Volumetric measurements in Graves’ orbitopathy

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Citation for published version (APA):
Summary
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Chapter 1
provides an overview of the current knowledge on pathogenesis, symptoms, natural history and diagnosis of Graves’ orbitopathy (GO). A survey of the development of CT scanning methods throughout time is given. At the end of this chapter the aims of the present thesis are outlined.

Chapter 2
describes the selection and validation of, commercially available, software (Mimics®) for the calculations of orbital fat and extraocular muscle (EOM) volumes from CT scans. Butter was chosen to mimic animal fat tissue because of its ability to be solid in cooled state and soft at room temperature. We inserted small muscles of chicken wings in the butter after placing the butter in thin foil. This ensemble was placed in the orbit of a human skull and an orbital CT scan was made. Two observers calculated the volumes independently. Their measurements showed a high level of observer agreement. To assess the intra- and inter-observer variability, the volumes of 10 patients were calculated by the same two observers. Since the Intra- and Inter-observer Correlation Coefficient (ICC; 0= no correlation, 1= very good correlation) were all above 0.986 the software was judged to be suitable. The method was described precisely step by step to allow other investigators to repeat the measurements.

Chapter 3
In order to establish reference values for orbital fat and muscle volumes, we calculated the orbital soft tissue volumes in 160 Caucasian orbits without disease. To also assess the influence of age, we took care to have at least 10 orbits per decade between 20 and 70 years. We eliminated the anatomical differences between genders by using ratios of fat volume/bony orbital cavity volume (FV/OV) and muscle volume/bony orbital cavity volume (MV/OV). In this way we were able to establish age-specific reference intervals for the ratios of fat and muscle volume. It turned out that, contrary to what was thought until now, the orbital fat volume increased with age instead of decreased. The MV/OV, however, decreased slightly, but only in women.

Chapter 4
We describe orbital volumetry in 95 patients with clinically diagnosed untreated GO, in order to establish the prevalence of each of four groups: group 1, no fat- or muscle increase, group 2, only fat increase, group 3, only muscle increase and group 4, fat- and muscle increase. In each patient we selected the orbit that was most affected by the disease. Contrary to our expectations, the increase in fat volume only was no more than 5.3%, the increase of fat volume in combination with muscle volume was seen in 8.4%. The largest group was the group 3, with only muscle volume increase (61.1 %), and group 4 without fat
or muscle volume increase finally accounted for 25.2%. However, within this group there may have been patients with an increase of fat or muscle volume as compared to their base-line, which did not exceed the upper border of the 95% confidence interval. Several clinical characteristics were compared between these groups. Comparing the groups with and without MV increase, we found that patients with increased MV were older, had more proptosis, more impaired ductions, more diplopia and higher TBII. Compared to patients without an increased FV, patients with increased FV had more proptosis and less diplopia.

Chapter 5
Since we observed a difference in structure in the orbital fat on our CT scans, we decided to look into the CT densities of orbital fat and muscle of controls and GO patients. The mean fat densities of the GO patients were significantly higher than in controls. The mean muscle densities were not different between both groups. There was a correlation between volumes and densities in GO patients: the higher the fat density, the smaller the fat volume and the larger the muscle volumes. We speculated that compression or absorption of orbital fat could be the explanation of this phenomenon.

Chapter 6
We studied the influence of smoking on the orbital volumes of GO patients. Analysis of muscle volume tertiles showed a higher prevalence of current smokers in patients with larger muscle volume but not in patients with larger fat volumes. Current smokers had larger muscle volumes when compared to never smokers and ex smokers. Contrary to earlier reports we found that current smoking is correlated with larger muscle volumes, not with fat volumes.

Chapter 7
In the general discussion, we discuss our findings against the background of current literature. We describe the technical aspects of volumetry and the differences in methods of calculating orbital soft tissue volumes in different reports. We compare our group of 160 control orbits with the, in general small, groups of controls in the literature. The differences between MV and FV in our GO patient group and groups described by previous observers are outlined. The finding that the fat volume is larger when the duration of the disease is longer (table 2, general discussion) could be supported by not volumetric data about Th1 and TH2 cytokines. Mean fat density increase is correlated with larger MV but smaller FV. This phenomenon is not described in the literature so we can only speculate on the nature and the mechanism.
In one report on volumetry in GO patients it was stated that smoking increased connective tissue containing fat. We found, on the contrary, an influence on MV and not on FV. Finally we propose future research in volumetry, especially longitudinal studies with the same patient group. The importance of volumetry is emphasized.