Optimization of Tissue Engineering Regeneration Conditions by the Method of Directed Bone Regeneration in Patients with Diabetes Mellitus

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Abstract:
Type 2 diabetes mellitus may compromise wound healing after dental implantation because of microcirculatory impairment, altered local immune response, dysbiosis of the oral cavity and reduced regenerative potential of bone tissue. In these conditions, guided bone regeneration requires not only mechanical restoration of the alveolar ridge volume but also biological support of tissue repair. Comprehensive bioregenerative support of guided bone regeneration in patients with type 2 diabetes mellitus may be regarded as a rational clinical strategy for controlling microbial burden, supporting tissue repair and individualizing the timing of functional loading through objective ISQ monitoring.

Keywords: *Type 2 diabetes mellitus; dental implantation; guided bone regeneration; hyaluronic acid; platelet-rich plasma; oral microbiota; implant stability quotient; osseointegration.*

Introduction

Dental implantation in patients with type 2 diabetes mellitus remains a clinically important challenge because treatment success depends not only on implant placement technique but also on the ability of tissues to develop a complete inflammatory, proliferative and remodeling response. Chronic hyperglycemia, microangiopathy, altered bone metabolism and a tendency toward oral dysbiosis may delay osseointegration and increase the risk of inflammatory complications [1,2,3].

The current concept of guided bone regeneration considers a bone defect not as an empty space that should simply be filled with grafting material, but as a biological system in which the final outcome depends on scaffold stability, cell migration, angiogenesis, molecular signaling and the stability of the wound environment. Therefore, tissue engineering in implant dentistry should combine surgical accuracy, proper selection of osteoplastic materials, microbial control, support of local immunity and objective assessment of implant stability.

Hyaluronic acid is a natural component of the extracellular matrix. It is capable of binding water, supporting cell migration, modulating the inflammatory response and participating in early matrix organization. In combination with autologous platelet concentrates, it may create a more favorable microenvironment for bone formation, especially in patients with systemic risk factors such as diabetes mellitus [4,5,6,7,8].

Outcome monitoring is of separate clinical importance. Bone density assessment in Hounsfield units helps correlate the clinical situation with the quality of the implant bed, while resonance frequency analysis allows non-invasive dynamic monitoring of implant stability. For patients with diabetes mellitus, this objective control is particularly important because premature functional loading may interfere with incomplete osseointegration [9,10,11].

Objective. The aim of the study was to perform a comprehensive assessment of the effectiveness of bioregenerative support for guided bone regeneration during dental implantation in patients with type 2 diabetes mellitus using clinical, microbiological, immunological, radiological and resonance frequency parameters.

Materials and Methods: The study included 40 patients with type 2 diabetes mellitus aged 20-65 years who had dentition defects and varying degrees of alveolar ridge atrophy. All patients underwent dental implantation combined with bone grafting and the use of a bioregenerative complex that included hyaluronic acid and platelet-rich plasma. Clinical observations were carried out in specialized dental and endocrinological institutions during 2014-2016.

Metodology

The study included 40 patients with type 2 diabetes mellitus aged 20–65 years with dentition defects and alveolar ridge atrophy. All patients underwent dental implantation combined with guided bone regeneration using hyaluronic acid and platelet-rich plasma. Inclusion criteria were confirmed type 2 diabetes mellitus, indication for implant-supported rehabilitation with bone augmentation, and possibility of follow-up. Exclusion criteria included acute infections, severe systemic decompensation, and noncompliance with follow-up. Clinical, microbiological, radiological and immunological assessments were performed. Microbiological samples were collected before surgery and on days 3, 7, 14 and 30, followed by anaerobic culture and susceptibility testing. Bone density was evaluated using CT in Hounsfield units and Misch classification. Implant stability was assessed using resonance frequency analysis (ISQ) at placement and follow-up up to 24 months. Data were processed using SPSS software. Statistical analysis included descriptive and comparative methods with significance level $p<0.05$ using SPSS version 26.0 for evaluation purposes only.

Result and descussion

The inclusion criteria were type 2 diabetes mellitus, an indication for implant-supported rehabilitation with bone grafting, the possibility of dynamic follow-up and microbiological monitoring. The exclusion criteria were acute purulent inflammatory processes, severe decompensation of systemic disease, inability to follow postoperative recommendations and absence of follow-up visits.

Table 1. Distribution of patients by age and sex.

Sex	20-30 years	31-40 years	41-50 years	50 years and older	Total
Men	2 (5%)	5 (12.5%)	7 (17.5%)	9 (22.5%)	23 (57.5%)
Women	1 (2.5%)	3 (7.5%)	5 (12.5%)	8 (20%)	17 (42.5%)
Total	3 (7.5%)	10 (25%)	12 (30%)	17 (42.5%)	40 (100%)

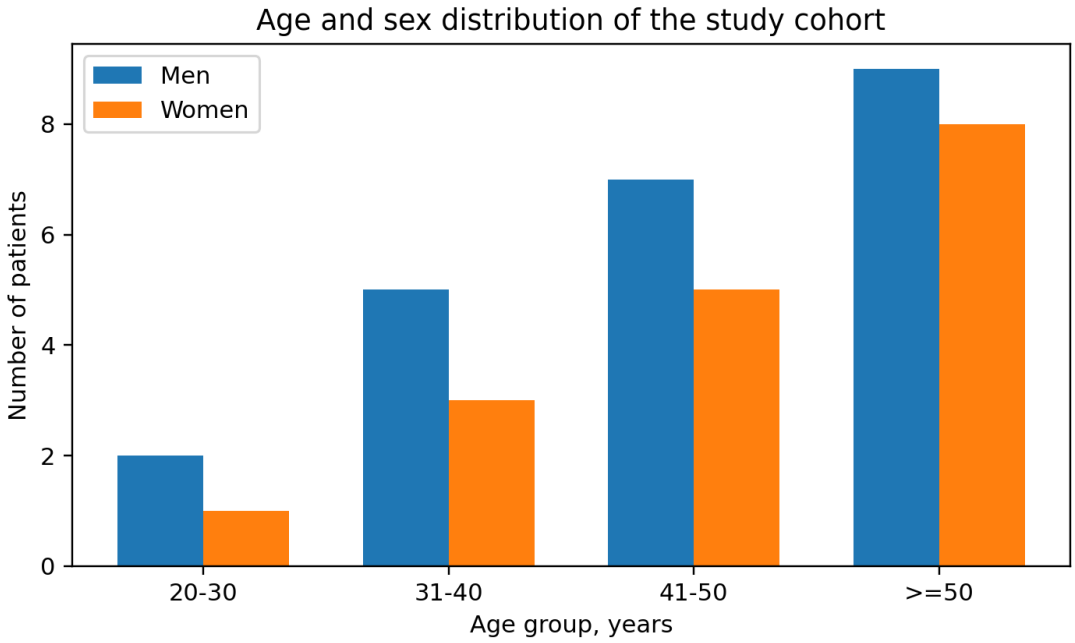

Figure 1. Age and sex distribution of the study cohort.

Preoperative preparation and microbiological monitoring. Before surgery, clinical sanitation of the oral cavity and laboratory assessment of the oral microbiocenosis were performed. The material was obtained from oral fluid after rinsing with sterile saline. Bacterial identification was performed using anaerobic cultivation. Samples were collected before surgery, after preoperative medication, and during the early postoperative period on days 3, 7, 14 and 30.

To evaluate in vitro microbial susceptibility, inhibition zones were analyzed after exposure to the studied medicinal agents. These data were used as the basis for targeted prevention of inflammatory complications in the early postoperative period[12,13,14].

Table 2. In vitro growth inhibition zones of microorganisms, mm.

No.	Microorganism	Metrolin/material	Metrogyl	Loroben	Cypress 500
1	Staphylococcus aureus	5.0 +/- 0.1	0	25.0 +/- 0.4	27.0 +/- 0.5
2	Staphylococcus epidermidis	0	7.0 +/- 0.1	17.0 +/- 0.3	35.0 +/- 0.5
3	Staphylococcus saprophyticus	0	7.0 +/- 0.1	5.0 +/- 0.1	35.0 +/- 0.5
4	Streptococcus pyogenes	0	5.0 +/- 0.1	12.0 +/- 0.2	27.0 +/- 0.5
5	Enterococcus faecalis	0	0	20.0 +/- 0.4	22.0 +/- 0.4
6	Escherichia coli LP	0	5.0 +/- 0.1	20.0 +/- 0.4	30.0 +/- 0.5
7	Escherichia coli LN	0	5.0 +/- 0.1	12.0 +/- 0.2	40.0 +/- 0.5
8	Proteus vulgaris	5.0 +/- 0.1	7.0 +/- 0.1	15.0 +/- 0.3	27.0 +/- 0.5
9	Klebsiella spp.	5.0 +/- 0.1	5.0 +/- 0.1	15.0 +/- 0.3	35.0 +/- 0.5

No.	Microorganism	Metrolin/material	Metrogyl	Loroben	Cypress 500
10	Pseudomonas aeruginosa	5.0 +/- 0.1	18.0 +/- 0.4	12.0 +/- 0.2	30.0 +/- 0.5
11	Candida albicans	0	0	12.0 +/- 0.2	5.0 +/- 0.1
12	Actinomycetae	5.0 +/- 0.1	7.0 +/- 0.1	15.0 +/- 0.3	40.0 +/- 0.5

Note: Values are presented as growth inhibition zones in millimeters.

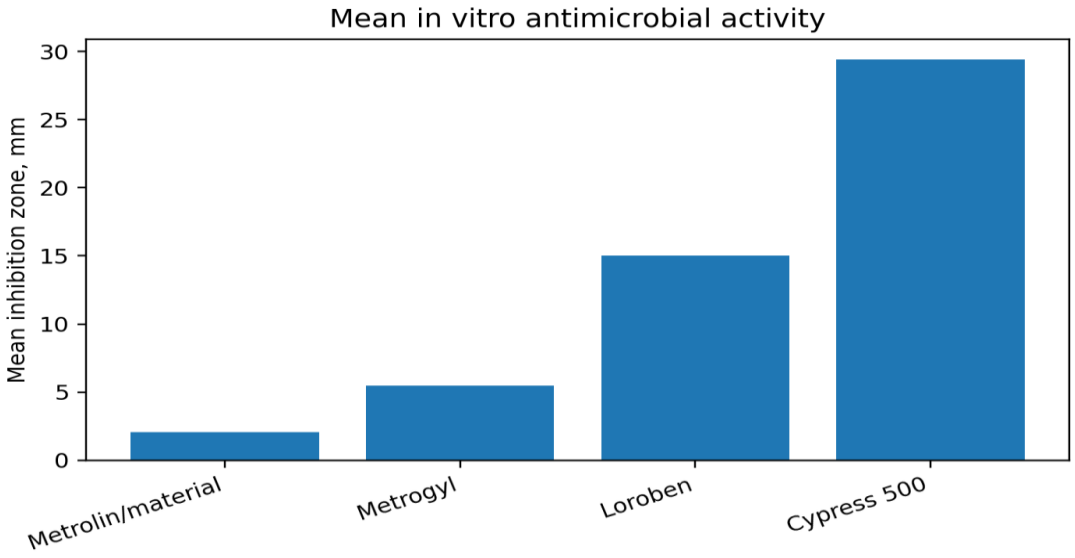

Figure 2. Mean in vitro antimicrobial activity of the studied agents.

Radiological and instrumental monitoring

Bone density and structure were assessed using three-dimensional computed tomography and radiovisiography. Hounsfield unit values were compared with the clinical Misch classification of bone quality: D1, dense cortical bone; D2, pronounced cortical and trabecular structure; D3, thin cortical plate with fine trabecular cancellous bone; and D4, loose cancellous bone with a minimal cortical component.

Implant stability was evaluated by resonance frequency analysis with registration of the implant stability quotient. Measurements were performed at implant placement and after 1, 2, 4, 6, 9, 12 and 24 months. An ISQ value above 70 units was considered a clinical reference point for safer transition to functional loading, taking into account the overall clinical situation and radiological findings[15,16,17].

Statistical processing. Quantitative data are presented as mean values and standard errors (M +/- m), or as absolute and relative values. Dynamic analysis across consecutive time points was used for clinical interpretation. In this translated manuscript, the original numerical values of the study were retained; additional calculated values were used only for graphical visualization.

Results

Before preoperative preparation, patients with diabetes mellitus showed an increase in several opportunistic microorganisms, including Staphylococcus aureus, Streptococcus mutans, Proteus spp., Escherichia coli and Candida spp[18,19,20]. After medication-based preparation, Staphylococcus aureus and Escherichia coli were eliminated, while Streptococcus mutans returned to the reference level. Persistently increased Candida values indicated the limited antifungal effect of the applied regimen and the need for separate evaluation of fungal flora in high-risk patients.

Table 3. Key oral microbiota parameters before surgery.

Microorganism	Reference, lg CFU/mL	At admission	After preparation
Staphylococcus aureus	0	3.15 +/- 0.14	0
Staphylococcus epidermidis	3.0 +/- 0.13	4.0 +/- 0.16	2.0 +/- 0.10
Streptococcus mutans	2.15 +/- 0.10	4.10 +/- 0.15	2.15 +/- 0.12
Proteus spp.	1.30 +/- 0.01	3.10 +/- 0.12	1.45 +/- 0.01
Escherichia coli	1.20 +/- 0.01	2.30 +/- 0.11	0
Candida spp.	2.0 +/- 0.15	4.10 +/- 0.21	3.0 +/- 0.15

After surgery, a temporary worsening of the microbial profile was observed on day 3, expressed as an increase in facultative flora and reappearance of Staphylococcus aureus. By day 7, positive changes were recorded: pathogenic staphylococci, Streptococcus mitis, Proteus spp., Escherichia coli and fungi were no longer detected. On day 14, a repeated increase in facultative flora was observed, which may clinically reflect completion of the active medication phase and the need for individualized monitoring in patients with diabetes. By day 30, the microbiological profile approached normal values[21,22].

Local protective factors

At admission, local protective parameters in patients with diabetes mellitus were reduced: lysozyme titer, phagocytic activity and secretory IgA levels did not reach reference values. After preoperative preparation, partial recovery of lysozyme and phagocytosis was observed. On postoperative day 3, the parameters decreased again, which may be associated with surgical trauma and the early inflammatory phase of wound healing. By month 1, a tendency toward recovery of local defense mechanisms was recorded[23,24].

Table 4. Dynamics of local protective factors in the oral cavity.

Parameter	**Reference**	**Admission**	**Preoperative**	**Day 3**	**1 week**	**2 weeks**	**1 month**
Lysozyme titer, mg/%	18.0 +/- 0.50	13.50 +/- 0.21	16.30 +/- 0.18	11.0 +/- 0.3	13.0 +/- 0.4	12.0 +/- 0.2	15.0 +/- 0.3
Phagocytosis, %	55.3 +/- 2.4	42.0 +/- 2.15	48.0 +/- 3.0	42.0 +/- 2.0	46.0 +/- 3.0	42.0 +/- 4.0	49.0 +/- 4.0
Secretory IgA, g/L	2.10 +/- 0.11	1.10 +/- 0.10	1.20 +/- 0.10	1.10 +/- 0.10	1.20 +/- 0.10	1.0 +/- 0.10	1.40 +/- 0.10

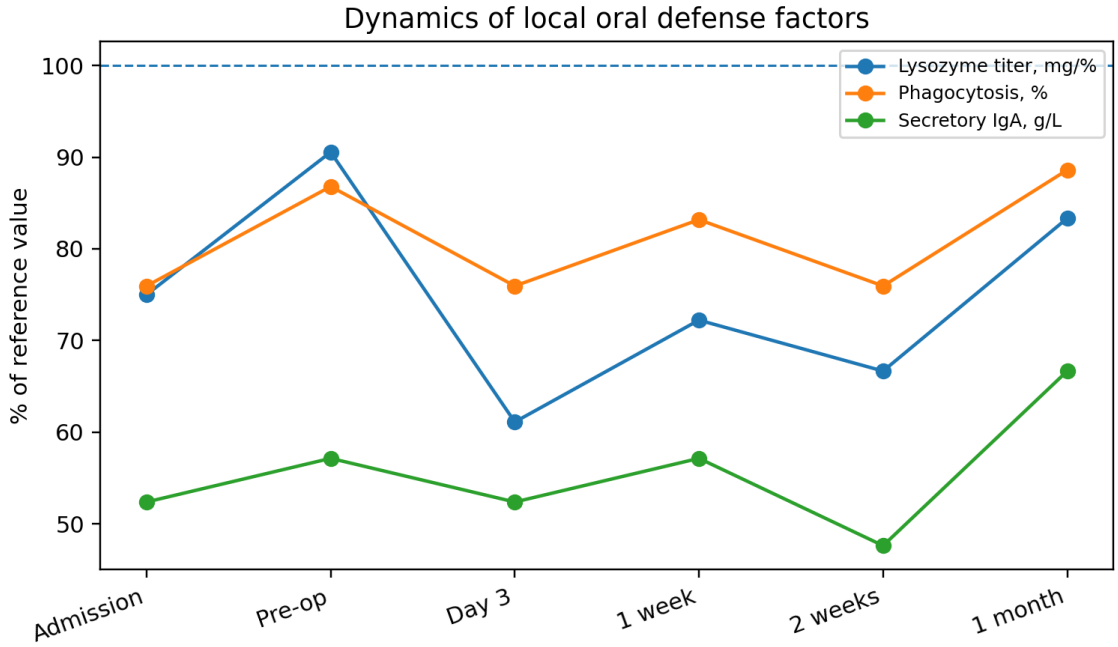

Figure 3. Local protective factors expressed as percentages of reference values.

Implant stability and timing of functional loading

Analysis of ISQ values showed that implant stability dynamics depended on baseline bone quality. In patients with D1 and D2-D3 bone, initial ISQ values were relatively high and subsequently increased gradually. The D4 bone group was the most clinically illustrative: after a low baseline value of 55 units and a decrease to 50 units at 1 month, stability increased to 68 units at 2 months, 74 units at 4 months and 84 units at 24 months. This pattern supports cautious selection of loading time in cases of low bone density and systemic metabolic risk.

Table 5. Mean ISQ values during follow-up.

Group	Placement	1 month	2 months	4 months	6 months	9 months	12 months	24 months
T2DM, D1	74	74	80	82	82	84	86	86
T2DM, D2-D3	73	71	78	83	84	84	85	88
T2DM, D4	55	50	68	74	78	80	82	84
Non-diabetic, D1-D2	71	65	68	74	78	82	83	84
Non-diabetic, D3-D4	50	48	50	60	70	72	76	80

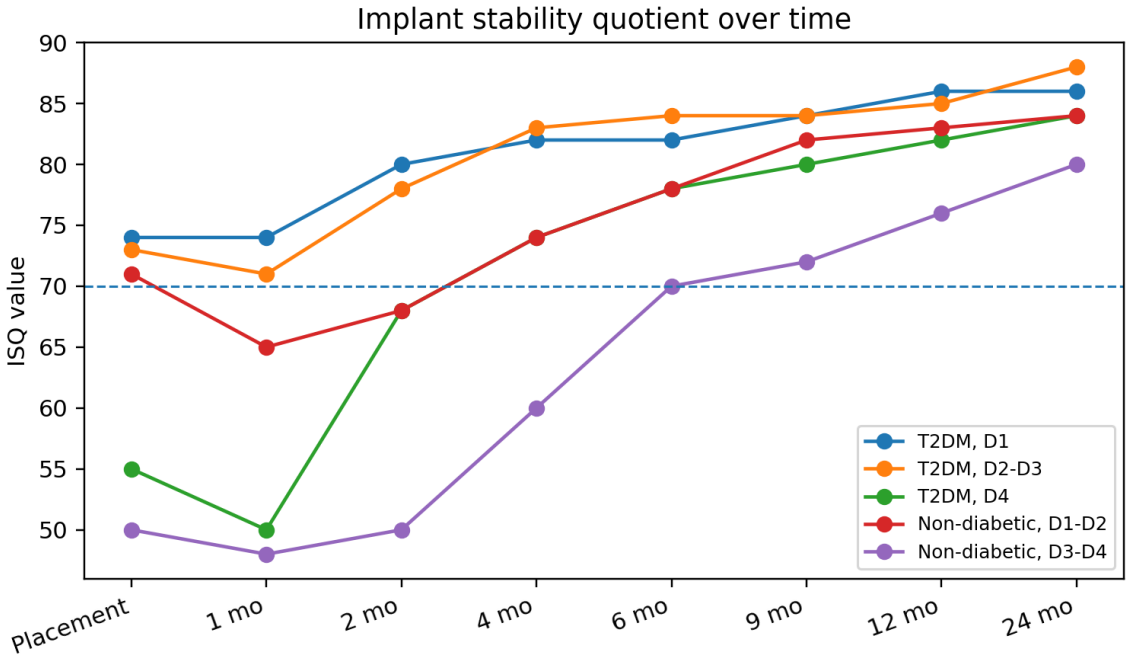

Figure 4. Dynamics of ISQ values according to bone quality.

Discussion

The obtained data confirm that dental implantation with bone grafting in patients with type 2 diabetes mellitus should be considered a multistage process in which the surgical outcome depends on three interrelated components: control of microbial burden, biological support of repair and instrumental monitoring of osseointegration. This approach is consistent with the modern understanding of implant-supported rehabilitation in patients with systemic risk factors.

Preoperative reduction of potentially aggressive flora is of major importance. The oral surgical field cannot be completely sterile, and local protective reactions are often impaired in patients with diabetes. Therefore, elimination of Staphylococcus aureus and reduction of enterobacteria before surgery represent important measures for preventing early inflammatory complications. At the same time, persistently increased Candida values indicate that standard antibacterial regimens should not automatically be considered sufficient for all components of the oral microbiocenosis[25,26].

In this context, hyaluronic acid acts not merely as an auxiliary filler but as a biological modulator of the wound environment. Through its role in extracellular matrix organization, water retention, cell migration and inflammatory regulation, it may contribute to conditions favorable for reparative regeneration. In combination with platelet-derived components, a local biologically active environment is formed in which osteogenic cells may receive more favorable conditions for migration and differentiation.

The dynamics of ISQ values confirm that the timing of prosthetic loading should be individualized. In dense bone, stability values were already high at early stages, whereas D4 bone showed a pronounced initial deficit of stability followed by gradual recovery. This is especially relevant for patients with diabetes mellitus, in whom morphofunctional remodeling of bone tissue may proceed more slowly than in systemically healthy patients.

Current systematic reviews also emphasize that dental implantation in patients with diabetes may be predictable when metabolic control is satisfactory; however, poorly controlled diabetes, peri-implant

inflammation and inadequate oral hygiene increase the risk of complications. Therefore, the present data should not be interpreted as proof of the universal superiority of a single adjunctive agent, but rather as support for a comprehensive clinical protocol for high-risk patients [1-3].

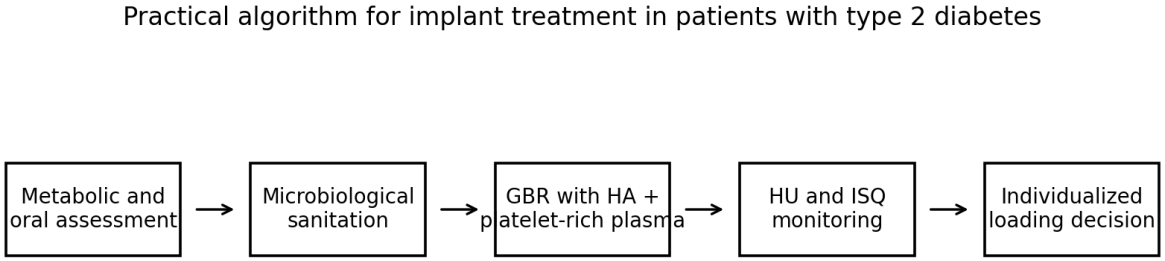

Figure 5. Practical algorithm for comprehensive implant treatment in patients with diabetes mellitus.

Clinical Recommendations

• Before implantation in patients with diabetes mellitus, it is necessary to assess not only bone volume but also oral microbiocenosis, local defense mechanisms and compensation of the underlying systemic disease.

• When pathogenic or opportunistic flora is detected, targeted preoperative sanitation followed by control testing is advisable.

• In low-density D3-D4 bone, the decision regarding early loading should be made after repeated ISQ assessment rather than only on the basis of the time elapsed after surgery.

• Hyaluronic acid and autologous platelet components may be considered biological adjuncts to bone grafting, especially in patients with delayed reparative potential.

• If Candida growth persists, antifungal correction and stricter oral hygiene control should be considered separately.

Limitations

This study has several limitations. First, it is based on clinical observation of a limited sample of patients with type 2 diabetes mellitus. Second, full randomization and separate comparison groups for each component of the bioregenerative complex were not available; therefore, the individual contributions of hyaluronic acid and platelet-rich plasma cannot be isolated. Third, HbA1c levels, diabetes duration and the type of glucose-lowering therapy were not detailed in the dataset, although these factors could influence regeneration time. Fourth, microbiological data mainly describe the early postoperative period and should be compared with long-term clinical outcomes in future studies.

Conclusions

1. In patients with type 2 diabetes mellitus, dental implantation with guided bone regeneration should be accompanied by comprehensive assessment of systemic, microbiological and bone status.

2. Preoperative medication-based preparation contributes to a reduction in potentially aggressive microorganisms and elimination of Staphylococcus aureus; however, fungal flora requires separate monitoring.

3. Hyaluronic acid and platelet-rich plasma may be considered components of bioregenerative support aimed at optimizing the wound environment and conditions for osteogenesis.

4. The dynamics of local protective factors confirm postoperative reduction of immunological parameters followed by partial recovery by the first month of observation.

5. Resonance frequency analysis using ISQ is a practical method for objective assessment of osseointegration and selection of functional loading time, especially in low-density D4 bone.

6. Combined HU and ISQ monitoring may reduce the risk of unjustifiably early implant loading and improve the predictability of prosthetic rehabilitation.

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