The effect of 4.5 gram methylprednisolone administered as weekly infusions for 12 weeks on bone metabolism in Graves' orbitopathy

Background

Systemic glucocorticoid (GC) (peroral or intraveous) is used in the treatment of numerous diseases. Treatment with GC is often long-term and many patients therefore develop side effects [1]. One such is decreased bone mineral density (BMD) [2] and increased risk of fractures [3]. There is solid evidence that a daily intake of GC equivalent to 5 mg prednisolone both decreases BMD and increases fracture risk [4], and epidemiological studies show that a yearly cumulative dose of 450 mg prednisolone is harmful [5]. Moreover, GC affect bone structure [6] which increases fracture risk independently of BMD [7]. A diagnosis of osteoporosis is usually given by a BMD T-score ≤ -2,5 but in case of GC treatment anti-osteoporotic treatment may be initiated already at a T-score < -1. It is common practice in Denmark to commence supplementation with calcium and vitamin D and measure BMD at planned treatment with GC of more than 450 mg prednisolone per year.

There are also studies, however, showing that the effect on bone with GC treatment for up to 20 weeks is largely reversible [8]. At present there is no evidence that short term high-dose GC treatment affects bone mass or increases fracture risk. An epidemiological study shows that daily rather that cumulated dose relates to fracture risk [9] and a recent Danish study shows that prednisolone at a cumulative dose of 1425mg given as 175mg once every 3. week followed by 100mg daily for three days every 3. Week as an adjunct to chemotherapy in treatment of breast cancer does not affect BMD [10].

Graves Orbitopathy (GO) is an eye disease seen with autoimmune hyperthyreosis (Grave's disease). If treatment is warranted intra-venous methylprednisolone with a weekly infusion for 12 weeks is used. Total dose amounts to 4500mg. The present study evaluates the effect of that treatment regimen on bone.

Purpose

To evaluate if high-dose intra-venous GC in GO affects BMD, bone turnover, or bone structure.

Studypopulation and methods

30 adult (age ≥ 18 år) patients with GO in whom GC treatment is indicated.

Primary end point:

- Change in lumbar spine BMD measured by Dual X-ray Absorptiometry (DXA)

Secondary end points:

- Change in BMD at the hip measured by DXA
- Change in bone turnover measured by CTx and P1NP
- Change in bone structure measured by High Resolution peripheral Quantitative Computed Tomography (HRpQCT)

Inclusioncriterion:

- Patients with GO commencing treatment with GC.

Exclusionscriteria:

- Treatment for osteoporosis
- Primary hyperparathyroidism
- Hypoparathyroidisme
- D-vitamin < 20mmol/L
- Chronic kidney disease with eGFR < 30 mL/min
- Liverdisease
- Peroral treatment with GC three months prior to study

Treatment of Graves´ orbitopathy

Patients are treated with intravenous methylprednisolone 500 mg once weekly for 6 weeks followed by 250 mg once weekly according to Danish national guidelines. Dose can be changed according to the clinical response at the discretion of the treating physician but if so the patient is excluded from the study. In addition al patients will be advised to take supplementation with 800 mg calcium and 40 µg 25-OH-vitamin D in 2 daily doses.

Treatment of thyrotoxicosis

Patients will be treated according to national guidelines.

Examinations

Bone Mineral Density is measured using DXA at the hip and spine regions at baseline and again after 12 and 24 weeks. Baseline DXA may be perforemd until 10 days after first dose of GC. Bone turnover is measured in blood samples using the bone markers P1NP and CTx. Blood samples are taken at baseline and after 3, 9, 12, and 24 weeks.

Bone structure is evaluated using high resolution peripheral quantitative computed tomography (HR-pQCT) at baseline and after 12 weeks.

In addition the following is measured at baseline to investigate for exclusioncriteria:

- Creatinine
- Na^+
- K^+
- Parathyroid hormone
- Calcium
- Vitamin D
- Alanine aminotransferase
- Alaline phosphatase
- Bilirubine

Studyplan:

	Baseline	W3	W9	W12	W24
Treatment	→→→→→→→→→→→→→→→→→→→→→→				
Informered consent	X				
Biochemistry	X				
Bone turnover markers	X	X	X	X	X
DXA	X			X	X
HRpQCT	X			X	
Thyroid function	X	X		X	X
Thyroid receptor antibodies	X			X	X

Statistics

Power calculation is based on the primary end point. From previous studies we know that the standard deviation on change in BMD is 3%. With a significance level of 5% and a power of 90% we need 30 participants to demonstrate a change in BMD of 2% using a paired samples t-test. A change below 2% is considered clinically insignificant. Change over time based on 2 measurements will be evaluated using paired samples t-test and change over time with more than two measurements will be calculated with ANOVA with repeated measures.

Recruitment

Participants will be recruited from Department of Endocrinology and Internam medicine, Aarhus University Hospital, Denmark during visits in the outpatient clinic. Here, written and oral information is given to the

potential participants in a closed room by one of the study doctors. Potential participants are encouraged to read the information thoroughly and are informed that they have the right to a bystander and are given a week to considerate participation before signing any informed consent form.

Biobanks

During the study a research biobank is formed to store blood samples (4 tubes with 2mL of both serum and plasma. To minimize analytical variance bone markers are analysed in batches when the last participant is finished. Thus, the research biobank is terminated in march 2021 and excess material is transferred to a biobank at Aarhus University Hospital for future research. Here, material is stored for future research for a maximum of 10 years before destruction. Participants are informed that at any time they can request their material to be destroyed.

Perspectives

Many patients are treated wit GC for a variety of disease with both intermitent or continuous dosing. It is therefore important to disclose which patients should receive a DXA and start medical fracture prevention, so that future treatment can be given with the greatest precision.

Etiske overvejelser

Blood sampling can give a bruise and in rare cases a skin infection. HR-pQCT and DXA gives a radiation dose of 80µSv and 12 µSv, respectively, which increases the life-time risk of cancer by 0,0005% from 25,0% to 25,0005%.

All participants are otherwise treated for their diseases according to national guidelines. We therefore believe that the benefit from the knowledge gained in the study outweighs the risks.

The project is approved by the Danish Data Protection Agency and Regional Ethics Comitee.

Economy

The study is initiated by the sponsor who already has acces to DXA and HR-pQCT and staff to use these. The costs for blood samples will be covered by the sponsors research account and does not call for additional funding. Participants will receive no participation fee.

Publications

All results (positive and negative) will be attempted to be published in a peer reviewed scientific journal. Participants will be given written information about the results and can get additional information by addressing the sponsor.

References

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