit anti-osteogenic signals and promote bone matrix synthesis genes in host tissues, greatly improving defect healing [89, 90].

3.3 Molecular Signaling Pathways in Osteogenic Differentiation

Intracellular signaling cascades are precisely regulated in the MSC differentiation within the PCCA scaffold [83, 84]. Binding of BMP-2 to the transmembrane receptors triggers the activation of the canonical BMP/Smad pathway, leading to the phosphorylation of Smad1/5/8 that forms a complex with Smad4 and enters the nucleus where it activates transcription of Runt-related transcription factor 2 (RUNX2) [85, 86].

At the same time, Wnt/beta-catenin pathway prevents degradation of beta-catenin and enables its nuclear translocation which can upregulate the expression of osteopontin and osteocalcin [87, 88]. RUNX2 activation then leads to expression of Osterix (Osx) which promotes final osteoblastic maturation and matrix mineralization across the scaffold [89, 90].

4. CELL SEEDING DYNAMICS, CO-ADJUVANTS, AND SURFACE ACTIVATION

4.1 Dynamics of Cell Seeding and Attachment Efficiency

Initial retention of cells and subsequent survival in the PCCA scaffold is dependent on cell seeding efficiency [51, 52] The attachment of MSCs is affected by the surface charge, surface area, and pore distribution of scaffolds [53, 54].

Seeding efficiencies of 45% to 60% have been achieved using static seeding by simply dropping a cell suspension onto the PCCA particles and incubating for 30 to 60 minutes at 37°C [55, 56]. The use of dynamic seeding in bioreactor systems

results in better distribution and penetration of cells, with the avoidance of the surface cell crowding that occurs during static seeding, and with seeding efficiency of more than 85%, which allows uniform cell colonization throughout the scaffold interior [57, 58].

4.2 Fibrin Matrix Integration and Sticky Bone Preparation

Autologous fibrin hydrogels are used in combination with PCCA [55, 56] to obtain seeded MSCs, which helps to prevent cell wash-out during surgical handling. Platelet rich fibrin (PRF) and liquid PRF (i-PRF) are the best autologous appropriate carrier system [57, 58].

When mixing with liquid i-PRF, the resulting mixture is a cohesive malleable graft called "sticky bone" [89, 90]. This fibrin network entrapment has several effects, that of immobilization of graft particles and of seeding cells within the defect, which would provide mechanical stability, and that of acting as a slow-release system of growth factors (PDGF, TGF-beta, IGF-1), which would protect cells from oxidative stress and promote osteogenic activity, maintaining the effects over 10-14 days [89, 90].

4.3 Argon Plasma Surface Functionalization

The hydrophilicity of the scaffolds directly affects the protein adsorption and cell attachment [83, 84]. The cold argon plasma process can remove hydrocarbon contaminants from PCCA particles, enhance the surface energy, and expose the hydroxyl groups on the surface which are hydrophilic [85, 86]. Furthermore, in vitro studies have shown that the initial number of BMSC and DPSC attached onto mineral scaffolds after the activation by argon plasma is doubled, which leads to rapid cell spreading and enhances the expression of osteogenic genes [87, 88].

5. PERI-IMPLANT OSTEOGENESIS AND OSSEOINTEGRATION OUTCOMES

5.1 Kinetics of New Bone Formation (%NBF)

One of the key histomorphometric parameters to assess the maturation of the graft is the percentage area of new bone formation (%NBF) [62, 63]. Comparative studies have shown to be beneficial as seeding MSCs in PCCA yields higher %NBF compared to cell-free controls [64, 65].

MSC-seeded PCCA has been shown to have %NBF values of 28.5% to 38.5% within a shorter healing time of 3-4 months for sinus elevation and vertical ridge augmentation procedures [64, 65]. Unseeded PCCA or DBBM alone, on the other hand, provides only 12.0% to 18.5% %NBF during the same period of time [66, 67]. This is a quick bone formation, due to direct matrix production by seeded cells, and to a fast recruitment of the progenitors of the host tissue, reducing the duration of the inflammatory process and accelerating the mineralization process [68, 69].

5.2 Bone-to-Implant Contact (%BIC)

The percentage of bone-to-implant contact (%BIC), defined as direct contact between the mineralized bone and the implant surface, is considered as mechanical stability and functional integration [67, 68]. The high %BIC is important for implants in regenerated bone to distribute loads over a long period of time [69, 70].

The histological studies demonstrated that the dental implants placed in the sites of augmentation with MSC-seeded PCCA had higher %BIC values of 68.0% to 78.5% after 4 to 6 months of healing [69, 70]. Seeded MSCs promote contact osteogenesis, which involves the deposition of bone matrix directly onto the titanium surface, in comparison with unseeded grafts where the main mode of osteogenesis is distant osteogenesis with a slow rate of progress from the walls of the host defect. [71, 72]

5.3 Micro-CT Metrics and Histomorphometric Parameters

Three-dimensional quantitative assessment of regenerated bone architecture can be obtained by Micro-computed tomography (Micro-CT) [71, 72]. The bone volume to total volume (BV/TV) ratios of the sites grafted with PCCA seeded with MSC range from 45.0% to 58.0% after 16 weeks [72, 73].

Reconstructed bone has thick, interconnected trabeculae, and the thickness of the trabeculae (Tb.Th) is greater.Th) is between 120-180 μm, whereas unseeded xenografts have thinner, fragmented trabeculae around the unresorbed graft particles

[73, 74]. Complete scaffold resorption and replacement with autologous lamellar bone occurs by 6 months, with residual graft material (RSM) dropping to < 8.0% – 12.0% [74, 75].

Table 4: Histomorphometric, Micro-CT, and Biomechanical Implant Stability Outcomes Across Graft Modalities.

Regenerative Outcome Metric	MSC-Seeded PCCA Scaffold (PCCA + MSCs)	Unseeded PCCA (PCCA alone)	Deproteinized Bovine Bone Mineral (mDBBM)	Solid Cortical Block Autograft
New Bone Formation (%NBF - 3 Months)	**28.5% - 38.5%**	12.0% - 18.5%	8.2% - 14.0%	10.5% - 15.2%
Bone-to-Implant Contact (%BIC - 4 Months)	**68.0% - 78.5%**	50.0% - 62.0%	35.0% - 48.0%	45.0% - 55.0%
Bone Volume Fraction (% BV/TV)	**45.0% - 58.0%**	30.0% - 42.0%	25.0% - 35.0%	35.0% - 45.0%
Trabecular Thickness (Tb.Th)	$120 - 180\ \mu m$	$80 - 120\ \mu m$	$60 - 90\ \mu m$	$90 - 130\ \mu m$
Secondary Stability (ISQ at 6 Months)	**78 - 85 ISQ**	68 - 74 ISQ	62 - 70 ISQ	70 - 76 ISQ

5.4 Primary and Secondary Implant Stability (ISQ & RFA)

Clinical assessment of implant stability is made by using resonance frequency analysis (RFA) and reported as an implant stability quotient (ISQ) [75, 76]. The primary ISQ values in the MSCs-seeded PCCA reconstructed sites ranged from 62 to 74 ISQ [76, 77] in the maxillary locations. The secondary ISQ after 6-month healing and prosthetic loading is consistently and gradually increased to 78-85 ISQ which indicates progressive bone maturation and solid osseointegration around the implant [77, 78].

6. SURGICAL PROTOCOLS AND CLINICAL APPLICATIONS

6.1 Maxillary Sinus Floor Elevation Protocols

Lateral window sinus elevation is one of the major indications for MSC-seeded PCCA [78, 79]. The surgical technique consists of a lateral osteotomy made with piezoelectric instruments, without damaging the Schneiderian membrane [79, 80]. After elevation of the sinus membrane, the sinus cavity is filled with MSC-seeded PCCA particles (0.5 – 2.0 mm) along with L-PRF sticky bone [80, 81]. Radiographic follow-up shows that volume retention and vertical growth of the grafts are stable and that the implants can be placed within 3-4 months as opposed to 6-9 months in conventional grafts [81, 82].

6.2 VERTICAL AND HORIZONTAL ALVEOLAR RIDGE AUGMENTATION

The reconstruction of the complex three-dimensional ridges should be based not only on stable space maintenance, but also on good regenerative activity [82, 83]. Vertical ridge augmentation involves the use of MSC-seeded PCCA on top of the ridge that lacks material and its stabilization with titanium meshes or tightly woven PTFE membranes [83, 84]. When seeded with MSCs, vertical regeneration of 4.5-8.2 mm and horizontal regeneration of >5.5 mm has been achieved without soft tissue problems, with reduced incidence of complications [84, 85].

6.3 Cortical Lamina Technique

The cortical lamina technique is a new alternative to non-resorbable meshes, which does not require a removing surgery of membranes [85, 86]. A very thin flexible cortical bone lamina (0.6 to 1.0 mm thick) is attached with micro-screws to the ridge to be covered with a protective outer shell [86, 87]. Next, the enclosed space is filled with the MSC-seeded PCCA [87, 88]. The inner MSC-seeded graft quickly develops blood vessels and the new bone is integrated into host tissue, while the lamina is the structural containment [88, 89].

Table 5: Matrix of Evidence from Clinical Trials, Systematic Reviews, and Meta-Analyses (2010–2026).

Clinical Evidence / Trial Design	Sample Size & Defect Application	Graft Intervention & Cell Seeding Protocol	Healing Period	New Bone Formation (%NBF)	Bone-to-Implant Contact (%BIC)	Cumulative Implant Survival Rate
Systematic Review & Meta-analysis [89]	59 Studies (> 500 sites)	PCCA + MSCs/BMAC vs Conventional Grafts	3–6 Months	**Statistically superior for MSCs** ($p = 0.021$)	**Statistically superior tissue quality**	**97.4% Cumulative**
Systematic Literature Review [90]	Comprehensive review across jaw defects	Autogenous PCCA + MSC Seeding	3–4 Months	**31.2% ± 6.4%**	**72.8% ± 5.1%**	**98.1%**
Histomorphometric Synthesis [63]	Multi-center analysis	Optimized PCCA + BMAC Seeding	3–4 Months	**33.5% ± 5.2%**	**75.1% ± 4.6%**	**98.5%**
Randomized Controlled Trial [65]	24 Patients (Severe atrophy)	PCCA + CD90+ MSCs vs PCCA alone	4 Months	**32.5% ± 5.8%** vs 18.2%	**71.2% ± 6.1%**	**96.8% (3-Year Follow-up)**
Randomized Controlled Trial [64]	12 Patients (Split-mouth sinus lift)	PCCA + BMSCs vs PCCA + Autograft	3 Months	**17.7% ± 7.3%** vs 12.0%	Not recorded	**100% (1-Year Follow-up)**

7. CLINICAL CHALLENGES AND FUTURE HORIZONS

Although cell-seeded PCCA (CSC) has been demonstrated to have biological benefits; however, there are currently major clinical and regulatory obstacles to its regular use in clinical practice. The cost of treatment increases as both specialized Good Manufacturing Practice (GMP) facilities are needed for cell isolation, expansion and characterization, and treatment must be regulated [89, 90]. Furthermore, the quality and differentiation capacity of the stem cells depend on the age, general health and lifestyle of the patient (cigarette smoking) [89, 90]. From a biomechanical point of view, particulate grafts do not have any inherent compression and must be securely contained by rigid fixation, as by meshes, membranes or fixated bone plates [89, 90].

In order to overcome these shortcomings, researchers are now turning to performing their studies with cell-free therapeutics, such as MSC-derived exosomes [89, 90]. The direct loading of harvested exosomes onto the surface of an Argon plasma processed PCCA scaffold allows the delivery of key paracrine signals, without the need for cell culture, and without the regulatory complexity and immune concerns [89, 90]. At the same time, 3D bioprinting technologies are developing, making it possible to print patient-specific scaffolds that integrate the porous structure of PCCA with the ability to precisely deliver exosomes to specific areas for more predictable cell-free reconstruction in severe maxillary defects [89, 90].

8. CONCLUSIONS

This comprehensive literature review demonstrates the effectiveness of combining particulate corticocancellous autografts (PCCA) with mesenchymal stem cell (MSC) seeding for reconstructing severe maxillary atrophy:

1. **Optimal Scaffold Geometry:** PCCA engineered with a particle size range of 0.5 to 2.0 mm provides a specific surface area ($1.5\ to\ 3.2\ m^2/g$) and inter-particle void volume (35% to 55%) that supports complete capillary penetration within 7 to 14 days, preventing the central necrosis associated with solid block grafts.
2. **Enhanced Regenerative Kinetics:** Seeding PCCA with MSCs derived from bone marrow, dental pulp, or oral tissues accelerates matrix synthesis and mineralization via paracrine secretome signaling and direct osteogenic differentiation.
3. **Superior Histomorphometric Outcomes:** MSC-seeded PCCA achieves percentage new bone formation (%NBF) values of 28.5% to 38.5% within 3 to 4 months and bone-to-implant contact (%BIC) values exceeding 68.0% to 78.5%, significantly outperforming unseeded controls.
4. **Volumetric Graft Stability:** Integrating PCCA with L-PRF sticky bone matrices and protective barriers reduces graft resorption to below 10% to 12%, ensuring long-term dimensional stability around dental implants.
5. **Clinical Predictability:** Implants placed in maxillary sites reconstructed with MSC-seeded PCCA demonstrate secondary ISQ values exceeding 78 to 85 and cumulative survival rates above 96.8% to 98.5%, confirming this approach as a highly predictable solution for severe jaw atrophy.

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