Obesity

The Metabolic Equivalent BMI in Patients with Familial Partial Lipodystrophy (FPLD) Compared with Those with Severe Obesity

Eden Koo[1,2], Maria C. Foss-Freitas[1], Rasimcan Meral[1], Muhammet Ozer[1], Abdelwahab J. Eldin[1], Baris Akinci[1,3], Nicole Miller[1], Amy E. Rothberg[1], and Elif A. Oral [1]

Objective: This study aimed to investigate the shortcoming of BMI as a measurement of adiposity in patients with familial partial lipodystrophy (FPLD).

Methods: Two different matching procedures were used to compare 55 FPLD versus control patients with severe obesity ($N = 548$ patients) to study the relationship between body weight, fat distribution, and metabolic diseases, such as diabetes mellitus, hypertriglyceridemia, and nonalcoholic steatohepatitis. In MATCH1, the patients with FPLD were matched to controls with obesity (OCs) by truncal mass, and in MATCH2, the patients with FPLD were matched to OCs with respect to glucose control.

Results: With MATCH1, the FPLD group had worse glycemic control (hemoglobin A1c 8.2% ± 1.6% vs. 5.9% ± 0.9%), higher triglycerides (884 ± 1,190 mg/dL vs. 139 ± 79 mg/dL), and lower leptin (20.5 ± 15.8 ng/mL vs. 41.9 ± 29.4 ng/mL, $P < 0.001$ for all comparisons). In MATCH2, metabolic comorbidity–matched FPLD patients had significantly lower BMI compared with OCs (29.5 ± 5.7 kg/m^2 vs. 38.6 ± 5.2 kg/m^2, $P < 0.001$).

Conclusions: Patients with FPLD with similar truncal mass have worse metabolic profiles than non-FPLD OCs. The differential BMI between the FPLD and OCs, when matched for their metabolic comorbidities, approximates 8.6 BMI units.

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Study Importance

What is already known?

- Besides the widespread use of BMI as a classification for obesity and its metabolic manifestations, it is increasingly more evident that there is a need to individualize the cutoff for different populations, such as the patients with familial partial lipodystrophy (FPLD) reported herein.

What does this study add?

- We demonstrate that patients with FPLD with similar truncal mass have worse metabolic profiles than controls with obesity.
- The metabolic disease burden of patients with FPLD is, on average, 8.6 (95% CI: 6.5-10.7) kg/m^2 higher than the observed BMI.

How might these results change the direction of research or the focus of clinical practice?

- Our data may change the goals for weight management in patients with FPLD.
- Here we suggest a BMI equivalent for categorizing individuals with FPLD with obesity and its related metabolic complications.
- More importantly, these data point out that BMI targets have to be adjusted according to fat cell compartment limitations, as observed in patients with FPLD to a point of extreme. However, this is a more generalizable observation that may be true for evaluating BMI targets in different ethnic groups or genders.

Introduction

Familial partial lipodystrophy (FPLD) is a group of rare, inherited syndromes characterized by the absence of adipose tissue in the extremities, with accumulation of fat in the upper body and ectopic sites. The exact prevalence of this syndrome can vary depending on whether monogenic versus polygenic forms are evaluated and whether there may be founder effects in certain geographic areas. Still, the estimated prevalence is accepted as rarer than 1 in 200,000 individuals with all the caveats (1). The limited adipose tissue capacity is responsible for spillover of excess fat at smaller total body weight, leading to increased risk for metabolic diseases either through impacting buffering capacity for excess energy or through secretion of adipokines (2). Metabolic abnormalities associated with FPLD include severe insulin resistance predisposing to diabetes mellitus, hypertriglyceridemia, and nonalcoholic steatohepatitis (3-5). Patients with FPLD have a disproportionately lower BMI compared with individuals with common obesity despite displaying

[1] Division of Metabolism, Endocrinology & Diabetes, University of Michigan, Ann Arbor, Michigan, USA. Correspondence: Amy E. Rothberg (arothber@med.umich.edu) and Elif A. Oral (eliforal@med.umich.edu) [2] University of Hawaii John A. Burns School of Medicine, Honolulu, Hawaii, USA[3] Dokuz Eylul University, Turkey.

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similar or worse metabolic state due to limited fat storage capacity (6). However, the extent and degree of metabolic abnormalities at comparable trunk mass (TM) or the "equivalent" BMI between the groups with similar metabolic abnormalities have not been examined.

In this study, we first matched a population of patients with FPLD with patients with severe obesity by TM and quantified the metabolic abnormalities between these populations. We hypothesized that patients with FPLD would have more metabolic abnormalities despite having comparable TM when compared with individuals with obesity with symmetric fat distribution. In a second step, we matched the two groups based on metabolic abnormalities and compared their BMI to gauge the "BMI equivalence" factor, i.e., the equivalent BMI at which similar metabolic abnormalities would occur in patients with FPLD.

Methods

We performed a retrospective case-control study comparing "cases" of FPLD against "controls" with severe obesity while matching for total TM or metabolic comorbidities. Baseline data were obtained from patients who participated in clinical studies of FPLD or who participated in our weight management program and made use of existing quality controlled prospective electronic databases. In brief, the weight management program is a 2-year intensive behavioral program that employs a very low-energy diet in the form of liquid meal replacement (Optifast (Nestlé) for 3 to 4 months to achieve a 15% reduction in body weight, followed by reintroduction of conventional food to maintain long-term weight loss. The program has been described in detail elsewhere (7).

All subjects in both groups provided written informed consent, and the protocols were approved by the Institutional Review Board at the University of Michigan. The patients with FPLD are part of a long-term observational, international, multicenter, prospective study collecting data on the natural history of different lipodystrophy syndromes (the LD-Lync study) registered at ClinicalTrials.gov, NCT03087253. The LD-Lync study represents a collaboration between endocrinology specialists, primary care providers, quality improvement personnel, and participants, all aiming to increase awareness, promote optimal disease management, and improve outcomes for lipodystrophy. Two primary types of data are collected: participant-reported data and clinical data. Participant-reported data are collected during clinical visits when patients are invited to complete an extensive survey assessing aspects of health, quality of life, and social elements in their lives.

The data collected and pooled for these analyses include demographics, vital signs, chemistry panels, descriptions of disease comorbidities and their treatment, and measurements of body composition. The available data on physical activity, quality of life, and self-perception were not included in these small-scale analyses.

Our cohorts consisted of 55 FPLD cases (9 male and 46 female, aged 37-57 years) and a pool of 548 non-FPLD controls with obesity (210 male and 338 female, aged 41-57 years). Clinical and body composition characteristics of the two cohorts are described in Table 1, and medication usage is shown in Table 2.

Using the MatchControls function of R's e1071 package, we performed two k:1 nearest neighbor case-control matches, which we refer to as MATCH1 and MATCH2, respectively. The strength of matching (as well as the selection of optimal match ratios for each model, i.e., 1:1 or 2:1) was evaluated by visualizing histograms that compared parameters between the two cohorts and by assessing probability values. We selected the matching cohort with the best histogram overlap. Statistical comparisons between these matched cohorts were made using the Wilcoxon rank sum test or a Fisher exact test as appropriate. We also determined the confidence intervals (CI) of the differences between the two cohorts from both match procedures.

We designed MATCH1 to have 2:1 matching, with two controls with obesity for each patient with FPLD as there were enough patients who could be selected to fit the set criteria. The matching criteria were baseline age, gender, and total TM with the hypothesis that patients with FPLD with similar TM would demonstrate worse metabolic abnormalities than controls with obesity. For MATCH2, an independent 1:1 "reverse match" was performed against age, gender, and the presence of comorbidities (hypertension, hypertriglyceridemia defined as >300 mg/dL, diabetes, liver steatosis, heart disease, arthritis, depression, anxiety, smoking history), with the additional consideration of concurrent glucose or lipid-lowering medications. We hypothesized that there would be a significant difference in BMI between the two populations. In this context, the difference provides a quantitative description of the missing body mass units needed to confer the same metabolic disease burden when peripheral fat depots are selectively absent.

Results

The results of the MATCH1 procedure demonstrated that patients with FPLD had worse glycemic control than the control group (hemoglobin A1c 8.2% ± 1.6%, 6.0% ± 1.0%, $P < 0.001$), higher triglyceride levels (884 ± 1,190 mg/dL, 139 ± 79 mg/dL, $P < 0.001$) (Figure 1), and (not unexpectedly) lower leptin levels (20.5 ± 15.8 ng/mL, 42.0 ± 29.4 ng/mL, $P < 0.001$), together with lower BMI (29.5 ± 5.8 kg/m^2, 34.3 ± 6.3 kg/m^2, $P < 0.001$) (median and interquartile ranges presented in Table 1). The estimated differences in the metabolic parameters were as follows: hemoglobin A1c (2.2%, 95% CI: 1.7%-2.7%) and triglyceride levels (745 mg/dL, 95% CI: 423-1,067 mg/dL). In contrast, the control group with obesity demonstrated an increase of 4.8 kg/m^2 (95% CI: 2.8-6.8 kg/m^2) in BMI, whereas leptin levels were higher with a difference of 21.5 ng/mL (95% CI: 9.6-33.4 ng/mL).

When we matched patients with FPLD to control patients with obesity for age, gender, presence of comorbidities, and medication usage with MATCH2 (full details available in Tables 1-2 and Figure 1), we observed a residual difference in triglyceride levels in patients with FPLD with a mean difference of 635 mg/dL (95% CI: 307-904 mg/dL). Moreover, the patients with FPLD had lower BMI (29.5 ± 5.8 kg/m^2) and lower leptin levels with a mean difference of 32.7 ng/mL (95% Cl: 15.1-50.3 ng/mL) compared with the control patients with obesity (38.1 ± 5.5 kg/m^2, $P < 0.001$). The difference in BMI between the two groups in MATCH2 was 8.6 kg/m^2 (95% CI: 6.5-10.7 kg/m^2).

Discussion

A phenotypic hallmark of FPLD is the absence of subcutaneous fat in the extremities with an accumulation of truncal adipose tissue. We show that patients with FPLD and similar TM compared with subjects with severe but common obesity have worse metabolic abnormalities. This

TABLE 1 Clinical characteristics of the cohorts before and after matching

	FPLD	Obesity
	n = 55	*n* = 548
Gender (M:F)	9:46	210:338
Age (y)	49 (37-57)	49 (41-57)
BMI (kg/m^2)	30.2 (24.6-33.1)	38.4 (35.2-42.3)
TMI (kg)	16.7 (13.3-19.0)	19.9 (17.7-22.4)
FMR	1.6 (1.5-1.9)	1.1 (1.0-1.3)
Body fat (%)	34.2 (26-38.9)	46.4 (40.8-50.9)
Leg fat (%)	23.8 (18.3-28.9)	44.1 (35.7-51.2)
HbA1c (%)	8.1 (7.05-9.2)	5.8 (5.5-6.8)
Total cholesterol (mg/dL)	228 (178-303)	181 (161-203)
LDL cholesterol (mg/dL)	84 (61-131)	102 (83-123)
AST (U/L)	27 (18-41)	28 (24-37)
ALT (U/L)	30 (21-49)	32 (25-45)
Triglycerides (mg/dL)	346 (245-1037)	137 (94-192)
Clinical characteristics after 1:2 match based on age, gender, total trunk mass (MATCH1)	*n* = 55	*n* = 110
BMI (kg/m^2)	30.2 (24.6-33.1)	35.2 (32.0-38.2)*
TMI (kg)	16.7 (13.3-19.0)	16.7 (15.6-17.7)
FMR	1.6 (1.5-1.9)	1.0 (1.0-1.1)
Body fat (%)	34.2 (26-38.9)	43.7 (41.7-35.4)
HbA1c (%)	8.1 (7.1-9.2)	5.6 (5.4-6.1)*
Triglycerides (mg/dL)	346 (245-1037)	125 (83-178)*
Leptin (ng/mL)	16.4 (9.4-24.9)	30.8 (19.7-66.8)*
Clinical characteristics after 1:1 match based on age, gender, comorbidities, concurrent medications (MATCH2)	*n* = 55	*n* = 55
BMI (kg/m^2)	30.2 (24.6-33.1)	39.8 (35.4-41.1)*
TMI (kg)	16.7 (13.3-19.0)	17.1 (16.5-17.8)
FMR	1.6 (1.5-1.9)	1.0 (1.0-1.1)
Body fat (%)	34.2 (26-38.9)	44.2 (42.8-45.7)
HbA1c (%)	8.1 (7.1-9.2)	7.5 (6.8-8.5)
Triglycerides (mg/dL)	346 (245-1037)	195 (153-288)*
Leptin (ng/mL)	16.4 (9.4-24.9)	41.2 (24.1-76.7)*

Data given as median (Q1-Q3). *P < 0.001 comparing groups with FPLD and with obesity.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; FMR, fat mass ratio; FPLD, familial partial lipodystrophy; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; TMI, trunk mass index.

TABLE 2 Presence of comorbidities and use of medications in the cohorts before matching

	FPLD	Obesity
Hyperlipidemia (%)	100	49.8 (45.5-54.1)
On lipid-lowering meds (%)	80 (67.0-89.6)	46.5 (40.5-52.6)
Presence of diabetes (%)	94.6 (84.9-98.9)	26.8 (23.2-30.7)
On insulin (%)	63.5 (48.9-76.4)	13.6 (8.5-20.2)
On insulin U500 (%)	17.3 (8.2-30.3)	1.6 (0.0-3.7)
On any glucose-lowering medications (%)	92.3 (81.5-97.8)	73.5 (65.6-80.4)
Presence of hypertension (%)	67.3 (53.3-79.3)	42.9 (38.7-47.2)

Data are presented as % (95% CI).
Abbreviation: FPLD, familial partial lipodystrophy.

result highlights the importance of the role that lower body fat depots would play in mediating overall energy homeostasis. We also attempted to quantify the "equivalent" BMI units contributed by the absence of subcutaneous adipose tissue. To our knowledge, no previous comparable studies have assessed these differences.

The current understanding of FPLD pathogenesis starts with inadequate adipose storage capacity, resulting in deficiencies in adipocytokine production, such as leptin, severe dyslipidemia, and severe insulin resistance (8,9). This understanding falls in line with our observed differences in hemoglobin A1c, triglyceride, and leptin levels between the two cohorts when perfectly matched for TM. We also believe that the "reverse match" performed in MATCH2 is a unique method of trying to estimate the BMI equivalent of the patients with FPLD if they had normal adipose tissue distribution. We interpret that the metabolic disease burden of the patients with FPLD is equivalent to that of those with non-FPLD

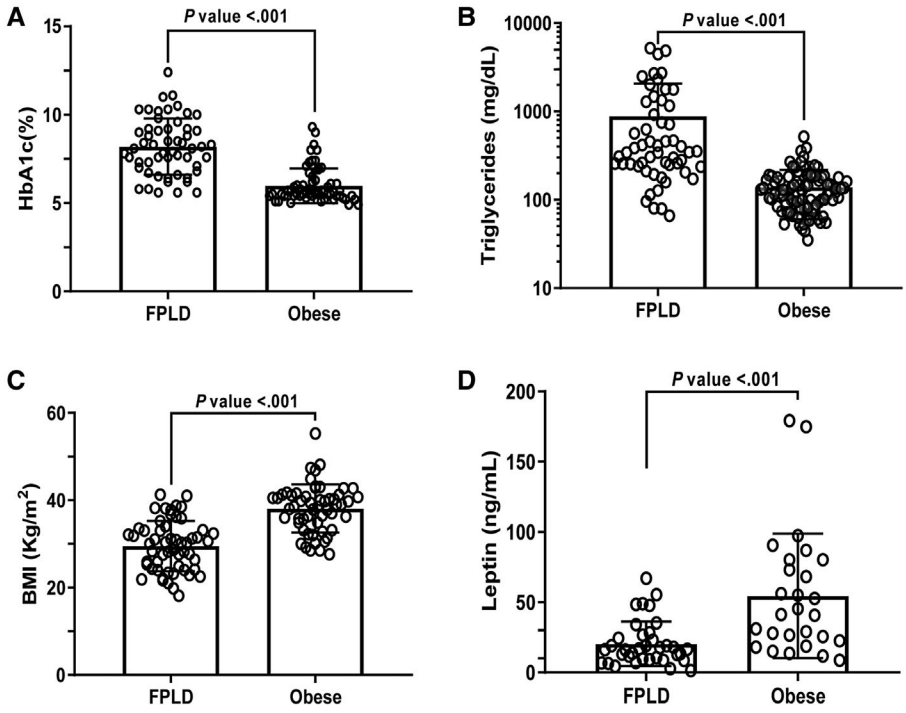

Figure 1 Differences between familial partial lipodystrophy (FPLD) and control groups with obesity when comparing individuals with (**A**,**B**) similar trunk mass (MATCH1) or with (**C**,**D**) similar metabolic disorders (MATCH2). Mean and SD values are shown.

obesity, that is, on average, 8.6 kg/m^2 (95% CI: 6.5-10.7 kg/m^2) higher than the observed BMI.

This latter finding may have important management implications and may fill a void that the current guidelines (10,11) do not address. If the metabolic disease BMI equivalent of the patients with FPLD is at least 6.5 to 10.7 kg/m^2 higher than the actual BMI noted, a patient with FPLD and BMI of 23 kg/m^2 would be categorized as having obesity. In comparison, a different patient with BMI of 33 kg/m^2 would be considered to have "severe obesity" with deficient storage capacity, as this patient's metabolic disease is equivalent to that degree of obesity. Ideal BMI in an individual with FPLD would more likely approximate the threshold for underweight (BMI = 18 kg/m^2) in order to avoid metabolic complications. Given that many patients with FPLD present with substantially higher BMI, earlier identification and referral to a high-intensity intervention to achieve and maintain weight loss (e.g., very low-energy diets, weight control medications, weight loss surgery) are imperative. Although recombinant leptin in the form of metreleptin is beneficial for treatment of generalized lipodystrophy (12,13), this treatment is not approved for partial lipodystrophy in the United States. It is, however, approved for treatment of metabolic complications in individuals with familial or acquired partial lipodystrophy in the European Union countries with a leptin level<12 ng/mL (2).

A limitation of our study is the retrospective design. Despite severe obesity, the control group was metabolically healthier, making it challenging to find sufficient numbers that matched our patients with FPLD in the extent of metabolic disease; therefore, we could not perform a 1:2 match for MATCH2. In fact, despite the match, the triglyceride levels were substantially higher in the FPLD cohort compared with those of the controls with obesity. Therefore, the metabolic disease "equivalent" BMI that we are reporting may underestimate the real equivalence value. In our analyses, we did not include physical activity, health care use, psychosocial factors, and personal perceptions because of the preliminary nature of this work. Despite these caveats, our data provide a quantifiable estimate of the metabolic burden contributed by the lack of peripheral (specifically lower body peripheral) depots. This BMI equivalence factor can be taken into consideration when defining weight goals for patients with FPLD.O

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Author contributions: EK collected and analyzed the data, designed the analysis, and wrote the manuscript. MCFF contributed to data analysis and wrote the manuscript. RM, MO, BA, and AJE designed the analysis, analyzed the data, and contributed to the writing. NM, AER, and EAO designed the study, supervised data analyses, and reviewed and edited the manuscript. EAO and AER are the guarantors of the manuscript.

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References

1. Gonzaga-Jauregui C, Ge W, Staples J, et al. Clinical and molecular prevalence of lipodystrophy in an unascertained large clinical care cohort. *Diabetes* 2020;69: 249-258.
2. Foss-Freitas M, Akinci B, Lou Y, Stratton A, Oral EA. Diagnostic strategies and clinical management of lipodystrophy. *Exp Rev Endocrinol Metab* 2020;15:95-114.
3. Kobberling J, Dunnigan MG. Familial partial lipodystrophy: two types of an X linked dominant syndrome, lethal in the hemizygous state. *J Med Genet* 1986;23: 120-127.
4. Dunnigan MG, Cochrane MA, Kelly A, Scott JW. Familial lipoatrophic diabetes with dominant transmission. A new syndrome. *Q J Med* 1974;43:33-48.
5. Bagias C, Xiarchou A, Bargiota A, Tigas S. Familial partial lipodystrophy (FPLD): recent insights. *Diabetes Metab Syndr Obes* 2020;13:1531-1544.
6. Garg A. Acquired and inherited lipodystrophies. *N Engl J Med* 2004;350:1220-1234.
7. Rothberg AE, McEwen LN, Fraser T, Burant CF, Herman WH. The impact of a managed care obesity intervention on clinical outcomes and costs: A prospective observational study. *Obesity*. 2013;21:11:2157–2162. http://dx.doi.org/10.1002/oby.20597
8. Akinci B, Onay H, Demir T, et al. Clinical presentations, metabolic abnormalities and end-organ complications in patients with familial partial lipodystrophy. *Metabolism* 2017;72:109-119.
9. Garg A, Misra A. Lipodystrophies: rare disorders causing metabolic syndrome. *Endocrinol Metab Clin North Am* 2004;33:305-331.
10. Brown RJ, Araujo-Vilar D, Cheung PT, et al. The diagnosis and management of lipodystrophy syndromes: a multi-society practice guideline. *J Clin Endocrinol Metab* 2016;101:4500-4511.
11. Araujo-Vilar D, Santini F. Diagnosis and treatment of lipodystrophy: a step-by-step approach. *J Endocrinol Invest* 2019;42:61-73.
12. Oral EA, Simha V, Ruiz E, et al. Leptin-replacement therapy for lipodystrophy. *N Engl J Med* 2002;346:570-578.
13. Oral EA, Chan JL. Rationale for leptin-replacement therapy for severe lipodystrophy. *Endocr Pract* 2010;16:324-333.