Multiple Symmetric Lipomatosis

A paradigm of metabolically innocent obesity?

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Excessive fat storage (obesity) is associated with insulin resistance and type 2 diabetes (1). Paradoxically, inability to store fat (lipodystrophy) is also associated with insulin resistance (2). In both obesity and lipodystrophy, the adipocyte's storage capacity is exceeded and lipids accumulate in liver, muscle, and β-cells. Hypothetically, if adipose tissue had an intrinsic propensity to proliferate, rather than passively respond to energy excess, calories should be extracted from the circulation and the system should become (or remain) insulin sensitive. Such a process would be particularly effective if it occurred preferentially in subcutaneous adipose tissue, which, metabolically, is the least harmful site (3).

RESEARCH DESIGN AND METHODS

— We performed extensive metabolic studies in two patients (Table 1) with multiple symmetric lipomatosis (MSL), a condition characterized by regional excess of subcutaneous adipose tissue (4).

Patient 1 had massive symmetrical subcutaneous fat accumulation in the thoracic, abdominal, and upper arm region (Fig. 1*A*) that had begun to develop about 15 years earlier. Patient 2 presented with fat accumulations in the thoracic, neck, and arm region in preparation of cosmetic surgery. In both patients, the onset of the disease coincided with a history of excessive alcohol consumption (>150 g/day for >10 years). At the time of these studies, both patients had been abstinent for several years. For comparison purposes, we created a healthy male control group for each patient from a preexisting database (5). The matching criteria were age, BMI, and percent body fat, with a maximal deviation of ±10, 7.5, and 5%, respectively.

RESULTS

— Both patients (Table 1) had normal glucose tolerance and a normal HbA_{1c}. Patient 2 had a lower 2-h glucose concentration than in the fasting state, which is usually an indication of excellent glucose tolerance and high insulin sensitivity. This was achieved with remarkably little insulin in both patients, strongly indicating a high degree of insulin sensitivity (Fig. 1*C* and *D*). While fasting free fatty acids (FFAs) were within the low normal range, suppressed FFAs at 2 h were substantially lower than in the control groups, especially in patient 1.

Insulin sensitivity (estimated from an oral glucose tolerance test [OGTT]) was markedly higher in both patients than in their respective control groups (Table 1). Insulin sensitivity, as measured by euglycemic-hyperinsulinemic clamp, was 40% greater in patient 1 than in his control group. Consistent with greater insulin sensitivity, serum adiponectin was elevated. This is particularly striking in patient 2, whose circulating adiponectin concentration ranged in the upper 10% of our entire database, which includes young, healthy subjects with BMI <18 kg/m^2. Both patients had normal plasma androgen and prolactin concentrations.

The body fat of patient 1 (Fig. 1*B*) was essentially confined to the subcutaneous compartment, and compared with a control subject, he had very little visceral fat. The subcutaneous-to-visceral ratio was 10:1 in patient 1 and 6:4 in the control subject. Liver fat was essentially absent in patient 1, and intramyocellular lipids in soleus and tibialis anterior muscles (measured by magnetic resonance spectroscopy) were less than half that in the control group.

In patient 1, greater insulin sensitivity was associated with very low lipid contents in liver and muscle cells and markedly reduced visceral adipose tissue (VAT) mass—lipid deposits that are generally associated with reduced insulin sensitivity. Moreover, the FFA concentrations indicate greater insulin sensitivity of adipose tissue to suppress lipolysis, consistent with the near absence of VAT.

CONCLUSIONS

— The two patients indicate that isolated subcutaneous fat accumulation is not necessarily accompanied by insulin resistance. On the contrary, it may actually permit a relatively high degree of insulin sensitivity and glucose tolerance, an assertion recently supported by higher HDL and lower LDL concentration in Mediterranean MSL subjects (6). There is a remarkable analogy to thiazolidinedione action, which also promotes subcutaneous fat deposition while improving insulin sensitivity and glucose tolerance. Thiazolidinedione treatment is accompanied by decreasing VAT and reduced intramuscular and intrahepatic lipids (7). In conclusion, these findings are consistent with the hypothesis that in a metabolic sense, fat depots such as in MSL may be meta-

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Abbreviations: MSL, multiple symmetric lipomatosis; OGTT, oral glucose tolerance test; VAT, visceral adipose tissue.

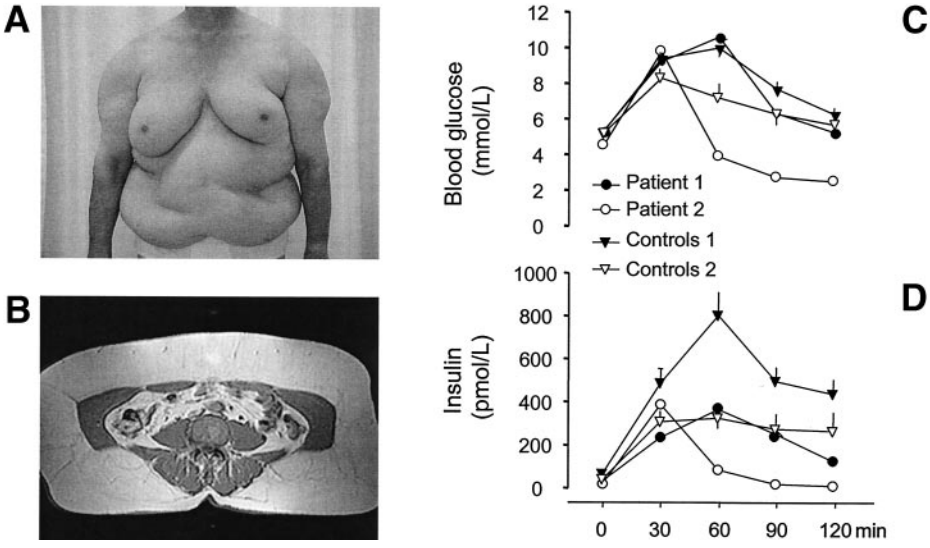

Figure 1—A*: The symmetric subcutaneous fat accumulations of patient 1 are concentrated in the upper chest and back, abdominal, and upper arm region. Face, forearms, hands, legs, and feet are spared ("pseudoathletic appearance").* B*: Axial T1-weighted magnetic resonance images (lumbar disc space 1/2) of patient 1 showing a paucity of visceral adipose tissue in the presence of massive subcutaneous fat masses. Blood glucose (*C*) and plasma insulin (*D*) concentrations during the OGTT in patients 1 and 2 and their respective control groups.*

Table 1—*Metabolic characteristics of two patients with MSL and their respective control groups*

	Patient 1	Control group 1	Patient 2	Control group 2
n	1	10	1	12
Age (years)	52	50 ± 2	56	54 ± 2.6
BMI (kg/m^2)	29.5	29.5 ± 0.6	21	23 ± 0.2
Percent body fat	28.5	28.4 ± 0.5	11.2	15.2 ± 1.1
Insulin sensitivity (OGTT)*	19.9	10.6 ± 1.8	50.4	22.3 ± 3.5
Serum leptin (ng/dl)	10.3	10.5 ± 1.2	1.9	3.6 ± 0.6
Serum adiponectin (μg/l)	7.2	6.9 ± 0.9	24.9	11.9 ± 1.3
Fasting free fatty acids (μmol/l)	345	433 ± 42	332	411 ± 44
2-h free fatty acids (μmol/l)	41	103 ± 18	79	65 ± 7
HbA_{1c} (%)	4.7	5.0 ± 0.1	4.8	5.1 ± 0.1
ISI (μmol · kg^{-1} · min^{-1} · pmol^{-1})†	0.070	0.050 ± 0.008		
GIR (μmol · kg^{-1} · min^{-1})†	38.9	25.3 ± 2.4		
$IMCL_{soleus}$ (au)	7.41	14.6 ± 1.6		
$IMCL_{tibialis\ anterior}$ (au)	1.76	4.5 ± 0.4		
Liver fat (% water signal)	0.8	7.8 ± 2.9		
Abdominal subcutaneous fat volume (l)	14.7	8.6‡		
Abdominal visceral fat volume (l)	1.4	5.5‡		

Data of control groups are means ± SE. *Estimated according to the equation of Matsuda et al. (8). †From euglycemic-hyperinsulinemic clamp. ‡One representative subject with identical percent body fat. 2-h refers to OGTT; au, arbitrary units; GIR, glucose infusion rate; IMCL, intramyocellular lipids; ISI, insulin sensitivity index.

bolically innocent, possibly by preventing lipotoxicity.

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References

1. Kahn BB, Flier JS: Obesity and insulin resistance. *J Clin Invest* 106:473–481, 2000
2. Reitman ML, Arioglu E, Gavrilova O, Taylor SI: Lipoatrophy revisited. *Trends Endocrinol Metab* 11:410–416, 2000
3. Montague CT, O'Rahilly S: The perils of portliness: causes and consequences of visceral adiposity. *Diabetes* 49:883–888, 2000
4. Enzi G: Multiple symmetric lipomatosis: an updated clinical report. *Medicine (Baltimore)* 63:56–64, 1984
5. Thamer C, Stumvoll M, Niess A, Tschritter O, Haap M, Becker R, Shirkavand F, Bachmann O, Rett K, Volk A, Haring H, Fritsche A: Reduced skeletal muscle oxygen uptake and reduced β-cell funtion: two early abnormalities in normal glucose tolerant offspring of patients with type 2 diabetes. *Diabetes Care* 26:2126–2132 2003
6. Busetto L, Strater D, Enzi G, Coin A, Sergi G, Inelmen EM, Pigozzo S: Differential clinical expression of multiple symmetric lipomatosis in men and women. *Int J Obes Relat Metab Disord* 27:1419–1422, 2003
7. Stumvoll M: Thiazolidinediones: some recent developments. *Expert Opin Investig Drugs* 12:1179–1187, 2003
8. Matsuda M, DeFronzo RA: Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care* 22: 1462–1470, 1999