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Calcium silicate bioactive cements: Biological perspectives and clinical applications☆

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ABSTRACT

Objective. To introduce and to examine the research progress and the investigation on hydraulic calcium silicate cements (HCSCs), well-known as MTA (mineral trioxide aggregate).

Methods. This review paper introduces the most important investigations of the last 20 years and analyze their impact on HCSCs use in clinical application.

Results. HCSCs were developed more than 20 years ago. Their composition is largely based on Portland cement components (di- and tri-calcium silicate, Al- and Fe-silicate). They have important properties such as the ability to set and to seal in moist and blood-contaminated environments, biocompatibility, adequate mechanical properties, *etc.* Their principal limitations are long setting time, low radiopacity and difficult handling.

New HCSCs-based materials containing additional components (setting modulators, radiopacifying agents, drugs, *etc.*) have since been introduced and have received a considerable attention from laboratory researchers for their biological and translational characteristics and from clinicians for their innovative properties.

HCSCs upregulate the differentiation of osteoblast, fibroblasts, cementoblasts, odontoblasts, pulp cells and many stem cells. They can induce the chemical formation of a calcium phosphate/apatite coating when immersed in biological fluids.

These properties have led to a growing series of innovative clinical applications such as root-end filling, pulp capping and scaffolds for pulp regeneration, root canal sealer, *etc.*

The capacity of HCSCs to promote calcium-phosphate deposit suggests their use for dentin remineralization and tissue regeneration. Several *in vitro* studies, animal tests and clinical studies confirmed their ability to nucleate apatite and remineralize and to induce the formation of (new) mineralized tissues.

Significance. HCSCs play a critical role in developing a new approach for pulp and bone regeneration, dentin remineralization, and bone/cementum tissue healing. Investigations of the next generation HCSCs for "Regenerative Dentistry" will guide their clinical evolution.

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1. Introduction

Interestingly, Portland cement appeared in dentistry before 1878 [1]. MTA (mineral trioxide aggregate), a Portland cement-based formulation was developed more than 20 years ago as a root-end filling material but its potential for new clinical applications later became evident thanks to its innovative hydraulic properties and sealing ability. We have now more information on its properties and many new MTA-derived materials have been developed.

This paper uses the term hydraulic calcium silicate cement (HCSC) to refer to the entire family of MTA-like cements. A long list of new materials based on the original formulation and/or with minor modifications has been introduced in routine clinical practice (Table 1). A light-curable HCSC is advisable in many clinical cases and at least one material is now on the market. Other experimental materials have been proposed, so many potential new products could soon be available and more very innovative HCSCs can be expected in the future.

Despite of the dearth of information from the first *in vitro* experiments and the lack of clinical studies, HCSC gained the trust of many operators who proposed its clinical use for apicogenesis, pulp capping and other procedure. Tay and Pashley [2] introduced the concept of "biomimetic remineralization" of partially demineralized dentin using MTA. This represented a major innovation and opened the way to potential new applications for HCSCs-based materials. At the moment the use of HCSCs-based technology for dentin remineralization is not far from the clinical application.

The history of calcium silicate Portland cements dates back to Roman times when a cement able to set in water made by grinding together lime and a volcanic product found at Puteoli (hence called *pozzolana*) around Neapolis (the places described by Pliny the Elder). Pozzolana helped Roman concrete set quickly even when submerged in water, allowing the construction of bridges, harbors, aqueducts, monuments and buildings. During the middle ages the secret of cement was lost. In the 18th century John Smeaton, an English engineer, rediscovered the correct proportions of cement using clay and limestone. In 1824, Joseph Aspdin, an English bricklayer, patented a process for making what he called Portland cement. The first great bridge built in the USA in the late 19th century was made of Portland–Pozzolanic cements. Modern Portland cement is made by mixing substances containing lime, silica, alumina, and iron oxide and then heating the mixture until it almost fuses. Pozzolana is still the main component of many Portland cements.

Calcium silicate Portland cements set through a hydration reaction after mixing with water or water-containing liquids. Various hydration products form during the reaction, namely different phases of calcium silicate hydrate (CSH) as porous colloidal CSH gel and radial acicular CSH crystals, rombohedral crystals of portlandite (calcium hydroxide), needle-like crystals of ettringite (hexacalcium aluminate trisulphate hydrate) (Fig. 1), and calcium monosulfoaluminate or calcium monocarboaluminate. Porous CSH hardens by the formation of a solid network within 1–6 h. The setting reaction requires several days to complete the hydration and hardening phases and includes dissolution and reprecipitation processes

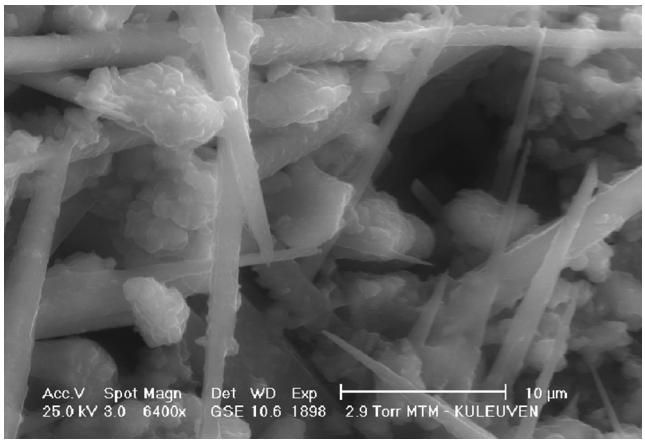

Fig. 1 – Morphology of the early phase setting reaction of a calcium silicate cement (HCSC) visualized by environmental scanning electron microscopy (ESEM) 10 min after the mixing procedures. The setting reaction has been described as dissolution–precipitation process with gradual dissolution of the unhydrated calcium silicate particles and the subsequent formation of hydration products as radial elongated needle-like calcium silicate hydrate crystals and calcium hydroxide (portlandite) within a calcium silicate hydrate (CSH) amorphous gel. At this time, the hydrated and unhydrated phases are still present and allow rapid ion exchange.

of the unhydrated di- and tri-calcium silicate phases (C_2S and C_3S) and formation of hydration products like calcium di- and tri-silicate hydrates and calcium hydroxide [4,5]. In this phase, CSH has layer structure, with a layer growing radially from the calcium silicate particles and resulting in a fibrous needle-like complex structure, and cuboidal calcium hydroxide crystals form among the hydrating cement compounds [4,5] (Fig. 2). This phase is difficult to inspect under standard SEM. As demonstrated by Gandolfi et al. [5], environmental SEM (ESEM) analysis can provide more information on the morphology of the early stage of Portland and dental calcium silicate/MTA cements (Fig. 3a and b). Original native Pozzolanic cements are very similar to HCSCs under ESEM (Fig. 4). Moisture (*i.e.* biological fluids) is essential to allow the setting reaction and to develop/activate the cement's bioactivity, such as the formation of apatite [3,6,7]. The following stages have been proposed by Gandolfi et al. [6,7] for the nucleation of calcium phosphates on the HCSC surface:

1. A solid–liquid interface forms on the mineral particles, and ion dissolution occurs almost immediately. Ca^{2+} ions rapidly migrate into the mixing solution and portlandite ($Ca(OH)_2$) forms.
2. Silicates are attacked by OH ion groups in an alkaline environment and a CSH phase forms on mineral particles. CSH is a porous, fine-grained/fibrous and disorganized hydrated silicate gel layer containing Si-OH silanol groups and negative surface charges that may act as nucleation sites for apatite formation.