

**REMINERALIZATION AGENTS ON EARLY STAGE OF CARIES COMPARISON
WITH DIFFERENT DIAGNOSTIC METHODS AND EVALUATE SURFACE
HARDNESS OF REMINERALIZATION AREA**

**BAŞLANGIÇ ÇÜRÜKLERİNDE REMİNERALİZE EDİCİ AJANLARIN
ETKİSİNİN ÇEŞİTLİ DİAGNOSTİK YÖNTEMLERLE KARŞILAŞTIRILMASI VE
YÜZEY SERTLİKLERİNİN DEĞERLENDİRİLMESİ**

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Makale Kodu/Article code: 3785
Makale Gönderilme tarihi: 05.07.2018
Kabul Tarihi: 14.02.2019

ABSTRACT

Aim: The aim of this study was to compare the extent of remineralization of permanent molar enamel with application of three remineralizing agents by employing QLF, microhardness and microcomputed tomography machine values.

Materials and Methods: An in vitro study was performed with 12 sound permanent molar teeth. The teeth were split in mesio-distal direction and two samples were obtained from each tooth (n=8). An artificial caries lesion (2x4 mm) was produced on enamel surfaces of sound molars using a previously reported demineralization model. Specimens were randomly divided into three groups: first group was treated using Tooth Mousse Plus (GC), the second group was treated using Clinpro Tooth Crème (3M ESPE) and the last group was treated using Sensodyne Protection and Repair (GSK). Demineralizing, remineralizing solutions and the tooth pastes were respectively applied the groups over a period of 14 days. The samples were subjected to QLF, microhardness, micro-computed tomography machine and electron microscope scanning.

Results: As compared with demineralization and remineralization values, in Tooth Mousse Plus group, micro-computed tomography showed no statistically significant difference (p>0,05) but QLF and micro hardness machines showed statistically significant difference (p<0,05). In Clinpro Tooth Crème and Sensodyne Repair and Protect groups; micro computed tomography, QLF and microhardness machines showed statistically significant difference (p>0,05).

Conclusion: Tooth Mousse Plus, Clinpro Tooth Crème and Sensodyne Repair and Protection are appropriated means of treating caries at early stages.

Keywords: Remineralization, CPP-ACP, micro-computed tomography, microhardness, QLF

ÖZ

Amaç: Bu çalışmanın amacı daimi molar dişlere uygulanan üç remineralize edici ajanın etkilerinin QLF, mikrosertlik ve mikrobilgisayarlı tomografi cihazları ile elde edilen değerlerin karşılaştırılmasıdır.

Gereç ve yöntem: Bu in vitro çalışmada sağlam 12 adet daimi molar diş kullanıldı. Dişler mezio-distal yönde ikiye ayrıldı (n=8). Yapay çürük lezyonu (2x4 mm) sağlıklı dişlerin minesinde demineralizasyon döngüsü ile oluşturuldu. Dişler rastgele 3 eşit gruba ayrıldı. 1. gruba Tooth Mousse Plus (GC), 2. gruba Clinpro Tooth Crème (3M ESPE) ve 3. gruba Sensodyne Onarım ve Koruma (GSK) uygulandı. 14 gün boyunca demineralizasyon, remineralizasyon solüsyonları ve diş macunları sırasıyla gruplara uygulandı. Numuneler QLF, mikrosertlik, mikrobilgisayarlı tomografi cihazları ile ölçüldü ve elektron mikroskopuyla değerlendirildi.

Bulgular: Tooth Mousse Plus uygulanan grupta demineralizasyon ve remineralizasyon değerleri kıyaslandığında, mikrobilgisayarlı tomografi istatistiksel olarak anlamlı bulunmamıştır (p>0,05) fakat QLF ve mikrosertlik cihazlarının değerleri istatistiksel olarak anlamlı bulunmuştur (p<0,05). Clinpro Tooth Crème ve Sensodyne Onarım ve Koruma uygulanan gruplarda; mikrobilgisayarlı tomografi, QLF ve mikrosertlik değerleri istatistiksel olarak anlamlı bulunmamıştır (p>0,05).

Sonuç: Tooth Mousse Plus, Clinpro Tooth Crème ve Sensodyne Onarım ve Koruma erken dönem çürüklerin tedavisinde kullanılabilir.

Anahtar kelimeler: Remineralizasyon, CPP-ACP, mikrobilgisayarlı tomografi, mikrosertlik, QLF

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INTRODUCTION

Dental caries are one of the most common and prevalent health problems among children and adults all around the world.^{17,23} The dentists therefore most frequently treat primary and secondary tooth cavities and renew previous restorations done on the teeth.^{36,11} The restorative therapy is costly and untreated caries cause chewing problems, pain (toothache) and life-long health problems.³² In recent years there has been a shift from invasive techniques to non-invasive ones in the field of dentistry.⁴ This may change the prevalence of caries in the population.^{22,25}

In initial caries, most of the hydroxyapatite crystals which constitute the dental structure are seen to remain unaffected. The dental enamel is remineralized due to calcium, phosphate and fluoride ions descending from the saliva. There are a number of theories on the fact that the dental enamel is more durable than the unaffected dental enamel.²⁹

Several agents are utilized to remineralize the teeth. Some of them are in the following: caseine phosphopeptide amorph calcium phosphate, tricalcium phosphate, calcium sodium phosphosilicate. The caseine phosphopeptide is formed when caseine calcium and phosphopeptide accumulate as a result of triptic decomposition of milk protein and contains anti-cavity agent.³³ The tricalcium phosphate is a form of calcium phosphate. It is formed when beta tricalcium phosphate and sodium lauric phosphate are combined. The tricalcium phosphate combine with fluoride ion, providing more fluoride and calcium ions to the surface of the enamel. It has been shown to cause remineralization on tooth enamel by both in vitro and in vivo studies.³⁷ Calcium sodium phosphosilicate contains bioactive glass particles and was first used regenerate bones. It can be activated in mouth-oral fluids to remineralize the tooth.⁵

New methods have been developed to detect cavities in the mouth thanks to rapid changes in medical technologies. These include QLF, DIAGNOdent have started to be widely used in relation to the increases in dental caries.²⁶

This study aims to compare the levels and effects of remineralization of various toothpaste that have remineralizing properties under pH cycle on the human molar teeth removed for several different

reasons using QLF, microhardness and micro-computed tomography (MCT) devices.

MATERIALS AND METHODS

Selection of the Research Sample

12 human molar teeth without cavity and restoration which were extracted because of periodontal or orthodontic reasons were selected for the study. The sample teeth were preserved in %1 thymol solution for less than 3 months until the study was carried out. After the soft tissue residues and debris on the teeth had been cleared, the dental roots were cut 1 mm below cervical line using a separator with low rotation.

Preparation of the Sample

The sample teeth were split in the center under watercooling using a separator with low rotation in mesiodistal direction. Then two specimens were prepared from each tooth. The specimens were embedded with their buccal or palatal surfaces upwards in an acrylic resin. The teeth were abraded using a sand paper of 600 grade and polished in order to prevent surface contamination and remove the hypermineralized structure on the surface. The buccal or palatal surfaces of the specimen were left open in dimensions of 2x4 mm and the other surfaces were covered by acid-resistant nail polish (Maybelline New York).

Demineralization of the Sample

The specimens were covered by acid-resistant varnish so as to make a window with the varnish and then demineralization solution was prepared to form primary cavity lesion. The demineralization solution consisted 1.5 mM calcium chloride (CaCl₂), 0,9 mM potassium-diphosphate (KH₂PO₄), 50 mM acetic acid (CH₃COOH) and 3 mM sodium nitride (NaN₃) and pH level was 4,8.³⁹ The specimens were stored in demineralization solution at 37°C in waterbath (Nuve BM 302, Ankara, Turkey) for 7 days. A specimen was randomly selected and the depth of lesion was examined by using micro-computed tomography device. Artificial cavities in the specimens were stored in %100 moisture settings.

Forming the groups

Group 1: Caseinphosphopeptide-amorphous calcium phosphate (CPP-ACP) fluoride with GC Tooth Mousse Plus (TMP)

Group 2: Sodium fluoride-tricalcium phosphate (f-TCP) with Clinpro Tooth Creme (3M ESPE)

Groups 3: Novamine (calcium sodium phosphosilicate) with Sensodyne Repair and Protection

Measuring Surface Microhardness (SMH) after demineralization

The measurement of the specimens microhardness after demineralization was performed in Cumhuriyet University Faculty of Engineering, Department of Metallurgy and Materials laboratory using microhardness machine (Shimadzu HVM-M3 Kyoto, Japan), The specimens received 200 gr force for 11 seconds with the tip of vickers diamond. The dentures formed on the demineralized windows were examined by using a microscope having a 40x magnifying power and calculated. The observers obtained results from four different zones of each specimen then the average values were recorded.

Evaluating the cavity formation

After the microhardness measurement was done, the demineralization values of the specimen were measured using QLF and MCT machines.

Evaluation by QLF

The QLF machine (QLF-D Biluminator 2, Amsterdam, The Netherlands) had a macrolens of Canon EFS 60mm f/2,8 USM (Canon Inc. Japan) a Canon Camera (EOS 550D Model) and a biluminator. The biluminator had 12 blue LED lamps and 4 white strong LED lamps. The specimens were evaluated on an x-y plane. Therefore, each specimen was measured at the same position. The specimens were washed and dried for 5 seconds before the procedure.

The QLF machine was fixed on the camera with an apparatus and the distance between the specimen and the lens was made stable. The specimens were measured and evaluated in the dark. The average fluorescence demineralization loss in the specimens was calculated using (% ΔF) QA2 version 1.18.

Evaluation by Micro Computed Tomography

Dental crowns were fixed in falcon tubes in the sample chamber on MCT device. The dental crowns were scanned via SkyScan 1172 on MCT device.

The device was calibrated for the procedure with the following settings: 100kV, 100mA, 8,5 pixel size, 0,4 rotational steps average imaging quality (as the number of frames) 3 and one images/1300 milliseconds. Each tooth was scanned for 99 minutes. The coronal images of the teeth were saved as TIFF image format. The images obtained were converted to make coronal fractions using NRecon Software (version1.6.5.2).

After this procedure, dental fraction images of each specimen were saved as bitmag file. The coronal, sagittal and axial fractions of the images were examined to find out defects on the teeth by using Data Viewer Software (version 1.5.1, Skyscan, Kontich, Belgium) and evaluated on the computer by the observers.

Remineralization of the Samples

pH cycle was applied to the samples to imitate the dynamic milieu in the mouth after creating primary cavity lesion. The pH cycle consists of demineralizing agents that represent acid attacks in the mouth (Calcium 2,0 mM, phosphate 2,0 mM, acetic acid 75,0 mM, pH 4,4) and remineralizing agents that represent the remineralizing effect of the saliva (1,5 mmol/l Ca⁺⁺, 0,9 mol/l phosphate, 130 mmol/l potassium chloride and 100 mmol/l tris tampon buffer, pH 7,0).

The toothpastes were stirred with 1/3 ratio water for 4 minutes (1 ml of therapeutic agent and 3 ml of water). After the samples were washed in deionized water, they were immersed into the mixture of 1/3 ratio water and 4 ml of toothpaste for 1 minute. Then they were washed with deionized water again. The samples were left in demineralization solution at 37°C for 6 hours so that each samples could have 40 ml of demineralization solution. After the procedure the samples were washed with deionized water and the mixture prepared before (1/3 ratio of water and toothpaste) was applied to the samples for 1 minute again. After being washed with deionized water again,

the samples were left in remineralization solution for 17 hours at night. The remaining one hour was spent by preparing the mixture and applying it to the sample. The procedure lasted 14 days. The remineralization solution was changed every two days and the demineralization solution was changed every five days.³⁴

Table 1. pH cycle

Treatment	Time
Washing with deionized water	
1. Tooth paste application and washing with deionized water	1 minute
Demineralization	6 hour
Washing with deionized water	
2. Tooth paste application and washing with deionized water	1 minute
Mineralization	17 hour

Microhardness measurement after application

The measurements of surface microhardness were done using vickers hardness testing after the pH cycle. The samples were measured from their 4 different demineralized zones. The average values were evaluated and recorded by the observers.

Evaluation of Remineralization

After the pH cycle performed the samples were measured again using QLF and micro computed tomography. The samples were left in deionized water for a week after the evaluation to show the consistency of the measurements. When the measurements showed consistency, the study continued.

Scanning Electron Microscope (SEM)

The remineralized surfaces were examined by scanning electron microscope (LEO 440 Computer Controlled Digital, UK). The Samples were placed on the metal holder using adhesive double layered selotapes and then fixed on the proposition machine. Here the vacuumed samples were covered in gold. After the surfaces were entirely covered in gold, the samples were ready to be examined. Then the

samples were examined using SEM working on 20 kV filamenttension under 150 millitorr low vacuum. The examined surfaces were photograped to obtain X 1000 and X 2000 sized images.

Statistical Methods

The findings of the study were analyzed in Cumhuriyet University, Faculty of Medicine, Department of Biostatistics. The data were analyzed by using SPSS (version 22) Parametrical assumptions couldn't be verified, so Mann-Whitney Utest, Kruskall-Wallis test and Mc Neman test were used. The error level was determined as $p=0,05$.

RESULTS

Remineralization and Demineralization Value of the Groups

The values in Table 2 were compared to each other QLF, SMH and MCT values were statistically significant.

The values in Table 3 were compared to each other, QLF, SMH and MCT values were statistically significant.

The values in Table 4 were compared to each other, QLF, SMH and MCT values were statistically significant.

Table 2. Demineralization and remineralization values of the group treated by tooth mousse plus.

Groups	Demineralization	Remineralization	p
QLF	-24,53±6,62 ^a	-10,61±3,43 ^b	0,001
SMH	72,87±30,53 ^a	134,62±26,37 ^b	0,001
MCT	150,75±77,99 ^a	80,62±28,11 ^b	0,047

Each column shows statistical differences with different letters (p<0,005).

Table 3. Demineralization and remineralization values of the group treated by Clinproo Tooth Creme.

Groups	Demineralization	Remineralization	p
QLF	-14,60±7,06 ^a	-10,87±4,30 ^b	0,023
SMH	94,25±56,38 ^a	136,12±61,43 ^b	0,048
MCT	133,62±47,09 ^a	82,62±43,05 ^b	0,038

Each line shows statistical differences with different letters (p<0,005).



Table 4. Demineralization and remineralization values of the group treated by Sensodyne Repair and Protection.

Groups	Demineralization	Remineralization	p
QLF	-43,00±64,05 ^a	-10,18±5,86 ^b	0,012
SMH	63,87±20,27 ^a	110,88±41,56 ^b	0,042
MCT	163,25±57,91 ^a	84,75±23,89 ^b	0,002

Each line shows statistical differences with different letters. (p<0,005)

Examination of SEM images

The evaluation of the SEM images showed that dentine tubules were highly clogged and had created accumulations indicating remineralization in all three groups.

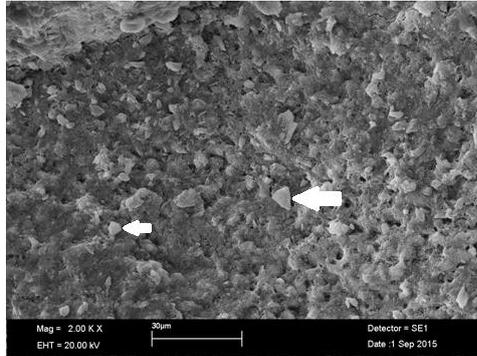


Figure 1. The image of sample under SEM randomly chosen from the group 1 (GC Tooth Mousse Plus) with x2000 times magnified state.

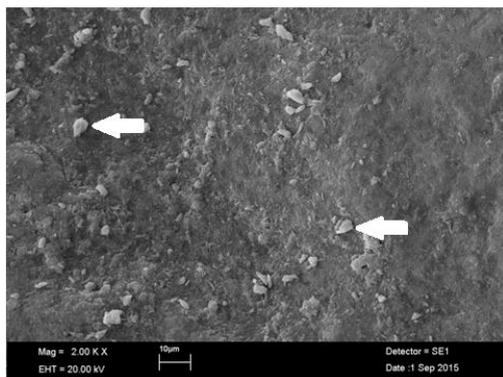


Figure 2. The image of sample under SEM randomly chosen from the group 2 (Clinpro Tooth Creme) with x2000 times magnified state.

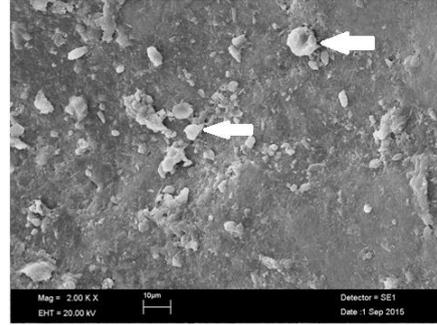


Figure 3. The image of sample under SEM randomly chosen from the group 3 (Sensodyne Repair and Protection) with x2000 times magnified state.

MCT Images

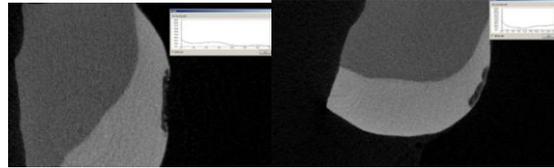


Figure 4. The image of a sample randomly selected from the group 1 (GC Tooth Mousse Plus) in demineralization (on the left) and the image of the same sample after remineralization on MCT.

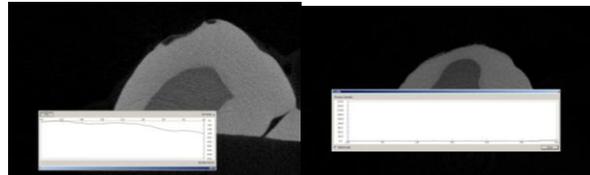


Figure 5. The image of a sample randomly selected from the group 2 (Clinpro Tooth Creme) in demineralization (on the left) and the image of the same sample after remineralization on MCT.

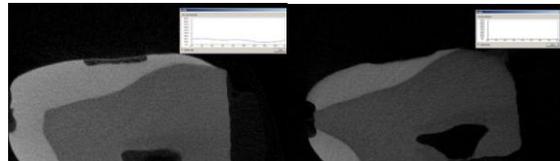


Figure 6. The image of a sample randomly selected from the group 3 (Sensodyne Repair and Protection) in demineralization (on the left) and the image of the same sample after remineralization on MCT.

According to MCT images the demineralized areas seemed to use remineralize.

DISCUSSION

Minimally invasive dentistry is to prevent the progression of the underlying disease and to protect the dental tissue. In the past century, dentists based on G.V. Black's principles, they have formed cavities according to the rule of 'expand to protect'. According to this view, all demineralised areas of the dental tissue should be removed and filled with restorative material. However, this concept causes the loss of the coronal structure during the restoration. For this reason, nowadays, minimally invasive technique is increasingly used.⁸

The most appropriate method for examining the efficacy of remineralization agents used in the non-invasive treatment of initial caries lesions is the inability to be in vivo experiments, the high number of participants, the long duration of the study, the persistence of participants and the ethical reasons constitute the main difficulties of these studies. The advantages of in vitro studies are that they are highly controlled, have fewer variations and can be selected for small samples.⁹ So in our study we choosed in vitro study model to make lower mistake.

The parameters for in vitro studies should be carefully selected, while the criteria for tooth retention, tooth retention times, initial demineralization process, imitation of the oral environment, and remineralization criteria should be carefully selected.¹⁶

When the efficacy of the remineralizing agents is tested, in vitro studies using bovine or human enamel. There are some differences between bovine and human enamel. Bovine enamel is more rough, soft, more carbonated and contains less fluoride than human enamel. Moreover, the arrangement of the prisms in the lower third quadrant of the minerals is different, the crystals are larger in bovine, but the prisms are smaller in diameter.¹³ In this study, human enamels were used to obtain closer data to the correct results.

The artificial caries solutions used to form the initial caries differ in the studies carried out. The mean duration of treatment varies from pH 4-5 to 32 hours to 8 weeks.^{19,24,7,1,2} This difference in demineralization times causes differences in the caries lesions that occur. As a result of the demineralization carried out in a short time, soft erosion-like structures occur on the

surface of the enamel. That lesions are different from initial lesions. Long-term demineralization causes more like the initial caries lesions that occurs in vivo conditions. This affects the content of demineralization solution, pH and demineralization duration.⁶ In our study, we stored the samples in demineralization solution with pH = 4.8 for 7 days to form the initial lesion. So we planned to make long term demineralization to make more closer initial caries lesions that occurs in in vivo condicions.

The pH cycle has been used for many years in in vitro studies to imitate the dynamic environment of the mouth and to create a caries, which histologically similar to the oral environment.^{38,28,15,18} In our study we make 14 days pH cycle. This cycle help us to make closer results. Our mineralization time is 17 hour this simulate salivas mineralization on teeth while sleeping or not eating or drinking. Demineralization time is 6 hours which is simulate acid attacks while eating and drinking.

Reynolds et al. argued that the effect of the fluorides used in the treatment of initial caries lesions during demineralization was sufficient in the presence of free calcium and phosphate ions in the environment.²⁷ We used fluoride-containing toothpastes that contain calcium and phosphate ions that we use in our work.

The first step of our study is the comparison of the effects of different remineralizing agents on the initial caries. In our study, we used group 1 Tooth Mousse Plus (GC), group 2 Clinpro Tooth Creme (3M espe), and group 3 Sensodyne Repair and Protection (GSK) as remineralizing agents. In a study by Elkassas et al. found that a toothpaste with triple calcium phosphate ions with 5% sodium fluoride formed a protective barrier in which fluoride and calcium coexisted during application to the tooth surface, after which they were attacked with calcium and fluoride ions.¹⁰ In our study, we found the remineralizing effect of tricalcium phosphate-containing toothpaste to be statistically significant. Balakrishnan et al. have shown that the remineralizing effect of CPP-ACP is shown in in situ and long-term controlled randomized in vivo studies. This remineralizing effect is explained by the release of free calcium and phosphate ions from the ACP on the tooth surface and the supersaturation of the miner.³ Shen et al. found that Clinpro contained sodium fluoride ions but that their



bioavailability was low when calcium ions and phosphate ions were added without stabilizer. In addition, calcium and phosphate ions in normal saliva have been shown to be limiting for continuous remineralization of subsurface lesions of the navel when applied topical fluoride.³⁰ In vitro studies by Shetty et al. have shown that CPP-ACP increases effective remineralization in enamel lesions with initial decay according to the results obtained in vickers surface hardness measurements obtained before and after treatment. However, compared to fluoride-supplemented CPP-ACP and NaF, efficacy is less. Fluoride-associated CPP-ACP was the most effective group followed by NaF.³¹

Mohanty et al., the clinical use of calcium and phosphate ions for remineralization was unsuccessful, suggesting that calcium and phosphate ions are difficult to dissolve and that 10 calcium and 6 phosphate ions should be present in the environment despite both fluoride ions. Nevertheless, novaminin is a bioactive glass molecule that is highly biocompatible and has been produced for bone regeneration. When they come together with body fluids, they point out that this molecule is converted to hydroxycarbonate apatite (HCA) which is close to the hydroxyapatite crystal in the structure of enamel and dentin, and that it provides remineralization.²¹

In the vast majority of these studies, the demineralization values of the groups treated with toothpaste were significantly higher than the remineralization values. In our study, the remineralization values of toothpastes that we applied to groups during the pH cycling were large and statistically significant in terms of demineralization values in accordance with the above studies. Gomez et al. reported that the agreement between fluoride dose response and QLF and surface hardness measurements was found to be statistically significant.¹² In our study, the difference between the groups with microhardness and QLF instruments was found to be statistically insignificant if vickers diamond tip was used. Mitropoulos et al. reported that ICDAS II visual inspection criteria and MCT are more compatible values, digital radiography and conventional radiography systems are comparable to each other and less compatible than other methods compared to the histological section of the rotator cuff.²⁰ Lo et al. argued that MCT could be used instead of polarised light microscope and transverse

microradiography in in vitro studies on caries.¹⁴ Soviero et al. MCT has been reported to show very high compliance when compared with histological examination. It has also been reported that compared to other methods of caries detection used in the study, both the enamel and dentin decay depth are better in diagnostic efficiency and that can be used as gold standard in the detection of interface decay.³⁵

CONCLUSIONS

The remineralizing effect of Tooth Mousse Plus (GC), Clinpro Tooth Creme (3M ESPE) and Sensodyne Repair and Protection (GSK) toothpastes on initial caries was sufficient. The efficacy of MCT, SMH and QLF devices in evaluating initial caries in vitro conditions was sufficient. Our study shows that both tooth pastes can be used in white spot lesions and early stages of caries.

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