ISSN: 2581-5989
PubMed - National Library of Medicine - ID: 101738774

*International Journal of Dental Science and Innovative Research (IJDSIR)*
*IJDSIR : Dental Publication Service*
*Available Online at: www.ijdsir.com*
*Volume – 5, Issue – 3, June - 2022, Page No. : 07 - 15*

# Effect of periodontal therapy on inflammatory biomarkers in patients with metabolic syndrome: a randomized controlled clinical trial

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**Citation of this Article:** Dr. Anjani Kumar Pathak, Prof Rishi Sethi, Dr. Kalpana Singh, Dr. Wahid Ali, Dr. Mili Jain, Dr. Manisha Verma, "Effect of periodontal therapy on inflammatory biomarkers in patients with metabolic syndrome: a randomized controlled clinical trial", IJDSIR- June - 2022, Vol. – 5, Issue - 3, P. No. 07 – 15.



**Type of Publication:** Original Research Article

**Conflicts of Interest:** Nil

## Abstract

**Introduction:** Metabolic syndrome refers to the combination of cardiovascular risk factors, including atherogenic dyslipidemia, obesity, hypertension, elevated glucose, a prothrombotic state, and a proinflammatory state. Atherogenesis, is a consequence of systemic and vascular inflammatory processes. Recent evidence suggests that periodontitis is associated with atherosclerotic vascular disease and its sequelae. A positive correlation between periodontitis and metabolic syndrome has been found in a population based survey and in case control studies. The chronic state of systemic inflammation that accompanies both periodontitis and metabolic syndrome may be a common denominator that underlies the association of these conditions with higher risk of atherosclerosis.

**Aims:** The present study is designed to determine whether treatment of periodontitis in patients with metabolic syndrome could reduce the serum CRP and and possibly contribute to reduced cardiovascular risk.

**Materials and methods:** Patients in the experimental group received scaling, and root planing and were given metronidazole (250 mg) and amoxicillin (500 mg) tablets, three times daily, for 7 days. Patients in the controlled group received treatment consisting of scaling and two placebo tablets thrice daily, for 7 days. Periodontal

procedures were repeated at 3, 6 and after 9 months. Blood samples will be collected after 10 hours of overnight fasting, at baseline and 9 months after therapy for the measurement of biochemical markers which includes high sensitive CRP, serum lipoproteins, and cholesterol. In addition to these total leukocytes count (TLC) will also be investigated.

**Results:** At baseline, no significant difference was found in mean hsCRP, serum lipoproteins, cholesterol values between the control and experimental groups (p=0.245), while at 9 months the mean hsCRP, serum lipoproteins and cholesterol level of experimental group was significantly less than the control group.

**Conclusion:** Reduction of periodontal inflammation with subgingival scaling, root planning and systemic antibiotics significantly reduces CRP levels.

**Keywords:** Metabolic syndrome, hsCRP, Atherosclerosis

**Introduction**

The metabolic syndrome (MetS) refers to the combination of cardiovascular risk factors, including atherogenic dyslipidemia, obesity, hypertension, elevated glucose, a prothrombotic state, and a proinflammatory state.[1] It has been estimated that people with MetS are at twice the risk of developing cardiovascular disease (CVD) than those without the syndrome.[2]

Atherogenesis, a condition of cardiovascular pathogenesis, is a consequence of systemic and vascular inflammatory processes.[3] Recent evidence suggests that periodontitis is associated with atherosclerotic vascular disease and its sequelae.[4] It has been proposed that the chronic inflammatory burden of periodontitis, characterized by elevated acute phase response proteins, such as C reactive protein (CRP) and fibrinogen[5] may represent a possible contributor to atherosclerosis.[6]

A positive correlation between periodontitis and metabolic syndrome MetS has been found in a population based survey[7] and in case control studies.[8, 9] Because atherosclerosis is an inflammatory disease,[3] circulating factors related to inflammation may increase the risk for CVD.[10, 11] The chronic state of systemic inflammation that accompanies both periodontitis[2, 5] and MetS[11] may be a common denominator that underlies the association of these conditions with higher risk of atherosclerosis.[12]

Reduction of systemic inflammation by the elimination of periodontitis in patients with metabolic syndrome may reduce the CVD risk. Some studies have also reported that intensive periodontal therapy results in periodontal and systemic reduction of inflammation in otherwise systemically healthy patients.[6, 13] However, a randomized, controlled trial by the same group did not find significant differences in the serum levels of CRP 6 months after intensive periodontal therapy.[14]

Other studies using standard nonsurgical or surgical periodontal therapy, in patients of good systemic health, have found either no significant changes in serum levels of CRP after periodontal therapy[15] or that the systemic inflammation responses to periodontal therapy[15] were heterogeneous and inconsistent across patients.[16]

Two systematic reviews concluded that there is either modest evidence[17] or no evidence that periodontal treatment may result in a reduction of serum CRP levels.[18] However, all but three[19-21] of the studies of the effect of periodontal treatment on systemic inflammation, excluded patients with known propensity for atherosclerosis. Thus, the potential benefits of periodontal treatment in patients with a high risk of CVD have not been completely explored. Therefore present study is designed to determine whether treatment of periodontitis in patients with MetS could reduce the serum CRP and and possibly contribute to reduced cardiovascular risk.

**Materials And Methods**

An interventional study done on periodontitis patients with MetS in the department of Periodontology, faculty of dental sciences KGMU Lucknow. The study was done as a parallel-arm; double-blind, randomized clinical trial of 1year duration among patients with a diagnosis of MetS who will be attending for treatment to reduce CVD risk in the department of cardiology. The inclusion criteria were, Patients aged between 35 to 65 years with features of periodontitis and MetS. Diagnostic determinants of MetS were Central obesity (>102 cm in males;>88 cm in females) or body mass index (BMI) > 30 $kg/m^2$ , Dyslipidemia defined by plasmatic triglycerides level >150 mg/dL, High density lipoprotein cholesterol (HDL) <40 mg/dL in males or <50 mg/dL in females, Blood pressure ≥130/85 mmHg, Fasting glucose ≥110 mg/dL.[22]The diagnosis of MetS will be made when ≥3 of the above risk determinants are present. Diagnostic criteria of periodontitis were; Presence of four or more teeth with one or more sites with probing depth (PD) ≥4 mm, and Clinical attachment loss of ≥3 mm.[23]Exclusion criteria for the study were**,** Patients with a history of Periodontal therapy for the last 6 months, Chronic or acute infections during the previous 6 months, Pregnant or lactating females, Systemic antibiotic treatment in the past 6 months, Regular use of nonsteroidal anti-inflammatory drugs or hormone replacement therapy.

**Investigative procedures**

All the patients received oral hygiene instructions. Patients in the experimental group received supragingival and subgingival scaling, crown polishing, and root planing using hand and ultrasound instruments. In addition, patients were given metronidazole (250 mg) and amoxicillin (500 mg) tablets, three times daily, for 7 days. Patients in the controlled group received treatment consisting of supragingival scaling with ultrasound instruments, crown polishing, and two placebo tablets thrice daily, for 7 days. The metronidazole, amoxicillin, and placebo tablets were packed in identical bottles. Periodontal procedures were repeated at 3, 6 and after 9 months. The subjects in both the groups were advised not to stop any medication which they were taking for MetS during the study period.

Blood samples will be collected after 10 hours of overnight fasting, at baseline and 9 months after therapy for the measurement of biochemical markers which includes high sensitive CRP, serum lipoproteins, and cholesterol. In addition to these total leukocytes count (TLC) will also be investigated.

**Sample size**

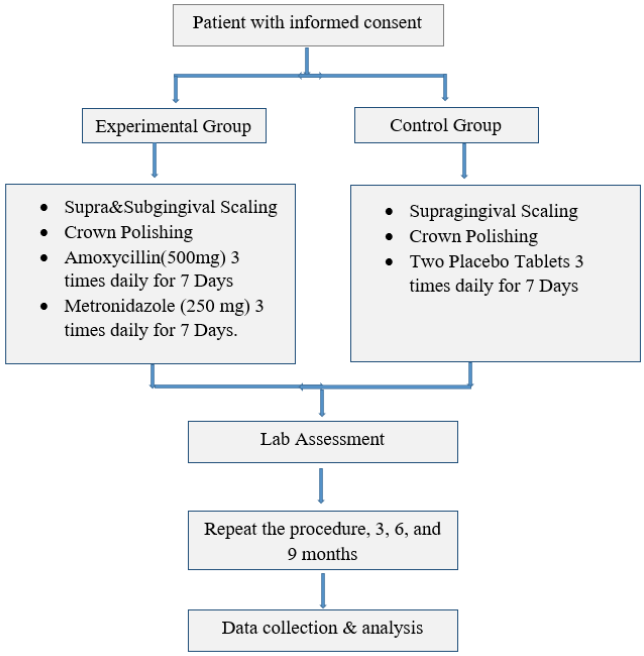
The total sample size is given by:

$$N = \frac{(r+1)\left(Z_{\alpha} + Z_{1-\beta}\right)^2 \sigma^2}{rd^2}$$

Where $Z_a$ and $Z_{1-b}$ are Normal deviates

Assuming a mean difference between groups in CRP of 0.60,[17] with a standard deviation of 1, it was calculated that with 120 patients, 60 in each group, we would have 90% power to detect this difference in CRP at a significance level (α) of 0.05.

**Project plan**




**Data management and analysis**

Difference between treatment groups in categoric variables at base line will be tested by the $\chi^2$ test, whereas continuous variables will be tested using Mann Whitney U test. The change from baseline to 9 month in the continuous variables will be tested for significance by using Wilicoxon test. The change in dichotomous variables will be compared by using Mc Nemar's test. The p value < 0.05 will be considered significant. All the analysis will be carried out by using SPSS 16.0 version.

The study protocol was approved by the University ethics committee (registration no. ECM IIB-IMR-F/P4 vide letter no 9890/Ethics/R.Cell-16. All participants provided written informed consent, and the study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2000.

**Results**

The baseline characteristics of both groups were similar. No significant changes in lifestyle factors, frequency of hypertension, BMI, serum lipoprotein cholesterol, and glucose levels were observed during the study period. No any significant change in diet and physical activity was determined during the study period. The mean age of experimental group was 36.47±10.91 years while the mean age of control group was 34.02±9.16 years. No significant difference was found in mean ages between the groups (p=0.264). In the experimental group 46.5% were females and 53.5% were males while in control group 37.2% were females while 62.8% were males. No significant difference was found in male and female proportion between the groups (p=0.382).

**Table 1: hsCRP level**

| hsCRP (mg/L) | Experimental Group | | Control Group | | Unpaired t Test | |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | t-value | p-value |
| Baseline | 7.78 | 0.38 | 7.87 | 0.30 | -1.17 | 0.245 |
| 9 month | 6.27 | 0.55 | 7.14 | 0.49 | -7.85 | <0.001 |
| Change | 1.51 | 0.50 | 0.72 | 0.33 | 8.69 | <0.001 |
| Intragroup | t=19.83, p<0.001 | | t=14.59, p<0.001 | | | |

At baseline, no significant difference was found in mean hsCRP values between the control and experimental groups (p=0.245), while at 9 months the mean hsCRP level of experimental group was significantly less than the control groups (p<0.001), however both control as well as experimental groups showed significant decrease in hsCRP level at 9 month from baseline (p<0.001). (Table.1, Figure .1)

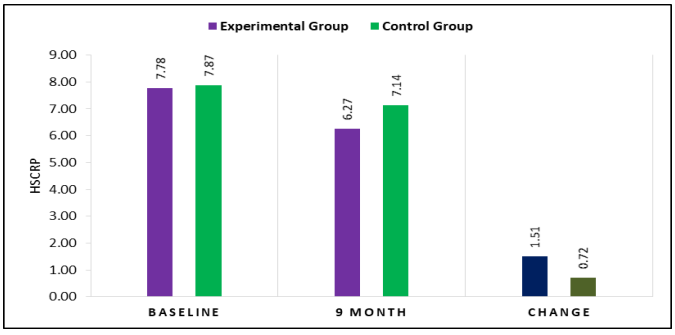



Figure 1

**Table 2: Serum triglyceride level**

| ST | Experimental Group | | Control Group | | Paired t Test | |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | t-value | p-value |
| Baseline | 166.09 | 108.24 | 173.40 | 106.50 | -0.32 | 0.753 |
| 9 month | 156.37 | 102.58 | 173.26 | 106.44 | -0.75 | 0.456 |
| Change | 9.73 | 46.54 | 0.14 | 0.50 | 1.35 | 0.180 |
| Intragroup | t=1.37, p=0.178 | | t=1.81, p=0.077 | | | |

Both control and experimental groups showed insignificant changes in Serum triglyceride level from baseline to 9 months (p>0.05). On comparing between the groups no significant difference was found in mean serum triglyceride values during assessed periods. (p>0.05) (Table.2, Figure .2)

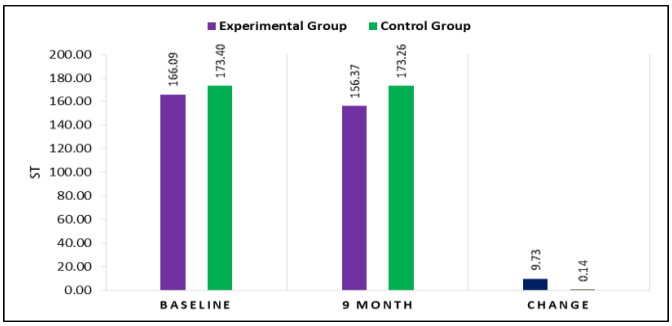



Figure 2

**HDL, LDL, and VLDL values**

Experimental group showed significant decrease in HDL (Table. 3), LDL (Table. 4) and VLDL (Table. 5) levels from baseline to 9 months (p<0.001). No significant difference was found in mean HDL, LDL and VLDL values between the groups (p>0.05), However the mean change in experimental group was significantly more than the control group (p<0.001).

**Table 3: HDL value**

| HDL | Experimental Group | | Control Group | | Paired t Test | |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | t-value | p-value |
| Baseline | 43.93 | 11.28 | 44.84 | 9.11 | -0.41 | 0.680 |
| 9 month | 42.70 | 11.46 | 44.76 | 9.05 | -0.93 | 0.357 |
| Change | 1.23 | 1.13 | 0.08 | 0.28 | 6.48 | <0.001 |
| Intragroup | t=7.17, p<0.001 | | t=1.93, p=0.060 | | | |

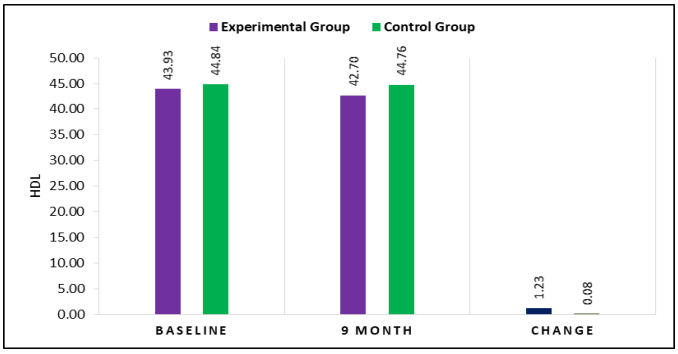



Figure 3

**Table 4: LDL values**

| LDL | Experimental Group | | Control Group | | Paired t Test | |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | t-value | p-value |
| Baseline | 86.77 | 32.59 | 86.33 | 32.53 | 0.06 | 0.950 |
| 9 month | 85.49 | 32.65 | 86.19 | 32.46 | -0.10 | 0.921 |
| Change | 1.28 | 1.16 | 0.14 | 0.56 | 5.80 | <0.001 |
| Intragroup | t=7.22, p<0.001 | | t=1.64, p=0.110 | | | |

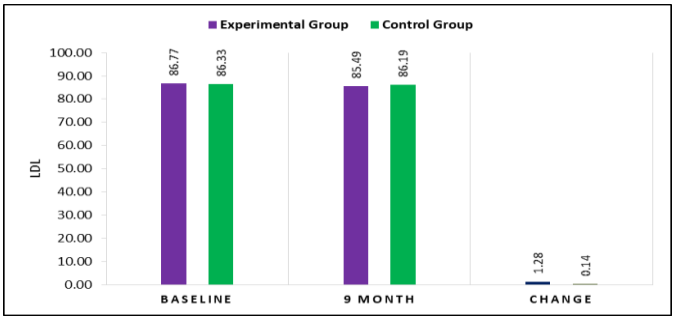



Figure 4

**Table 5: VLDL values**

| VLDL | Experimental Group | | Control Group | | Paired t Test | |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | t-value | p-value |
| Baseline | 30.16 | 14.19 | 29.60 | 12.94 | 0.19 | 0.849 |
| 9 month | 28.70 | 13.96 | 29.44 | 12.92 | -0.26 | 0.798 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Change | 1.47 | 1.30 | 0.16 | 0.48 | 6.17 | <0.001 |
| Intragroup | t=7.41, p<0.001 | | t=2.20, p=0.033 | | | |

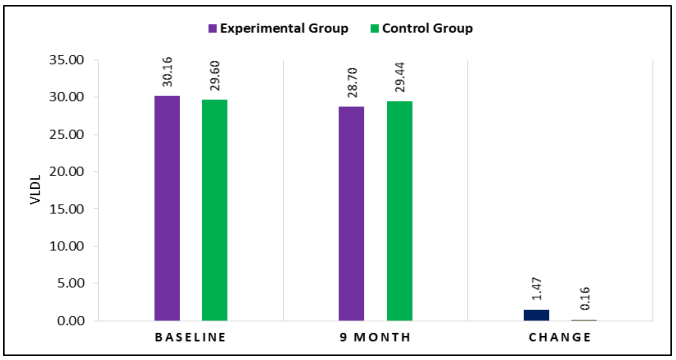



Figure 5

**Table 6: S. Cholesterol Level**

Experimental group showed significant decrease in S.Cholesterol level at 9 month from baseline (p<0.01), however no significant difference was found in mean S.Cholesterol values between the groups (p>0.05), at baseline and 9 months both.

| S.Chol | Experimental Group | | Control Group | | Paired t Test | |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | t-value | p-value |
| Baseline | 162.20 | 41.42 | 162.77 | 37.25 | -0.07 | 0.947 |
| 9 month | 161.66 | 41.45 | 162.29 | 37.01 | -0.07 | 0.942 |
| Change | 0.54 | 1.30 | 2.23 | 14.21 | -0.78 | 0.440 |
| Intragroup | t=2.71, p=0.010 | | t=1.00, p=0.322 | | | |

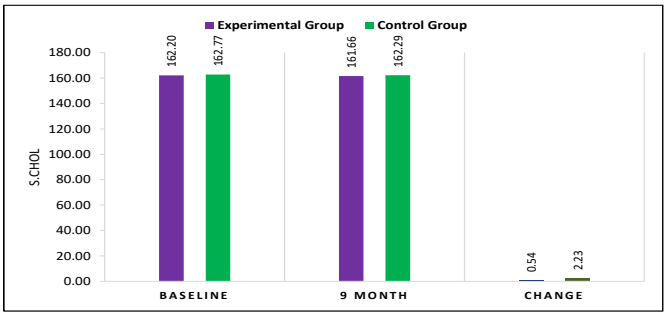



Figure 6

**Table 7: Total Leucocyte Count**

| TLC (/mm3) | Experimental Group | | Control Group | | Paired t Test | |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | t-value | p-value |
| Baseline | 7548.84 | 1967.40 | 7741.86 | 1998.72 | -0.45 | 0.653 |
| 9 month | 5099.72 | 2024.96 | 7741.86 | 1998.72 | -6.09 | **<0.001** |
| Change | 2449.12 | 743.56 | 0.00 | 0.00 | 21.60 | **<0.001** |
| Intragroup | t=21.60, p<0.001 | | NA | | | |

At baseline, no significant difference was found in mean TLC values between the groups (p=0.653), while at 9 months the mean TLC of experimental group was significantly less than the control group (p<0.001). Further experimental group showed significant decrease in TLC at 9 month from baseline (p<0.001). (Table. 7 Figure .7)

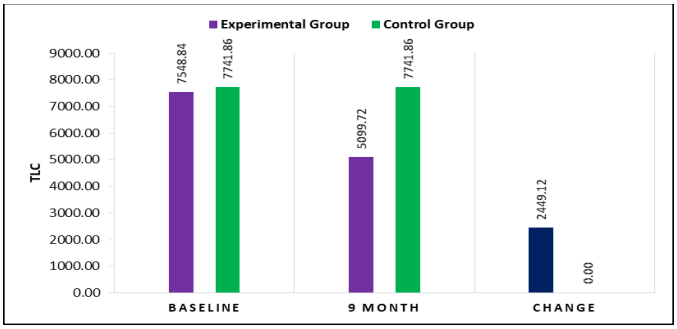



Figure 7

**Discussion**

Periodontitis is most common Gm –ve oral infection which result into severe inflammation and it has potential for vascular dissemination. Studies have established that levels of systemic markers of inflammation including CRP, fibrinogen, Interleukin-6 are associated with the pathogenesis of atherosclerosis and the risk of cardiovascular diseases.[24] Particularly CRP is a key marker of atherosclerosis and elevated level constitute a risk predictor of CVD. In addition, leukocyte count is considered as a good predictor of ischemic heart disease.[25]It has also been proposed that these

inflammatory markers could be elevated in chronic infections like periodontitis and the elevated levels of markers in blood aggravate other ongoing inflammatory processes which in turn increases the risk of atherosclerosis leading to cardiovascular events.

In the present study, patients in the control group received treatment consisting of supragingival scaling, polishing and two placebo tablets for 7 days while patients in experimental group received treatment consisting of supra- and subgingival scaling, polishing and antibiotics (Amoxicillin and metronidazole) for 7 days. In the study, the authors found that the treatment of periodontitis is associated with significant reduction in serum CRP and improvement in periodontal inflammation in patients with metabolic syndrome (MetS). Although the reduction in serum CRP and improvement in periodontal inflammation were significantly higher in the experimental group. The results of this study support with the findings of studies done by Offenbacher et al[20] who reported that periodontal treatment showed significant reduction in CRP levels. Noack et al[26] also observed the similar results. In the present study most of the patients had elevated levels of baseline CRP because both metabolic syndrome and periodontitis are associated with systemic inflammation.[26] No any significant changes in habits or lifestyle were observed during the study. So improvement in the CRP values may be attributed to the reduction of periodontal inflammation in the subjects. There are evidences that systemic inflammation associated with periodontitis may contribute to atherosclerosis in healthy individuals.[4,5] Increase in systemic inflammation in response to periodontitis may increase the metabolic changes in patients with metabolic syndrome promoting dyslipidemia and thus increasing the risk of cardiovascukar accidents. The plausible significance of this study results is that the burden of systemic inflammation caused by periodontitis may be controlled with a relatively simple treatment and thus decreasing the risk of cardiovascular disease.

On comparing serum lipoproteins and serum cholesterol levels authors concluded that the experimental group showed significant decrease in HDL, LDL, VLDL and cholesterol levels from baseline to 9 months but no significant difference was found in mean HDL, LDL and VLDL values between the groups. Again this may be attributed to reduction of systemic inflammation in both the groups.

At baseline slightly elevated levels of leucocyte count was observed in both the groups and the difference was statistically insignificant on comparison between the groups. While at 9 months the mean TLC of experimental group was significantly less than the control group. Many studies reported elevation of TLC in periodontitis.[27 28] The results obtained from our studies showed significant decrease in TLC in experimental group as compared to control group, which is in accordance with the study conducted by Loose et al in 2000.[28] In a study done by Twig et al[29] concluded that a measurement of leucocytes in healthy young men may predict coronary artery diseases independently from other risk factors such as elevated lipid levels and positive family history. Sweetnam PM et al[25] reported that increased count of leucocyte increases the blood rheology there by increasing the risk for cardio vascular accidents.

**Conclusion**

Present study showed that elimination of periodontal inflammation by using scaling, root planing and systemic antibiotics significantly reduces CRP in patients with metabolic syndrome. The reduction of the inflammation in periodontitis in patients with MetS may contribute to reduce cardiovascular risk.

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