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Exophthalmos Caused by Excessive Fat: CT Volumetric Analysis and Differential Diagnosis

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CT has proven to be excellent in identifying orbital pathology responsible for proptosis. Occasionally, no discrete mass or extraocular muscle enlargement to explain the exophthalmos is found, only an appearance suggestive of an abnormal increase in orbital fat volume. Fifteen patients were studied with proptosis apparently resulting from increased orbital fat. Clinical follow-up revealed that four of them had Graves orbitopathy, unilateral in one; two had Cushing disease/syndrome; and nine were obese without endocrinopathy. The orbital volume and percentage orbital fat volume were measured by CT software analysis in these patients and in a control group of 16 patients without proptosis. Measurements of proptosis and thickness of the scalp fat pad at the inion level were also performed. Significantly greater values for orbital fat volume, percentage fat volume, and proptosis were found in the proptosis group compared with the control group. There was excellent correlation between proptosis and percentage fat volume, supporting the contention that increased orbital fat is responsible for the proptosis. The thickness of the scalp fat pad at the inion level was significantly greater in obese and Cushing patients than in control subjects, but the thickness was not significantly greater in Graves patients than in controls. Proptosis and inion fat were well correlated (r = 0.74) in the control and obese patients, which suggests a relation between general body fat and orbital fat volume.

Exophthalmos, unilateral or bilateral, is a frequent indication for orbital CT scanning and medical evaluation. CT has proven to be excellent in identifying orbital pathoogy responsible for proptosis. Occasionally, no discrete mass or extraocular muscle enlargement to explain the proptosis is found, except for an appearance suggestive of an abnormal increase in orbital fat volume [1–8]. There are a few reports of exophthalmos resulting from excessive orbital fat in patients with Graves disease [1–6], Cushing disease or syndrome [1, 7], and obesity [1, 8–10]. No previous report investigates all three etiologies or considers differential diagnoses.

It is the intention of this study to document a greater orbital fat volume in patients with a CT diagnosis of excess orbital fat proptosis compared with a control group of people without proptosis; to correlate orbital fat volume with the amount of proptosis; and to investigate whether a measurement of the thickness of scalp fat at the level of the inion is predictive of obesity and thereby might serve as a CT differential diagnostic sign between Graves disease versus obesity or Cushing disease/syndrome when clinical data are unavailable.

Subjects and Methods

Fifteen patients with exophthalmos determined by CT and clinical criteria in whom CT did not reveal an orbital mass or enlargement of the extraocular muscles represent the proptosis group. Clinical follow-up showed that four had Graves disease, unilateral in one; two had Cushing disease/syndrome (one from chronic steroid administration for sarcoidosis; the other from an ACTH-producing pituitary adenoma); and nine were grossly obese with no endocrine

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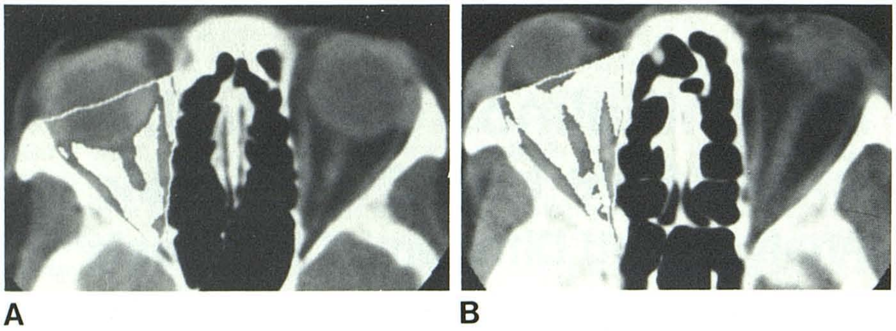

Fig. 1.—Orbital boundaries and volume measurements. **A**, Midorbital axial CT section, control subject. No evidence of proptosis. Volume measurements were performed on right orbit. Anterior orbital boundary is defined by white line passing through globe from zygoma to lacrimal bone. Traced line continues along edge of orbital bony margin. Patches of white within these boundaries represent pixels with density values in range of fat. White areas conform to areas filled with fat in opposite orbit. **B**, Slightly higher section in patient with proptosis caused by excess orbital fat. Considerably more orbital fat compared with control patient.

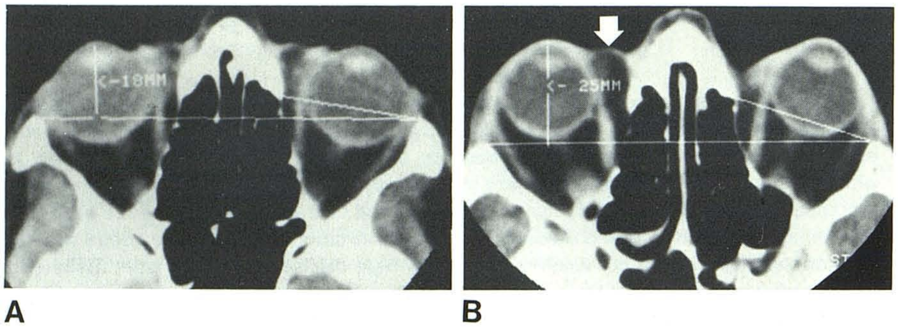

Fig. 2.—CT proptosis measurements and guidelines. **A**, Axial orbital CT section including lenses, control subject. Interzygomatic line is drawn. Length of perpendicular line from anterior margin of globe to this line in millimeters represents proptosis measurement, as illustrated for right orbit. In this case, measurement of 18 mm falls well below upper limit of normal (21 mm). **B**, Patient with excess fat exophthalmos. Proptosis measurement is 25 mm. Anterior bowing of right medial orbital septum (*arrow*) is well seen.

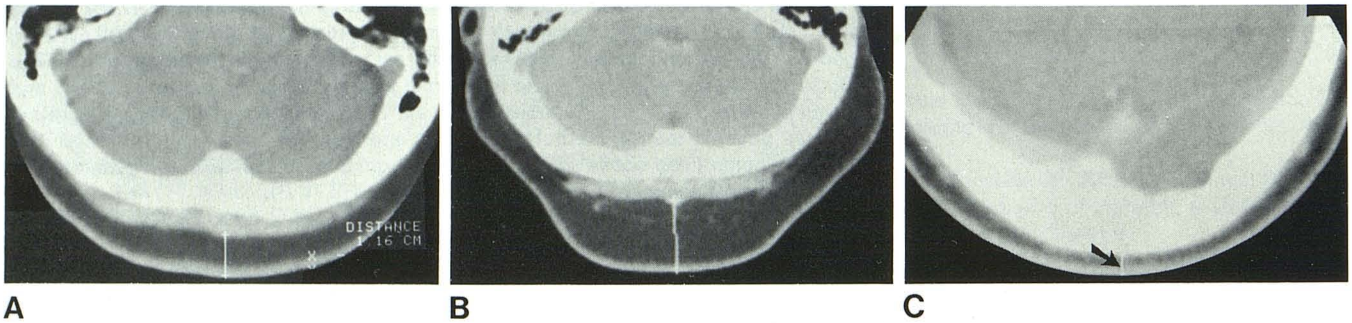

Fig. 3.—Measurement of scalp fat thickness at inion level. **A**, Obese patient with excess fat exophthalmos. Measurement shown by line between cursors, which extends from scalp margin posterior to inion to muscle. Fat thickness (1.16 cm or 11.6 mm) is recorded beneath *DISTANCE* in lower right corner. **B**, Scalp fat measures 24 mm in patient with Cushing syndrome caused by long-term steroid treatment. **C**, Scalp fat measurement (*arrow*) of 3.4 mm in patient with Graves ophthalmopathy was smallest scalp fat measurement in any patient, including control group.

abnormality. A control group of 16 subjects without exophthalmos by either clinical or CT criteria were randomly obtained from 74 patients with untreated unilateral primary choroidal melanoma limited to the globe. These patients all had complete axial CT orbital examinations available for analysis on floppy disks.

All scanning was performed on a GE 8800 CT/T scanner. The orbits were scanned with either contiguous 1.5 or 5-mm-thick slices in the axial plane at 0° to −10° to the orbitomeatal line.

Measurements of orbital volume and orbital fat volume were made for both orbits using the volume measurement function in General Electric Display (GEDIS) experimental software (General Electric, Milwaukee). This program requires the examiner to define on a CT section the boundaries of the area of interest with the trace CT console function and to designate a density range in Hounsfield units for the tissue whose volume is to be determined. The computer sums the voxels within the prescribed density range to derive the partial volume of the tissue of interest. The total volume within the traced boundaries, the density of the tissue of interest, and the percentage of the total volume occupied by the tissue of interest are also calculated. This operation was performed for all CT orbital sections to obtain total orbital volume and orbital fat volume. For this study, the orbital boundaries for orbital volume determination were defined by tracing along the edge of the bony walls of the orbit. On slices where the anterior boundary of the orbit was not defined by bone, the anterior aspects of the medial and lateral orbital bony margins were connected by a straight line to form the anterior boundary (fig. 1). By choosing the anterior boundary in this fashion, in cases of marked proptosis, some of the postseptal orbital fat would be excluded from measurement, but erroneous inclusion of periorbital fat would be avoided and identical boundaries could be used for all patients. A density range of −200 to −3 H was chosen for the measurement of orbital fat volume since no other intraorbital tissue lies within this density range, as shown by initial trials (fig. 1). The percentage of total orbital volume (OV) occupied by fat (FV) was

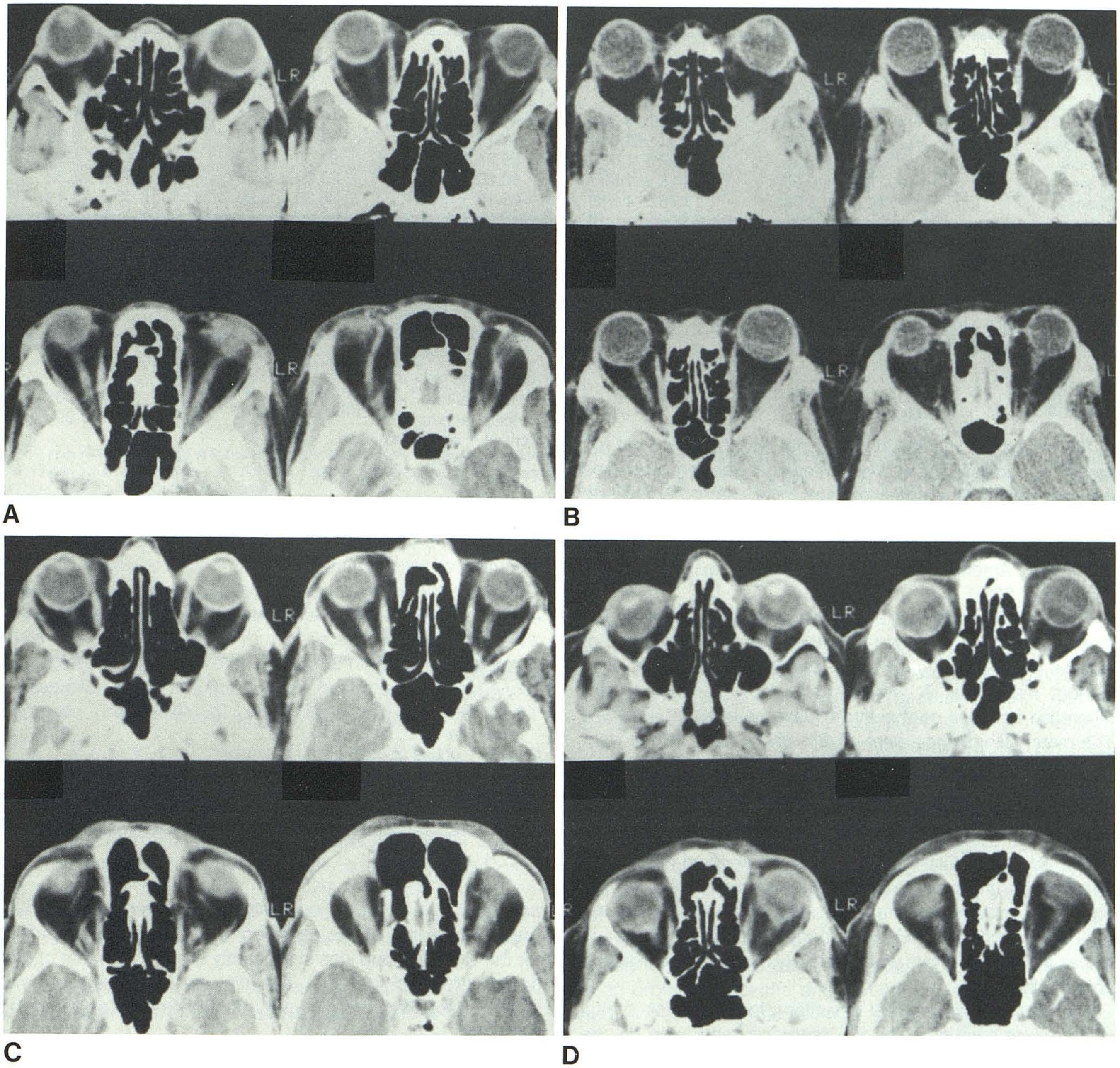

Fig. 4.—CT appearance of excess fat exophthalmos. **A**, Axial orbital CT sections in obese patient. Bilateral proptosis, normal extraocular muscles, and no evidence of discrete orbital mass. Orbital septa bowed anteriorly. Apparent bilateral increase in orbital fat. **B**, Orbital scans in patient with Cushing syndrome show same findings as in **A. C**, Graves ophthalmopathy. No detectable enlargement of extraocular muscles, and CT findings are essentially identical to **A** and **B. D**, Graves ophthalmopathy. Excess fat exophthalmos only on left.

obtained by $\%FV = FV/OV \times 100$.

Proptosis in millimeters was measured by dropping a perpendicular line from the most anterior aspect of the globe on a section including the lens to a line drawn between the anterior tips of the frontal processes of the zygomas (fig. 2).

The thickness of the scalp fat pad in millimeters was measured posterior to the inion on a slice that also included the sella using the CT cursor measure distance function (fig. 3).

Statistical analysis of the data was performed in several ways: Paired Student *t* tests were used for comparing the percentage of fat in the right versus left orbit and in the orbit containing the choroidal melanoma versus the normal orbit of the control group. Independent Student *t* tests were used for comparing measurements of orbital volume, orbital fat, percentage orbital fat, proptosis, and inion fat from the control group with measurements from the proptosis group and its subdivisions. Linear and multiple regression analyses were used for correlation of percentage orbital fat, proptosis, and inion fat for all 31 subjects and a subgroup without endocrinopathy composed

TABLE 1: **Measurements by Patient Group**

Group	Mean ± SD				
	Orbital Fat (cm^3)	Orbital Volume (cm^3)	% Orbital Fat	Proptosis (mm)	Scalp Fat Pad (mm)
Control	8.16 ± 1.68	19.82 ± 3.68	41.51 ± 7.6	15.44 ± 2.52	6.78 ± 1.34
Proptosis	11.04 ± 1.76	18.97 ± 2.00	58.15 ± 6.85	24.77 ± 2.45	10.84 ± 5.39
Obesity	11.34 ± 1.4	18.93 ± 1.93	59.84 ± 4.54	25.03 ± 2.07	10.42 ± 1.95
Graves	9.60 ± 0.63	19.15 ± 1.59	50.20 ± 4.73	23.90 ± 3.85	8.20 ± 3.82
Cushing	12.53 ± 3.64	18.75 ± 4.31	66.15 ± 4.31	25.30 ± 0.99	18.00 ± 14.14

of the control and obese patients. Values of $p > 0.05$ derived from the t tests were interpreted as demonstrating a lack of significant difference between the groups being compared.

Results

The orbital CT findings in excess fat exophthalmos did not vary with etiology (fig. 4). These findings were proptosis, no enlargement of the extraocular muscles nor any other discrete orbital mass to account for the proptosis, and the subjective impression that there is more than the usual amount of fat in the orbit(s). Anterior bowing of the orbital septa is an ancillary finding (fig. 2B).

The control group was examined for possible influence of their melanoma on orbital fat content. The mean volume of fat was 41.4% for eyes with melanoma and 41.7% for eyes without melanoma. A paired t test showed no significant difference between normal and melanoma eyes ($p = 0.687$). The mean fat volumes were 41.8% and 41.2% for the right and left eyes, respectively, in the control group, and again no significant difference was found (paired t test, $p = 0.538$). The values for the right and left orbit for each patient were averaged for orbital fat, percentage orbital fat, proptosis, and orbital volume for further analysis. It is recognized that for the patient with unilateral Graves ophthalmopathy who had an orbital fat volume of 9.7 cm^3 (51.9%) for the abnormal left orbit and 7.8 cm^3 (44.4%) for the right orbit, using the average values for the two orbits would partially obscure this unilateral abnormality.

The means and standard deviations for orbital fat, orbital volume, percentage orbital fat, proptosis, and inion fat are shown in table 1 for the control and proptosis groups and for the etiologic subdivisions of the proptosis group. Comparison by independent t tests of the control and proptosis groups for percentage orbital fat, proptosis, and inion fat showed significantly higher values in the proptosis group for these variables ($p < 0.001$). There was no significant difference between the orbital volume of the proptosis and control groups. Comparison of the control group versus the group of nine obese patients for these same variables yielded essentially the same results, with significantly greater percentage orbital fat, inion fat, and proptosis in the obese group ($p < 0.001$) and no significant difference in orbital volume. For the two patients with Cushing disease/syndrome, orbital and inion fat and proptosis were also significantly greater than in the control group ($p < 0.001$), again with no significant difference in orbital volume. The percentage of orbital fat of the four patients with Graves ophthalmopathy was significantly greater than that of the control group ($p = 0.02$), proptosis for the Graves group was significantly greater than that of the control group ($p < 0.001$), but inion fat and orbital volume were not significantly different for the Graves and control subjects.

TABLE 2: **Multiple Regression Analyses of Proptosis versus Orbital Fat and Scalp Fat Pad**

Group: Variable	Coefficient	Probability
All subjects ($n = 31$):		
%Orbital fat	0.35	0.001
Scalp fat pad	0.09	0.60
Control + obese ($n = 25$):		
%Orbital fat	0.26	0.001
Scalp fat pad	0.91	0.007

Note.—For all subjects, intercept = 1.75; multiple correlation = 0.77; multiple $r^2 = 0.59$ ($F = 19.8$; $p < 0.001$). For control plus obese subjects, intercept = −0.78; multiple correlation = 0.86; multiple $r^2 = 0.73$ ($F = 30.4$; $p < 0.001$).

TABLE 3: **Correlations of Orbital Fat, Scalp Fat, and Proptosis**

Group: Variable	% Orbital Fat	Scalp Fat	Proptosis
All subjects ($n = 31$):			
% Orbital fat	1	0.46	0.76
Scalp fat	...	1	0.41
Proptosis	...	...	1
Control + obese ($n = 25$):			
% Orbital fat	1	0.61	0.79
Scalp fat	...	1	0.74
Proptosis	...	...	1

Table 2 shows the results of multiple regression analysis of proptosis versus percentage orbital fat and inion fat for all 31 patients. The correlation between proptosis and orbital fat was 0.76 ($p < 0.001$), with moderate correlation between proptosis and inion fat at 0.41 and between orbital fat and inion fat at 0.46 (table 3). The multiple regression model shows that 59% of the variance of proptosis can be explained by percentage orbital fat and inion fat together (table 2).

Table 2 also shows the multiple regression analysis for the control group plus the obese group, eliminating the patients with Graves and Cushing. All three correlations are greater than when all patients were included, with 73% of the variance now explained by the multiple regression model. The coefficients for percentage orbital fat and inion fat are highly significant. A scatter diagram with best-fitted line is shown for proptosis versus percentage fat volume for all 31 patients in

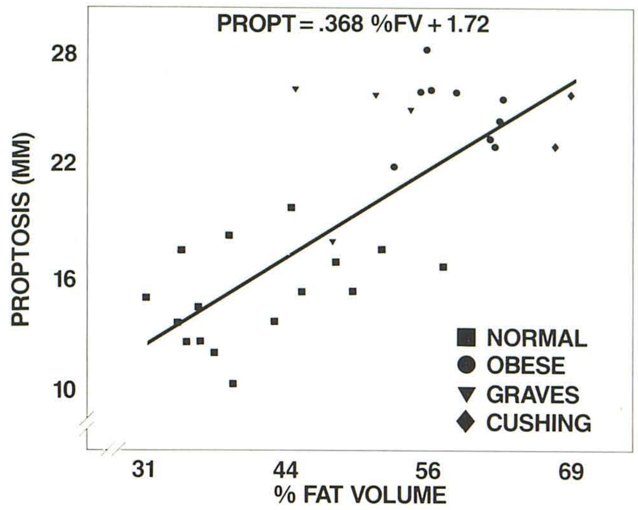

Fig. 5.—Scatter diagram with best-fitted line for proptosis versus percentage fat volume for all 31 patients. As indicated by data and line, proptosis increases with increase in percentage fat volume.

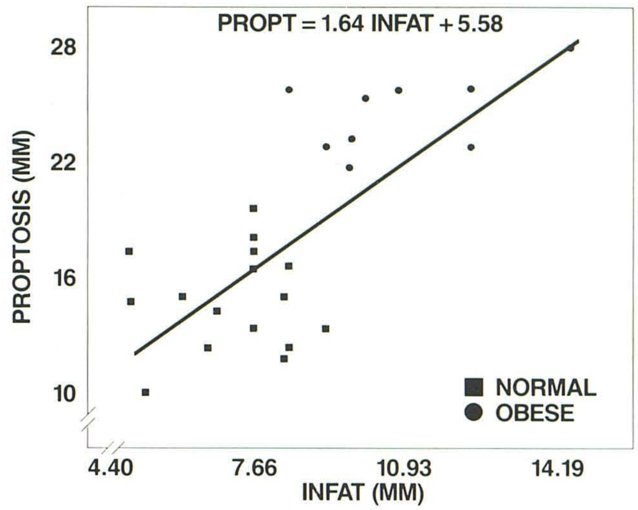

Fig. 6.—Scatter diagram with best-fitted line for proptosis versus thickness of scalp fat pad at inion level (INFAT) for control and obese patients. Proptosis increases with increase in scalp fat. Control patients, all of whom had proptosis measurements less than 21 mm, are grouped in lower left, and obese patients, all of whom had proptosis measurements exceeding 21 mm, are grouped in upper right.

figure 5. It may be seen that the Graves patients had, among the proptosis group, relatively lower values for orbital fat; the Graves subject with unilateral disease showed a mean proptosis measurement of 18 mm because of the influence of averaging in the normal orbit. A scatter diagram for proptosis versus inion fat for the normal plus obese group is shown in figure 6. The density of orbital fat was normal in all 31 subjects.

Discussion

Exopthalmos resulting from an increase in orbital fat volume has been described in Graves ophthalmopathy [1–6], in Cushing disease/syndrome [1, 7], and with obesity [1, 8–10]. No previous report has discussed all etiologies of this condition nor attempted to establish CT criteria to distinguish between them.

The results of our report demonstrate that the 15 patients with CT diagnoses of exophthalmos considered to be caused by an increase in orbital fat have a significantly greater proportion of their orbits occupied by fat than do the 16 control subjects lacking proptosis. The number of cases in each subcategory of the proptosis group, particularly Graves and Cushing diseases, unfortunately, is small. Despite this, statistically significant differences for percentage orbital fat between the proptosis versus the control subjects, and for inion fat between the obese and Cushing versus control subjects, were obtained. We hope to have the opportunity to study more subjects with excess fat exophthalmos to increase our confidence in generalizing our conclusions regarding the populations of patients in each etiologic subcategory of this condition.

Several previous studies have used CT to measure orbital volume and intraorbital soft-tissue volume [2, 11–13]. Forbes et al. [2] measured the volume of orbital fat and muscle in 19 normal subjects and in 19 patients with Graves ophthalmopathy. They found two distinct groups among the patients with Graves ophthalmopathy. Nine patients constituted their type A Graves, in which there was a marked increase in orbital muscle volume and a decrease, compared with their normal group, in orbital fat volume. This group had little or no clinical proptosis. Their type B Graves group consisted of 10 patients, most of whom had increase in both orbital fat volume and extraocular muscle volume, but some of whom had exclusive increase in orbital fat volume. Exophthalmos was clinically evident in this group. Feldon et al. [12] measured extraocular muscle volume in 50 patients with Graves ophthalmopathy and found relatively poor correlation between proptosis and the extent of muscle enlargement. This observation would suggest that increase in nonmuscular orbital soft tissue, namely fat, must influence the degree of proptosis. While the mean orbital fat volume and percentage orbital fat volume were higher in the patients in our study with Graves ophthalmopathy than in the control group, even higher values for these measurements were found among the obese patients and those with Cushing disease/syndrome. Proptosis was well correlated with the quantity of orbital fat in our study, which supports the contention of a cause-and-effect relation between the increase in orbital fat and the proptosis noted in the proptosis group, as was suspected from the CT appearance of their orbits.

There is no satisfactory explanation in the literature regarding the pathogenesis of increased orbital fat volume occurring with Graves ophthalmopathy. It has been proposed that infiltration of the fat by edema and inflammatory cells is responsible for the increase in fat volume [2, 13, 14]. Trokel and Jakobiec [6] reviewed biopsy material including orbital fat in patients with Graves ophthalmopathy and were unable to find evidence for inflammatory infiltration of the fat. They also stated that, in their experience, the CT density of orbital fat in Graves disease is identical to normal orbital fat, which suggests against infiltration of the fat. The density of the orbital fat was normal in our three cases of Graves ophthalmopathy. There is generalized increase in body fat in obesity and Cushing disease/syndrome [7, 8]. An increase in orbital fat in these two conditions presumably reflects this generalized fatty accumulation. The relatively strong correlation between scalp fat thickness, orbital fat volume, and extent of proptosis noted in our study would support this hypothesis. Little is known about the circumstances under which orbital fat pads will participate along with other fat depots in increased fat accumulation; racial, genetic, and developmental factors may be involved. Excess fat exophthalmos is not seen in most patients on steroid therapy who manifest other cushingoid changes [7]. The percentage of obese patients that would exceed normal limits of measurement for proptosis, either by CT or exophthalmometry, is unknown.

In cases of Graves ophthalmopathy with combined increases of extraocular muscle and orbital fat volumes, CT diagnosis is not difficult. In cases with isolated increase in orbital fat volume, differential diagnosis from obesity and Cushing disease/syndrome becomes more challenging. Clinical and laboratory evidence, when available, of Graves disease or Cushing disease/syndrome will establish the diagnosis in these patients. In obese patients with excess fat exophthalmos, one must first exclude endocrinopathy before blaming the obesity for the proptosis. When the radiologist is faced with a CT scan suggestive of excess fat exophthalmos without immediate access to the patient or clinical data, certain information on the scan may aid in differential diagnosis. Unilateral excess fat exophthalmos has not been reported with obesity or Cushing disease/syndrome, nor is it logical that it should occur in these conditions. While unilateral orbital involvement in Graves ophthalmopathy is uncommon, occurring in about 5% of cases [4, 5], it remains the most common cause of unilateral proptosis [8, 14] and should be the favored diagnosis in cases of unilateral excess fat exophthalmos. The thickness of the scalp fat pad at the inion level was significantly greater among the obese patients than in the control group in our study. This finding is perhaps made more significant since no effort was made to exclude overweight subjects from the control group. The patients with Cushing disease/syndrome also had large inion fat measurements, significantly greater than those of the control group. The mean inion fat measurement for the patients with Graves ophthalmopathy was not significantly greater than that of the control group; in fact, one of the patients with Graves disease had the smallest inion fat measurement (3.4 mm) of any patient studied. A large inion fat measurement in a patient with excess fat exophthalmos is not helpful in the differential diagnosis, since patients with Graves ophthalmopathy can also be obese. However, our data suggest that a small inion fat measurement associated with excess fat exophthalmos is unlikely to be found in obesity or Cushing disease/syndrome, and a diagnosis of Graves ophthalmopathy should be suggested under these circumstances.

The density of the orbital fat appeared normal in all of our subjects. There are conditions, however, such as orbital pseudotumor, leukemia, lymphoma, and, in children, metastatic neuroblastoma, that can diffusely infiltrate orbital fat, inhomogeneously raising its density (the "dirty orbit"), and cause proptosis [8, 15–17]. It is important to recognize the alteration of the appearance of the orbital fat in these conditions to distinguish them from those entities described above, which cause proptosis by increasing the volume of normal orbital fat.

In summary, this study has shown that there is an increased amount of orbital fat in patients with Graves orbitopathy, Cushing disease/syndrome, and obesity with proptosis and a CT scan showing no orbital mass other than an appearance suggesting excessive orbital fat to account for exophthalmos. The larger inion fat measurements in the obese and Cushing subjects suggest that the amount of scalp fat may reflect total body fat and that a small scalp fat measurement in a patient with excess fat exophthalmos would favor a diagnosis of Graves orbitopathy over obesity or Cushing disease/syndrome.

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