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Reduction of Falls in Elderly. The central role of Alfacalcidol in a multi-dimensional paradigm

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Abstract

Fractures in the elderly represent a major threat in terms of life expectancy and quality of life. Modern therapeutics in the fight against fractures in the elderly require pluripotent efficacy in both preserving bone mineral density and limiting falls. Indeed, epidemiological evidence has recently highlighted that agents with a targeted action on bone only may fail to prevent up to 50% of the fractures observed in patients over 60 years. Furthermore, there are growing fundamental and clinical evidences that native vitamin D is unable to reduce falls and fractures in vitamin-D replete patients and patient with deficient renal function.

D-hormone analogs (Alfacalcidol and Calcitriol) have been scrutinized for two decades for their abilities to prevent BMD loss, fractures, and, more recently, falls. Alfacalcidol (1alpha (OH) D3), notably by bypassing the renal endogenous feedback loop regulation, is a synthetic vitamin D derivative with more favourable pharmacokinetic and tolerability profiles as compared to calcitriol (1,25 (OH)2 D3). Encouraging results from pilot studies have driven research, and led to modern data able to support a pseudo Copernician change by switching from supplementation with vitamin D to actively treat bone, muscle, and neurocoordination with Alfacalcidol.

This systematic narrative review browses the current pilot, clinical and meta-analytical data to demonstrate, in an evidence-based fashion, that the D-Hormone analog Alfacalcidol is an excellent candidate in preventing falls and fractures to a greater extent as compared to native vitamin D. The continuum of evidence synthesized in this paper highlights the necessary change in medical paradigm to efficiently prevent fractures in the elderly, and opens new research pathways, notably in combination therapies with Alfacalcidol.

Age-related fractures; a multifactorial paradigm

Clinical experience and epidemiological data demonstrate that mobility and balance are key determinants of improved quality of life in worldwide aging populations. Falls currently tends to be a primary outcome in clinical trials given their consequences, in terms of fractures, quality of life and psychological consequences, including deconditioning and kinesophobia. A significant number of osteoporotic fractures are associated with falls, independently of bone mineral density (BMD) [1].

Fractures are of the most conservative outcome in the fight against osteoporosis. Recently it was shown that 54% of women aged 65 years or older with incident hip fractures were not osteoporotic [2]. Established osteoporosis in older patients of both sexes is characterized by decoupled bone remodelling induced by a deficit in sex hormones, as well as by a somatopause (insulin-like growth factor [IGF]-deficit), but also by a lack of circulating vitamin D, a reduced synthesis of D-Hormone in the kidneys and bones and by a lack of receptors and/or receptor affinity for D-Hormone (VDR's) in the target organs leading to increased parathormone (PTH) levels and a higher bone turnover [3].

In parallel to decreased bone strength, a loss of muscle power and performance (sarcopenia), neuromuscular deficiencies, deterioration in gait and postural stability appears in the age of 65-70 years in both genders and are very common. These deficiencies, together with slower response times lead to an increase of intrinsic, non-syncopal, locomotoric falls with no or only minimal contributions of external obstacles during normal daily activities. Together with a higher incidence of bone loss, differences in the types of falls, more often sideways instead of forward, and therefore, the direct impact of force on the hip together with the loss of soft tissue covering also explain the increased in hip fractures in elderly people over the age of 75.

There is a current consensus that the combination of reduced bone strength and increased fall risk account for most of the variability for the different types of age-, fall- and osteoporosis-related peripheral, and, to a lesser extent, vertebral fractures [4,5].

Physiology of falls: muscle, kidney,

nerves and bone interaction

Age-related sarcopenia is, besides of reduced physical activity, the consequence of a reduction of fast-twitch type II muscle fibres, decreased IGF-1 and increased cytokine levels, e.g., interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α). Increasing IL-6 and decreasing IGF-1 are synergistic factors for functional disability [6]. High PTH-levels and low circulating D-Hormone levels also play major roles as proximal muscle weakness is associated with hyperparathyroidism, vitamin D metabolism disorders, diabetes, chronic inflammatory diseases and reduced kidney function [7,8]. Vitamin D-Hormone receptors (VDR's) have been found in skeletal muscles and nerves and are implicated in correct muscle contraction and relaxation and in muscle protein synthesis [9,10]. Murine models of VDR depleted mice have confirmed that VDR's absence causes a reduction of skeletal muscle fiber size based on an increased expression of myogenic regulation factors (Myf5, Myogenin, E2A) through which the strict regulated differentiation and maturation of muscle cells will be disturbed [11]. The muscular abnormalities are independent from secondary, metabolic changes, e.g. hypocalcaemia or hyperparathyroidism, confirming the direct involvment of VDR's. The fact that a treatment with D-Hormone of VDR-positive myoblasts in vitro downregulates the mentioned myoregulating transcription factors, points out in addition the important role of D-Hormone and VDR's in muscle development [11].

Older age is significantly associated with decreased VDR expression in human skeletal muscle tissue [12]. A positive correlation was found between femoral muscle strength and function and D-Hormone serum levels in the elderly [13,14]. This interaction was strongly supported by the fact that higher D-hormone serum levels were correlated, on a clinical perspective, with lower fall rates in elderly women [15]. These data suggest that the age-related and the corticosteroid/inflammation-induced decline in muscle strength and function and the increase of falls could be in part explained by a decrease of VDR's and a decrease of D-Hormone in serum and/or at receptor level.

Impaired renal function is detrimental to the activation of D-Hormone. Dukas et al. found in multivariate-controlled analyses that in community-dwelling elderly women and men over age of 70, a creatinine clearance (CrCl) of < 65 ml/min, calculated from serum creatinine by the Cockcroft-Gault formula, was significantly associated with low D-Hormone serum levels and with a significant four times increased risk of falls compared to participants with normal CrCl [16].

It has been postulated that this increased risk of falls is due to the associated significant lower D-Hormone and/or increased PTH serum levels. To test this hypothesis it was investigated in a double-blind randomized study

whether treatment with Alfacalcidol can reduce the high risk of fallers and the high risk of falls associated with low CrCl. As a result 36 weeks of treatment with Alfacalcidol (1 µg daily) significantly and safely reduced in community-dwelling elderly men and women with a CrCl of < 65 ml/min the low CrCl associated high risk of falls by -71% compared to placebo [17]. The treatment with Alfacalcidol was, compared to placebo, associated with a significant reduction in the number of fallers (OR 0.26, 95% Cl, 0.08-0.80, P=0.019) and a significant reduction of the number of falls (0.29, 95% Cl, 0.09-0.88, P=0.028). The treatment effect of Alfacalcidol became significant after 24 weeks in participants with a CrCl < 65ml/min. Alfacalcidol reduced the frequency of fallers and falls to the frequency of fallers and falls observed in participants with a CrCl ≥ 65ml/min and normal D-Hormone serum levels, which supports the basic hypothesis of the role of low D-Hormone levels and high risk of falls [17] It was confirmed in a cross-sectional study that also in osteoporotic patients (5313 women and men) a CrCl of less than 65 ml/min is a significant and independent risk factor for falls [18]. Furthermore it could be shown for the first time that a low CrCl is also associated with a significantly increased risk of vertebral, hip and radial fractures [18].

Recently Dukas et al found a significant correlation between decreasing CrCl and lower performance in validated balance and muscle power tests, like chairrising-test, timed – up and go test and tandem stand [19]. Furthermore they found that a low CrCl < 65 ml/min is, independent from the performance in muscle and balance tests, a significant risk factor for falls. In addition the same group found for the first time an stepwise increased risk for fall-associated fractures with a decreasing CrCl associated with first a decrease of D-hormone serum levels (CrCl < 70 ml (min) and second with an increase of PTH serum levels (CrCl < 40 ml/min) [20].

Ensrud *et al*. tested the hypothesis that community-dwelling older women (>65 years) with low CrCl, calculated by the Cockcroft–Gault formula, are at increased risk of hip and vertebral fractures [21]. There was an independent, graded association between reduced renal function and the risk of hip fractures. Women with a less than 60 ml/min CrCl compared to women with normal renal function (>60 ml/min CrCl = 1.0 as reference) had an increased risk, adjusted for age, weight and calcaneal BMD, between 1.6 (45–59 ml/min CrCl: Hip fractures (Fx) OR, 1.6; 95% CI, 0.9–2.8) and 2.3 (<45 ml/min CrCl: Hip Fx OR, 2.3;95%CI, 1.2–4.7). The correlation between renal function and vertebral fractures was not significant. The increased risk of hip fractures induced by low CrCl can obviously not be sufficiently explained by renal-induced bone quality impairment but primarily by increased risk of falls.

The pathogenetic relevance of decreased CrCl for falls and non-vertebral fractures and the advantageous therapy with D-hormone analogs have been

confirmed recently by two independent research groups [21,22,23]. In a double-blind placebo-controlled 3 year-study [24] the effect of age-related decline in renal function on fall incidence by comparing groups with a CrCl less or more than 65 ml/min in placebo and calcitriol treated women was tested [22]. In elderly women aged 65–77 years with osteopenia, the cumulative number of falls per subject on placebo was 1.60 for less than 65 ml/min CrCl and 1.16 for more than 65 ml/min CrCl ($P = 0.05$). CrCl was calculated by the Cockcroft–Gault formula and by measurement from a 24 h urine without any difference concerning the outcome (pers. comm., J.C. Gallagher 2005). Comparing the groups with less than 65 ml/min CrCl, the OR of a fall was 1.8 times greater (95% CI, 1.2–2.8) on placebo than on calcitriol. The group with less than 65 ml/min CrCl had significantly lower ($P < 0.001$) serum 1.25(OH)2 D3 levels than women with more than 65 ml/min CrCl. On placebo women with a less than 60 ml/min CrCl, using the National Kidney Foundation definition of stage III chronic renal failure, had a 63% increase in falls per person ($P = 0.05$) compared to women with a more than 60 ml/min CrCl [23]. On calcitriol, the mean cumulative number of falls was 53% lower ($P < 0.003$) compared to the placebo group. The group with less than 60 ml/min CrCl had significantly lower 1.25(OH)2D3 serum levels, lower calcium absorption and lower physical performance measurements. There were no significant differences in serum PTH or serum 25(OH)D levels [23].

Rationale for preventing falls using D-hormone analog Alfacalcidol

Modern therapeutic approaches in fracture prevention should be focused on both enhancing bone strength and reducing fall risk [25]. Increasing muscle strength and neurocoordination means therefore improving bone strength and reducing falls simultaneously [26]. Besides adequate exercising there is a strong need for drugs with positive effects on muscle function and postural capacity.

Alfacalcidol (1α (OH) D_3) is a synthetically produced, inactive pro-Hormone, and is completely metabolized in the liver and in the target organ bone into Calcitriol 1.25$(OH)_2D_3$). Alfacalcidol induces active absorption of calcium and phosphate, improves mineralization of the skeleton and facilitates normal neuromuscular functioning. D-Hormone analogs indirectly reduce PTH, which is commonly high in elderly patients, through increased calcium absorption. D-Hormone directly acts on PTH levels by inhibiting the proliferation of the parathyroid gland through the induction of apoptosis, as well as by reducing PTH synthesis and release [3]. These reduced negative effects of continuously increased PTH on bone and muscles are notable. D-Hormone also reduces the release of pro-inflammatory cytokines, which are partly increased in the elderly and are factors for osteoclast activation and

increased bone resorption, but also for muscle wasting [3,27]. It is unclear to what extent the impairment of the immune system due to increased pro-inflammatory cytokine levels and decreased suppressor cells is responsible for age-related bone loss and muscle weakness, however, the positive effect of Alfacalcidol on regulating the cytokine homeostasis and increasing T-suppressor cells has been showed [28,29,30]. An increase of serum levels of IGF-1, a strong muscle-activating factor, has been shown after 14 days of treatment with high dosages of D-Hormone [31]. These elements of knowledge support the hypothesis that several pathogenetic factors of age-related sarcopenia can be counterbalanced by Alfacalcidol therapy.

Pilot studies

There is a growing consensus that D-Hormone analogs are suitable for a pharmacological intervention with positive effects on muscle function and postural capacity and falls [32], based on a continuum of evidence ranging from in vitro studies to meta-analysis of clinical data. Histochemical classification based on muscle biopsies from Vastus lateralis of the fibre composition revealed that a treatment of osteoporotic patients with 1 µg Alfacalcidol daily for 3 to 6 months induced a significant increase in the relative number of fast-twitch type II A fibres, which are responsible for fast reactions in the body. The cross-sectional area of the fast twitch type II A fibres also increased [33]. The serum concentrations of Calcidiol (25(OH) D) were constant during the study and therefore increased D-Hormone levels are solely responsible for the positive muscle fibre alterations. Alfacalcidol improved muscle power and functional ability (walking distance over 2 minutes) significantly after 6 months of treatment in elderly D-Hormone deficient women [34]. Patients with rheumatoid arthritis, osteopenia and normal vitamin D levels (49-59 nmol/l), who received a daily dose of 1 µg of Alfacalcidol showed a significant increase in muscle power (60%), as compared to only an 18% increase in those patients who received a daily dose of 1000 IU of plain vitamin D [28].

Clinical studies

In a prospective study 489 osteopenic women, aged 65-77 years with normal Calcidiol serum levels (25(OH)D = 31 ng/ml), were randomized in a double blind trial using treatment with a placebo, Calcitriol 0.25 µg twice daily, conjugated equine oestrogens (CEE) 0.625 mg (ERT or HRT) daily and a combination of CEE and Calcitriol [35]. The cumulative number of fallers in each group was 64% taking the placebo vs 50% on D-Hormone ($P<0.04$), 58% on ooestrogen, 57% on combination of oestrogen and D-Hormone [24]. The three-year incidence rate for falls was 0.43 on placebo vs 0.27 on Calcitriol ($P=0.0015$), 0.39 on ERT/HRT and 0.35 on the combination. This

was a statistically significant reduction of 38%. The difference between the D-Hormone and the placebo treated group was already apparent at the end of the first year [24]. The incidence of fractures due to falls was 7% on placebo, 4.6% on D-Hormone, 11.7% on oestrogen and 4.8% on the combination. If the data were combined for the two groups on Calcitriol there was a near significant difference (P=0.05) between the D-Hormone groups compared to the two groups not on D-Hormone [24].

In a large randomized, Placebo-controlled clinical study in elderly osteopenic women aged 72 at baseline it was demonstrated that the physical performance tests declined with age, but the decline was less in the D-Hormone-treated group compared to placebo for the chair-rising test and the timed walk test (over 5 m at normal and fast speed) [24].

In a cross-sectional study it has been claimed, that the effect of a long-term therapy with Alfacalcidol can improve body sway in elderly women and may reduce falls by improving postural stability and lateral balance [36]. A treatment with Alfacalcidol (1 mcg daily) of patients with increased fall risk and decreased creatinine clearance of ≤ 65 ml/min leads after 3 months (+ 53%) and after 6 months (+79%) to an impressive increase of muscle power and balance [37]. In addition Dukas et al. found in this open, prospective study that a 6 months therapy with Alfacalcidol decreased the mean time used for the TUG by 2.01 sec., by 2.29 sec. the mean time used for the Chair Rising Test (CRT) and increased by 2.02 sec. the mean time used for the Tandem Standing Test (TST). The Alfacalcidol treatment reduced significantly the number of fallers by 48.1% ($p < 0.001$) and the number of falls by 51.3% ($p< 0.001$) [38], compared to the 6 months prior to the therapy.

On the other hand, in a recently published, randomized, double-blind, Placebo-controlled study in elderly aged over 80 years it has been shown that a single oral dose of 300'000 IU plain vitamin D over 6 months failed to reduce the fall rate [39]. A confirmative, randomised, placebo-controlled clinical study including 9440 community-dwelling elderly women and men aged >75 years has been recently proven, that an annual intramuscular application of 300'000 IU of plain vitamin D over 3 years is not able to reduce falls and the risk of hip and other non-vertebral fractures [40]. Another new randomized controlled trial of orally given vitamin D (800 IU daily) in combination with calcium (1 g daily) to 3322 women aged over 70 years with at least one risk factor for hip fracture showed after 25 months of treatment no significant difference between the supplementation group and the unsupplemented group concerning falls and hip fractures [41]. The findings of the newest randomized placebo-controlled trial of daily oral vitamin D (800 IU) and/or calcium (1 g) in 5292 women (85%) and men aged 70+ with established osteoporosis followed-up for 24 and 62 months also do not support oral supplementation with calcium, plain vitamin D or their combination for the prevention of falls and further osteoporotic fractures as a

monotherapy [42].

378 Swiss community-dwelling women (n=191) and men (n=187), averaging 75 years of age, were randomized to receive in a double-blind trial either 1µg Alfacalcidol or placebo daily for 9 months. Falls and dietary calcium intake were assessed using questionnaires. Baseline Calcidiol and Calcitriol serum levels were within the normal ranges. When compared to the group taking the placebo, those being treated with Alfacalcidol had a significant reduction both in the number of fallers by - 55% (odds ratio (OR), 0.45; 95% CI, 0.21 – 0.97; P = 0.04) and in the number of falls by – 54%(OR 0.46, 95% CI 0.22-0.99, P=0.045) provided with a total calcium intake of more than 500 mg calcium daily [43].

Meta-Analyses

A systematic review and meta-analysis of 40 randomized clinical trials has been performed [44]. A multifactorial fall risk assessment and management programme to prevent falls in older adults was the most effective component on risk of falling (adjusted relative risk RR = 0.82; 95% Cl, 0.72 - 0.94). Exercise interventions also had a beneficial effect (adjusted RR = 0.86; 95% Cl, 0.75 - 0.99). The effect size is small and immediately after stopping the exercise programs the risk of falls returns [44].

A comparison of the clinical efficacies of Alfacalcidol and Calcitriol based on a meta-analysis of randomized, controlled clinical studies didn't show any significant difference [45].

A recently published important meta-analysis of the efficacy of "Vitamin D" on falls in elderly supports at first view the effect of "Vitamin D" in comparison to calcium and placebo [46]. Based on 5 prospective, randomized controlled clinical studies a 22% reduction of the fall rate could be shown (OR 0.78; 95% Cl, 0.64-0.92). This meta-analysis included a subgroup analysis to differentiate between the effect-sizes of plain vitamin D and D-Hormone analogs [46]. For 3 studies involving 613 participants treated with cholecalciferol, the corrected OR of falling was 0.83 (95% Cl, 0.65-1.06). In contrast the reduction of fallers was statistically significant based on two studies involving 626 patients treated with D-Hormone analogs (OR 0.71, 95% Cl, 0.55-0.92). It is worth to be mentioned that most participants in the plain vitamin D group have been vitamin D-deficient in opposite to the participants treated with D-Hormones, which had normal serum vitamin D levels.

Richy et al therefore performed a comparative meta-analysis to clarify the open question of differentiation of the efficacy of plain vitamin D in comparison to D-Hormone analogs on falls. Based on randomised, double-

blind controlled clinical studies, the reduction of the absolute risk of falls was 3.5 times higher with D-Hormone analogs (Alfacalcidol, Calcitriol) than with plain vitamin D and the number needed to treat to avoid a fall was 12 and 52 [47] In detail D-Hormone analogs provided a statistically significant lower level of risk of falling compared to plain vitamin D: RR= 0.79 (95% CI 0.64-0.96) vs. RR= 0.94 (95% CI 0.87 – 1.01) (inter group difference P= 0.049) [47]. Upon current evidence, D-Hormone analogs seem to prevent falls to a greater extent than their native compound.

Vitamin D or Alfacalcidol in preventing falls and fractures?

The individual and respective efficacies of native vitamin D compared to D-Hormone analogs in osteoporosis remained debated till the publication of recent meta-analyses [47,48]. The effects of vitamin D and calcium have been undoubtedly shown in patients with vitamin D deficiency, while the evidence supporting the efficacy of that treatment in vitamin-D replete subjects remains limited. Currently, supplementation with plain vitamin D is not considered as a pharmacological therapy, but as a dietary substitute. Due to the feedback-regulation of the final activation-step of 25-hydroxyvitamin D (25(OH)D) in the kidneys into the active hormone 1.25-dihydroxyvitamin D oral supplements of plain vitamin D have a limited ability to increase the D-Hormone level [49,50,51]. That means that in vitamin D-replete patients, therapeutic effects on bone, muscle or other target organs have better chances to be achieved using D-Hormone analogs. D-Hormone deficient patients (inhibition of 1-alpha-hydroxylase in the kidney), e.g. elderly patients, patients with decreased kidney function, nephropathies, hypertension or patients with chronic inflammatory diseases (rheumatoid arthritis, chronic obstructive lung diseases), type 1 diabetes, arteriosclerosis and heart failure, are likely to be resistant to plain vitamin D treatment. The same pattern can also be found in patients with a lack of receptors or less receptor affinity for D-Hormone (VDR deficits) in the target organs, e.g., GI-tract, bones, muscles, in old age or by high glucocorticoid therapy [49,50,51]. As Alfacalcidol is activated in the liver and in other target organs like bones and is a so-called prodrug of the D-hormone, it allows for bypassing the metabolic limitations of native vitamin D pathways [49,50,51]. Regarding safety, and following a baseline and longitudinal monitoring of calcemia, the safety of Alfacalcidol is considered very good. Indeed, no harmful D-Hormone levels can be found in the serum, because of the direct binding of the D-Hormone to the receptors of the target organs. This is one of the reasons for the low observed rates of hypercalcemia in clinical trials with Alfacalcidol, as well as in head-to-head studies compared with plain vitamin D [52]. A post marketing surveillance study of Alfacalcidol on 13550 osteoporotic patients showed 1.1% side effects, including only 0.22% patients with hypercalcemia

without kidney stone [53]. Hypercalcemia could be completely avoided by checking the serum calcium levels at the beginning and then all 3-6 months after commencement of therapy.

The superiority of Alfacalcidol versus plain Vitamin D on reduction of falls can be also explained by the known fact of expression of its own receptor by D-Hormone in muscles and brain. By this way it can be hypothesized an improvement of muscle power and functions in the brain, e.g. promotion of balance performance, reduction of depression and increase of cognitive capabilities, which all would result in a reduction of falls and fractures.

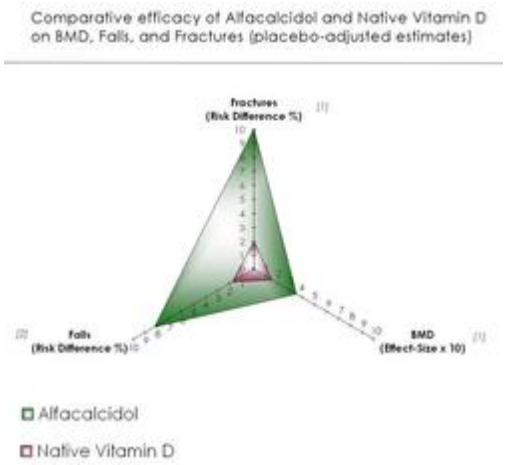

Figure 1 [47,48]

$$\frac{[\Delta BMD_{Treatment} - \Delta BMD_{Placebo}]}{SD(\Delta BMD_{Treatment}, \Delta BMD_{Placebo})}$$

Effect-Size=

$$\frac{[Events_{Treatment}]}{N_{Treatment}} - \frac{[Events_{Placebo}]}{N_{Placebo}}$$

Risk Difference=

In general Alfacalcidol was able to increase bone mineral density (BMD) in primary and secondary osteoporoses and to reduce vertebral and non-vertebral fractures to a greater extent as compared to plain vitamin D [24,45,48,51,54,55,56,57,58]. The rate of hip fractures was reduced significantly and very quickly after only 6 months treatment with 1µg Alfacalcidol daily in stroke patients and after 18 months in elderly patients with Parkinson's disease, e.g. in patients with high risk of falls [59,60].

SERMs and bisphosphonates are not able to reduce the rate of falls. These

antiosteoporotics acting as bone-specific, combination therapies with Alfacalcidol offer a new and unique way to provide an cost-efficient and safe way to fight against fractures in the elderly [24,61,62,63,64].

Conclusion

D-Hormone analogs, particularly Alfacalcidol, have pluripotent effects in different target organs, including bone, muscle and nerves. Alfacalcidol reduces vertebral and peripheral fractures in different types of osteoporosis. Its mode of action on muscle power and the reduction of falls is unique and differentiates this form of therapy from all other antiosteoporotic drugs, which have no influence on falls. On the other hand, plain vitamin D seems to be active only in vitamin D deficient patients and/or with normal kidney function and is accepted worldwide as a preventive measure in elderly, but cannot be recommended as a monotherapy for reduction of falls and osteoporotic fractures.

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