

Mild Primary Hyperparathyroidism

Long-term effects of parathyroidectomy versus observation – with emphasis on skeletal outcomes

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentligen försvaras i Förmaketen, Vita Stråket 12, den 22 april 2022, klockan 09.00

av Karolina Lundstam

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Avhandlingen baseras på följande delarbeten

- I. Lundstam K, Heck A, Mollerup C, Godang K, Baranowski M, Pernow Y, Varhaug JE, Hessman O, Rosén T, Nordenström J, Jansson S, Hellström M† and Bollerslev J† on behalf of the SIPH study group.
Effects of parathyroidectomy versus observation on the development of vertebral fractures in mild primary hyperparathyroidism.
Journal of Clinical Endocrinology and Metabolism 2015;100(4):1359-67.
- II. Lundstam K, Heck A, Godang K, Mollerup C, Baranowski M, Pernow Y, Aas T, Hessman O, Rosén T, Nordenström J, Jansson S, Hellström M† and Bollerslev J† on behalf of the SIPH study group.
Effect of surgery versus observation: Skeletal 5-year outcomes in a randomized trial of patients with primary HPT (the SIPH study).
Journal of Bone and Mineral Research 2017;32(9):1907-14.
- III. Lundstam K, Godang K, Pretorius M, Markwardt P, Hellström M, Bollerslev J and Heck A.
The influence of DXA hardware, software, reference population and software analysis settings on the bone mineral density and T-Score relationship.
Journal of Clinical Densitometry 2022;25(1):24-33.
- IV. Lundstam K‡, Pretorius M‡, Bollerslev J, Godang K, Fagerland MW, Mollerup C, Fougnier SL, Pernow Y, Aas T, Hessman O, Rosén T, Nordenström J, Jansson S, Heck A† and Hellström M†.
Positive effect of parathyroidectomy compared to observation on BMD in a randomized controlled trial of mild primary hyperparathyroidism.
In manuscript.
- V. Pretorius M‡, Lundstam K‡, Heck A, Fagerland MW, Godang K, Mollerup C, Fougnier SL, Pernow Y, Aas T, Hessman O, Rosén T, Nordenström J, Jansson S, Hellström M† and Bollerslev J†.
Mortality and morbidity in mild primary hyperparathyroidism: Results from a 10 year prospective randomized controlled trial of parathyroidectomy vs observation.
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SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR KLINISKA VETENSKAPER



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Abstract

Background: The majority of patients with primary hyperparathyroidism (PHPT) in developed countries today present with no obvious symptoms, i.e. the mild form of the disease. As the only curative treatment is parathyroidectomy (PTX), it has been debated whether this intervention is reasonable in this patient category and if observation is a safe alternative. There are surgical criteria for patients with mild disease. However, these criteria are not based on long-term randomized studies since such studies have been lacking, and non-randomized studies are at risk of selection bias. Also, many studies have not been limited to mild disease.

Aims and methods: The randomized controlled trial, *The Scandinavian Investigation of Primary Hyperparathyroidism (SIPH)*, included patients with mild PHPT. The aim was to compare PTX with observation (OBS) on mortality and disease-specific morbidities (bone health, renal health, cardio- and cerebrovascular disease and malignancies) during a follow-up of 10 years. Bone mineral density (BMD) was followed by dual-energy x-ray absorptiometry (DXA) and prospectively obtained thoracolumbar spine radiographs were assessed for vertebral fractures (VFs) by two radiologist. Peripheral fractures as well as kidney stones and other pre-specified morbidities were structurally inquired at baseline and after two, five and 10 years. With long-term follow-up, DXA data had to be validated and the BMD-T-score-plot was invented for that purpose.

Results: In Paper I (5-year fracture data), all new VFs were found in the OBS group, however not reaching statistical significance in comparison with PTX ($P=0.058$). Peripheral fractures were equally distributed between groups. In Paper II (5-year BMD data), a significant treatment effect of PTX could be seen for all analyzed compartments except radius 33% (Rad33). In paper III (validation of DXA data), we found systematic differences in the BMD-T-score relationship, and the factors causing them were accounted for. In Paper IV, the DXA results (BMD and T-scores) of the 10-year evaluation are presented. In Paper V, the end of study (10 years) mortality data and morbidity data (fractures including VFs, kidney stones, cardio- and cerebrovascular disease and malignancies) are presented.

Conclusion: In a 5-year perspective, no effect of PTX compared to OBS could be seen for mortality or any hard endpoint morbidity event, however with very few events. Even though PTX had a positive effect on BMD evolution, no effect on fracture outcome could be seen. Thus, observation could be an alternative to PTX in a 5-year perspective. For 10-year data see the conclusion of Paper IV and V. Longitudinal BMD data is at risk for systematic differences and the BMD-T-score-plot is an effective tool in the validation process.

Keywords: primary hyperparathyroidism, parathyroidectomy, observation, vertebral fractures, peripheral fractures, kidney stones, radiography, bone mineral density, dual-energy x-ray absorptiometry, mortality