

GUIDE FOR PATIENTS ON HIGH DOSES OF

"VITAMIN" D

(a thorough read on these recommendations is fundamental)

1 Cholecalciferol was mistakenly named as "vitamin (D) in the beginning of XX when its presence was noticed in cod's liver as substance with an unknown chemical structure, able to promote recovery and cure of children's rickets, promoting absorption of calcium present in food (necessary for skeleton development) providing, through this effect, the absorption of needed amount of calcium for full skeleton development, without delay and deformities caused by rickets. Currently Cholecalciferol is not only recognized as a steroidal substance (hormonal), but also as a necessary substance for adjustment of 229 functions (genes) in all our cells. It is primarily produced by exposure of the skin to the sun, and it is found only in minimal quantities in foods, which are insufficient for the execution of its numerous biological functions:

2 Lack of sun exposure due to a modern urban life (associated to indiscriminate use of sun screens) led to an increase in occurrence of a growing number of diseases that affect all the organs and systems of the human body', where the most notorious ones are: infectious and autoimmune illnesses, cancer, cardiovascular illnesses, hypertension, diabetes, depression, autism, infertility, spontaneous miscarriages, and pre-eclampsia.

3 "Vitamin" D deficiency leads to loss of control of 229 functions (genes) as well as in cells of the immune system, reducing the system's potency to fight infections and allowing immune aggression against the organism. Individuals prone to develop autoimmune illnesses are partially resistant to Vitamin D. Once they get ill, higher doses of Cholecalciferol are needed in order to make the illness inactive, not only to compensate this partial resistance, but also to "erase" the false information that part of the body must be seen as a micro-organism intruder by the immunological system memory.

4 Contrary to what occurs with high doses of steroids and with the use of immunosuppressive agents used as part of traditional treatment, the administration of Cholecalciferol ("vitamin" D) increases the power of Immunological system in combating infections.

5 The use of higher doses of Cholecalciferol ("vitamin" D) is only viable through prevention of its feared side-effect: the absorption of excessive amounts of calcium present in food. It's like these higher doses of vitamin D "open completely the

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door" to allow the passage of calcium from the interior of the bowel to the blood stream, obliging the organism to get rid of excess calcium through urine elimination. Calcium excess, concentrated during urine formation, could be deposited in the kidneys, and could cause loss of renal function and make the individual dependent on haemodialysis to survive.

6 To avoid renal lesion is fundamental that the patient does not ingest calcium rich food (and "vegetable milks rich in calcium such as: soy, rice or oat) as these foods cannot be present in the bowel when "the door" to the passage of calcium to blood is completely "open" by "vitamin" D in higher doses. If there is not calcium excess in the other side of the door (i.e. intestine's interior), only the normal amount of calcium (present in other foods) will pass to the blood flow (when the door is open by higher doses of "vitamin" D); and the elimination of excess calcium through kidney is not necessary, which avoids risks to renal function and allows patients to have a normal life, with no lesions or sequels (if these sequels are not too old).

7 The patient should take special care with suppliers of vitamin D. Use reliable compound chemists (specifically reliable in the manipulation of "vitamin" D) or industrialized product (Over the counter). Doses above those prescribed ones (by manipulation mistake) can cause very serious problems. On the other hand, if the compound chemist use expired Cholecalciferol from stock, no beneficial effect will be obtained, and lots of months of treatment will be wasted. Also during these months an aggression of the immunological system against the organism will continue, with consequent risk of cumulative sequels.

8 DIET: The recommended diet involves COMPLETE RESTRICTION of dairy intake (foods that are integrally formed by milk, cheese, cheese spread, yoghurt, curdled milk, cream of milk, caramel, milk pudding, condensed milk) and of soy milk enriched with calcium (for reduction of the amount of calcium ingested due to the use of high doses of vitamin D in your treatment). Foods that include milk in their preparation (mashed potato, breads, cakes, biscuits, etc.), as well as butter and margarine, are liberated. It is only advisable, but not mandatory, the restriction of poultry, meat and pork meat (for reduction of the quantity of heterocyclic amines in the diet - information on these substances are easily found by typing the expression "heterocyclic amines". It is recommended egg-vegetarian diet with fish, using (as sources of protein) soy protein, tofu, egg white and fish (especially bred in captivity to avoid the presence of high levels of mercury in the diet) which should be preferably (but not invariably) prepared as stews or in steam as sources of protein. What must be avoided: excessive consumption (routine) of bananas, star fruit and anonaceas: sweet sop, sour sop and atemoya. Recommended intake of raw green leaves daily.

9 HYDRATION: Ingest high amounts of liquids (at least 2 and a half litres of liquids daily, including water, juices, soft drinks, teas, etc.). This higher quantity of liquids assures a urine volume around 2.000 ml which allows calcium dilution eliminated in the urine, and avoids excessive concentration of urinary calcium (as when calcium is diluted it does not get deposited in the kidney, preserving renal function).

10 INITIAL DOSE. The initial dose of "vitamin" D to be administered in the first appointment is calculated taking into consideration various factors, especially patient's weight and height, age, colour of skin and seriousness of autoimmune manifestations. The most fundamental functions to quality of life (i.e., vision, in case of MS) influences the prescription of initial doses, and the doctor can opt for an initial therapy including much higher doses.

11 Smoking worsens auto-immune diseases, and may reduce or even undo the protective effect of high doses of "vitamin" D. The patient should quit smoking not to harm or even compromise completely (undo) the effectiveness of your treatment.

12 For the same reason consumption of distillates should be avoided. Limit consumption of alcohol to a glass of wine (or 2 cans of beer) once a week. Alcohol inhibits the enzyme that converts vitamin D to its active form (hormonal) and routine consumption of alcohol limits the effectiveness of the treatment.

13 FAKE RELAPSE: "HEATED SCARS". Every time a MS patient with the disease in remission caused by the use of high doses of vitamin D (Cholecalciferol) has emotional stress, or practices exhausting physical exercises, or has sleep deprivation or is submitted to excessive environmental heat, the patient may have old symptoms (caused, for example, by a scar still present in their nervous system) that return (on a milder way), and may occur in the same place where it has previously occurred, or (if they had not disappeared) may be intensified partially and temporarily. It is as if emotional stress (or any of the other factors) "heats" the scar. As soon as the patient is calm, the symptoms start to cool down. If you get stressed, afflicted, worried and think that you are having a new relapse of the disease, you will extend the symptom.

14 A GENUINE NEW RELAPSE. A new relapse is generally characterized by a new symptom, different, that has never occurred. It is unlikely (not impossible) to have a new relapse after the first 2 months of treatment with high doses of Cholecalciferol that was prescribed, calculated (estimated) according to age, weight and height. In rare cases in which this happens, it is verified that it is the case of a mild relapse, identified then by the fact that this is a new symptom, that has never occurred (or by a symptom that has already occurred, but then occurs in an area of the body

where it had not happened before), that sometimes gets spontaneously resolved and that invariably does not leave sequels. Throughout the period in which the dose of Cholecalciferol ("vitamin" D) is being adjusted, new relapses may occur, which are treated in accordance with the traditional procedure (pulse therapy with intravenous or oral corticosteroid, according to its severity).

15

ADJUSTING THE DAILY DOSE OF CHOLECALCIFEROL
Adjusting the dose of vitamin D (Cholecalciferol) - according to the specific needs of each patient - is done by the physician in the

appointment (recommended after 2 months after start of treatment), through tests results comparison (blood and urine)

collected before the start of the treatment (first round of tests) with the tests results (also blood and urine) collected during the treatment of at least 2 months (second round of tests). Both pathology requests (containing a complete tests list) are delivered to the patient or to the family member at the first appointment with the doctor. In other words, the interval between the beginning of treatment and the collection of the second round of tests may not be less than 2 months so that the adjustment calculation of daily doses for the patient's specific needs does not get compromised; during the first 2 months after the treatment's beginning or after the adjustment of Cholecalciferol daily doses the vitamin D levels are not stabilized yet (they are still raising), therefore blood and urine tests collection are not adequate before this period, except if THIRST happens, then test on calcium in the urine will be done independently from the other tests (SEE BELOW). On the other hand, you must allow at least 1 month from the last collection of tests until the appointment date for evaluation of these tests to ensure that all the tests will be ready on the date of the second appointment

18

To make the adjustment of cholecalciferol doses ("vitamin" D) the patient or their family member must check that all the required tests have been made available by the pathology lab and must bring the printed tests on the date of the appointment. It is not recommended that the patient brings only a number of identification and a password provided by the pathology lab for the secretary to try to access results via internet on the occasion of the appointment. Often labs website pages are congested by other patients internet access or your medical centre may have internet problems, which don't allow the adjustment of the dose on the appointment date. When knowing that the tests will not be available on the scheduled date for the appointment, the patient or their family member should call the clinic in advance to postpone the appointment's date

16 The maximum effect (which almost always represents the remission of the disease) is reached after the course of 2 months from the date of this adjustment (from the dose adjustment done in the second appointment). Over the months until the maximum effect is reached, disease relapses may still occur (in general they are mild and of short duration), and must be treated with intravenous pulse therapy or orally with steroids, according to the severity of the manifestations.

17 During the period of adjustment of the final dose of "vitamin" D, the cooperation of the patient in seeking the maximum level of calm is absolutely vital as relapses or exacerbations from autoimmune diseases are in general (around 85% of cases) triggered by emotional stress ("stressing life occasions"). On the other hand, the emotional stress level also influences the final dose, and is often necessary to achieve higher levels of vitamin D and an even more restricted diet in patients who remain emotionally disturbed. If necessary, anti-depressants or tranquilizers are used. Depression is knowingly facilitated by low circulating levels of "vitamin" D and it seems to be associated with the progressive form of the disease, and should be appropriately treated with antidepressants.

19 The levels of vitamin D (25OHD3" or " 25-hydroxy-vitamin D") must be high (above the reference values indicated as normal by the pathology) from the second tests collection. That is expected and it should not cause concerns. On the other hand, calcium levels in the blood must be within normal limits if the patient is strictly observing the diet and hydration recommended.

20 When ingested, the vitamin D (Cholecalciferol) should not be diluted in juice or water (being insoluble in water, part of the dose would be lost, stuck to the glass walls), nor dripped onto directly in the mouth (to avoid eye-dropper contamination during accidental contact with the oral mucous and the consequent growth of bacteria in the solution, spoiling the expiry date of the preparation). The dose of the solution to be ingested (measured with a dropper or with a syringe) should be placed directly in a spoon and ingested on a pure form.

21 IN CASE OF TRAVEL. During the journeys, the non-encapsulated form of Cholecalciferol (manipulated, diluted in sunflower oil) does not need to be refrigerated, but should not be exposed to heat (such as inside a car that was parked in the sun). On air plane trips the vitamin D (Cholecalciferol) should be placed in checked baggage (in the baggage compartment the temperature is low and the passenger does not need to worry about the limit of liquids in hand luggage). When getting to your destination, place it in the hotel's refrigerator.

22 The use of nephrotoxic drugs must be avoided; they may limit the elimination of calcium through the kidneys, accumulating in the bloodstream, as "the door" between the intestine and the blood current is "open" by higher circulating levels of "vitamin D. Avoid taking unnecessary medications. Be especially careful with anti- inflammatory drugs and antibiotics, especially administered by parenteral (intravenous or intramuscular injection). If you are prescribed any medication as absolutely necessary, read the leaflet and request information from the doctor and pharmacist about its nephrotoxicity. If it is verified that the medication is in fact nephrotoxic, discuss alternatives with the physician who has prescribed the drug. If it is irreplaceable or absolutely necessary, hydration should be intensified to reduce drug concentration as much as possible in the urine that is formed in the kidneys. Special care must be taken with parenteral antibiotics (such as the aminoglycosides - intra-muscular or intra-venous) in case of serious respiratory or urinary infections - these latter are common in patients prone to urinary retention that are repeatedly using catheter to empty their bladder.

23

During the treatment, the patient should pay special attention to the symptom of excessive thirst, because thirst may indicate that the calcium is being eliminated in excessive quantity in the urine, putting in risk the renal function.

Firstly, the patient must differentiate the real thirst from "dry mouth" sensation, which can occur due to the low humidity of the air, or in association with periods of stress, among other causes. In the case of thirst the patient needs to consume a quantity of liquids well above their standard to obtain relief of discomfort (quench). In the "dry mouth" case (which can occur, for example, due to the low relative humidity of the air or temporarily in a situation of emotional stress), the discomfort disappears with a "wet" mouth, not being necessary to swallow water. In case of excessive and persistent thirst the patient has a need to take several glasses of water to feel satiated.

24

As thirst may be caused by other factors (such as the intake of salted foods, for example), there is no other way to clarify its cause except through total calcium measure eliminated in the urine collected over 24 hours (" 24-hour calcium urine test") using one of the forms that are provided by the physician on the occasion of your appointment.

25

In the event of excessive THIRST (not "dry mouth"), the patient should use the Calcium-Urine 24 hours form that was delivered during their appointment and show it to the lab staff, who will then supply a bottle for urine collection. Normally, the first urine is not used (and eliminated in toilet), then all the urine over the next 24 hours must be collected. While the urine is being collected, the daily dose of Cholecalciferol should not be changed, because, if it is suspended or reduced (before or during the collection of the urine) the result of the examination would no longer represent what was occurring with the urinary calcium in response to daily dose that was been taken.

26

When receiving the result of the 24-hour Calcium in the urine test The patient (or family member) must calculate the concentration of calcium in the urine, dividing the total quantity that was eliminated in 24 hours by the volume of urine (in litres) that was delivered to the lab. For example, assuming that the result of 24-hour calcium in the urine test was of 400 mg per 24 hours, and that the volume was 2,000 ml (equivalent to 2 litres) the value of

400mg is divided by 2 litres and the result of 200mg per litre indicates that there is no risk to renal function, as it is below the recommended maximum value (concentration).

27

The concentration of calcium in the urine is considered adequate (i.e. the calcium is sufficiently diluted to the point of not causing renal lesion) if it is

less than 250 mg per litre of urine (calculated through the 24-Hour calcium urine test or verified through the isolated sample - the latter associated with the weighing of geriatric diaper or absorbent urinary pads changed over 24 hours - see below). Abundant hydration (greater than or equal to 2 litres and a half of liquid ingested over 24 hours) is essential to maintain the calcium sufficiently diluted in the urine to the point of not causing renal lesion.

28

If the calcium concentration is higher than 250 mg per litre of urine, the patient should interrupt the daily doses of Cholecalciferol for 3 days, which is usually the necessary time to obtain the disappearance of excessive thirst. On the fourth day the patient should restart taking a lower daily dose of vitamin D, as per medical recommendation.

29

It is possible that thirst (not the sensation of "dry mouth") may return after some days or some weeks following the reduction of the vitamin D dose even if in the use of lower doses of Cholecalciferol. In this case, the patient should repeat the Calcium urine 24 hours test (without suspending the Cholecalciferol) and, as the concentration of calcium in the urine exceeds again 250 mg per litre of urine, the patient should repeat what was recommended in the previous item. Thus, suspending the daily administration of Cholecalciferol for 3 days and restarting on the fourth day with a once more reduced dose as per medical recommendation. It may be necessary to lower the dose IF THIRST occurs again and IF the concentration of calcium in the urine is once more still higher than 250 mg per litre of urine.

30

In case of patients who have urinary incontinence and use geriatric diaper or absorbent pads, a request form should be used for Calcium in the urine in an isolated sample, where the

the absorbent pad (diaper) is simultaneously weighed at each change over the course of 24 hours. The estimate of 24-hour Calcium urine test is made through a calculation, where it is assumed that 1 kg of diaper or absorbent pad is equivalent to 1 litre of urine. Thus, for example, if 4 pads were changed over 24 hours, weighing 550, 600, 450 and 700 grams, it is understood that the total (2,300 grams) equals 2,300 ml = 2.3 litres. The total weight of diaper changed over the 24 Hours may not be less than 2 kg if the patient is being properly hydrated (ingesting a minimum volume 2 litre and a half of liquid per day). Assuming that the concentration of calcium in isolated sample was 10 mg/dL (10 mg per 100 ml), you will have eliminated 100 mg per litre (230 mg in 2,3 litres of urine). As verified in the previous item, with this result the calcium is sufficiently diluted in urine to the point of not causing renal injury.

31 Patients who present urinary urgency or incontinence reduce the intake of liquids in order to minimize the occurrence of embarrassing situations, such as having to leave suddenly in the midst of a meeting at work, or during visits to family or friends in order to go to the toilet, with the risk of not arriving in time to the toilet, and "wetting" their clothes (incontinence). The hydration (minimum intake of 2 litres and a half of liquid over 24 hours), however, is non-negotiable, as it is essential to protect renal function. Thus, it is recommended that the patient seek urinating frequently and preventively, if going to a meeting or visiting a shopping centre, you should try to urinate before you leave. If you are in a meeting (or during a visit to the shopping centre, or during a dinner or lunch out of the house) that can be extended for a longer time than the usual interval between two consecutive visits to the toilet, you must excuse yourself and go to the toilet, before you feel any need to urinate, as a preventive measure to empty urine as often as necessary, without prejudicing to the recommended hydration.

32 The physician that monitors the patient can also prescribe medication to reduce urinary urgency, and the schedules of these medications can be settled in order to make that the maximum effect coincides with outdoor lunch or dinner time (in restaurants or at friends or family home) or in scheduled reunions. The effect of one of the doses can also coincide with the hours of sleep at night to reduce the frequency of visits to the toilet at night, which breaks up sleep, and reduces quality of life. In some cases, a single preventive visit to toilet during the night can avoid the use of night time nappies (diaper) (or the patient can even avoid the discomfort of having a wet nappy/diaper or absorbent pad). It is recommended that the patient sets an alarm clock to be awake before being under any urinary urgency (with the risk of having incontinence before reaching the toilet). All these preventive measures can be done in order to make recommended hydration viable.

33 Patients with neurogenic bladder, on the contrary, due to urinary retention (and therefore even require repeated use of catheters to empty the bladder) also are used to reduce ingestion of liquids as a way to reduce the frequency of use of catheters. This habit causes a great risk when they make use of high doses of Cholecalciferol, because the calcium that potentially is eliminated in excess in the urine should be diluted to avoid being deposited in the kidneys, as already emphasized in this text.

34 On the other hand, periodically eliminating urine by spontaneous contraction of the bladder is an important defence against infections, because it is a mechanism that intermittently expels (sweeps) potential germ invaders

out of the urinary tract. A patient with urinary retention has a mechanism already impaired. If additionally the patient maintains the urine in the interior of the bladder for a longer time due to a reduction (intentional) of liquid intake to reduce the frequency of use of catheters, the patient provides the time necessary for bacteria to multiply, and to transform the stagnated urine residue on the inside of the bladder for long hours in an environment of bacterial culture. In addition, if it is true that bladder catheterization can carry germs to the interior of the bladder, this negative effect is probably supplanted by elimination of urine residue where growing germs may be already present. This residue is then replaced by new urine (newly formed). Maximum care should be taken in the perineum hygiene, with use of antiseptics (anti-septic soap, appropriate anti-septic solution) and disposable catheters. In addition, at each intestinal evacuation, the peri anal region should be cleaned with anti-septic soap and hygienic douche (or, where this is not possible, if you are not at home, with baby wipes moistened with antiseptic solution, sold in pharmacies). Most of the germs that cause urinary infections originate in microscopic waste faeces that are not eliminated by simple use of toilet paper; mixed with sweat, these germs are spread all over the perineum reaching the opening of urinary tract (urethra) and causing cystitis and pielonefritis

35 If the urinary infection that is installed is sufficiently serious, the patient may be hospitalized for use of potentially nephrotoxic antibiotics intravenously, configuring the situation potentially disastrous described in item " 22" of this text.

36 If preventive measures recommended here are not effective in the prevention of recurrent urinary infections, patients with neurogenic bladder caused by tendency of urinary retention may discuss with a urologist about recommended local administration of botulinum toxin

onto the urinary sphincter, allowing the spontaneous emptying of the bladder. Even if this procedure causes a mild urinary incontinence (preferable to urinary retention and multiple use of daily catheters, with a higher risk of infections), the social constraints caused by incontinence can be avoided or minimized through urinary absorbents use.

37 The recurrence of infections (respiratory, urinary or of any other nature), when maintaining aggressiveness of the immune system, affect the beneficial effect of high doses of Vitamin D in the disease control auto-immune. The patient (woman) can, additionally, chat with a gynaecologist to receive additional guidance to keep sexual activity without triggering new urinary infections.