Does adipocyte hypercellularity in obesity exist?

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Summary and conclusions

Adipose tissue samples were biopsied from three subcutaneous sites in 80 obese and 27 non-obese patients. Additional samples were taken from intra-abdominal sites in 44 of the patients. There was a small increase in the calculated number of fat cells in the more obese patients, but there was no relation between fat-cell number and obesity of childhood onset. Omental fat cells were one-third the size of subcutaneous cells. Thus the calculated number of fat cells, usually based solely on subcutaneous samples, is an underestimate of the true number, and most obese patients can accommodate their fat without needing to recruit new cells.

The diagnosis of "hyperplastic" obesity—that is, an excess number of fat cells—is unreliable and its relation to infantile obesity doubtful.

Introduction

Studies on fat cells in obesity have been stimulated by the hypothesis that an excess number of cells is found in patients whose obesity begins in childhood and that there are one or more critical periods during development when overfeeding may lead to an abnormal increase in adipocytes, which then have a lifelong tendency to retain triglyceride.¹⁻⁵ Björntorp *et al* claimed that obese adults with an excess number of cells—that is, with hyperplastic obesity—found it particularly hard to slim,⁶ which increased the emphasis on the need to change infant feeding practices in order to prevent adult obesity.

We have re-examined the problem of measuring the number of fat cells and find that many ideas on fat-cell number are incorrect and that the prevalence and significance of hyperplastic obesity have been much exaggerated.

Patients and methods

We studied 107 patients (83 women and 24 men) aged 16-80 years with weights ranging from 13% underweight to 225% overweight. Desirable weight was defined as that corresponding to the midpoint of the weight range for medium frame size listed by the Metropolitan Life Insurance Company,⁷ and obesity was defined as 20% or more above the desirable weight. Sixty-one of the obese men and women were attending an obesity clinic, having tried various therapeutic measures without success; they therefore represented a selected group of obese people. Fat cells were sampled by aspirating subcutaneous tissue under local anaesthesia from the epigastric, supra-iliac, and femoral areas. The remaining 46 obese and non-obese

patients were undergoing elective abdominal surgery, during which samples of subcutaneous fat were removed; in 44 cases intra-abdominal fat samples were also taken during the operation. Patients gave informed and written consent for the procedure, which was approved by the hospital and unit ethical committees.

The mean diameter of the fat cells and hence the triglyceride content were determined as previously described⁸ from frozen sections fixed in 10% formol saline. Cell size varied considerably at each site, 20% of the sites having a non-Gaussian distribution; the distribution of sizes was taken into account when calculating the number of fat cells. Total body fat was derived from skinfold measurements,⁹ but almost identical values were obtained from whole-body potassium measurements made in 61 of the patients.

Results

Figure 1 shows that there was a considerable range in the mean triglyceride content of the fat cells in both normal and obese patients. Despite this variation, a progressive rise in the lipid content of the adipocytes occurred with increasing obesity until patients were about 80% overweight. Above this weight there was no further increase, the mean $\pm$ SE of mean triglyceride content of the fat cells remaining at 1.0 ± 0.15 μ g, with few values above 1.5 μ g. Many patients showed differences in the sizes of the fat cells removed from the three subcutaneous sites, and in 30 (28%) there was more than a twofold variation in adipocyte lipid content between sites. In patients whose maximum deposition of fat was on the abdomen the largest adipocytes were those in the epigastric sample, whereas in patients with fat predominantly on the limbs the femoral fat cells were largest. Thus the distribution of fat seemed to be related to the characteristics of the adipocytes, and fat deposition in any one area did not appear to depend on the presence of an excess of cells. Differences in regional fat-cell size also occurred between men and women (table I). In men the epigastric fat cells were larger than the iliac and femoral cells, whereas in women the femoral cells were largest. Women of equivalent relative weight to men had more lipid per cell, and this difference was apparent in both normal-weight and obese patients.

To calculate the total number of fat cells we ignored regional differences in the sizes of the subcutaneous cells and divided the total body fat by the mean cell lipid content. Figure 2 shows that in both men and women of normal weight there was a wide scatter in the number of fat cells, but there was a positive relation between this number and the degree of obesity ($r=0.342$; $P<0.001$). When the obese patients were subdivided according to the age at onset of obesity (table I) there was no suggestion that those with obesity originating in

FIG 1—Relation between mean size of subcutaneous fat cell and body weight. ● = Women. △ = Men.

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childhood had more cells than those with obesity of short duration, and the correlation between the number of fat cells and the age at onset of obesity was insignificant ($r=0.08$; $P>0.5$). There was, however, a positive relation ($P<0.001$) between the degree and duration of obesity.

FIG 2—Total number of fat cells related to body weight.
● = Women. △ = Men.

FIG 3—Comparison between sizes of subcutaneous and omental fat cells and their relation to body weight.
● = Women. △ = Men.

The values calculated for the "apparent" number of fat cells were obtained by assuming that fat cells in all areas of the body were about equal in size. Measurements of omental cells (fig 3) showed that this was not true, many subjects having omental cells only one-third the size of the subcutaneous cells. In the more obese patients omental cells were noticeably larger, but in only one obese patient was the cell size expanded sufficiently to match the size of the subcutaneous cells. Thus all subjects of normal weight have a greater number of fat cells than that calculated on the basis of subcutaneous sampling, and the error will depend on the relative proportion of fat located internally.

Discussion

We suggest that the differentiation of obesity into two types—namely, hyperplastic obesity of childhood onset and hypertrophic obesity of adult onset^{3,4}—is unwarranted for three reasons. Firstly, when the number of fat cells is calculated from measurements taken from subcutaneous samples the true number of cells in the tissue is seriously underestimated in both normal-weight and moderately obese patients. Secondly, the inclusion of a series of normal-weight patients of equivalent age shows that the number of fat cells in a control group is so scattered that most obese patients (in our series every one) fall within the 95% confidence limits for normal values. The limit of normality has been taken as the mean +1 SD—namely, 5×10^{10} —number of fat cells in non-obese women.⁶ This, therefore, includes only 67% of the population. The more appropriate 95% confidence limit for our non-obese patients was 7.1×10^{10} , so that no obese patient was hyperplastic. Thirdly, we found no relation between the calculated number of fat cells and the age at onset of obesity.

Hirsch and Batchelor found no hypercellularity in obese patients weighing under 170% of the ideal weight for their height whether the obesity was lifelong or of recent onset.¹⁰ Many of the original data related to severely obese patients weighing 136 kg (300 lb) or more¹; these patients represent the extreme end of the obese range, perhaps less than 0.1% of the obese population. Recent epidemiological evidence casts doubt on the claim that fat babies necessarily become fat children.¹¹ Thus "programming" of fat cells, if it occurs in infancy, is not an overriding factor in maintaining obesity.

Our finding, confirmed by others,^{3,12} that the omentum normally contains cells much smaller than those found subcutaneously offers an explanation for the hyperplastic obesity found in other studies. Methods for calculating the number of fat cells ignore the small omental cells, but as these expand in obesity the measured total body fat rises and there is an apparent but spurious increase in number. This occurs particularly in patients who preferentially deposit fat in the abdominal area and may be seen in both sexes. The discrepancy between the

TABLE 1—Details of obese and non-obese patients and size and number of fat cells. (Figures are means $\pm$ SE of mean)

Age at onset in years	No of patients	% above ideal weight	% body fat	Size of subcutaneous fat cell (μ g of triglyceride)			Apparent number of fat cells based on mean size of subcutaneous cell ($\times 10^{10}$)
				Epigastric	Suprailiac	Femoral	
Obese women							
<2	16	69.85 $\pm$ 6.03	42.01 $\pm$ 1.36	0.80 $\pm$ 0.06	0.86 $\pm$ 0.06	0.93 $\pm$ 0.06	4.60 $\pm$ 0.294
2–	8	76.34 $\pm$ 10.06	41.23 $\pm$ 0.94	0.87 $\pm$ 0.13	0.90 $\pm$ 0.09	1.00 $\pm$ 0.08	4.49 $\pm$ 0.353
9–	13	96.96 $\pm$ 17.09	43.63 $\pm$ 1.06	1.03 $\pm$ 0.10	1.03 $\pm$ 0.08	1.12 $\pm$ 0.07	4.43 $\pm$ 0.351
≥ 20	28	68.42 $\pm$ 7.14	43.21 $\pm$ 0.96	0.78 $\pm$ 0.06	0.93 $\pm$ 0.06	0.99 $\pm$ 0.07	4.50 $\pm$ 0.186
Obese men							
<2	4	75.45 $\pm$ 21.87	32.78 $\pm$ 2.79	1.03 $\pm$ 0.08	0.81 $\pm$ 0.22	0.94 $\pm$ 0.24	4.29 $\pm$ 0.411
2–	2	54.55 $\pm$ 13.55	35.05 $\pm$ 2.75	0.97 $\pm$ 0.04	0.90 $\pm$ 0.10	0.84 $\pm$ 0.16	3.71 $\pm$ 0.105
9–	4	79.15 $\pm$ 9.80	38.28 $\pm$ 3.40	0.99 $\pm$ 0.14	0.61 $\pm$ 0.12	0.55 $\pm$ 0.10	5.49 $\pm$ 0.348
≥ 20	5	44.27 $\pm$ 15.01	32.80 $\pm$ 3.76	0.77 $\pm$ 0.10	0.70 $\pm$ 0.13	0.62 $\pm$ 0.10	4.26 $\pm$ 0.461
Non-obese women							
	18	6.93 $\pm$ 1.94	30.8 $\pm$ 1.17	0.32 $\pm$ 0.04	0.45 $\pm$ 0.05	0.60 $\pm$ 0.05	4.30 $\pm$ 0.33
Non-obese men							
	9	1.87 $\pm$ 3.79	21.36 $\pm$ 1.99	0.45 $\pm$ 0.09	0.33 $\pm$ 0.04		3.95 $\pm$ 0.434*

*Calculated from mean of two sites only as no femoral fat could be aspirated.

TABLE II—Total body fat, size of fat cells (mean ± SE of mean), and true and apparent numbers of fat cells in obese and non-obese patients

	Total body fat derived from skinfold measurements (kg)	Size of fat cells (μg of triglyceride)		Apparent number*	Number of fat cells (× 10 ¹⁰)		
		Subcutaneous	Omental		True number		
					Subcutaneous	Omental	Total
Obese women (n = 14)	30.5	0.729 ± 0.068	0.293 ± 0.046	4.19	2.81	3.44	6.25
Obese men (n = 5)	26.0	0.602 ± 0.062	0.406 ± 0.107	4.32	2.89	2.11	5.00
Non-obese women (n = 16)	17.8	0.458 ± 0.040	0.134 ± 0.022	3.90	2.61	4.39	7.00
Non-obese men (n = 9)	14.6	0.408 ± 0.063	0.189 ± 0.044	3.58	2.40	2.55	4.95

*Based on subcutaneous sites only.

apparent and true numbers of fat cells depends not only on the difference between the sizes of omental and subcutaneous adipocytes but on the relative proportions of fat in the two areas. Many authors have commented on the distribution of subcutaneous and internal fat, and the calculated proportions vary considerably.⁹ Detailed studies on fat distribution suggest that the ratio of subcutaneous to internal fat is two to one and that this does not alter appreciably in moderate obesity.¹³ The amount of fat in muscle probably accounts for less than 4% of the total body fat and has little effect on the calculation of the number of fat cells.

We assumed a ratio of two to one for fat distribution, and table II shows the importance of this compartmentalisation of fat in determining the number of fat cells. There was a substantial underestimate of the true number of cells in both men and women. If the true number calculated for non-obese subjects is assumed to remain constant as obesity develops then, by multiplying this number by the increased lipid content of the fat cells in the obese, the total body fat is derived—namely, 31.9 kg for women and 24.8 kg for men. These values are similar to those derived from skinfold measurements (table II). This suggests that in moderate obesity there is little need to recruit additional fat cells to accommodate the excess fat. If it is assumed that internal cells plateau at the same value as the subcutaneous cells—that is, at 1.1 μg—then existing cells can accommodate extra fat until body fat has exceeded 77 kg in women and 55 kg in men. Above these high values recruitment of pre-adipocytes from stromal cells may become necessary. Other internal fat depots—for example, retroperitoneal, epicardial, and anterior extraperitoneal areas—tend to have adipocytes intermediate in size between those of the omental and subcutaneous cells.⁹ Nevertheless, the omentum seems to account for an appreciable proportion of internal fat, and the tendency when calculating the number of fat cells to average the

values from the subcutaneous sites and ignore the internal sites is unwarranted.

In our view the whole concept of adipocyte hypercellularity as a causal factor in obesity has been overemphasised. If hypercellularity appears to occur it may reflect merely the inadequacy of our assessment techniques; even if these are not at fault, from our observations hypercellularity is so unusual that it does not merit the research interest it has received and is unlikely to facilitate understanding of the everyday problem of simple obesity.

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ONE HUNDRED YEARS AGO Dr T Gaillard Thomas (*New York Hospital Gazette*) read a paper on the intravenous injection of milk as a substitute for blood before the New York Academy of Medicine. The operation was first performed by Dr Hodder of Toronto about 1850, who employed it three times in the treatment of collapse in Asiatic cholera. Next, Dr J W Howe of New York injected six ounces of goat's milk into the cephalic vein in a case of phthisis, but with no benefit to the patient. Dr Howe, also, injected cow's milk into the veins of five dogs, and they all died. The experiments of Dr Eugene Dupuy, made at the suggestion of Dr Thomas, proved that milk could be injected without any baneful results. In these experiments it was found that cases of intravenous injection of milk which had been removed from the cow for an hour or two invariably proved fatal, while the injection of perfectly fresh milk was followed by marked benefit.

The method employed by Dr Thomas may be best illustrated by relating briefly one of his cases. A healthy cow was driven into the yard of the hospital, and eight and a half ounces of milk, drawn from her udder into a porcelain dish surrounded with warm water, was permitted to flow slowly into the median basilic vein of the patient from a glass funnel, to which was attached an India-rubber tube and a suitable nozzle to be introduced into the opening in the blood-vessel.

A rigor followed the operation; the temperature rose to 104 degs Fahr, but these symptoms soon passed off, and the patient, who was moribund at the time of the operation, rallied, and left the hospital in about three weeks. Dr Thomas has employed it in seven injections, and arrives at the following conclusions. 1. Injection of milk into the circulation in place of blood is a perfectly feasible, safe, and legitimate operation. 2. None but healthy milk, drawn from the udder of the cow within a few minutes of its introduction into the circulation, should be employed. It should be tested with litmus paper, and, if found to be acid, should be made alkaline by the addition of carbonate of soda. 3. A glass funnel, with an India-rubber tube and a suitable pipe attached, was much better and safer than a more elaborate apparatus. 4. Intravenous injection of milk was an infinitely easier operation to perform than transfusion of blood. 5. Intravenous injection of milk, like that of blood, was commonly followed by a chill and rapid rise in temperature; but these symptoms soon subsided, and were replaced by a great improvement in the general condition of the patient. 6. He would not limit lacteal injections to cases in which profuse and exhausting hæmorrhage had occurred, but recommended their use in certain cases of typhoid fever, pneumonia, cholera, etc. (*British Medical Journal*, 1878.)