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Adipose Tissue Cellularity in Relation to Metabolism in Juvenile Onset Diabetes Mellitus

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Summary. Adipose tissue cellularity was determined by a microscopic method in 18 men suffering from insulin dependent, juvenile diabetes mellitus for several years. These results were set in relation to the degree of clinical control estimated from the average urinary glucose output or fasting blood glucose during the year preceding the investigation. Furthermore, the results were compared with controls of comparable age and of the same sex. Both young and middle-aged diabetic men had smaller fat cells than non-diabetic men. Fat cell size was correlated to the degree of clinical control, small fat cells indicating a poor control. It was suggested that fat cell size might be included as a measure of the long-term metabolic control in patients with insulin dependent diabetes mellitus.

Key words: Diabetes mellitus, body fat, fat cells, insulin, insulin, glucose, control.

In clinical practice the metabolic condition of a patient with diabetes mellitus is usually followed by measurements of fasting blood glucose and/or glucose output over a day. This gives an impression of the metabolic situation over a short period of time. Juvenile onset diabetes mellitus, however is characterized not only by aberrations in glucose metabolism, but constitutes, when not in control, a catabolic state with derangements of protein and lipid metabolism. The long-term effects of diabetes mellitus on these variables have been comparatively little studied.

Recent advances in methods have made it possible

Table 1. *Clinical data. Young diabetic patients*

Patient	Age (y)	Duration of disease (y)	Body weight (kg)	Height (cm)	Nephropathy	Retinopathy	Insulin (I.U./day)	Blood sugar (mg/100 ml)	Urine sugar (g/d)	Average blood sugar during recent year (mg/100 ml)	Average urine sugar during recent year (g/d)
1	20	7	54	176	a	a	52	155	29	180	60
2	23	7	75	186	a	a	40	205	7	251	100
3	23	9	61	174	b	d	52	189	49	160	27
4	24	11	76	184	a	c	40	195	0	191	29
5	25	12	56	164	a	a	40	160	72	255	50
6	25	17	65	174	b	d	68	94	3	193	37
7	27	24	88	169	b	d	60	190	95	291	99
8	28	21	66	177	b	d	32	84	2	148	2
9	30	16	76	174	a	b	92	165	36	292	49
10	32	19	52	178	b	d	52	227	18	155	40
11	38	19	57	184	b	d	72	40	118	251	142
					Middle-aged diabetic patients						
12	40	29	53	170	b	d	52	125	63	183	24
13	44	20	75	168	a	b	32	140	0	120	8
14	44	24	62	–	a	b	64	71	31	184	61
15	45	24	76	182	b	d	60	237	102	235	74
16	49	11	85	182	b	d	52	119	3	73	0
17	51	12	104	184	a	c	88	202	60	261	160
18	59	33	59	168	b	d	40	189	22	203	73

Grading of nephropathy: a = normal findings; b = proteinuria without signs of urinary tract infection.
Grading of retinopathy: a = normal findings; b = microaneurysms; c = microaneurysms and exudates; d = proliferative changes

to study these questions. Isotope dilution methods allow estimations of body compartments, including body fat [1, 2], which are of interest pertinent to the questions of long-term energy metabolism in diabetic patients. Methods are now also available allowing determination of adipose tissue cellularity which allows a better understanding of the metabolic condition of adipose tissue than if only body fat is determined.

To elucidate these questions adipose tissue cellularity was determined in a group of juvenile onset diabetic patients treated with insulin and these results set in relation to the estimated metabolic situation as measured during routine clinical control.

Clinical Data

Eighteen diabetic men were examined. Their clinical data are listed in Table 1. The mean age was 35 ± 3 years (mean ± SEM) with a range of 20–59 years. They all had diabetes mellitus requiring insulin treatment for 7–33 years. They had been admitted to the hospital when the disease started and later all were routinely examined at the outpatient department of Sahlgren's Hospital, as a rule at 3 months' interval. At the visits urinary glucose loss over a 24 hr period was determined as well as fasting blood glucose. Urine testing at home with test-tape or similar techniques had usually not been carried out. All patients were recommended to follow a diet in addition to their insulin treatment. This diet aimed at caloric balance and contained approximately 20, 30 and 50% of calories as protein, fat and carbohydrate respectively. The diet was checked occasionally by a dietician. Two patients (no 7 and 17) admitted that they did not follow these recommendations and ate ad libitum. Insulin was prescribed according to the values of blood and urinary glucose. The best possible clinical control was aimed at, but the results were variable in different individuals (cf. Table 1) for various reasons. All were in good general condition with full capacity to perform ordinary work and in a state of general well-being. Ketonuria occurring accidentally was not accepted without increasing the insulin dose. Tendencies to decrease in weight were met by increasing caloric intake and insulin. Urinary glucose output of less than 40 g per day was considered desirable but larger glucose losses had frequently to be accepted (cf. Table 1). Manifestations of the late diabetic syndrome were found in most patients (Table 1).

Comparisons were performed with non-diabetic control groups. The diabetics below the age of 40 years (27 ± 2, mean ± SEM, years) were compared with young control men with an average age of 23 years, previously described [3]. The diabetic men above the age of 40 years (47 ± 2, mean ± SEM, years) were compared with randomly selected 55 year old men from the same city. This group too has been described previously [3].

Table 2. *Results of determinations in young and middle-aged diabetic patients compared with controls. Means ± SD.*

	n	Age (years)	Body weight (kg)	Height (cm)	Body fat (kg)	Fat cell weight (gluteal) (μg)	Fat cell number ($\times 10^{10}$)
Young diabetics (<40 years)	11	27 ± 5	68 ± 10	176 ± 7	7 ± 9	0.28 ± 0.18	2.8 ± 2.7
Young controls	11	22 ± 24	69 ± 7	180 ± 7	13 ± 4	0.44 ± 0.10	3.1 ± 0.7
p	—	—	n.s.	n.s.	< 0.05	< 0.02	n.s.
Middle-aged diabetics (≤ 40 years)	7	47 ± 6	73 ± 18	176 ± 8	9 ± 7	0.39 ± 0.14	2.6 ± 1.9
Middle-aged controls	49	55	75 ± 11	175 ± 6	16 ± 5	0.62 ± 0.21	3.2 ± 1.4
p	—	—	n.s.	n.s.	< 0.01	< 0.01	n.s.

Material and Methods

Body fat was determined by isotope dilution methods. Exchangeable potassium was obtained by administration of ^{42}K and total body water with the aid of tritiated water [4,5]. From body weight, total exchangeable potassium and total body water, body fat could be estimated as described by Berg and Isaks-

son [2]. In the randomly selected middle-aged men body fat was determined by anthropometric measurements and calculations from a regression equation as previously described [3].

Fat cell size was measured in needle biopsy specimens obtained from the subcutaneous adipose tissue layer of the upper lateral quadrant of the gluteal region. In 10 subjects determinations were performed also on the subcutaneous fat depot in the middle of a line between the umbilicus and the anterior superior iliac spine and there was on average no difference between the two cell sizes. Therefore only the gluteal size was used for further calculations. Fat cell size was determined by a microscopic method described by Sjöström *et al.* [6]. Fat cell number was estimated by dividing body fat by an average fat cell weight.

Blood and urinary glucose was determined in clinical practice according to Härtel *et al.* [7]. The metabolic condition of the diabetic patients over the last year before examination of body composition and adipose cellularity was estimated by averaging blood glucose values and urinary glucose values at all visits during the preceding year, usually 3–4 visits.

The statistical method used was Students' t-test.

Results

Table 2 shows that in the younger groups the diabetic patients had less body fat. The fat cells in the gluteal region were somewhat smaller in the diabetics than in the controls. Otherwise no significant differences were found in the young subjects investigated. The middle-aged diabetic patients also had less body fat due to smaller fat cells than controls.

Fat cell size is plotted versus average urinary glucose loss at visits during the past year in Fig. 1. The correlation reached borderline values of significance ($p<0.10$) in the whole material. The two patients, who were not following dietary advice and ate freely, clearly fell outside the other observations. Without these two patients the correlation is fully significant

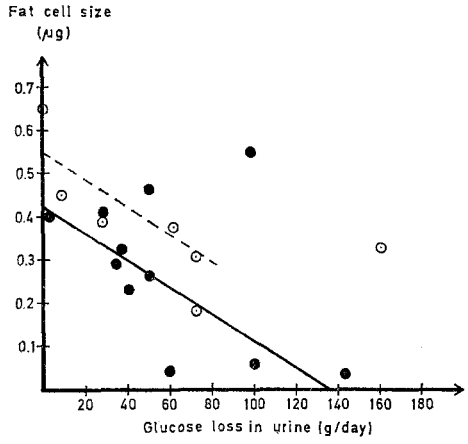

Fig. 1. The relation between the average glucose loss in urine during the year preceding the investigation, and fat cell size in young (filled symbols) and middle-aged (open symbols) men with juvenile insulin dependent diabetes mellitus. Patients on 160/0.33 and 99/0.55 ate ad libitum

Group	Regression equation	n	r	p_{t_b}	Regression line
All	$y = -0.0016\,x + 0.42$	18	0.44	<0.10	
Young	$y = -0.0019\,x + 0.39$	11	0.46	n.s.	
Middle-aged	$y = -0.0013\,x + 0.47$	7	0.52	n.s.	
All (except ad lib. diet)	$y = -0.0035\,x + 0.48$	16	0.79	<0.001	
Young (except ad lib. diet)	$y = -0.0031\,x + 0.42$	10	0.77	<0.01	(solid line)
Middle-aged (except ad lib. diet)	$y = -0.0032\,x + 0.55$	6	0.86	<0.05	(hatched line)

Table 3. *Regression analyses*

Correlations	r	p_{t_b}
Fat cell size vs. blood glucose, all	−0.42	<0.10
Fat cell size vs. blood glucose, young	−0.08	n.s.
Fat cell size vs. blood glucose, middle-aged	−0.83	<0.05
Fat cell size vs. daily insulin dose, all	0.04	n.s.

for the whole material and for the young and older subgroups separately.

The results of other regression analyses are shown in Table 3. Fat cell size showed a significant negative correlation with average fasting blood glucose at visits during the past year in the middle-aged men, and of borderline significance in the total material. Fat cell size and daily dose of insulin were not correlated.

Discussion

There was no difference in height and body weight between diabetics and controls, and consequently no difference in relative body weight. Nevertheless, body fat was lower in the diabetic patients. These findings imply that an increase in weight of other body components must have made up for the smaller body fat mass in the diabetics. Preliminary analyses indicate that this may well be due to an increase in body water because body cell mass does not seem to be increased (Isaksson *et al.*, to be published). There was no clinically demonstrable edema in the subjects examined.

These findings furthermore imply that body weight or weight indices of different kinds are poor indicators of the long-term metabolic status of the diabetic patient, because they were not different between groups in spite of the fact that body fat was lower in the diabetic subjects. A small fat cell size was responsible for this diminution of body fat, while the estimated number of fat cells was not different. It has previously been reported that adipose tissue metabolism in insulin dependent diabetic patients in clinical control shows aberrations in glucose metabolic pathways [8], and increased lipid mobilization [9, 10]. Both these metabolic abnormalities, which are explainable by a relative deficiency of insulin, lead to a decreased triglyceride content of the fat cells and therefore to smaller fat cells.

Two diabetic patients admitted that they did not follow dietary instructions and ate freely. These two patients had comparatively large fat cells and a considerable loss of glucose in the urine. They also required relatively large doses of insulin for control of their diabetes and it seems likely that the combination of an excess of calories and of exogenous insulin explains their relative fat cell enlargement.

The smaller fat cells of the insulin treated diabetic patients thus indicate a state of long-term relative insulin deficiency. The negative correlation between the average urinary glucose output over the last year and fat cell size is in agreement with this.

The finding of smaller fat cells in insulin treated diabetic patients is of interest from at least two points of view. First, it re-emphasizes the fact that diabetic patients in a state of metabolic control, which probably often must be accepted in clinical practice, are by no means metabolically normal, but are on average in a state of insulin deficiency. Second, measurements of fat cell size may prove to be a convenient way to estimate the long-term metabolic condition of a patient with diabetes mellitus requiring insulin treatment.

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