Dentin decalcification during lithium treatment: case report

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Introduction

Depressive and bipolar disorders (BD) treatments have long been associated with a range of oral problems, notably caries, and periodontal disease, that result in partial or total edentulousness. Additionally, antipsychotics and antidepressants may induce xerostomia through anticholinergic effects, while chronic lithium therapy has been associated with hypercalcemia and hypernatremia.

Following early reports of dental decay in lithium treated patients, Tatsch et al. retrospectively identified 96 cases of dental or periodontal problems among 209 consecutive cases of patients with BD, schizoaffective or depressive disorders. In approximately 20% of the patients, the dental problems started after the introduction of lithium. The authors suggested that patients submitted to lithium treatment for mood disorders could present significant dental problems.

The reasons for such aggressive lesions on mineralized tissues are still unknown. This paper reports the chemical and ultrastructural dentinal changes in a patient receiving lithium maintenance therapy who has been currently treated for severe tooth decay.

Case report

A 30-year-old woman, diagnosed with BD, was treated over 14 months with lithium carbonate (Carbolitium®, 300 mg, once a day) in association with sertraline (Zoloft®, 50 mg, twice a day) and alprazolam (Frontal®, 1 mg, at bedtime). Carbamazepine (Tegretol®, 200/400 mg, once a day) was subsequently prescribed. Serum dosages of phosphorous, magnesium, calcium, lithium, and parathormone were recently done, in which no alterations were observed. However, the patient was also submitted to bone densitometry of lumbar spine (L1–L4), right femoral neck, and right total femur, and osteopenia in lumbar spine was detected.

After 12 months of treatment, the patient reported the development of uncommon dental changes. She also complained of severe and unexplained pain in region of the molars and canine (teeth 26, 27, and 33). Following the removal of the canine’s restorative material, the drill reached the dentin, exposing a soft tissue that suggested internal changes coming from the pulp and clinically different from those of caries lesions. After the interruption of the lithium treatment, the patient had a pain relief. However, softened dentin...
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continued to be observed when treating any of her teeth over the following 4 years. After 5 years of lithium treatment, the extractions of teeth 26 and 27 were indicated.

In order to check for possible chemical and morphological changes in tooth structure, electron microscopy and mineral chemical composition studies were contrasted between dentin samples form the index patient (“lithium”) and from an immediately extracted third molar of a healthy 30-year-old-man (“control”). Both patients gave informed consent for such studies.

**Scanning electron microscopy analysis and energy**

Dispersive Spectroscopy (EDS) X-ray Microanalysis Dentin samples from two molars (teeth 26 and 27) were collected from the index case. The sample from the healthy volunteer was obtained from his molar (tooth 38—indicated for extraction). Samples were fixed and immersed in hexamethyldisilazane (HMDS). Specimens were mounted on aluminum stubs and sputter-coated with gold (Balzers SDC-050, Bal-Tec AG, Liechtenstein). Samples were examined in an LEO 440I scanning electron microscope and selected areas were analyzed under EDS X-ray to investigate the presence of some chemical elements. Samples from the control tooth exhibited a normal structure with numerous dentinal tubules surrounded by a homogeneous wall of peritubular dentin (Figure 1a). In contrast, samples from the index case exhibited peritubular walls with irregular contour and absence of peritubular dentin in some regions (Figure 1b).

The EDS X-ray microanalysis revealed that concentrations of calcium and phosphorous were approximately twofold in control teeth than those in the lithium-treated teeth. Interestingly, no lithium content was detected in samples from the lithium-treated patient (Figure 2).

**Transmission electron microscopy analysis**

Samples from lithium teeth (#26 and #27) obtained prior to extraction were fixed, left undecalcified and processed for embedding in Spurr resin. Eighty-nanometer-thick sections were cut at an ultramicrotome (Leica Ultracut R, Leica Inc, Buffalo, NY, USA) collected onto 200-mesh copper grids, stained with uranyl acetate and lead citrate, or left unstained, and examined under transmission electron microscopy.
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An almost 10-fold decrease in Mg$^{2+}$ and a 3-fold increase of Zn$^{2+}$ concentrations were detected in the index dentin samples in comparison with the control dentin (Figure 4a). Neither sample had any trace of lithium. The contents of P$^{3-}$ (~35%) and Ca$^{2+}$ (~44%) were also strikingly lower in the index case (Figure 4b).

Discussion
The dentin decalcification verified in this patient contributes to clarify the
peculiarly severe dental decay observed in some patients with BD undergoing lithium treatment. The clinically softened appearance of dentin was firstly confirmed when undecalcified samples were processed for ultrathin sectioning. Scanning electron microscopy (SEM) examination confirmed the inconsistent presence of peritubular dentin. In addition, this approach combined with EDS X-ray microanalysis revealed less amount of calcium than in the control teeth. Some reports have described this dental disease as similar to caries lesions. 7-9 However, microscopic evaluation of the carious dentin has demonstrated that the transparent layer is not sclerotic but is part of the demineralized softened dentin. The crystal precipitation in the tubules is an intermediate product in a slow demineralization process. 10 Also, in the transparent zone of carious lesion, both peritubular and intertubular dentin consists of nano-size apatite crystallites with smaller size in the former. The peritubular mineral phase in the transparent zone is chemically similar to the intertubular dentin. 11 According to the findings of this study, the structural aspects of the dentin of a patient submitted to lithium treatment do not match with any other hard tissue pathology previously found in clinical dentistry. As enamel did not exhibit abnormal changes, it indicates that dissolution of hydroxyapatite crystals took place at its pulpal side. Mineralized dentin is separated from the odontoblast layer by the predentin, a 10- to 40-µm-thick layer of unmineralized matrix. Predentin is similar to osteoid that separates the bone mineralized matrix from the osteoblasts/bone lining cells. 12 While continuous remodeling takes place in bone, dentin is not resorbed under normal conditions. Nevertheless, dentinal inner resorption would require the presence of clastic cells at the dentin–pulp interface and the lost of dentinal mass. The phenomenon observed in this lithium-treated patient revealed that dentin did not lose its mass, but gradually lost its mineral content. An interesting feature is the absence of lithium in dentin even in the treated group, while the demineralized dentin showed a threefold increase of Zn2+ concentration. It has been demonstrated that dentin mineralized matrix contains some matrix metalloproteinases (MMPs), mainly MMP-2, MMP-3, MMP-8, and MMP-9, which are zinc-dependent enzymes. Thus, it is conceivable that Zn2+ could appear in demineralized dentin after the dissolution of mineral crystals. Therefore, the present results suggest that dentin decalcification may contribute to the increased levels of serum calcium observed in some patients. Several calcium-related complications that may contribute to hypercalcaemia have been reported in patients receiving lithium therapy. 6 Although hypercalcaemia has been reported in these patients, no relation to osteoporosis has been established. 14 In general, the above disorders ultimately increase the reabsorptive activity by clastic cells with the consequent lost of tissue mass, which was not observed in dentin, as discussed above. It is important to mention that not all the patients diagnosed with BD and that undergo the treatment with lithium develop such type of dentinal lesion. 9 Tatsch et al. 9 evaluated 209 private patients with mood disorders (bipolar, scizoaffective, or depressive) and exposed to lithium. In 63 (30.1%) patients, dental or periodontal problems proceeded exposure to lithium. In approximately 20% of the patients (43 patients) these lesions were diagnosed and in 11 patients, these lesions were very severe. 7 This suggests that the method by which the lithium treatment leads to dentin decalcification is not only medication-dependent but may be related to some predisposing conditions.

The mechanisms responsible for the observed dentinal changes remain unknown, and deserve further investigation. Long-term controlled clinical studies should be conducted in order to establish the safety of lithium in respect to adverse effects on dental health. Meanwhile, careful monitoring and management of dental lesions in patients on long-term lithium treatment is mandatory.

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