Protocol Summary - Adherence in Global Airways – the relationship between steroid intake and the impact on the endocrine axis, bone density, and structure in patients with chronic sinusitis and asthma

Trial Responsible Nurse

Christiane Haase, Clinical Nurse Specialist and Ph.D. Student

Department of Otorhinolaryngology and Audiology

Inge Lehmanns Vej 8

2100 Copenhagen Ø

Phone: 35459565

Christiane.holbaek.haase.01@regionh.dk

Trial Responsible Physician

Vibeke Backer, Professor and Chief Physician

Department of Otorhinolaryngology and Audiology

Inge Lehmanns Vej 8

2100 Copenhagen Ø

35 45 60 33

Nina.vibeke.backer@regionh.dk

Purpose:

The purpose is to investigate the relationship between high total intake of systemic steroids in patients with upper and lower airway disease, low endogenous cortisol production, and reduced bone density and structure. Additionally, through an exploratory follow-up (pilot project) study, to investigate whether improved adherence to local steroid treatment and biologic medication would decrease the patient's endogenous cortisol production.

Method, Design, and Investigation Procedures:

Patients referred for evaluation at the Luftvejsklinik~~Airway clinic~~, Department of ENT, Rigshospitalet with possible chronic sinusitis with or without asthma are offered participation in the project. The project consists of 1) a cross-sectional study and 2) an exploratory follow-up (pilot project) after four months. The patient population includes all newly referred patients who are offered evaluation and assessment for CRS, without polyps (CRSnNP) or with polyps (CRSwNP), and possible concurrent asthma with regards to potential biological treatment.

Inclusion/exclusion criteria for the cross-sectional study:

Inclusion criteria:

- Diagnosed with CRS and possible asthma
- Aged over 18 years

Exclusion criteria:

• Unable to read or speak Danish

• Serious psychiatric comorbidities

• Patients who have never taken systemic steroids

• Not able to participate or fulfill local treatment according to the investigator's assessment

• Does not give permission for access to FMK-online

Inclusion/exclusion criteria for the exploratory study - 4-month follow-up (pilot project):

Inclusion criteria:

• Diagnosed with CRS and possible asthma

• Aged over 18 years

• Low adherence: Foster score, i.e. number of treatments taken compared to prescribed <80% (4 weeks out of 16 weeks) and/or measured on MARS-5 L/N ≤35 at first visit (corresponding to under 80%). If the patient does not have asthma, it is MARS-5N ≤19.

• If asthma: ACQ ≥1.2 or ACT≤17 (partially uncontrolled asthma)

• SNOT-22 score ≥35 (partially uncontrolled CRS)

• Participation in the cross-sectional study at the initial visit to the Airways Clinic

Exclusion criteria:

• Adherence: Foster score >80% and/or MARS-5-L/N >35 points at the first visit

• Unable to read or speak Danish

• Serious psychiatric comorbidities

• Patients who have never taken systemic steroids

• Not able to participate or fulfill local treatment according to the investigator's assessment

• Does not give permission for access to FMK-online

Side effects, risks, and disadvantages:

Synacthen test: There are no serious side effects or risks associated with undergoing a synacthen test. When injecting Synacthen (ACTH), one may experience short-term side effects such as a feeling of warmth, and in rare cases, transient nausea. In rare cases (0.01-0.1%), there may be reactions to ACTH, which can manifest as an allergic swelling of the face, mouth, and larynx, and in extremely rare cases (0.001-0.1%), this can progress to an anaphylactic reaction. Safety precautions are taken for each test, including the presence of a doctor on call with emergency contact information for treating an allergic or anaphylactic reaction. The test is performed in accordance with the recommendations from the endocrinology department at Rigshospitalet, where training also takes place. Safety measures are taken for each test, and

there is an agreement with the on-call ENT doctor. This includes calling a doctor for treatment of an allergic reaction (often with prednisolone Solucortef 40 mg and antihistamine (Tavegyl), as well as possible adrenaline inhalation) or an anaphylactic reaction (intramuscular adrenaline with 0.3 mg in an Epipen).

Economic considerations:

The mentioned research group has initiated the project. There is no increased financial consumption associated with the project, as it involves patients who are part of the clinical outpatient treatment at the Luftvejsklinik~~Respiratory Clinic~~, ENT, RH. Funding has been sought for extra work for a nurse at the Danish Lung Association, Rigshospitalet's research fund, and other small and large funds. A final response to these applications is awaited in the spring of 2023. Included patients and the Regional Ethics Committees will be informed of the name of the sponsor and the amount of support, if obtained.

Recruitment of study participants:

Patients are recruited at their initial visit to the Luftvejsklinik~~Airway Clinic~~. A nurse from the clinic will provide information about the project and ask if the patient is interested in participating. If the patient is interested, an information meeting with a researcher from the group will be arranged. If the patient wishes to participate, they will receive verbal and written information about the project. If the patient wishes to participate, they must complete a written consent form for participation in the project.

Publication of trial results:

All results, whether positive, negative, or inconclusive, will be published via www.clinicaltrials.gov.

Scientific Ethical Statement:

Participants have the right to self-determination to choose whether they want to participate in the project and a "no" will be respected. They will be adequately informed about the purpose of the project. They will be informed that their participation is voluntary, and they can withdraw from the project at any time without consequences for their future treatments and consultations in the healthcare system. They will receive verbal and written information about the project. They will also be made aware that they have at least 24 hours to consider before giving consent for participation. If they choose to participate, written informed consent will be obtained once they have decided. The project has been approved by the Capital Region's Data Protection Agency P-2022-493. The project is also being conducted on the basis that the research group has an expectation that the results will be useful for future treatments of this group of patients. For example, if they have a severely affected endocrine axis (low P-cortisol) and will need supportive steroids in, for example, cases of surgical treatment under general anesthesia.

Protocol - Adherence in Global Airways – the relationship between steroid intake and the impact on the endocrine axis, bone density, and structure in patients with chronic sinusitis and asthma

Research Group:

Clinical Nurse Specialist, Cand. Cur, Christiane Haase (PI)

Clinical Nurse Specialist, Cand. Cur, Ditte Gertz Mogensen

Chief physician and Ph.D., Ear-Nose-Throat, Kasper Aanæs

Professor and Chief physician, Endocrinology, Peter Schwarz

Professor and Chief physician, Pulmonology, Vibeke Backer

Introduction:

There has been a significant focus on ensuring treatment of diseases in both upper and lower airways (global airways) simultaneously because they have the same inflammatory disease mechanism. Approximately 9% have chronic sinusitis (CRS), 4% of the Danish population is diagnosed with CRS with nasal polyps (CRSwNP)(1), and 7-10% have asthma. Over the years, some of these patients have been treated with systemic and/or locally acting steroids (glucocorticoids). These patients referred have moderate to severe disease with a significant disease burden, and therefore continue to be treated with steroids. The risk of developing secondary adrenal insufficiency is high with prolonged use of systemic high-dose and potent glucocorticoids but can also occur with locally administered glucocorticoids (2). It has recently been demonstrated that treatment of eczema with steroid-containing creams has indications of side effects not only on the skin but also on the bones (3). Moreover, there is an additive effect, so that it is the total burden of steroid intake that is significant for the development of side effects, but whether it also affects cortisol response to ACTH is unknown (4). Treatment with steroids currently affects the endocrine axis (P-cortisol), increasing the risk of osteopenia, osteoporosis, and possibly diabetes. Our knowledge of which preparations, doses, and modes of administration cause these side effects is inadequate, and whether the total dose over time is significant is unknown. This gives rise to conducting a cross-sectional study to determine the significance of these side effects, followed by an exploratory follow-up study of patients with global airway diseases and high adherence (80%) to local treatment.

Purpose:

The purpose is to investigate the relationship between high total intake of systemic steroids in patients with upper and lower airway disease, low endogenous cortisol production, and reduced bone density and structure. Additionally, through an exploratory follow-up (pilot project) study, to investigate whether improved adherence to local steroid treatment and biologic medication would decrease the patient's endogenous cortisol production.

Hypothesis/research question:

Patients with CRS/CRSnNP/CRSwNP who have received systemic steroids have an impact on the adrenals with low basal P-cortisol (below 500nmol), abnormal response to stimulation with ACTH (synacthen test) measured at the final P-cortisol. Additionally, a reduced increase (delta value) in P-cortisol is expected in connection with a synacthen test. These patients also have an affected bone density and structure with a higher incidence of osteopenia and osteoporosis than expected for this age group. Patients with CRS/CRSnNP/CRSwNP who can improve their adherence to >80% have an increasing impact on P-cortisol.

Primary outcome:

The primary outcome is to investigate whether newly referred patients with upper and possible lower respiratory tract diseases have an impact on their own cortisol production after prolonged use of systemic steroids. That is, the baseline level of plasma cortisol is <500 nmol, and a correlation with lifelong use of systemic steroids can be demonstrated.

Secondary outcomes:

Cross-sectional study:

1: After a stimulation test, plasma cortisol is not above 500 nmol.

2: The increase in plasma cortisol is associated with the intake of systemic steroids.

3: Demonstration of the correlation between lifelong use of systemic steroids and the degree of osteopenia and osteoporosis (T-score). T-score from DEXA scanning is used to measure bone density and structure. An affected T-score is defined as follows: T-score between -1.0 and -2.5 = osteopenia and score ≤ -2.5 = osteoporosis.

4: The number of patients with osteoporosis/penia of the spine and femur is increased compared to expected findings in age-matched individuals.

Exploratory follow-up at 4 months (pilot project):

5: Patients with CRSwNP/CRSsNP/CRS with and without asthma who have shown low adherence <80% after the cross-sectional study and who have achieved adherence over 80% at follow-up have also developed adrenal function impairment with a reduction in plasma cortisol of at least 8% (exploratory study).

Study design (brief description):

The study design is a cross-sectional study of newly referred patients to the Luftvejsklinik, ENT, RH for investigation and treatment of CRS and possibly asthma. And an exploratory follow-up (pilot project) study of patients who attend 4-month control.

Background:

Chronic rhinosinusitis (CRS) is a condition with chronic inflammation in the nose and sinuses. CRS can be with both nasal polyps (CRSwNP) and without polyps (CRSsNP) (5). 9% of the Danish population is affected by CRS, and about 4% are estimated to be diagnosed with CRSwNP (1). The diagnosis is based on the patient's symptoms and objective signs of inflammation in the nose and sinuses. The symptoms are a blocked nose or nasal secretion, reduced airflow, reduced sense of smell, pain/pressure around the nose, forehead, or eyes. The above symptoms must have been present for more than 12 weeks, and one of the symptoms must be secretion or reduced airflow through the nose to make a diagnosis (6). About 40% of CRS patients in primary care have asthma, whereas 65% referred for treatment at the hospital have asthma (7). CRSwNP that is not satisfactorily controlled particularly affects quality of life (8). It is often characterized by type-2 inflammation, i.e., an increased number of eosinophils in the mucous membranes in the sinuses and nasal polyps - as well as comorbidities such as asthma, ASA/NSAID intolerance (N-ERD), and allergies (5). CRS can be treated both surgically and medically. The basic medical treatment of CRS includes daily saline irrigation and use of nasal steroids. If there is a lot of secretion, antibiotic treatment can also be added to the basic treatment. In the case of nasal polyps, systemic corticosteroid treatment (prednisolone tablets/injection betamethasone) can also be added (5,6). If the medical treatment is not

optimal, patients can be offered surgical treatment - endoscopic sinus surgery (ESS) (5). The goal is to aim for the removal of polyps in the nose and sinuses.

Comorbidity:

In patients with CRSwNP, one should also focus on comorbidity due to the interaction between the upper and lower airways. Patients with uncontrolled CRSwNP are often burdened with a high disease burden. CRSwNP and asthma often have a negative impact on each other. Therefore, patients should be evaluated for asthma. Patients with CRSwNP with type-2 inflammation (high eosinophil cell count in the blood or nasal mucosa) have more frequent recurrence of CRSwNP after surgery than patients with low eosinophil cell count (5). Patients with asthma may also experience faster recurrence of their polyps than patients who do not have asthma.

Asthma:

Asthma is a chronic respiratory disease characterized by chronic inflammation in the airways, airway hyperresponsiveness, and variable airflow obstruction (9). It is estimated that over 300 million people worldwide suffer from asthma, which has a significant impact on the economy (10). Symptoms of asthma include cough, wheezing, shortness of breath, and chest tightness, among others, and can vary in intensity. The diagnosis is based on the medical history, symptoms, and objective findings, such as spirometry, FeNO measurement, provocation tests, and peak flow test (9).

Adherence:

The term adherence describes the patient's adherence to the treatment strategy developed in consultation with a healthcare provider. The patient is considered an active participant in their treatment. Adherence can be measured both for pharmacological and non-pharmacological treatment. The WHO categorizes adherence measurements into subjective and objective measurements (11,12). Objective measurements include measurements such as pill counting, electronic monitoring (shared medical record), or biochemical measurements (e.g., blood tests) (11). Subjective measurements require an assessment by a healthcare professional or the patient themselves. Self-reporting by the patient or assessment by the healthcare provider is the most common method used to assess patient adherence. Foster's score and MARS-5 are subjective tools for measuring patient adherence. With Foster's score, the patient is asked a single question, "How many days out of seven do you take your medicine as recommended?" Starting at 0, the score is calculated as the number of days of taking the prescribed amount. Zero days are equal to 0% assessed adherence and taking the medication every day for seven days is equal to 100% assessed adherence (13). MARS-5 - developed by Professor Rob Horne (14,15). MARS-5 is a generic tool. It has been validated in many different clinical settings, including patients with asthma (16).

Poor adherence is especially seen with prolonged treatments among chronically ill patients, underscoring the importance of focusing on sustained adherence in these patients (17). Some patients discontinue their treatment once they have symptom control, after which an exacerbation occurs. They resume their treatment with the feeling that "it does not help" because they experience worsening symptoms (18). WHO estimates that only 50% of patients receiving long-term pharmacological treatment for their chronic illnesses are adherent to their treatment (18,19). Adherence to asthma and COPD has been found to range from 22% to 78% (10,18). In connection with "usual care," patients with asthma receive information, education, and training in relation to their disease in many places. Adherence to pharmacological treatment depends on age, educational level, knowledge of asthma, how many times medication is to be taken, whether the medication is easy to take, and how their communication is with the healthcare

provider (18,19). Adherence to inhalation medication is lower than with treatment with tablets taken orally or medication given by injection. The more complex and the more times the patient has to remember to take the medication, the more difficult it is to maintain optimal adherence (18,19). In a recent study, adherence was investigated in patients with asthma and pregnancy. The most interesting finding was that patients had a perception of being somewhat adherent. However, upon checking their electronic medical records, it turned out that patients did not buy as much medication as they thought. Thus, they were less adherent than they perceived themselves to be (20).

CRSwNP is a chronic disease like asthma, where low adherence is often seen in mild to moderate cases of CRS compared to severe cases of CRSwNP (21). However, the clinical perception is that not all patients take all their daily doses, but few scientific studies have focused on this. The difficulty in treating CRS is that the patient must use nasal steroids 1-2 times daily and combine it with nasal saline irrigation at least once daily. Reduced adherence is accompanied by poor disease control. Therefore, it is important to support and strengthen patients' adherence in relation to CRS with or without asthma to achieve good disease control (21).

Glucocorticoid-induced adrenal insufficiency and osteoporosis:

The use of steroids is a part of medical treatment for CRSwNP and asthma, and systemic steroid use is often seen in moderate to severe cases. It can affect the body's own production of hormones, which at different doses can trigger adrenal insufficiency. The condition is divided into primary and secondary adrenal insufficiency (22). Primary adrenal insufficiency involves the body's reduced or complete lack of hormone-producing cells in the adrenal cortex. Secondary adrenal insufficiency is caused by reduced production or effect of ACTH from the pituitary gland in the brain (2, 22, 23). The most common form of secondary adrenal insufficiency develops during external steroid treatment with pharmacological doses for a non-endocrine disease, such as CRSwNP and asthma. About 25% of patients receiving long-term steroid treatment develop long-term adrenal insufficiency - the higher the dose and treatment duration, the greater the risk (2, 23). Adrenal insufficiency can also occur with locally administered steroids - for example, it has been shown that 8% of patients treated with inhaled steroids, 52% after intramuscular injection, and more than a third of patients in long-term low-dose steroid treatment develop insufficiency (23, 24). In addition, steroid creams have been shown to have systemic side effects in a previously unknown high number of patients (3). Reduced production of steroids from the adrenals is a situation that should be considered in connection with acute illness, but also surgery (22, 25). Many patients with CRSwNP are offered 1-3 injections of steroids annually, in addition to high doses of nCS. Surgical intervention is also performed in between these injections. Here, one could consider supplementing preoperatively with steroids as protection against the stress of surgery if the endocrine axis is affected. Systemic glucocorticoids are used as treatment for a wide range of diseases, such as inflammatory diseases like CRSwNP or asthma either as needed or chronically (26-28). Glucocorticoid-induced osteoporosis is the most common secondary cause of osteoporosis and is a global public health problem, where fractures contribute to significant morbidity and mortality (29). The frequency of secondary glucocorticoid-induced osteoporosis is unknown in patients with CRSwNP (26). Prevention of this and negative consequences should be a focus point for healthcare professionals in these patients due to long-term treatment with systemic glucocorticoids (28).

Method:

Regarding 1) In the cross-sectional study, patients will receive the standard investigation and treatment at the Luftvejsklinik. This includes investigation for airway disease and possible type-2 inflammation,

treatment, etc. Measurement of their adherence and possible optimization of CRS and asthma treatment. The total amount of systemic steroids will be calculated and included in the study.

Experimental intervention (synacthen test): To investigate how prolonged use of systemic steroids and adherence affect cortisol production, all patients who agree to participate in the project will undergo a synacthen test. A synacthen test is used to assess whether the body's adrenal glands produce cortisol satisfactorily (i.e., own production). Cortisol is a hormone produced in the adrenal glands and is therefore called adrenal cortex hormone. It has a few effects, including on muscles, supportive tissues and bones, and nutrient metabolism. Therefore, the adrenal glands' ability to produce hormones is important. Reduced or absent production of adrenal cortex hormones can be seen with prolonged treatment with systemic steroids (adrenal cortex hormones). A synacthen test will be performed twice in total on all patients. The first time is at the 1st visit (preliminary examination) and the second time at the 4-month follow-up.

Ad 2) Exploratory investigation/4-month follow-up (pilot project): The experimental intervention in the follow-up involves measuring P-cortisol in patients who have now achieved high adherence (> 80%). Patients will receive standard follow-up/monitoring and treatment in the respiratory clinic.

Study population:

The study population consists of patients referred to the Luftvejsklinik, ENT, RH, for evaluation of CRS/CRSwNP/CRSnNP and with or without asthma for biological treatment. They are classified according to the type of inflammation they have (type-2 or non-type-2), whether they have CRSwNP or CRSsNP, their adherence, comorbidity with asthma, and finally the severity of the disease. All patients are given standard questionnaires to assess CRS/CRSwNP/CRSnNP and asthma (STARR-15, SNOT22, ACQ, ACT, MARS-5-L/N, Fosterscore - routine questionnaires for all patients in the Luftvejsklinik).

Patients for the project are recruited at the initial visit to the ~~Luftvejsklnik~~Luftvejsklinik. A nurse from the clinic~~e~~ will inform about the project and ask if the patient is interested in participating. If the patient is interested, a meeting will be arranged with a researcher from the research group (see section on information).

Inclusion/exclusion criteria for the cross-sectional study:

Inclusion criteria:

• Diagnosed with CRS and possibly asthma

• Age over 18 years

Exclusion criteria:

• Do not read or speak Danish

• Severe psychiatric comorbidities

Patients who have never taken systemic steroids

• According to investigators' experience, cannot participate or comply with local treatment.

• Do not give permission to access FMK-online

Inclusion/exclusion criteria for exploratory study - 4 months follow-up (pilot project):

Inclusion criteria:

• Diagnosed with CRS and possibly asthma

• Age over 18 years

• Low adherence: Foster score, i.e. number of treatments taken compared to prescribed <80% (4 weeks out of 16 weeks) and/or measured on MARS-5 L/N ≤35 at first visit (equivalent to less than 80%). If the patient does not have asthma, it is MARS-5N ≤ 19.

• If asthma: ACQ ≥1.2 or ACT ≤17 (partially uncontrolled asthma)

• SNOT-22 score ≥35 (partially uncontrolled CRS)

• Participation in cross-sectional study at initial visit to Respiratory Clinic

Exclusion criteria:

• Adherence: Foster score> 80% and/or on MARS-5-L/N> 35 points at first visit

• Cannot read or speak Danish

• Severe psychiatric comorbidities

• Patients who have never taken systemic steroids

• According to investigators' experience, cannot participate or comply with local treatment

• Do not give permission to access FMK-online

Method of investigation:

Demographic information:

Height, age, gender, weight, lung function.

Blood tests:

Leukocytes and differential count, allergy blood tests with a package of specific allergens (routine). Research blood test plasma cortisol.

Synacthen test:

The Synacthen test is performed by inserting a venous catheter at time 0, and then a blood sample is taken to determine the plasma cortisol level. Subsequently, 0.25 mg of ACTH is injected into the venous catheter, and 5 ml of iso NaCl is flushed. After 30 minutes, a blood sample is taken to determine the plasma cortisol level. The first mL should be discarded before obtaining a new P- Cortisol is taken. The 0-sample and 30-sample belong to the same Sampling Test Form (PTB). Scanned with PDA corresponding to the actual sampling time. The blood samples are sent together with their corresponding PTBs for analysis at the Clinical Biochemical Department, RH. Results will appear in the patient's medical record under laboratory results. The patient must not have ingested hydrocortisone or steroid inhalation at least 12 hours before the test and should not have received treatment with injection (i.m) steroid such as diprospan within the last three months (30). The entire procedure for the synacthen test takes approximately 1 hour and 15 minutes, including preparation and completion. The test itself takes about 30 minutes. This applies to both the cross-sectional study and exploratory follow-up.

DEXA scan:

Patients with CRS/CRSsNP/CRSwNP receive a DEXA scan as part of their clinical evaluation. This group has received larger amounts of nasal steroid for often more than 10 years, as well as 1-3 times systemic steroid annually over several years. Therefore, it is good clinical practice to refer to a DEXA scan to examine bone density and structure and any need for treatment with calcium and vitamin D. These investigations are included in the project.

Questionnaires:

Patients are required to complete the following questionnaires as part of the standard treatment in the Respiratory Clinic:

- STARR-15
- SNOT-22:
- ACQ
- ACT
- MARS 5-L/N:
- Foster score

Data processing:

Data will be entered into REDCap (Research Electronic Data Capture), which is a secure web application for building and managing databases and online questionnaires. The system was developed at Vanderbilt University, which released the first version in 2008 (31). The use of REDCap is a requirement from Region Hovedstaden.

Statistical analysis:

Statistical analysis of the data will be performed using IBM SPSS Statistics. Results will be presented as mean, SD, median, range, and 95% CI. Parametric data will be compared using paired tests, and non-parametric data using Mann-Whitney Test. Categorical variables will be tested using the chi-square test.

Power calculation for cross-sectional study and exploratory follow-up at 4 months (pilot project):

Rationale: In a recent study on severe asthma, patients received daily tablet prednisolone (>5 mg) for 3 months. 60% of the patients had adrenal insufficiency, 33% had total insufficiency, and 27% had partial insufficiency (32). Patients with CRS are often treated with steroid injections in Denmark, receiving an average of three steroid injections per year (clinical observation, REDCap, Global airways incl. biological treatment). Some receive up to six injections per year, with an effect lasting approximately 6-8 weeks per injection. This means that patients with CRS are only covered for about 6 months out of 12 months per year. This is different from severe asthma with daily treatment. Therefore, we estimate that we can detect half of the findings from the asthma study (32). We therefore expect that half of the 60% who develop insufficiency in the asthma study = 30% of the CRS patients will have adrenal insufficiency. As some will have received steroid injections several months ago, a slight reduction is estimated to 25%. But no less than 25%, as many receive high-dose nasal steroids, which, like steroid cream, may cause adrenal insufficiency (3). The 25% is our best estimate. It may be higher but not lower. The literature has documented that 8% of a population have adrenal insufficiency without having received supplemental steroids before the test. To

demonstrate a difference between the background population and our population with 25% adrenal insufficiency, we will need to investigate 72 patients with an alpha value of p <0.05 and a power of 80%, and with a dropout rate of 10%, we will need to test around 80 patients (cross-sectional study).

In the exploratory follow-up at 4 months (pilot project), we will investigate whether good adherence (>80%) to nasal steroids versus continued poor adherence (<80%) changes in P-cortisol compared to measurement of P-cortisol from the cross-sectional study. It is not known whether good adherence (>80%) changes adrenal function. This pilot project will be used for a possible future study, where the effect of adherence will be the primary focus. Therefore, we will include all 80 patients from the cross-sectional study and divide their results into good and poor adherence.

Extraction of biological material:

A maximum of 14 ml of blood is extracted during each Synacthen test (minimum 0.5-3.5 ml maximum split tube x 2-, and 3.5-ml maximum x 2 for the first blood sample for P-cortisol baseline and for the second blood sample for P-cortisol determination). The first blood sample is collected for P-cortisol measurement before the IV injection of ACTH and a minimum of 0.5 ml and a maximum of 3.5 ml of blood is extracted. The second blood sample is collected after 30 minutes following the IV injection of ACTH, and a minimum of 0.5 ml and a maximum of 3.5 ml of blood is extracted. The material is destroyed after analysis. Therefore, no research biobank will be established.

Information from patient records:

Patient information will be collected during the participant's visit to the Luftvejsklinik. Information about the participant, such as medical history, examinations, and medication use, will be obtained from the medical records. The information will only be used to screen whether the participant can participate in the project. Journal information used in the project before the participant has given consent will be disclosed to the researcher, as the researcher does not have access to obtain the information from the journal before consent. Once the participant has given consent, the responsible trial sponsor and any regulatory authority will have direct access to obtain information about the participant's medical records to see information about the participant's health conditions that may be necessary for the implementation of the project. Additionally, this is also for monitoring purposes, including self-monitoring, quality control, and monitoring that they are obligated to perform. If the participant has undergone blood tests and DEXA scans before the initial pre-examination and signing of the consent form, this data will be obtained from the patient's medical records if the participant wishes to participate in the project. Thus, unnecessary examinations will not be performed when data already exists. Data obtained from patient records after consent will be used in the project. This includes medical history, age, height, weight, objective clinical examinations, DEXA scans, blood test results, lung function values, and data from patient-completed questionnaires. The same data will be used in the exploratory follow-up study.

Treatment of personal information and information:

The project will be carried out in submission with the General Data Protection Regulation and the Data Protection Act. The researcher will ensure that the information meeting takes place in an undisturbed location in the department. They will be informed that participation is voluntary and that they will have at least 24 hours to consider their decision. Participants will also be made aware that they have the right to have a support person present during the information meeting to ensure that the participant feels safe, or to assist with relevant questions, keeping track of what was said and decided during the meeting. However, participants can also sign the consent form on their own request before the meeting. They will also be

informed that they can withdraw from the project at any time without a reason and with immediate effect. If they wish to participate, they must fill out a written consent form for participation. If the participant wishes to take part in the project, they will receive oral and written information. They will also be informed that the project manager may withdraw a participant from the project at any time, regardless of the reason. The participant will be informed that they may be withdrawn from the project if they have another significant illness, do not comply with the protocol, or have a lack of ability to read and understand Danish.

Finance:

The mentioned research group has initiated the project. There is no increased financial consumption associated with the project as it involves patients who are part of the clinical outpatient treatment process at the ~~Respiratory Clinic~~Luftvejsklinik, ENT, RH. Funding has been sought for additional work for a nurse at the Lung Association, Rigshospitalet's research fund, and other small and large foundations. A final response is awaited in the spring of 2023. Included patients and the Regional Ethics Committee for the Capital Region will be informed of the name of the donor and the amount of support if support is obtained.

Conflicts of Interest:

There are no financial conflicts of interest to report related to this project.

Publication of Results:

All results, whether positive, negative, or inconclusive, will be published via www.clinicaltrials.gov.

Scientific Ethical Considerations:

The participant's right to self-determination to choose to participate in the project will be respected. They will be sufficiently informed about the purpose of the project. They will be informed that their participation is voluntary and that they can withdraw from the project at any time without it having consequences for their future treatments and consultations in the healthcare system. They will receive oral and written information about the project. They will also be informed that they have at least 24 hours to consider before giving consent or not to participate. If they wish to participate, written informed consent will be obtained when they have decided whether or not to participate. The project has been approved by the Capital Region Data Protection Center P-2022-493. The project is also being carried out based on the researcher group's expectation that the results will be useful for future treatments.

Information on Compensation:

The trial is covered by the hospital's patient compensation.

Bibliography:

1. Lange B, Holst R, Thilsing T, Baelum J, Kjeldsen A. Quality of life and associated factors in persons with chronic rhinosinusitis in the general population: a prospective questionnaire and clinical cross-sectional study. Clin Otolaryngol. 2013;38(6):474–80.
2. Lindholm J. Binyreinsufficiens og behandling med glukokortikosteroid. Ugeskr Laeger. 2016;178(12):V10150788.
3. Egeberg A, Schwarz P, Harsløf T, Andersen YMF, Pottegård A, Hallas J, et al. Association of Potent and Very Potent Topical Corticosteroids and the Risk of Osteoporosis and Major Osteoporotic

Fractures. JAMA Dermatology. 2021;157(3):275–82.

4. Aasbjerg K, Torp-Pedersen C, Backer V. Specific immunotherapy can greatly reduce the need for systemic steroids in allergic rhinitis. Allergy Eur J Allergy Clin Immunol. 2012;67(11):1423–9.
5. Jensen MR, Arndal E, Von Buchwald C. Kronisk rinosinuitis. Ugeskr læger [Internet]. 2019;181(16):1505–8. Available from: www.rhinologiskselskab.dk
6. Dansk Rhinologisk Selskab. Klinisk retningslinje: Kronisk rhinosinuitis [Internet]. 2015. Available from: http://dsohh.dk/wp-content/uploads/2015/04/DSOHH-KKR-kronisk-rhinosinutitis.pdf
7. Frendø M, Håkansson K, Schwer S, Rix I, Ravn AT, Backer V, et al. Asthma in ear, nose, and throat primary care patients with chronic rhinosinusitis with nasal polyps. Am J Rhinol allergy Off J Am Rhinol Soc Int Rhinol Soc. 2016;30(3):67–71.
8. De Prins L, Raap U, Mueller T, Schmid-Grendelmeier P, Haase CH, Backer V, et al. White Paper on European Patient Needs and Suggestions on Chronic Type 2 Inflammation of Airways and Skin by EUFOREA [Internet]. Vol. 3, Frontiers in Allergy . 2022. Available from: https://www.frontiersin.org/article/10.3389/falgy.2022.889221
9. Reddel HK, Bacharier LB, Bateman ED, Boulet L-P, Brightling C, Brusselle G, et al. GINA-Main-Report-2021-V2-WMS.pdf. 2021. p. 1–217.
10. Bårnes CB, Ulrik CS. Asthma and adherence to inhaled corticosteroids: current status and future perspectives. Respir care Off J Am Assoc Respir Ther. 2015;60(3):455–68.
11. Lam WY, Fresco P. Medication Adherence Measures: An Overview. Biomed Res Int. 2015;2015:217047–12.
12. Organization WH. Adherence to Long-term Therapies. Geneva: World Health Organization; 2003.
13. Hedegaard BO, Håkansson KEJ, Jensen FF, Ulrik CS, Weinreich UM. Determining Persistence with an Inhaled Corticosteroid in Asthma: Assessment Using an Objective Measurement vs the Self-Reported Foster Score. J Asthma Allergy. 2022;15:25–33.
14. Chan AHY, Horne R, Hankins M, Chisari C. The Medication Adherence Report Scale: A measurement tool for eliciting patients' reports of nonadherence. Br J Clin Pharmacol. 2020;86(7):1281–8.
15. Horne R, Weinman J. Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. J Psychosom Res. 1999 Dec 1;47(6):555–67.
16. Cohen JL, Mann DM, Wisnivesky JP, Horne R, Leventhal H, Musumeci-Szabó TJ, et al. Assessing the validity of self-reported medication adherence among inner-city asthmatic adults: the Medication Adherence Report Scale for Asthma. Ann Allergy, Asthma Immunol. 2009 Oct 1;103(4):325–31.
17. Morrison D, Mair FS, Yardley L, Kirby S, Thomas M. Living with asthma and chronic obstructive

airways disease: Using technology to support self-management – An overview. Chron Respir Dis. 2017 Nov 1;14(4):407–19.

18. Ulrik CS, Backer V, Søes-Petersen U, Lange P, Harving H, Plaschke PP. The patient's perspective: adherence or non-adherence to asthma controller therapy? J asthma Devoted to asthma Relat Cond Off J Assoc Care Asthma. 2006;43(9):701–4.
19. Mäkelä MJ, Backer V, Hedegaard M, Larsson K. Adherence to inhaled therapies, health outcomes and costs in patients with asthma and COPD. Respir Med. 2013;107(10):1481–90.
20. Baarnes CB, Hansen AV, Ulrik CS. Enrolment in an Asthma Management Program during Pregnancy and Adherence with Inhaled Corticosteroids: The "Management of Asthma during Pregnancy" Program. Respiration. 2016;92(1):9–15.
21. Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S, et al. Epos 2020. Vol. Suppl 29, Official Journal of the European and International Rhinologic Societies and of the Confederation of European ORL-HNS. 2020.
22. Husebye ES, Pearce SH, Krone NP, Kämpe O. Adrenal insufficiency. The lancet. North American ed. 2021;397(10274):613–29.
23. Broersen LHA, Pereira AM, Jørgensen JOL, Dekkers OM. Adrenal insufficiency in corticosteroids use: Systematic review and meta-analysis. J Clin Endocrinol Metab. 2015;100(6):2171–80.
24. Borresen SW, Klose M, Baslund B, Rasmussen ÅK, Hilsted L, Friis-Hansen L, et al. Adrenal insufficiency is seen in more than one-third of patients during ongoing low-dose prednisolone treatment for rheumatoid arthritis. Eur J Endocrinol. 2017;177(4):287–95.
25. Dansk Endokrinologisk Selskab. Binyrebarkinsufficiens [Internet]. Available from: https://endocrinology.dk/nbv/hypofyse-og-binyresygdomme/binyrebarkinsufficiens/
26. Winblad L, Larsen CG, Håkansson K, Abrahamsen B, von Buchwald C. The risk of osteoporosis in oral steroid treatment for nasal polyposis: a systematic review. Rhinology. 2017 Sep;55(3):195–201.
27. Compston J. Glucocorticoid-induced osteoporosis: an update. Endocrine. 2018 Jul;61(1):7–16.
28. Weare-Regales N, Hudey SN, Lockey RF. Practical Guidance for Prevention and Management of Glucocorticoid-Induced Osteoporosis for the Allergist/Immunologist. J allergy Clin Immunol Pract. 2021 May;9(5):1841–50.
29. Ebeling PR, Nguyen HH, Aleksova J, Vincent AJ, Wong P, Milat F. Secondary Osteoporosis. Endocr Rev. 2022;43(2):240–313.
30. (CKO) R> HS. Synacthentest (ACTH-test) [Internet]. 2023. Available from: https://vip.regionh.dk/servlet/GeneratePDF?openservlet&server=172.20.157.23:63148&host=188.2

44.78.177&pdfdb=VIP/Admin/PDFDMS30.nsf&database=VIP/Redaktoer/130171.nsf&docid=XC2008
4EB49E1ED56C1257988003895F5&readeraccess=false&hmargin=18mm&vmargin=15mm&foote

31. Schneider B. Hvad er REDCap og hvilken funktionalitet indeholder det REDCap funktioner. Region Hovedstaen; 2017. p. 1–3.

32. Menzies-Gow A, Gurnell M, Heaney LG, Corren J, Bel EH, Maspero J, et al. Adrenal function recovery after durable oral corticosteroid sparing with benralizumab in the PONENTE study. Eur Respir J [Internet]. 2022;60(6). Available from: http://dx.doi.org/10.1183/13993003.03226-2021

Informed consent for participation in a health science research project

Research project title: **Adherence in Global Airways – the relationship between steroid intake and the impact on the endocrine axis, bone density, and structure in patients with chronic sinusitis and asthma**

Trial participant declaration of consent:
I have received written and oral information and I know enough about the purpose, the method, the advantages, and the disadvantages of the trial to give my consent to participate in the trial.
I know that it is voluntary to participate and that I can withdraw my consent at any time without losing my present and future rights to receive treatment. I give my consent to participate in the research project and have received a copy of the declaration of consent, as well as a copy of the written information about the project.
Name of the trial participant: _____

Date: _____ Signature: _____

You will be informed if significant new information regarding your health is disclosed during the research project. If you request to not be informed about significant new information regarding your

health that is being disclosed during the research project, please tick here: _____(x)

Would you like to be informed about the results of the research project and any consequences it might have for you?
Yes (x) _____ **No (x)** _____

Would you like to receive text messages from Department of Otorhinolaryngology, Head and Neck Surgery & Audiology with reminders to take your medication and fill out and complete the diary?

Yes (x) _____ **No (x)** _____

Declaration from the person providing information:

I declare that the trial participant has received oral and written information about the trial.
I believe that sufficient information has been provided in order to make a decision regarding participation in this trial.
Name of the person providing information: _____

Date: _____ **Signature:** _____