European Review for Medical and Pharmacological Sciences 2013; 17: 2254-2256

Insulin sensitivity in familial multiple lipomatosis

M. D'ETTORRE, D. GNIULI*, C. GUIDONE*, R. BRACAGLIA, D. TAMBASCO, G. MINGRONE*

Department of Plastic and Reconstructive Surgery, Catholic University, Rome, Italy
*Department of Metabolic Diseases, Institute of Internal Medicine, Catholic University, Rome, Italy

Abstract. – BACKGROUND: Familial Multiple Lipomatosis (FML) is a mainly autosomal dominant rare benign condition. Excessive fat storage (obesity), as well as the inability to store fat (lipodystrophy), is associated with insulin resistance.

AIM: Our study aimed to document if also patients affected by regional excess of subcutaneous adipose tissue as in FML show this feature.

PATIENTS AND METHODS: Metabolic studies were performed in four brothers. A standard 75 g oral glucose tolerance test (OGTT) was submitted to each patient, with blood sampling at 0, 30, 60, 90, 120 and 180 min. Insulin sensitivity was calculated from the OGTT as the oral glucose insulin sensitivity index (OGIS), using the 2-h OGIS equation. Eight obese, non-diabetic subjects matched for BMI, age and sex, were used as controls.

RESULTS: All the patients revealed a normal glucose tolerance and a normal HBA1c.

CONCLUSIONS: Isolated subcutaneous fat accumulation is not necessarily associated with insulin resistance, on the contrary it may even allow a relatively high degree of insulin sensitivity.

Key Words:
Familial lipomatosis, Insulin sensitivity, Diabetes.

Introduction

Lipomas are the most common type of soft tissue tumor, with a prevalence of 2.1 per 1000 people. Familial Multiple Lipomatosis (FML) is a quite rare benign condition, with a prevalence of 0.002 percent in the general population[1]. It is characterized by regional excess of subcutaneous adipose tissue in members of the same family and it is usually transmitted by the autosomal dominant route of inheritance, although cases with recessive inheritance have also been reported. Some authors claim that FML is particularly prevalent in males, but the female-to-male ratio is usually close[2]. In FML, lipomas are usually painless. However, sometimes they become a problem for an ordinary life, reason for their surgical excision. According to the literature, FML lipomas usually appear in the third decade, and rarely in the fourth or fifth decades[3,4].

Excessive fat storage (obesity), as well as the inability to store fat (lipodystrophy), is associated with insulin resistance. The aim of our study was to document if also patients affected by regional excess of subcutaneous adipose tissue as in FML show this feature.

Patients and Methods

Extensive metabolic studies were performed in four brothers: 3 males and 1 female.

Patient 1 had massive symmetrical subcutaneous fat accumulation in the trunk, arms and thighs, that had begun to develop at the age of 10. He was an occasional alcohol consumer with a history of heavy smoking 20 years before. He had 4 sons (aged 5, 5, 13 and 18) in good conditions.

Patient 2 had massive symmetrical subcutaneous fat accumulation in the trunk, that had begun to appear when he was 20, he was an occasional alcohol consumer and smoker. Two sons respectively aged 27 and 21 in good health.

Patient 3 had massive symmetrical subcutaneous fat accumulation in the trunk, that had begun to develop at the age of 20, he was an occasional alcohol consumer and heavy smoker. Patient 4 had massive symmetrical subcutaneous fat accumulation in the same region, that had begun to develop at the age of 16, she denied alcohol and cigarettes consumption. She had one daughter affected by lipomatosis, firstly appeared in the retroauricular region since she was 12 years old.

A standard 75 g oral glucose tolerance test (OGTT) was performed in each patient, with blood sampling at 0, 30, 60, 90, 120 and 180 min.

Insulin sensitivity was calculated from the OGTT as the oral glucose insulin sensitivity (OGIS) index[5], using the 2-h OGIS equation, a validated and widely used test[6]. This method pro-

Corresponding Author: Marco D'Ettorre, MD; e-mail: marco.dettorre@hotmail.it

vides an insulin sensitivity index that is an estimate of the glucose clearance during a euglycaemic-hyperglycaemic clamp, expressed in milliliter per minute per square meter of body surface area. Normal reference values for insulin sensitivity were obtained from a group of 8 obese, non-diabetic subjects matched for BMI, age and sex.

Results

The clinical and metabolic characteristics of the study subjects are shown in Table I.

All the patients revealed a normal glucose tolerance and a normal HBA_{1c}. Their glucose levels at 0' (88.00 ± 6.98 mg/dl), 120' (111.50 ± 20.49 mg/dl) and 180' (60.00 ± 12.75 mg/dl), as well as insulin levels at 0' (10.35 ± 8.39 μU/ml) and 120' (54.05 ± 24.28 μU/ml) were lower than controls. Consequently, the OGIS test revealed an insulin sensitivity of 476.00 ± 81.00 $ml \cdot min^{-1} \cdot m^{-2}$, which is significantly ($p < 0.01$) higher than 348.98 ± 56.23 $ml \cdot min^{-1} \cdot m^{-2}$ recorded in the control group. The pedigree analysis revealed a transmission by the autosomal dominant route of inheritance (Figure 1).

Discussion

Glucose and lipid metabolism is closely related to visceral adipose tissue (VAT)[7]. Conversely, subcutaneous adipose tissue (SCAT) may have a protective effect on glucose and lipid metabolism[8], but the underlying mechanism(s) remain(s) poorly defined. SCAT may secrete some "beneficial factors" such as adiponectin and leptin, which have been shown to improve glucose and lipid metabolism[9]. Previously, obesity with mainly SCAT has been called "benign obese" and that with mainly VAT "non-benign obese" by some authors[10]. However, removal of VAT from mice results in decreased insulin resistance, whereas removal of SCAT does not result in improved glucose and lipid metabolism.

Whether the subcutaneous fat is really capable of antagonizing some adverse effects of visceral obesity is still to be defined but we expect that concepts of good and bad fat would be implemented in the future.

Unlike lipomas, lipomatous tissue in this syndrome is non-encapsulated, with the ability to infiltrate spaces between adjacent subcutaneous and muscular structures. The lipomatous tissue is characterized by normal-sized or smaller than expected fat cells[11-12], consistent with an ongoing recruitment and maturation of preadipocytes to explain adipose tissue growth.

Gokalp et al[13] observed that differences in adipocyte cell size were closely related to glucose and lipid metabolism,with smaller-sized adipocytes having a protective effect on glucose and lipid metabolism, while largersized ones had the opposite effect. Possibly, smaller adipocytes have a higher affinity to free fatty acids and triglycerides and prevent their accumulation in non-adipose tissue, e.g. skeletal muscles, pancreas and liver and, thus, play a role as powerful "buffers" to alleviate glucose and lipid metabolism dysfunction. Furthermore, smaller-sized adipocytes can secrete more adiponectin, a recently discovered plasma protein with many associations to glucose and lipid metabolism[14].

Conclusions

Our study started from the assumption that excessive fat storage is closely linked to the con-

Table I. Anthropometric and biochemical parameters of the studied population.

Parameters	Pt. 1	Pt. 2	Pt. 3	Pt. 4	Mean ± SD	Controls (mean ± SD)
Sex	M	M	M	F		6 M and 2 F
Age (years)	41	56	38	48	45.75 ± 8.02	46.25 ± 7.84
Weight (kg)	71.90	97.70	85.5	136.5	97.90 ± 27.81	96.12 ± 21.83
Height (m)	1.62	1.71	1.72	1.69	168.5 ± 0.5	168.2 ± 0.4
BMI (kg/m^2)	27.39	33.41	28.90	47.79	34.37 ± 9.30	34.08 ± 8.32
Body fat (%)	39.50	40.01	34.70	45.70	39.98 ± 4.50	40.50 ± 7.13
Waist circumference (cm)	87	118	102	147	113.50 ± 25.67	114.12 ± 21.45
Hip circumference (cm)	103	111	105	134	113.25 ± 14.24	113.62 ± 10.86
OGIS ($ml\ min^{-1}\ m^{-2}$)	587	403	480	432	475.50 ± 80.83	348.98 ± 56.23[#]

[#] $p < 0.01$.

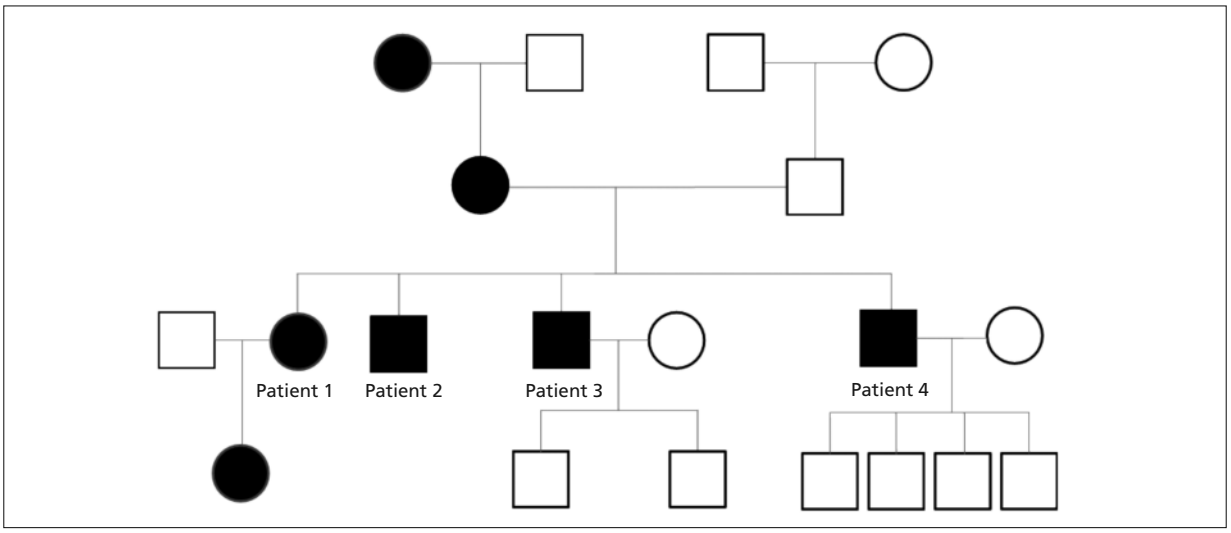

Figure 1. In the pedigree scheme a transmission by the autosomal dominant route of inheritance was evidenced.

cept of altered insulin sensitivity. Our findings showed that isolated subcutaneous fat accumulation is not necessarily associated with insulin resistance, on the contrary it may even allow a relatively high degree of insulin sensitivity.

Adequate and demonstrable explanations justifying such a high insulin sensitivity in patients affected by FML are still awaited and further studies are needed.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Ronan SJ, Broderick T. Minimally invasive approach to familial multiple lipomatosis. Plast Reconstr Surg 2000; 106: 878-880.
2) Keskin D, Ezirmik N, Celik H. Familial multiple lipomatosis. Isr Med Assoc J 2002; 4: 1121-1123.
3) Rabbiosi G, Borroni G, Scuderi N. Familial multiple lipomatosis. Acta Derm Venereol 1977; 57: 265-267.
4) Mohar N. Familial multiple lipomatosis. Acta Derm Venereol 1980; 60: 509-513.
5) Mari A, Manco M, Guidone C, Nanni G, Castagneto M, Mingrone G, Ferrannini E. Restoration of normal glucose tolerance in severely obese patients after bilio-pancreatic diversion: role of insulin sensitivity and beta cell function. Diabetologia 2006; 49: 2136-2143.
6) Hatunic M, Finucane FM, Norris S, Pacini G, Nolan JJ. Glucose metabolism after normalization of markers of iron overload by venesection in subjects with hereditary hemochromatosis. Metabolism 2010; 59: 1811-1815.
7) Misra A, Garg A, Abate N, Peshock RM, Stray-Gundersen J, Grundy SM. Relationship of anterior and posterior subcutaneous abdominal fat to insulin sensitivity in nondiabetic men. Obes Res 1997; 5: 93-99.
8) Porter SA, Massaro JM, Hoffmann U, Vasan RS, O'Donnel CJ, Fox CS. Abdominal subcutaneous adipose tissue: a protective fat depot? Diabetes Care 2009; 32: 1068-1075.
9) Banerjee RR, Rangwala SM, Shapiro JS, Rich AS, Rhoades B, Qi Y, Wang J, Rejala MW, Pocai A, Scherer PE, Steppan CM, Ahima RS, Obici S, Rossetti L, Lazar MA. Regulation of fasted blood glucose by resistin. Science 2004; 303: 1195-1198.
10) Gabriely I, Ma XH, Yang XM, Atzmon G, Rajala MW, Berg AH, Scherer P, Rossetti L, Barzilai N. Removal of visceral fat prevents insulin resistance and glucose intolerance of aging: an adipokine-mediated process? Diabetes 2002; 51: 2951-2958.
11) Enzi G, Inelmen EM, Baritussio A, Dorigo P, Prosdocimi M, Mazzoleni F. Multiple symmetric lipomatosis: a defect in adrenergic-stimulated lipolysis. J Clin Invest 1977; 60: 1221-1229.
12) Enzi G, Favaretto L, Martini S, Fellin R, Baritussio A, Baggio G, Crepaldi C. Metabolic abnormalities in multiple symmetric lipomatosis: elevated lipoprotein lipase activity in adipose tissue with hyperalphalipoproteinemia. J Lipid Res 1983; 24: 566-574.
13) Gokalp D, Bahceci M, Ozmen S, Arikan S, Tuzcu A, Danis R. Adipocyte volumes and levels of adipokines in diabetes and obesity. Diab Metab Syndr Clin Res Rev 2008; 2: 253-258.
14) Taksali SE, Caprio S, Dziura J, Dufour S, Calí AM, Goodman TR, Papademetris X, Burgert TS, Pierpont BM, Savoye M, Shaw M, Seyal AA, Weiss R. High visceral and low abdominal subcutaneous fat stores in the obese adolescent: a determinant of an adverse metabolic phenotype. Diabetes 2008; 57: 367-371.