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The metabolic equivalent BMI in Familial Partial Lipodystrophy (FPLD) patients compared to those with severe obesity

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Authors' contribution: 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, reviewed, and edited the manuscript. EAO and AER are guarantors of the manuscript.

Answer to the Study Importance Questions

- What is already known about this subject?
  - Besides the widespread use of BMI as a classification for obesity and its metabolic manifestations, it is increasingly more evident the need to individualize the cut off for different populations such as the familial partial lipodystrophy (FPLD) patients reported here.
- What are the new findings in your manuscript?
  - We demonstrate that FPLD patients with similar truncal mass have worse metabolic profiles than obese controls.

- The metabolic disease burden of FPLD patients is, on average, 8.6 (CI: 6.5-10.7) kg/m^2 higher than the observed BMI.

- How might your results change the direction of research or the focus of clinical practice?
  - Our data may change the goals for weight management in FPLD patients.
  - 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 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.

Abstract:

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

RESEARCH DESIGN AND METHODS: We used two different matching procedures comparing 55 FPLD versus control patients with severe obesity (OC) (total=549 patients) to study the relationship between body weight, fat distribution and metabolic diseases, such as diabetes mellitus, hypertriglyceridemia and non-alcoholic steatohepatitis (MetS). In MATCH1, the FPLD patients were matched to Obese controls (OC) by truncal mass and in MATCH2, the FPLD patients were matched to OC with respect to glucose control.

RESULTS: With MATCH1, FPLD group had worse glycemic control (HbA1c=8.2±1.6% vs. 5.9±0.9%), higher triglycerides (884±1190 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 to OC: 29.5±5.7 kg/m2 vs. 38.6±5.2 kg/m2, $p<0.001$).

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

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 (MetS) associated with FPLD include severe insulin resistance predisposing to diabetes mellitus, hypertriglyceridemia, and non-alcoholic steatohepatitis (*3-5*). FPLD patients have a disproportionately lower body mass index (BMI) compared to individuals with common obesity despite displaying similar or worse MetS due to limited fat storage capacity (*6*). However, the extent and degree of MetS at comparable truncal mass (TM) or the “equivalent” BMI between the groups with similar MetS have not been examined.

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

Methods and Procedures

We performed a retrospective case-control study comparing “cases” of FPLD against “controls” with severe obesity while matching for total trunk mass or metabolic

comorbidities. Baseline data were obtained from subjects who participated in clinical studies of FPLD or who participated in our weight management program (WMP) making use of existing quality controlled prospective electronic databases. In brief, the WMP is a 2-year, intensive, behavioral weight management program that employs very-low energy diet in the form of liquid meal replacement (Optifast, Nestlé, SW) for three-four months to achieve 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. https://www.ncbi.nlm.nih.gov/pubmed/?cmd=historysearch&querykey=4)

All subjects in both groups provided written informed consent, and the protocols were approved by the institutional review board (IRB) at the University of Michigan. The FPLD patients are part of a long-term observational, international, multi-center, prospective study collecting data on the natural history of different lipodystrophy syndromes (LD-Lync) registered at ClinicalTrials.gov with NCT03087253. 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 being 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 the patient's life.

The data collected and pooled for these analyses included demographics, vital signs, chemistry panels, descriptions of disease comorbidities and their treatment and measurements of body composition. The available data on physical activity and quality of life, 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, obese controls (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 sequentially refer to as MATCH1 and MATCH2. 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 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's exact test as appropriate. We also determined the confidence intervals of the differences between the two cohorts from both match procedures.

We designed MATCH1 to have a 2:1 matching, with 2 obese controls for each FPLD patient as there were enough patients that could be selected to fit the set criteria. The matching criteria were baseline age, gender, and total trunk mass with the hypothesis that FPLD patients with similar trunk mass would demonstrate worse MetS than those of obese controls. 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 the patients with FPLD had worse glycemic control than control group (HbA1c=8.2±1.6%, 6.0±1.0%, $p<0.001$), higher triglyceride levels (884±1190 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, respectively, $p<0.001$) together with lower BMI (29.5±5.8 kg/m^2, 34.3±6.3 kg/m^2, $p<0.001$), (Table 1). The estimated differences in the metabolic parameters were as follows: HbA1c (2.2%, 95% confidence interval (CI): 1.7-2.7%) and triglycerides levels (745 mg/dL, CI: 423-1067 mg/dL). In contrast, the obese control group demonstrated an increase of 4.8 kg/m^2 (CI:2.8-6.8 kg/m^2) in BMI, while leptin levels were higher with a difference of 21.5 ng/dL (CI: 9.6-33.4 ng/dL).

When we matched FPLD patients to obese control patients for age, gender, presence of comorbidities and medication usage with MATCH2 (full details available in Table 1, Table 2 and Figure 1), we observed a residual difference in triglyceride levels in FPLD with mean difference of 635 mg/dL (CI: 307-904 mg/dL). Moreover, the FPLD patients had lower BMI (29.5±5.8 kg/m^2), and lower leptin levels s with mean difference of 32.7 ng/mL (CI: 15.1-50.3 ng/mL compared to the obese control patients (38.1±5.5 kg/m^2, p<0.001). The difference in BMI between the two groups in MATCH2 was 8.6 (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 to subjects with severe but common obesity have worse metabolic abnormalities (MetS). This result highlights the importance of the 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 (*7, 8*). This understanding falls in line with our observed differences in HbA1c, triglycerides, and leptin levels between the two cohorts when perfectly matched for truncal mass. We also believe that the "reverse" match performed in MATCH2 is a unique method of trying to estimate the BMI equivalent of the FPLD patients if they had normal adipose tissue distribution. We interpret that the metabolic disease burden of the FPLD patients is equivalent to non-FPLD obesity, that is, on average, 8.6 (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 (*9, 10*) do not address. If the metabolic disease BMI equivalent of the FPLD patients is at least 6.5 to 10.7 kg/m2 higher than the actual BMI noted, an FPLD patient with a BMI of 23 kg/m2 would be categorized as obese. In comparison,

another one with a BMI of 33 kg/m2 would be considered “severely obese” with their deficient storage capacity, as their metabolic disease is equivalent to that degree of obesity. Ideal BMI in an FPLD individual would more likely approximate the threshold for underweight (BMI of 18 kg/m2) in order to avoid metabolic complications. Given that many FPLD patients present with substantially higher BMIs, earlier identification and referral to a high-intensity intervention to achieve and maintain weight loss (e.g., very-low energy diets, weight control medications, and weight loss surgery) are imperative. While recombinant leptin in the form of Metreleptin is approved for treatment of generalized lipodystrophy, this treatment is not approved for partial lipodystrophy in the US. It is, however, approved for treatment of metabolic complications in individuals with familial or acquired partial lipodystrophy in the EU countries with a leptin level<12 ng/dL (*11, 12*).

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 FPLD patients 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 to the obese controls. 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, healthcare utilization, psychosocial factors and personal perceptions due to 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 FPLD patients.

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Legend for Figure 1:

Differences between Familial Partial Lipodystrophy (FPLD) and obese control groups when comparing individuals with similar trunk mass (MATCH1, panels a and b) or with similar metabolic disorders (MATCH2, panels c and d). Patients with FPLD have higher HbA1c (a) and serum triglycerides levels (b) when compared to obese patients of similar trunk mass. FPLD patients and controls with similar comorbidities and medications have a BMI difference of 8.6 (CI 6.5-10.7) kg/m^2 (c) associated with lower serum leptin levels (d).

Table 1: Clinical Characteristics of the Cohorts Before and After Matching

	FPLD	**Obese**
	n=55	n=548
Gender (M:F)	9:46	210:338
Age (years)	49 (37-57)	49 (41-57)
BMI (kg/m2)	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 a 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) *
Triglyceride (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 a 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) *

	FPLD	Obese
Hyperlipidemia (%)	100	49.8 (45.5-54.1)
On Lipid Lowering Meds (%)	80 (67.0-89.6)	46.5 (40.5-52.6)
Diabetics (%)	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 Glucose Lowering Meds (%)	92.3 (81.5-97.8)	73.5 (65.6-80.4)
Hypertensive (%)	67.3 (53.3-79.3)	42.9 (38.7-47.2)
Data presented as % (95% CI)		
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)
Triglyceride (mg/dL)	346 (245-1037)	195 (153-288) *
Leptin (ng/mL)	16.4 (9.4-24.9)	41.2 (24.1-76.7) *

** p<0.001 comparing FPLD and obese groups.*

FPLD: Familial Partial Lipodystrophy; BMI: Body Mass Index; TMI: Trunk Mass Index; FMR: Fat Mass Ratio; HbA1c: Hemoglobin A1c; LDL: Low-density lipoprotein; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase.

Table 2: Presence of comorbidities and use of medications in the Cohorts before matching

FPLD: Familial Partial Lipodystrophy

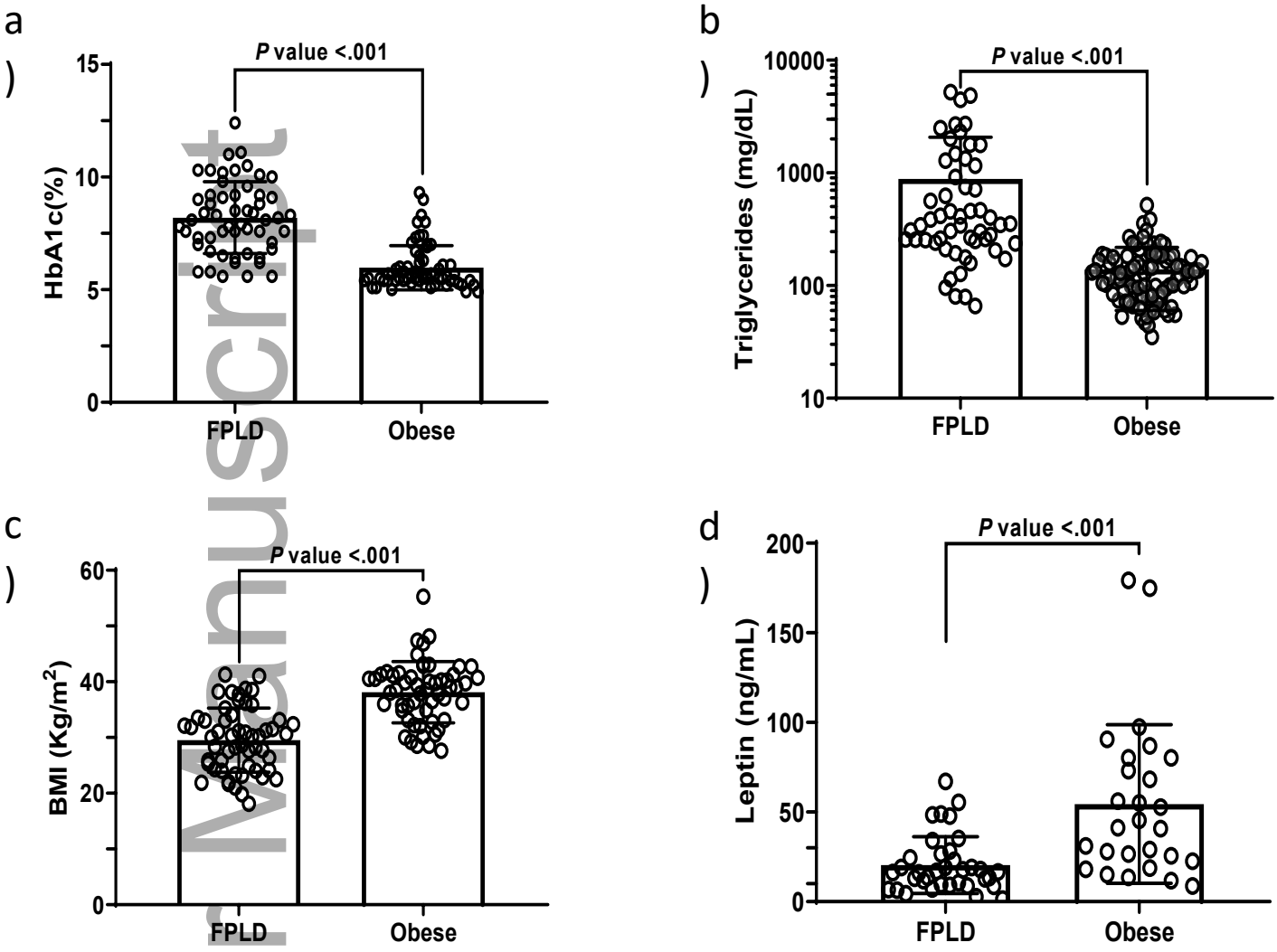

Figure 1