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Involvement of IL-23 and IL-12 Levels in the Development of Peri–Implantitis

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ABSTRACT

Dental implants: a surgical component that interfaces to the jaw or skull bone to support a dental prosthesis such as a crown, bridge, denture, or facial prosthesis.

The aim of this study was to detect the role and related inflammatory cytokines IL-23 and IL-12 in the initiation and progress and evaluate their implication in peri-implant inflammation and their influence upon osseointegration.

Material and Methods: 80 subjects (15 peri-implantitits patients and 35 successful implants and 30 healthy controls); the mean age was 43.91 ± 11.33 years, (49 male and 31 female), were attending the department of Oral and Maxillofacial Surgery in the Dental College Teaching Hospital/ Baghdad University, and Shahid Ghazi Hariri Hospital/ Medical City Baghdad, Iraq.

Enzyme-linked immunosorbent assay (ELISA) kits were used for the analysis and detection of IL-12 and IL-23.

Results: The elevated PISF levels of selected inflammatory cytokines is a result of their activation in the inflammatory process of the peri-implantitis, however, this activation may contribute to peri-implant supportive tissue destruction and bone loss.

Conclusion: These results suggest that IL-23 may play an important role in inflammation-mediated bone loss. However, IL-12 exhibits potential as a target for the treatment of pathological bone diseases.

Key words: Dental implants, Peri–implantitis, Per-implant sulcular fluid, IL-23/ IL-12

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INTRODUCTION

Dental implants are one of the most well-established and reliable treatments in contemporary dentistry. This surgical component connects with the jaw or skull bone to support a dental prosthesis such as a crown, bridge, denture, facial prosthesis, or function as an orthodontic anchor. The most common and proven implant materials are titanium and titanium alloys, which have demonstrated excellent tissue integration. For materials like titanium to develop a close relationship with the bones, osseointegration is required [1]. A load-bearing implant and organized live bone form a direct structural and functional link [2]. Insufficient osseointegration by the host tissue may contribute to implant failure [3]. Implant failures are classified as early or late failures, or as infectious or noninfectious. Also, Early failures occur due to surgical damage, premature loading of the implant, or bacterial infection, whereas late failures occur due to the implant's inability to sustain osseointegration [3-5]. However, removing the tooth and implanting it causes inflammation in the jawbone and body, leading to uneventful recovery and implant stability [6]. An inflammatory response is used to contain pathogenic bacteria, draw cells and their products to injured regions, and start the healing process. It includes various pathological processes and cell types. Despite the unpleasant symptoms, these responses help to isolate a disease and prevent it from spreading [7]. Pathogenic bacteria may colonise dental implants, causing inflammation

of the supporting tissues [8]. Contrary to popular belief, bacterial biofilm production does not cause tissue harm in peri implantitis. Multiple studies have indicated that titanium implants may create chronic inflammation in the surrounding tissue, causing local and systemic health issues [9]. On the basis of immunological vulnerability to Th I and macrophage reactivity which may eventually lead to titanium implant failure, peri-implant illness, peri-implant mucositis, and peri-implantitis have been postulated [6]. Peri-implantitis is an inflammatory condition that causes soft tissue inflammation and gradual bone loss [10]. Its progression has hampered implant survival and success [11-13].

Interleukins and TNFs have been linked to osteonecrosis [14-16]. Pro-inflammatory cytokines (interleukin 1 [IL 1], IL 6, IL 8, TNF, and interferon gamma) They activate the immune system, the central nervous system, and hormone release (or repression). Although more research is needed on cytokines, the relevance of their numerous roles is now completely understood [17,18]. While these cytokine-induced reactions are typically beneficial, too much of them may be dangerous. Surplus pro-inflammatory cytokines may cause hypotension, multi-organ failure and death. The body has a sophisticated system of checks and balances to regulate cytokine production and activity, significantly more complex than those that govern endocrine activities [18].

The activation of CD4+ cells produces effector populations that may contribute to the advancement of the inflammatory response [19]. The activation of the adaptive immune response was formerly thought to be mediated by two effector CD4+ T cell subpopulations, namely Th 2 responses, which are prevalent in periodontitis gingiva. Others claim that periodontitis and peri implantitis patients' gingival difficulties have greater Th0 and/or Th1 responses. Since the discovery of TH 17 generating IL-17 in the presence of IL-23, an important cytokine implicated in the growth of the Th17 lineage linked to various immune-related destructive tissue disorders, this paradigm has been updated. The Th17 Pathway and IL-23 in Periodontitis [20,21]. IL-12 induces IFN-expression from T-cells and leads TH cells to become TH1 cells. IFN- also inhibits osseointegration by interfering with the RANKL-RANK signaling pathway [22].

MATERIALS AND METHODS

A total of 80 subjects (15 peri-implantitis patients and 35 successful implants and 30 healthy controls) were enrolled in this cross-sectional study.

The inclusion criteria of patients were required to have an unremarkable medical history, no known allergies, and no metabolic diseases. They also had no history of any antibiotic treatment for the prior 3 months, no use of anti-inflammatory drugs in the 6 months preceding the beginning of the study and no radiographic evidence of periodontal bone loss after a full-mouth radiographic periapical examination. The periodontal health of the patients was also evaluated using the plaque index (PI), gingival index (GI), pocket depth (PD) and bleeding on probing (BOP) by a dentist.

Subjects were grouped into 3 groups: group1 consisted of 15 patients (9 males and 5 females, mean age 39 years) with peri-implantitis patients, group 2 consisted of 35 Subject with working Osseo integrated implants i.e. successful implants, (21 males and 15 females, mean age 47 years)and group 3 consisted of 30 Subject randomly taken healthy control adult subjects (19 males and 11 females, mean age 41 years). The study protocol and informed consent forms were approved by the Faculty of Medicine, University of Baghdad.

Sample collection

Patients were scheduled for sample collection during the morning hours that is, from 9 AM to 11 AM. The patients were instructed to refrain from food and vigorous oral hygiene measures 90 minutes prior to sample collection. To avoid salivary contamination, the selected sites were rinsed with water, isolated by cotton rolls, and dried with a gentle air spray. The fluid sample was collected from the test groups by standardized absorbent paper strips (Perio Paper). The supragingival plaque was removed with dry gauze, and a standardized paper strip was inserted 1-2 mm into the sulcus. The strip was held in place for 30 seconds. Strips contaminated by blood were excluded from the sampling group. After 30 seconds of sampling time, paper strips were immediately placed

in sterile Eppendorf tubes containing 0.5 ml preservative (PBS) then centrifuged at (3000) rpm for ten minutes, and carefully wrapped to be stored in −80°C until laboratory analysis [23]. Enzyme-linked immunosorbent assay (ELISA) kits were used for analysis and detection of IL-23 and IL-12 in the patient their peri-implant sulcular fluid specimens.

Statistical analysis

SPSS version 26, Microsoft Excel 2010, Using normality tests, the present study's data was carefully examined to determine if it was parametric or non-parametric. As a result, appropriate statistical tests were employed. One-way ANOVA and LSD were achieved to evaluate considerable differences. ROC data and person correlation were used to assess the applied parameters as perfect or excellence markers for the studied case together with their association as (v. strong, strong, moderate or weak negatively or positively).

RESULTS

Fifteen patients with Peri-implantitis were rolled in this study, the age of patients with peri-implantitis ranged between (20-70) years with a mean of (39.93 ± 8.21) years. Furthermore, there was a significant male's predominance (61.0%) among the patient's group, no statistically significant differences (P=0.888) in age or gender existed between patients and controls. as shown in Table 1.

PISF levels of IL-23 (pg\ml) in healthy subjects, successful implant and patients with peri-implantitis

The peri-implant sulcular fluid level of IL-23 in 15 patients with peri-implantitis was compared to the healthy subject as the control group, and in the successful implant group. PISF level of IL-23 showed highly significant increase (P=0.0001) in the group of patients having peri-implantitis (609.056 ± 17.080) in comparison with both healthy control and successful implant group (119.947 ± 13.033), (143.438 ± 12.284) respectively, as illustrated in the Tables 2 and Table 3 and Figure 1.

PISF levels of IL-12 (pg\ml) between healthy subjects, successful implant and patients with peri-implantitis

The PISF level of IL-12 detected in 35 patients with Peri-Implantitis and compared to the healthy subjects as the control group, IL-12 level was increased significantly (P=0.0001) in groups of Peri-Implantitis patients (255.485 ± 10.828 pg/ml) in comparison with (154.443 ± 8.263) in the control group as shown in Table 4 and Figure 2.

Also the PTSF level of IL-12 was significantly increased (P=0.0001) in peri-implantitis patients group (255.485 ± 10.828pg/ml) in comparison with (191.713 ± 7.788) successful implant group pg/ml.

The three study groups showed a slight difference level in IL-12 the three study groups show slight difference level in IL-12 as illustrated in Table 5 and Figure 2.

Table 1: Demographic data of patients and Successful implant, healthy control.

Gender		Study groups			Total	P. value
		Healthy control No. (%)	Implant successful No. (%)	Peri-Implantitis No. (%)		
Female		11 (36.7)%	15 (41.7)%	5 (35.7%)	31 (38.8)%	0.888NS
Male		19 (63.3)%	21 (58.3)%	9 (64.3%)	49 (61.3)%	
Total		30 (100.0)%	36 (100.0)%	14 (100.0)%	80 (100.0)%	
Age	Mean ± SD	41.67 ± 13.15	47.33 ± 9.95	39.93 ± 8.21	43.91 ± 11.33	
	Range	(24–69)	(27–66)	(28–56)	(24–69)	

Table 2: Comparison of IL-23 levels (pg/ml) in PISF between healthy subjects and patients with peri-implantitis.

	Peri-implantitis patients		Healthy Control		P value
Number	N=15		N=30		-
peri-implant sulcular fluid level of IL 23 (pg/ml)	Mean	SE	Mean	SE	0.0001
	609.056	± 17.080	119.947	± 13.033	

Table 3: Comparison of IL-23 levels (pg/ml) in PISF between successful implant group and patients with peri-implantitis.

Number	Peri-implantitis patients		successful implant		P value
	N=15		N=35		-
peri-implant sulcular fluid level of IL 23(pg/ml)	Mean	SE	Mean	SE	0.0001
	609.056	± 17.080	143.438	± 12.284	

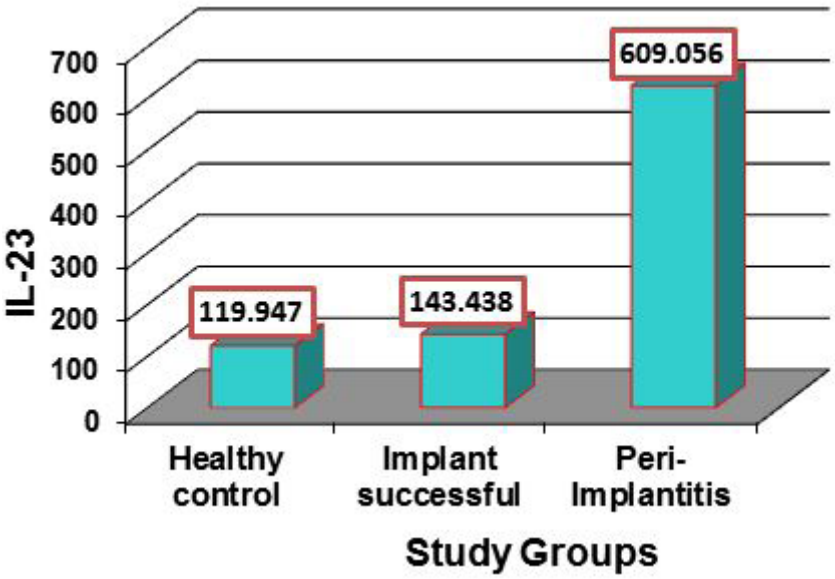

Figure 1: Comparison between the three study groups in IL-23 level.

Table 4: Comparison of IL-12 levels (pg/ml) in PISF between healthy subjects and patients with peri-implantitis.

Number	Peri-implantitis patients		Healthy Control		P. value
	N=15		N=30		-
peri-implant sulcular fluid level of IL 12(pg/ml)	Mean	SE	Mean	SE	0.0001
	255.485	± 10.828	154.443	± 8.263	
One way ANOVA					

Table 5: Comparison of IL-12 levels (pg/ml) in PISF between successful implant group and patients with peri-implantitis.

Number	Peri-implantitis patients		Successful implant		P value
	N=15		N=35		-
peri-implant sulcular fluid level of IL 12(pg/ml)	Mean	SE	Mean	SE	0.0001
	255.485	± 10.828	191.713	± 7.788	
	One way ANOVA				

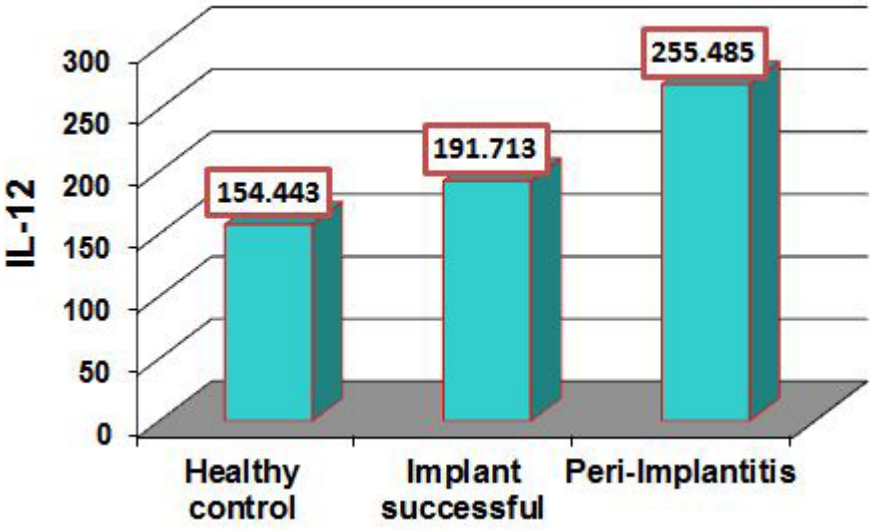

Figure 2: Comparison between the three study groups in IL-12 level.

Correlation between the PISF levels of IL-12 and IL-23 in the three study groups

The results in Table 6 and Figure 3, summarize the correlation between IL-12 and IL-23 in PISF among Healthy control and successful implant groups which were revealed non-significant

Table 6: Correlation coefficient between IL-12 and IL-23 in the three study groups.

Groups	Correlation coefficient-r between IL-12 and IL-23	P-value
Healthy control	-0.12 NS	0.503
Implant successful	-0.10 NS	0.546
Peri-Implantitis	0.61 **	0.011

** (P≤0.01), NS: Non-Significant

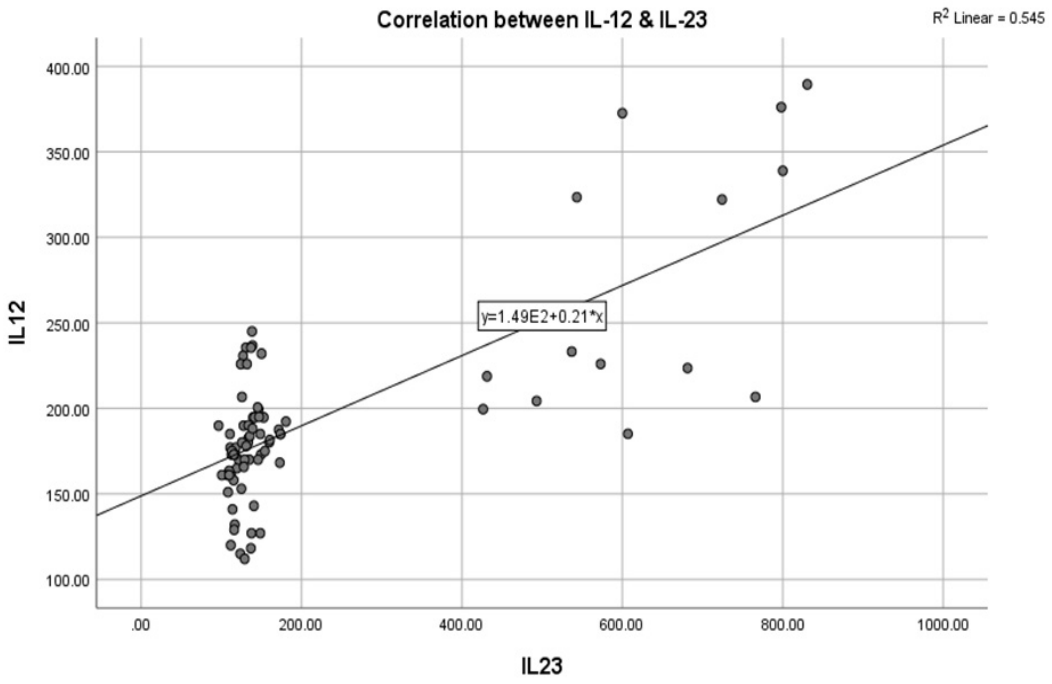

Figure 3: Correlation of PISF levels of IL-12 and IL-23 in patients with three study groups.

inverse correlation (r=-0.12)(P=0.503),(r=-0.10) (P=0.546) respectively. In the peri-implantitis patients a statistic significant difference was observed in the correlation between IL-12 and IL-23, indicating a positive relation(r=0.61) (P=0.011).

DISCUSSION

Peri-implantitis: is a pathological condition occurring in tissues around dental implants, characterized by inflammation in the peri-implant connective tissue and progressive loss of supporting bone. the exact causes for the development of peri-implant mucositis to peri-implantitis is not clear . The onset of peri-implantitis may occur early during follow-up and the disease progresses in a non-linear and accelerating pattern [24].

PISF levels of IL-23 (pg\ml) in healthy subjects, successful implant and patients with peri-implantitis.

PISF is a physiological fluid and an inflammatory exudate originating from the gingival plexus of blood vessels in the gingival corium, The composition of PISF can potentially be used to detect subclinical alterations in tissue metabolism, inflammatory-cell recruitment, inflammatory mediators and biomarkers and connective tissue remodeling [25].

It is well known that IL-23 its pro-inflammatory properties. Its ability to potently enhance the expansion of T helper type 17 (Th17) indicates its responsibility for many of the inflammatory autoimmune responses and chronic infections, in addition, different antigens can stimulate IL-23 production and some other cytokines [26].

In the present study, the levels of IL-23 were determined in PISF obtained from three groups – healthy subjects, patients with Peri-implantitis, and those with successful implants – using an ELISA kit. The study revealed that there was a highly significant increase in PISF level of IL-23 in the patients group having peri-implantitis (P=0.0001) in comparison with both healthy control and successful implant groups. The high level of IL-23 and related loss of its protective

effect on the gingival tissue may be explained due to the dysregulation of the IL-23/IL-17 pathway which occur during the progress the peri-implant disease, however, very little data is known about the exact reason for this dysregulation, which warrants further investigations.

Unfortunately, no previous studies concerning peri-implantitis are available to compare with, however, our result was compatible with previous findings detected by Lester et al. [27] who found a significant elevation in the level of IL-23 in GCF and serum among patients with periodontitis, in addition, they reported the association of the IL-23 concentration with increased progression of Periodontitis (PPD).

Other studies agree with previous study by Vernal et al. [28], Cardoso et al. [29], Ohyama et al. [30], Rohaninasab et al. [31] and Althebeti et al. [32], who found significant elevation of IL-17 and IL-23 in cases with moderate to severe chronic periodontitis particularly in regions adjacent to the bone loss and they concluded that the activity and stimulation of Th17 cells could be observed in periodontal inflammatory lesions.

In addition, several studies than by Schenkein et al. [33]; Borch, et al. [34] and Graves et al. [35] on periodontal inflammation support our study, they stated higher levels of IL-17, IL-23 cytokines in serum and GCF samples.

Where they said that The enhanced systemic inflammatory response caused by local cytokine generation leads to periodontal tissue destruction.

Our result agrees with Chen et al. [36] and Ju et al. [37] who reported that IL-23 boosted osteoclast development by directly increasing RANK in precursor cells and indirectly increasing RANKL expression on CD4 T cells leading to bone resorption

While Dutzan et al. [38] examined the mRNA of IL-23 and showed a significant overexpression of this cytokine in periodontal disease-affected tissues compared to healthy gingival tissues. Jafarzadeh et al. [39] assumed that the raised IL-23 levels might add to the systemic inflammatory burden a predisposing factor to cardiovascular complications, also may lead to a lack of osseointegration and bone loss or implant failure [40-42].

Other investigators as Himani et al. [43], Cifcibasi et al. [44] described a decrease in IL-23 after periodontal therapy, other studies as Duarte, et al. [45], Santos et al. [46], de Ribeiro et al. [47], Reports conflicting results they found almost no change in the levels of IL-23 after therapy.

As the IL-23 level in the gingival crevicular fluid is directly proportional to relative attachment loss , it may be considered as an active factor in guiding and progression of periodontal disease, thus can be regarded as a marker for the inflammatory activity in the periodontium during the process of tissue destruction [43]. It can be postulated that the greater the extent of peri-implant tissue destruction, the higher the concentration of IL-23 in the gingival crevicular fluid signifies the pro-inflammatory role of this cytokine in such diseases.

PISF levels of IL-12 (pg\ml) in healthy subjects, successful implant and patients with peri-implantitis

Several studies reported that immunologic factors particularly interleukins and TNFs might influence the development of osteonecrosis [14,48,49]. The usefulness of IL-12 as a marker of peri-implant disease including mucositis and peri-implantitis has been investigated, this cytokine has pro-inflammatory functions and induces bone reabsorption. Nevertheless, it Promotes other cytokine production, predominantly of IFN-γ, from NK and T cells, it functions as a growth factor for activation of these cells, improves the cytotoxic activity of NK cells, and favours cytotoxic T lymphocyte formation [50-52].

BMMSC osteogenesis is inhibited by IL-12. IL-12 and IFN- are effective osteoclast differentiation inhibitors [53-55]. In BMMs and RAW264.7 cells, IL12 modulates NFATc1 expression and suppresses RANKL's osteoclast genic activity [56]. IL-12 also increases TNF-induced osteoclast apoptosis through Fas/Fas ligand interaction [57].

In the present study, the mean level of IL-12 in PISF was obviously higher in the peri-implantitis group when compared to healthy controls and successful implant groups. The high level of this cytokine in patients may be explained since the IL-12 is considered as a pro-inflammatory mediator involved in the inflammatory response. However, IL-12 alone does not activate the

osteoclast activity and may inhibit the activity of RANKL. This means that level of IL-12 has no direct and strong effect on inflammation-induced bone loss.

Our result agrees with previous findings reported by Spyrou et al. [58]; Liskmann et al. [59], Konttinen et al. [60] and Duarte et al. [61] that showed significant elevation in level of IL-12 in PISF and GCF among patients with peri-implantitits as compared to successful implant groups and healthy controls, they also described the significant role of this interleukin in gingival inflammation and its unique protective character against bone loss.

Our result disagree with other studies conducted by Mengel et al. [62], Salcetti et al. [63] and Campos et al. [64] which reported no significant relationship between peri-implant disease and early implant loss concerning the level of IL-12 .

Correlation between the PISF levels of IL-12 and IL-23 in the three study groups

Based on data in this study the correlation between IL-12 and IL-23 in PISF among peri-implantitis patient groups were revealed a significant and positive correlation and in the three study groups. Unfortunately, there is no study evaluating the correlation between these two cytokines in this context. However, this correlation was consistent with Xu et al. [65] who detect the effects of IL-12 and IL-23 on bone mass maintenance and formation in mice, they stated that These two interleukins share cytokine subunits and receptor chains, in which IL-23 is formed by two p19 and p40 subunits, The later subunit is which placed between IL-12 and IL-23, have different functions in autoimmune diseases, cancer and pathologies associated with bone disorders and osteoarthritis. And stated that the combination of IL-12, IL-23 and other cytokines specially IL-17 and IFN-γ will promoted osteoclast differentiation, suggesting that the osteoclast-inducing ability of IL-23 should be significantly stronger than that of IL-12, IL-17 and IFN-γ [66]. Our result can be explained by the strong ability of IL-23 to promote osteoclast formation and differentiation, especially when combined and assisted by IL-12. In addition to IL-17 this strengthens osteoclast ability to induce bone loss.

CONCLUSION

In summary, the IL-23 can act as a biomarker to predict diseases and treatment efficacy and can be used as an effective therapeutic drug to combat inflammatory bone disorders. Targeting IL-12 can promote tissue repair and protect bone mass, whereas IL-12 deletion paradoxically mediates bone loss.

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