# Interactions between Fluorides and Magnesium

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## Zusammenfassung

Magnesium ist in der Lage leicht lösliche Komplexe wie Magnesiumfluorid ($MgF_2$) zu bilden. Es hat einen hemmenden Effekt auf die Kristallbildung von Calciumphosphat, einer Verbindung, die eine wichtige Rolle in der Physiologie lebender Organismen spielt.

Nach Fluorid-Gabe ist die Mobilisierung von Calcium-Ionen aus den Knochen anfangs als Ergebnis einer erhöhten Calciumphosphat-Bildung vermindert.

Wird jedoch während der Fluorid-Therapie Magnesium einige Zeit nach der Fluorid-Applikation gegeben, ist die Kristallbildung von Calciumphosphat vermindert und die Kristalle erscheinen kleiner, zeigen eine irreguläre Struktur und eine erhöhte Löslichkeit.

Die Entdeckung einer spezifischen Interaktion zwischen den beiden Substanzen stellt die theoretische Basis für die Gabe von Magnesium als unterstützende Maßnahme in der Fluorid-Therapie der Osteoporose dar, wie sie bei uns schon seit vielen Jahren durchgeführt wird.

Die Löslichkeit von Calciumphosphat-Kristallen und die Calcium-Homeostase bleiben unbeeinflußt.

Die zweckmäßigen Konsequenzen können ohne weiteres durch den klinischen Fall einer Patientin gezeigt werden, die chronisch hohe Fluorid-Dosen bekommen hatte. Im Fall einer über 10 Jahre dauernden Fluorid-Therapie wurde Calciumapatit in Fluorapatit umgewandelt, wie die Kristallographie zeigt. Das Ergebnis war eine hypocalcämische Tetanie verbunden mit Krämpfen und multiplen Knochenfrakturen. In einer der tetanischen Episoden starb die Patientin.

## Summary

Magnesium has a tendency to form slightly soluble complexes such as magnesiumfluoride ($MgF_2$). It exerts an inhibitory effect on the crystallisation of calcium phosphate, a compound which plays an important role in the physiology of living organisms.

After administration of fluorides, the mobilization of calcium ions from bone is initially diminished as a result of an enhanced calcium phosphate formation. If, however, during fluoride therapy magnesium is given with a certain time lag after fluoride application, crystallisation of calcium phosphate is decreased and crystals appear to be smaller showing an irregular structure and an increased solubility.

These findings of a specific interaction between the two substances are the theoretical basis for the use of magnesium as a supporting measure in fluoride therapy of osteoporosis as practiced by us for many years now.

Thus, solubility of calcium phosphate crystals and calcium homeostasis remain unimpaired.

The practical consequences can be readily demonstrated by the clinical cause of a female patient who had received a chronic medication of high doses of fluoride. In the course of more than ten years of continuous fluoride treatment, calcium apatite was converted into fluoroapatite as evidenced by crystallography. The result was hypocalcemic tetany with concomitant convulsions and multiple bone fractures. In one of the tetanic episodes the patient died.

## Résumé

Le magnésium est capable de former des complexes facilement solubles tels que le fluorure de magnésium ($MgF_2$). Il a un effet inhibitif sur la cristallisation du phosphate de calcium, un composé qui joue un rôle important dans la physiologie des organismes vivants.

Après avoir administré des fluorures la mobilisation des ions de calcium à partir des os est d'abord diminuée suite à une formation élevée de phosphate de calcium.

Cependant, si du magnésium est administré pendant la thérapie aux fluorures quelque temps après l'application des fluorures, la cristallisation du phosphate de calcium est réduite et les cristaux apparaissent plus petits et montrent une structure irrégulière ainsi qu'une solubilité plus élevée.

La découverte d'une interaction spécifique entre les deux substances est la base théorique pour l'administration du magnésium en tant que mesure de support dans la thérapie aux fluorures de l'ostéoporose telle qu'elle est appliquée chez nous depuis plusieurs années.

La solubilité des cristaux de phosphate de calcium et l'homostéase de calcium ne sont pas influencées.

Les conséquences pratiques peuvent être démontrées sans problèmes à la lumière d'un cas clinique d'une patiente qui a reçu une application chronique de doses trop élevées de fluorure. Dans le cas d'une thérapie aux fluorures pendant plus de 10 ans l'apatite de calcium a été changée en apatite de fluor tel que le montre la cristallographie. Il en est résulté une tétanie hypocalcémique liée à des spasmes et des fractures d'os multiples. La patiente est morte durant une de ces périodes tétaniques.

Fluoride forms complexes with alkaline earth metals in aqueous medium. Measurements demonstrate that the most stable fluoride complex is formed with magnesium (Fig. 1).

This is one way to explain that chelated magnesium is able to neutralize the effects of fluoride in a certain degree (Fig. 2).

Interactions between fluorides and magnesium have gained clinical significance in the management of various forms of osteoporosis. The administration of fluorides today represents the standard therapy of this kind of disorder. Adjuvant Mg application has first been advocated by *Münzenberg*. After many years of clinical practice in treating osteoporosis with a combination of fluorides and magnesium we have frequently been reporting on our experience (*Anders, Münzenberg* and *Menge*, 1979).

Improved crystallinity and larger size of calcium phosphate crystals is not a consistent fluoride effect. Only if fluoride concentrations keep within the rather narrow range of $3 \times 10^{-5}$ to $2 \times 10^{-3}$ mol (= 0.03 to 2 mmol) precipitation of calcium phosphate is facilitated and cristallinity of mineral particles improved (*Wadkins* et al.). At lower fluoride levels of $10^{-6}$ to $2 \times 10^{-5}$ mol (0.001 to 0.02 mmol) or at concentrations exceeding $10^{-2}$ mol in vitro inhibition of calcium phosphate formation occurs (Fig. 3).

Magnesium ions in contrast are strong in vitro inhibitors of calcium phosphate precipitation on the collagen matrix. Both, nucleation and growth of mineral particles are greatly reduced. At Mg concentrations of about $4 \times 10^{-6}$ mol (0.004 mmol) only minute quantities of small crystals are traceable which by means of x-ray-diffraction will be identified as apatite of poor crystallinity. If Mg concentrations are even higher, no anorganic crystals will be detected at all with the x-ray-diffraction displaying nothing but the pattern of the organic collagen matrix.

As *Wadkins* et al. fount out, Mg and fluorides affect mineralization at different phases of apatite formation. Mg is suspected to exert its inhibitory action predominantly in the initial phase by enhancing formation of calciumphosphates of lower acidity such as brushite and octacalciumphosphate and at the same time inhibiting the conversion of these apatite precursors into apatite. Fluoride in contrast is active in the final phase where it is in tegrated into the crystal lattice of apatite instead of hydroxyl. The resulting fluoro-apatite is less soluble than normal hydroxyapatite.

The inhibitory effect on apatite maturation in the presence of an excess of fluorides is a dual one: the amount of apatite particles available to be resolved in the course of recrystallization is reduced and at same time the chemical reactivity lowered which is mainly a function of ion-channels within the apatite particle where the fluoride-ions are localized.

Further evidence for this hypothesis is provided by the calcergic reaction which was seen in our studies of the mechanism by which Mg and fluorides affect mineralization. After heattreating of the calcergic precipitations at 900° C it became evident that in the presence of fluoride there is merely a formation of apatite whereas in the Mg group a considerable amount of whitlockite is seen. The conclusion was that under the influence of magnesium the stayingtime of brushite and octocalciumphosphate in tissue is prolonged.

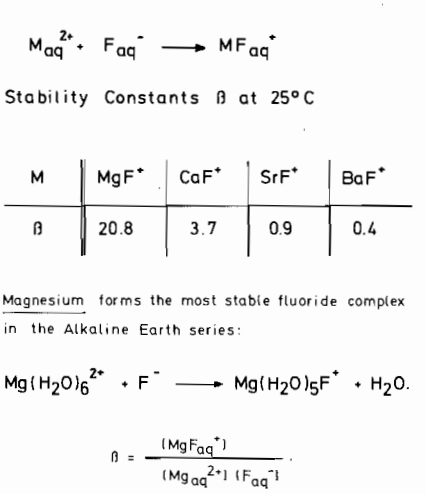


Fig. 1: Fluoride Complexes of Alkaline Earth Metals in Aqueous Medium

Mg seems to exert only indirect influence on crystallization of calciumphosphates. An important feature of Mg effect is the smaller size of the individual calciumphosphate crystals which allows for the minerals to be rapidly resorbed in calcium homeostasis even when fluorides are present.

Osteoblast activity as well as — to a minor extent — osteoclast activity are enhanced by Na-fluoride. The trabecular osteoid seams are thicker and their histologic structure resembles that of osteomalacia with its low degree of mineralization.

One side effect of fluorides appears to be the hyperplasia of the parathyroid glands accompanied by a rise in circulating PTH as has been demonstrated by *Faccini* and *Care* (1965) in sheep and by *Cohen* and *Rubini* (1965) in humans.

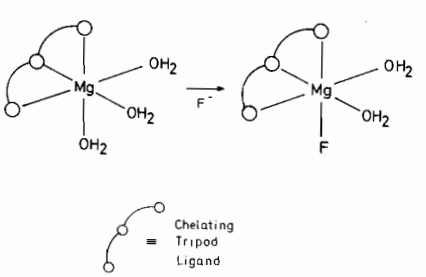


Fig. 2: **Model System:** Fluoride Incorporation into a Chelated Magnesium Complex

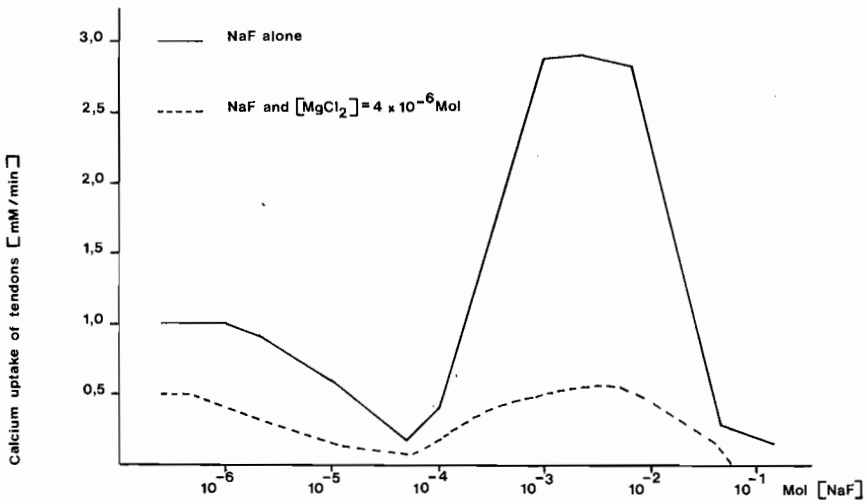


Fig. 3: Crystallinity of calcium phosphate dependent upon concentration of fluoride (Abszisse)

*Jowsey* concluded from these findings that the stimulating effect of fluorides on parathyroid glands is mediated by a temporary drop of calcium levels. The influence of fluoride on parathyroid function is discussed controversially. The disparate results reported in the literature on the influence of Mg on parathyroid function are also still a matter of discussion as is the case with Mg effect on parathyroids (Fig. 4).

In a number of publications of different investigators an inhibitory effect of Mg on parathyroid function has been described. On the other hand a drop in parathormone-secretion can be seen in Mg deficiency states. *Estep* (1966), *McManus* and co-workers (1971) postulate that normal Mg levels are necessary for secreted parathormone to be effective.

*Freemans* findings (1978) suggest that the effect of Mg on parathyroid activity in persons with normal renal function can be differ depending on the activity status of the gland: an increased secretory activity will be reduced as opposed to a state of minor PTH activity where secretion can be expected to be stimulated.

In our study reported here rabbits were divided into 4 groups. The first group (8 animals) was the control. Group 2 (6 animals) was given Mg parenterally whereas the fourth group of 8 rabbits received parenteral Mg in combination with oral fluoride.

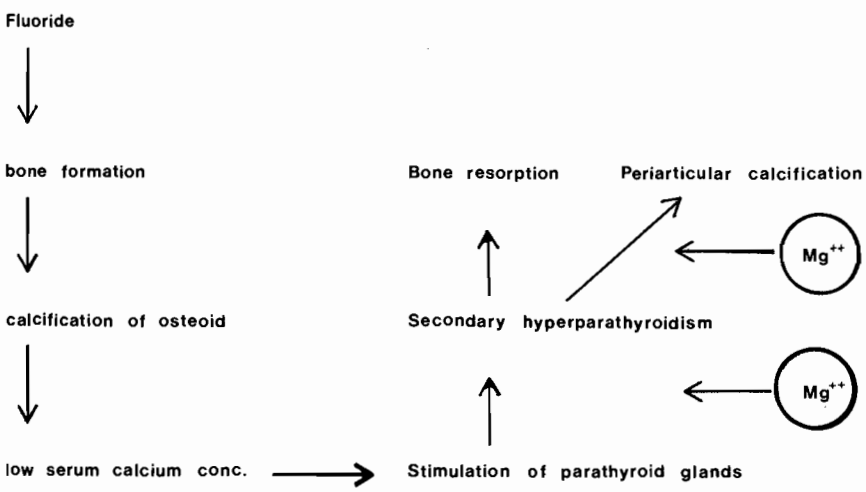


Fig. 4: Sequence of events by administration of fluoride

After high doses of parenteral Mg we saw the expected rise of serum-Mg-levels. In the presence of fluoride serum-Mg remained unchanged with no evidence of interactions between Mg and fluorides. After Mg injections serum calcium dropped significantly. The same phenomenon was encountered after application of fluorides.

The additional application of fluoride or Mg respectively was not capable of lowering serum calcium any further.

The histological studies of Na-fluoride treated animals revealed newly formed osteoid seams resembling in structure those found in osteomalacia. The picture paralells in part the histology of clinical rickets.

Assuming fluoride did in fact exert an activating influence on parathyroid function it seems plausible that a concomitant administration of Mg outweighs this untoward fluoride effect.

The fluoride induced stimulation of PTH leads to subperiosteal erosions of bone thus aggrevating osteoporotic changes in bone architecture and counteracting rather than supporting the therapeutic efforts to increase bone mass.

Over and above the stimulation of parathyroid function previously mentioned fluoride has another adverse effect of clinical significance.

Patients under Na-fluoride therapy often complain about severe pain in joints which we think is caused by depositions of calcium phosphates in periarticular tissue. In three instances we were able to demonstrate these metastatic calcifications by radiology. In the course of more than ten years of continuous fluoride treatment, calcium apatite was converted into fluoroapatite as evidenced by crystallography. The result was hypocalcemic tetany with concomitant convulsions

and multiple bone fractures. In one of the tetanic episodes the patient died.

If Mg is administered as an adjuvant measure in fluoride therapy of osteoporosis, joint pain is significantly diminished and periarticular calcium phosphate deposits are resorbed. A group of 57 patients receiving sodium fluoride was compared with 108 cases treated additionally with magnesium (Magnesium Verla®, Verla-Pharm, 8132 Tutzing) administered in doses of 15 to 20 mM. at intervals of not less than four hours. In the first six months of treatment, seven patients receiving sodium fluoride alone and two subjects treated additionally with magnesium complained of periarticular disorders, which may be regarded as symptoms of secondary hyperparathyroidism. Thus, the adverse effects of fluoride therapy may be reduced when magnesium is used as an adjunct and given in adequate amounts. Our results are statistically significant at a 1 % level and they are confirmed by the findings of *C. E. Schmidt* from Australia (1985).

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