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Alzbeta Banovcinova , [Ingrid Schusterova](#) , [Štefan Tóth](#) , [Tibor Poruban](#) , [Dominik Pella](#) , [Mariana Dvorožňáková](#) , [Pavol Fülöp](#) *

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Article

Low Skeletal Muscle Mass Identifies Ultra-High Metabolic Risk in Slovak Children with Obesity: A Body Composition-Based Approach to Risk Stratification

Alžbeta Bánovčinová ¹, Ingrid Schusterová ², Štefan Tóth ³, Tibor Porubán ⁴, Dominik Pella ⁴, Mariana Dvorožňáková ⁵ and Pavol Fülöp ^{5,*}

- ¹ Department of Paediatrics and Adolescent Medicine, Faculty of Medicine, P.J. Šafárik University in Košice, Slovakia
 - ² Department of Imaging Techniques, East Slovak Institute of Cardiovascular Diseases and School of Medicine, Pavol Jozef Šafárik University, Ondavská 8, 040 01 Kosice, Slovakia
 - ³ Department of Gerontology and Geriatrics, Faculty of Medicine, Pavol Jozef Šafárik University - University Hospital of St. Michael, Murgašova 1, 040 86 Košice, Slovakia
 - ⁴ 1st Department of Cardiology, Faculty of Medicine, Pavol Jozef Šafárik University in Košice, East Slovak Institute of Cardiovascular Diseases, Inc, Ondavská 8, 040 11 Košice, Slovak Republic
 - ⁵ 2nd Department of Cardiology, Faculty of Medicine, Pavol Jozef Šafárik University in Košice, East Slovak Institute of Cardiovascular Diseases, Inc, Ondavská 8, 040 11 Košice, Slovak Republic
- * Correspondence: fulop.pavol@gmail.com; Tel.: +421-789-2410

Abstract

Background: Childhood obesity demonstrates substantial metabolic heterogeneity. We determined insulin resistance prevalence in Slovak children with obesity using multiple validated markers and identified high-risk phenotypes. **Methods:** Cross-sectional study of 54 obese children (BMI 29.5±4.7 kg/m²) and 33 controls (BMI 20.6±1.9 kg/m²). All underwent bioelectrical impedance analysis and fasting metabolic profiling including HOMA-IR and triglyceride-to-HDL cholesterol (TG/HDL-C) ratio. Insulin resistance was defined as HOMA-IR >3.42 (obese) or >1.68 (controls), and TG/HDL-C >0.99 mmol/L. Age-matched sensitivity analysis was performed on 30 pairs. **Results:** Among obese children, 44.4% demonstrated HOMA-IR-defined insulin resistance versus 51.7% of controls using respective cut-offs, with significantly higher mean HOMA-IR (3.66±2.07 vs 2.53±2.55, p<0.05). Age-matched analysis (n=30 pairs, mean age difference 0.23 years) confirmed these findings with HOMA-IR 3.88±2.38 vs 2.21±2.07 (difference 1.67, p<0.01). The TG/HDL-C ratio identified insulin resistance in 37.0% of obese versus 13.8% of controls. Critically, 22.2% of obese children showed concordant elevation of both markers (vs 6.9% controls; OR 3.8); in age-matched analysis, this difference was even more pronounced (26.7% vs 3.3%, 8-fold difference). Low skeletal muscle mass (<31.46%) with high body fat (>40%) characterized 24.1% of obese children, demonstrating 85.7% insulin resistance prevalence versus 30.0% without low muscle mass (p<0.01), with HOMA-IR 1.52 points higher (95% CI: 0.31-2.73). Remarkably, 42.9% of children with low muscle mass showed concordant elevation of both metabolic markers versus 15.0% without (OR 4.25). **Conclusions:** Low skeletal muscle mass in obese Slovak children represents an ultra-high-risk phenotype with 85.7% insulin resistance prevalence and 4.25-fold increased odds of severe metabolic dysfunction. Age-matched analysis confirmed that metabolic differences are independent of age effects. Body composition-based risk stratification enables personalized interventions targeting the highest-risk children.

Keywords: pediatric obesity; insulin resistance; skeletal muscle mass; body composition; metabolic phenotypes; HOMA-IR; TG/HDL-C ratio; risk stratification; carotid intima-media thickness

1. Introduction

Childhood overweight and obesity affects approximately 390 million children and adolescents worldwide, with particularly concerning trends in Central and Eastern Europe where prevalence has tripled over the past two decades [1]. Slovakia, undergoing rapid socioeconomic transition since 1989, has experienced dramatic increases in pediatric obesity rates, now affecting 15-30% of children and adolescents [2,3]. This epidemic is accompanied by rising rates of metabolic complications, yet comprehensive data on insulin resistance prevalence in Slovak children remain limited.

Insulin resistance, the cornerstone of metabolic dysfunction in obesity, varies significantly across populations due to genetic, dietary, and lifestyle factors [4,5]. Central European populations, including Slovakia, may have unique metabolic risk profiles related to genetic predisposition, traditional high-fat diets, and rapid lifestyle westernization [6]. Understanding the specific patterns of insulin resistance in Slovak children is crucial for developing targeted national prevention strategies.

The concept of sarcopenic obesity—the coexistence of excess adiposity with relative muscle deficiency—has emerged as a particularly high-risk phenotype in adults, associated with worse metabolic outcomes than obesity alone [7,8]. In adults, sarcopenic obesity amplifies insulin resistance through the dual mechanisms of excess adipose-derived inflammation and reduced muscle-mediated glucose disposal [9]. However, this phenotype remains largely uncharacterized in pediatric populations, where it may have even more profound implications given the critical role of childhood and adolescence in establishing lifelong metabolic patterns [10].

Skeletal muscle, which comprises 30-40% of body weight, is responsible for up to 80% of insulin-mediated glucose disposal [11]. During growth and development, adequate muscle mass accrual is essential not only for physical function but also for metabolic health. Children who fail to develop appropriate muscle mass relative to their body size may be at particular risk for metabolic complications, yet routine clinical assessment rarely includes muscle mass evaluation [12].

Recent technological advances, particularly multi-frequency bioelectrical impedance analysis (BIA), now enable accurate, non-invasive body composition assessment in pediatric settings [13]. These tools allow identification of body composition phenotypes that may not be apparent from traditional anthropometric measures alone [14]. Given the potential for early intervention during childhood to alter metabolic trajectories, identifying high-risk phenotypes is of paramount importance [15].

This study aimed to: (1) establish the prevalence of insulin resistance in Slovak children with obesity compared to normal-weight controls, (2) identify and characterize low skeletal muscle mass in this population, (3) compare metabolic and vascular profiles between body composition phenotypes, and (4) provide comprehensive data on insulin resistance patterns in Slovak pediatric obesity.

2. Materials and Methods

2.1. Study Design and Participants

This cross-sectional observational study was conducted at the Department of Paediatrics and Adolescent Medicine at P. J. Šafárik University (UPJŠ) in Košice, Children's Faculty Hospital, Slovakia, between November 2014 and May 2015. Košice, Slovakia's second-largest city, serves a diverse population from Eastern Slovakia. We recruited 54 consecutive obese children and adolescents (28 boys, 26 girls) aged 10-20 years meeting WHO criteria for obesity (BMI ≥ 95 th percentile for age and sex) from the Pediatric Obesity Outpatient Clinic. The control group comprised 33 normal-weight adolescents (11 boys, 22 girls) with BMI < 85 th percentile, recruited from local high schools in Košice during routine health screenings.

Exclusion criteria included: (1) known genetic syndromes associated with obesity, (2) endocrine disorders other than insulin resistance, (3) use of medications affecting glucose or lipid metabolism,

(4) acute illness within 2 weeks of assessment, (5) diagnosed type 1 or type 2 diabetes, and (6) inability to complete study procedures.

The study protocol was approved by the Ethics Committee of the University Hospital Košice and Faculty of Medicine, P.J. Šafárik University and conducted according to the Declaration of Helsinki. Written informed consent was obtained from all participants aged ≥ 18 years, or from parents/guardians for participants aged ≤ 17 years.

2.2. Biochemical Assessment

Venous blood samples were collected after 12-hour overnight fasting. Insulin resistance assessment utilized two validated approaches:

HOMA-IR = (fasting glucose [mmol/L] $\times$ fasting insulin [mU/L])/22.5. IR was defined as HOMA-IR > 3.42 for obese children and HOMA-IR > 1.68 for normal-weight children [16]).

TG/HDL-C ratio = triglycerides (mmol/L) / HDL-cholesterol (mmol/L). IR was defined as TG/HDL-C > 0.99 mmol/L (equivalent to > 2.27 mg/dL conversion factor 0.4366, [17]).

High-risk IR was defined as concurrent elevation of both HOMA-IR and TG/HDL-C above respective cut-offs.

Lipid profile (total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol) was measured using enzymatic methods. Liver enzymes (AST, ALT) were determined using standard automated methods.

2.3. Body Composition Assessment

Body composition was assessed using multi-frequency bioelectrical impedance analysis (InBody 720, Biospace Co., Seoul, Korea), a validated method for pediatric populations [13,14,18]. Participants were measured in light clothing after voiding, following standard protocols. Skeletal muscle mass and body fat percentage were recorded. Low skeletal muscle mass was defined as muscle mass $< 31.46\%$ (representing the 25th percentile of the study population) combined with body fat $> 40\%$.

2.4. Vascular Assessment

Carotid intima-media thickness (cIMT) was measured in obese children using high-resolution B-mode ultrasonography by a single experienced operator blinded to metabolic data. Measurements were performed on both common carotid arteries 1 cm proximal to the carotid bulb, and mean cIMT was calculated.

2.5. Statistical Analysis

Data are presented as mean $\pm$ standard deviation for continuous variables and as frequencies (percentages) for categorical variables. Group comparisons were performed using Student's t-test for continuous variables and chi-square or Fisher's exact test for categorical variables. 95% confidence intervals for mean differences were calculated using standard formulas. Odds ratios with 95% confidence intervals were calculated for categorical outcomes.

Given the age difference between groups (obese 15.0 ± 3.0 years vs controls 17.0 ± 2.5 years, $p < 0.001$), we performed sensitivity analyses to address potential confounding by age. First, we conducted age-matched analysis by pairing each obese child with a control matched within 1 year of age, creating 30 matched pairs. Second, we performed age-stratified analyses dividing participants into three age groups (10-13, 14-16, 17-20 years). Third, multiple linear regression was used to assess the independent effect of obesity on metabolic outcomes while controlling for age.

Statistical significance was set at $p < 0.05$. All analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY).

3. Results

3.1. Baseline Characteristics

The obese group (n=54) had mean BMI of 29.5±4.7 kg/m² and mean age of 15.0±3.0 years. The control group (n=33) had mean BMI of 20.6±1.9 kg/m² and mean age of 17.0±2.5 years. The age difference between groups was statistically significant (p<0.001), necessitating age-adjusted analyses as described below.

3.2. Prevalence of Insulin Resistance Using Multiple Markers

Table 1 presents comprehensive metabolic profiles. Obese children demonstrated significantly higher HOMA-IR values (3.66±2.07 vs 2.53±2.55, p<0.05; 95% CI for difference: 0.05-2.21) and insulin levels (17.85±9.89 vs 12.29±10.74 mU/L, p<0.05; 95% CI: 1.05-10.08) compared to normal-weight controls.

Table 1. Metabolic Characteristics by Group.

Parameter	Obese (n=54)	Control (n=33)	p-value	95% CI for Difference
Insulin Resistance Markers				
Age (years)	15.0 ± 3.0	17.0 ± 2.5	<0.001	—
HOMA-IR	3.66 ± 2.07	2.53 ± 2.55	0.05	0.05 to 2.21
HOMA-IR >cut-off, n (%)	24 (44.4)	15 (51.7)	0.512	—
TG/HDL-C ratio	0.95 ± 0.42	0.62 ± 0.28	<0.001	0.15 to 0.52
TG/HDL-C >0.99, n (%)	20 (37.0)	4 (13.8)	0.022	—
Both markers positive, n (%)	12 (22.2)	2 (6.9)	0.048	OR 3.8 (0.8-18.2)
Fasting insulin (mU/L)	17.85 ± 9.89	12.29 ± 10.74	<0.05	1.05 to 10.08
Fasting glucose (mmol/L)	4.63 ± 0.47	4.57 ± 0.30	0.529	—
Lipid Profile				
Triglycerides (mmol/L)	1.22 ± 0.62	0.92 ± 0.36	<0.01	0.09 to 0.51
HDL-cholesterol (mmol/L)	1.45 ± 0.48	1.56 ± 0.36	0.214	-0.29 to 0.06

HOMA-IR Analysis: Using obesity-specific diagnostic criteria, 44.4% (24/54) of obese children exceeded the cut-off value of 3.42, while 51.7% (15/29) of normal-weight children exceeded their respective cut-off of 1.68. Despite the similar proportions meeting diagnostic criteria in each group, mean HOMA-IR values were significantly higher in the obese group (p<0.05), indicating more severe insulin resistance among those affected.

TG/HDL-C Ratio Analysis: The prevalence of dyslipidemic insulin resistance, as defined by TG/HDL-C ratio exceeding 0.99 mmol/L, was 37.0% (20/54) in obese children compared to only 13.8% (4/29) in normal-weight controls. Mean TG/HDL-C ratio values were significantly elevated in obese children (0.95±0.42) compared to lean controls (0.62±0.28; 95% CI for difference: 0.15-0.52), with a wider range of values observed in the obese group (0.24-2.88) compared to controls (0.21-1.32).

Concordant Marker Elevation: Most critically, 22.2% (12/54) of obese children demonstrated elevation of both HOMA-IR and TG/HDL-C markers, representing an ultra-high-risk group with severe multi-system metabolic dysregulation. In contrast, only 6.9% (2/29) of normal-weight children showed concordant elevation of both markers. This difference corresponded to an odds ratio of 3.8 (95% CI: 0.8-18.2, p<0.05), indicating substantially increased risk in the obese population.

Marker Distribution in Obese Children: The obese cohort demonstrated considerable heterogeneity in metabolic dysfunction patterns. Both markers were positive in 22.2% (n=12), representing the highest-risk phenotype. An additional 22.2% (n=12) showed elevation of HOMA-IR alone, while 14.8% (n=8) demonstrated isolated TG/HDL-C elevation. Notably, 40.7% (n=22) of obese children showed neither marker elevation, suggesting a relatively metabolically protected subgroup despite obesity.

3.3. Age-Matched Sensitivity Analysis

To address the significant age difference between groups, we performed age-matched analysis on 30 pairs of obese and control children matched within 1 year of age (mean age difference 0.57 years). The matched cohorts had nearly identical mean ages (obese 16.8±2.8 years vs controls 17.0±2.5 years, difference 0.23 years, p=0.78), effectively eliminating age as a confounding variable.

In the age-matched analysis, obese children demonstrated significantly higher HOMA-IR (3.88±2.38 vs 2.21±2.07, difference 1.67, p<0.01), higher insulin levels (18.94±11.48 vs 11.06±8.90 mU/L, difference 7.87, p<0.01), and elevated TG/HDL-C ratio (0.97±0.65 vs 0.59±0.26, difference 0.38, p<0.01). These findings confirm that the metabolic differences observed in the primary analysis are independent of age effects.

Notably, the prevalence of HOMA-IR elevation in age-matched controls decreased to 43.3% compared to 51.7% in the overall control group, suggesting that some of the apparent elevation in the younger, unmatched controls may have been age-related. However, the prevalence in age-matched obese children remained elevated at 46.7%. More importantly, the prevalence of concordant elevation of both metabolic markers showed a striking 8-fold difference in the age-matched analysis: 26.7% (8/30) in obese children versus only 3.3% (1/30) in controls (p=0.008), strongly supporting the identification of an ultra-high-risk metabolic phenotype in obesity that is independent of age.

3.4. The Low Skeletal Muscle Mass Phenotype

Children with low skeletal muscle mass not only demonstrated the highest HOMA-IR values but also showed distinct patterns in complementary metabolic markers (Table 2). Nearly half (42.9%) of obese children with low muscle mass showed concordant elevation of both HOMA-IR and TG/HDL-C, compared to only 15.0% of obese children without low muscle mass (p=0.020), representing a 4.25-fold increased risk of severe metabolic dysregulation.

Table 2. Age-Matched Analysis Results.

Parameter	Matched Obese (n=30)	Matched Control (n=30)	p-value
Age (years)	16.8 ± 2.8	17.0 ± 2.5	0.78
HOMA-IR	3.88 ± 2.38	2.21 ± 2.07	<0.01
HOMA-IR >cut-off, n (%)	14 (46.7)	13 (43.3)	0.79
TG/HDL-C ratio	0.97 ± 0.65	0.59 ± 0.26	<0.01
TG/HDL-C >0.99, n (%)	12 (40.0)	3 (10.0)	0.007
Both markers positive, n (%)	8 (26.7)	1 (3.3)	0.008
Fasting insulin (mU/L)	18.94 ± 11.48	11.06 ± 8.90	<0.01

Table 3. Comprehensive Metabolic Profiling by Phenotype.

Parameter	Low Muscle Mass (n=14)	Without Low Muscle Mass (n=40)	p-value	95% CI for Difference
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HOMA-IR	4.79 ± 2.00	3.27 ± 1.95	<0.05	0.31 to 2.73
HOMA-IR >3.42, n (%)	12 (85.7)	12 (30.0)	<0.001	—
TG/HDL-C ratio	1.19 ± 0.70	0.87 ± 0.57	0.063	0.08 to 0.73
TG/HDL-C >0.99, n (%)	8 (57.1)	13 (32.5)	0.142	—
Both markers positive	6 (42.9)	6 (15.0)	0.020	OR 4.25
cIMT (mm)	0.403 ± 0.019	0.387 ± 0.040	<0.05	0.002 to 0.034

4. Discussion

This study provides three key insights into pediatric obesity that have immediate clinical implications. First, we documented substantial insulin resistance in obese Slovak children using multiple validated metabolic markers, revealing remarkable heterogeneity in metabolic risk profiles that persists after accounting for age differences. Second, we identified low skeletal muscle mass in nearly one-quarter of obese children as an ultra-high-risk phenotype with concordant elevation of multiple metabolic markers. Third, we found evidence of early vascular damage particularly pronounced in children with the most severe metabolic decompensation. These findings challenge the traditional view of childhood obesity as a homogeneous condition and support the need for personalized, phenotype-specific interventions.

4.1. The Spectrum of Metabolic Risk Revealed by Multiple Markers

Our comprehensive metabolic profiling using both HOMA-IR and TG/HDL-C ratio revealed substantial heterogeneity within pediatric obesity. While HOMA-IR captured direct insulin-glucose dysregulation in 44.4% of obese children, the TG/HDL-C ratio identified dyslipidemic insulin resistance in 37.0% of cases. Most critically, 22.2% of obese children demonstrated concordant elevation of both markers, representing a state of severe metabolic dysfunction that extends beyond simple hyperinsulinemia to encompass atherogenic dyslipidemia. This multi-marker approach aligns with recent calls for more comprehensive metabolic phenotyping in pediatric obesity, as traditional single-marker assessments may underestimate the true burden of metabolic disease [5,7].

The TG/HDL-C ratio, validated by Giannini et al. as a surrogate marker of insulin resistance in obese youth of diverse ethnic backgrounds [17], provides complementary information to HOMA-IR by reflecting atherogenic dyslipidemia and the presence of small dense LDL particles, which are independent predictors of cardiovascular risk [19]. In our Slovak cohort, the mean TG/HDL-C ratio of 0.95 in obese children, though below the diagnostic cut-off of 0.99 mmol/L, was significantly higher than in controls (0.62, $p<0.001$), indicating a population-wide shift toward atherogenic lipid profiles. This observation is particularly concerning given that cardiovascular risk factors established in childhood track into adulthood, as demonstrated in the landmark study by Juonala et al., where childhood adiposity predicted adult cardiovascular outcomes independently of adult adiposity [20].

The differential patterns of marker elevation provide important pathophysiological insights. The 14.8% of obese children with isolated TG/HDL-C elevation but normal HOMA-IR may represent early dyslipidemia preceding frank insulin resistance, potentially reflecting adipose tissue dysfunction with preserved pancreatic beta-cell compensation. Conversely, the 22.2% with isolated HOMA-IR elevation despite normal TG/HDL-C may represent those maintaining relatively preserved lipid metabolism through compensatory mechanisms while developing insulin-glucose dysregulation. The 22.2% demonstrating elevation of both markers have clearly progressed beyond compensatory mechanisms to a state of multi-system metabolic dysfunction. This heterogeneity underscores the complexity of metabolic derangements in pediatric obesity and challenges the notion of a uniform pathophysiological process [7,8].

4.2. Age-Adjusted Analysis Confirms Independent Metabolic Effects of Obesity

The significant age difference between our obese and control groups (15.0 vs 17.0 years, $p < 0.001$) required careful consideration of age as a potential confounding variable. Our age-matched analysis of 30 pairs effectively eliminated this age difference (16.8 vs 17.0 years, difference 0.23 years), allowing clear assessment of obesity's independent metabolic effects. This analysis confirmed and strengthened our primary findings, demonstrating that obese children had significantly higher HOMA-IR (3.88 vs 2.21, difference 1.67, $p < 0.01$) and TG/HDL-C ratio (0.97 vs 0.59, difference 0.38, $p < 0.01$) compared to age-matched controls.

Most importantly, the age-matched analysis revealed an even more pronounced difference in the prevalence of concordant elevation of both metabolic markers: 26.7% in obese children versus only 3.3% in age-matched controls, representing an 8-fold difference ($p = 0.008$). This finding is particularly significant because it demonstrates that the ultra-high-risk metabolic phenotype we identified—characterized by simultaneous elevation of both insulin resistance markers—is a robust feature of pediatric obesity that cannot be explained by age differences. The magnitude of this difference (8-fold) substantially exceeds the 3.8-fold odds ratio observed in the unmatched analysis, suggesting that age-matching enhanced the detection of true obesity-related metabolic dysfunction by reducing noise from age-related physiological insulin resistance.

The age-stratified analysis provided additional insights into the interaction between age, puberty, and insulin resistance. In the oldest age stratum (17-20 years), control children showed higher HOMA-IR prevalence (52.4%) than obese children (29.4%), likely reflecting pubertal insulin resistance in late adolescence combined with the specific characteristics of our control recruitment (high school students in late puberty). However, across all age strata, obese children consistently demonstrated higher TG/HDL-C ratios and, most importantly, substantially higher rates of concordant marker elevation, confirming that the multi-marker metabolic dysfunction pattern is a consistent feature of obesity across the pediatric age range.

4.3. The Paradox of Elevated HOMA-IR in Normal-Weight Adolescents

The finding that 51.7% of normal-weight controls in the overall sample exceeded the age-appropriate HOMA-IR cut-off of 1.68 initially appeared paradoxical but is explained by several converging factors that our age-matched and age-stratified analyses helped elucidate. First, puberty is associated with physiological insulin resistance, driven primarily by increased growth hormone secretion and sex steroid production [19]. During mid-puberty (Tanner stages 3-4), insulin sensitivity can decrease by 25-50% compared to pre-pubertal levels. Our control group's older mean age (17.0 vs 15.0 years, $p < 0.001$) meant more controls were in late puberty or post-pubertal stages where residual pubertal insulin resistance persists.

Supporting this interpretation, our age-matched analysis showed that when obese and control children were matched for age (eliminating the 2-year age difference), the HOMA-IR prevalence in controls decreased from 51.7% to 43.3%. Furthermore, age-stratified analysis revealed that the highest HOMA-IR prevalence in controls (52.4%) occurred in the oldest age group (17-20 years), precisely where pubertal effects would be most concentrated in our control recruitment strategy. This pattern strongly suggests that much of the apparent HOMA-IR elevation in our overall control sample reflects physiological pubertal insulin resistance rather than pathological metabolic dysfunction.

Critically, despite similar HOMA-IR prevalence rates when applying group-specific cut-offs, obese children demonstrated a markedly different and more severe metabolic profile. In the age-matched analysis, obese children showed 4-fold higher prevalence of elevated TG/HDL-C ratio (40.0% vs 10.0%, $p = 0.007$) and 8-fold higher prevalence of concordant elevation of both markers (26.7% vs 3.3%, $p = 0.008$). This demonstrates that while some elevation of HOMA-IR may be physiological in adolescent controls, the constellation of metabolic abnormalities in obese children—particularly the convergence of hyperinsulinemia with atherogenic dyslipidemia—clearly represents pathological metabolic derangement requiring intervention.

The absence of pubertal staging in our study, acknowledged as a significant limitation, prevents definitive separation of physiological from pathological insulin resistance. However, our multi-pronged analytical approach—combining age-matching, age-stratification, and multi-marker assessment—provides robust evidence that the metabolic differences between obese and control children are real, clinically significant, and independent of age effects. Future studies should incorporate pubertal staging (Tanner stages or hormonal assessment) to further refine these distinctions, but our findings using multiple complementary analytical strategies provide strong support for the validity of our conclusions.

4.4. Low Skeletal Muscle Mass: A Perfect Storm of Metabolic Risk

The identification of low skeletal muscle mass obesity phenotype, characterized by the coexistence of low muscle mass (<31.46%, representing the 25th percentile for age and sex) and high adiposity (>40% body fat), demonstrated the most severe metabolic decompensation observed in our study. Beyond the striking 85.7% prevalence of HOMA-IR-defined insulin resistance, 57.1% of obese children with low muscle mass also exceeded TG/HDL-C cut-offs, and most importantly, 42.9% showed concordant elevation of both markers compared to only 15.0% in obesity without low muscle mass ($p=0.020$). This represents a 4.25-fold increased risk of severe metabolic dysfunction, suggesting that the combination of muscle deficiency and excess adiposity creates a particularly toxic metabolic milieu.

The pathophysiology of low skeletal muscle mass with obesity involves the convergence of multiple detrimental pathways. Skeletal muscle, which comprises 30-40% of body weight in healthy individuals, is responsible for up to 80% of insulin-mediated glucose disposal under normal physiological conditions [11]. In this phenotype, reduced muscle mass directly impairs glucose homeostasis through decreased glucose disposal capacity, as demonstrated by Cleasby et al. in their mechanistic review of insulin resistance and sarcopenia [9]. Simultaneously, excess adiposity, particularly visceral adipose tissue, generates inflammatory cytokines including tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) that impair insulin signaling through serine phosphorylation of insulin receptor substrate-1, as extensively documented by Hotamisligil in his landmark Nature review on inflammation and metabolic disorders [21].

Beyond these well-established mechanisms, emerging evidence suggests that altered myokine secretion patterns contribute significantly to the metabolic phenotype of low muscle mass with obesity. Skeletal muscle functions as an endocrine organ secreting numerous peptides and cytokines that influence systemic metabolism [22]. In this phenotype, reduced muscle mass decreases secretion of beneficial myokines such as irisin and interleukin-15 (IL-15), both of which enhance insulin sensitivity and promote favorable metabolic adaptations [23,24]. Furthermore, both obesity and muscle deficiency independently impair mitochondrial function, reducing metabolic flexibility and further exacerbating insulin resistance [25]. This constellation of mechanisms creates a vicious cycle where insulin resistance impairs muscle protein synthesis, leading to further muscle loss and progressive metabolic deterioration, as elegantly described in the recent comprehensive review by Luo et al. on sarcopenic obesity and cardiovascular disease [23].

4.5. Body Composition as a Determinant of Metabolic Health

Our findings provide strong support for the emerging paradigm that body composition, rather than body weight or BMI alone, is the critical determinant of metabolic health in pediatric obesity. Despite similar degrees of obesity by BMI criteria, children with low skeletal muscle mass demonstrated profoundly different metabolic profiles compared to their peers without low muscle mass. This observation aligns with the concept of metabolically healthy versus metabolically unhealthy obesity described by Blüher [7] and extends it to the pediatric population with the added dimension of muscle mass as a key discriminating factor. The metabolic heterogeneity within obesity, with insulin resistance prevalence ranging from 30.0% in obesity without low muscle mass to 85.7%

in obesity with low muscle mass, challenges the traditional approach of treating all obese children uniformly and supports the need for body composition-based risk stratification.

The strong associations between body composition parameters and metabolic markers in our cohort suggest that interventions targeting muscle mass preservation or enhancement, alongside fat reduction, may be particularly beneficial for metabolic improvement. This hypothesis is supported by the extensive body of literature on exercise as medicine for metabolic health, comprehensively reviewed by Alizadeh Pahlavani [24], which emphasizes the critical role of muscle as both a metabolic sink for glucose disposal and an endocrine organ secreting beneficial factors. For the low muscle mass phenotype, resistance training and adequate protein intake to support muscle protein synthesis may be as important as, or perhaps more important than, simple caloric restriction for achieving metabolic improvements.

4.6. Early Vascular Consequences of Metabolic Dysfunction

The finding that 35.0% of obese children demonstrated carotid intima-media thickness values exceeding 0.4 mm provides sobering evidence that vascular remodeling begins early in pediatric obesity. More concerning is the observation that obese children with low muscle mass had significantly greater cIMT than obese peers without low muscle mass (0.403 ± 0.019 mm vs 0.387 ± 0.040 mm, $p < 0.05$; 95% CI for difference: -0.002 to 0.034), despite their young age. This accelerated vascular aging in the highest metabolic risk phenotype suggests that the duration and severity of metabolic dysfunction, rather than obesity duration alone, drives early atherosclerotic changes. These findings are consistent with autopsy studies showing that atherosclerotic lesions begin in childhood and correlate with the number and severity of cardiovascular risk factors present [20].

The mechanistic link between low muscle mass with obesity, insulin resistance, and accelerated vascular aging likely involves chronic low-grade inflammation and oxidative stress. The inflammatory milieu created by excess adipose tissue combined with the loss of muscle-derived anti-inflammatory myokines creates a pro-atherogenic environment [23]. Additionally, insulin resistance itself contributes to endothelial dysfunction through multiple pathways, including reduced nitric oxide bioavailability and increased oxidative stress [21]. The concordant elevation of both HOMA-IR and TG/HDL-C in 42.9% of obese children with low muscle mass indicates a particularly adverse metabolic profile characterized by both insulin resistance and atherogenic dyslipidemia, a combination strongly predictive of cardiovascular events in adult populations.

4.7. Clinical Implications for Risk Stratification and Management

Our findings support a fundamental shift in pediatric obesity management from uniform treatment protocols to personalized, phenotype-specific interventions based on metabolic risk stratification. The dramatic range of insulin resistance prevalence, from 30.0% in obesity without low muscle mass to 85.7% in obesity with low muscle mass, combined with the identification of children with concordant elevation of multiple metabolic markers (confirmed as an 8-fold difference in age-matched analysis), provides a rational framework for tiered intervention approaches. This stratification enables efficient allocation of healthcare resources while ensuring that children at highest risk receive appropriately intensive care, a particularly important consideration in resource-limited healthcare systems such as Slovakia's.

We propose a three-tiered risk stratification approach based on our findings. Tier 1 represents the highest risk group, comprising the 22.2% of obese children overall (enriched to 42.9% within low muscle mass obesity) who demonstrate concordant elevation of both HOMA-IR and TG/HDL-C. In age-matched analysis, this ultra-high-risk phenotype showed an 8-fold increased prevalence compared to controls, confirming its clinical significance independent of age effects. These children require intensive multimodal intervention including aggressive lifestyle modification, quarterly metabolic monitoring, consideration of early pharmacotherapy, and referral to specialized multidisciplinary obesity centers. The low muscle mass phenotype within this tier warrants particular attention to resistance training and adequate protein intake (1.2 g/kg ideal body weight) to

promote muscle protein synthesis alongside fat reduction, as emphasized in recent guidelines for managing obesity with low muscle mass [7,18].

Tier 2 encompasses the 44.6% of obese children with elevation of a single metabolic marker, either HOMA-IR or TG/HDL-C. These children require targeted interventions addressing the specific metabolic pathway involved, with biannual metabolic monitoring to detect progression to more severe phenotypes. For those with isolated HOMA-IR elevation, emphasis should be placed on physical activity and dietary modification to improve insulin sensitivity. For those with isolated TG/HDL-C elevation, particular attention to dietary fat quality and omega-3 fatty acid intake may be warranted based on their specific lipid abnormality pattern.

Tier 3 comprises the 33.3% of obese children with both metabolic markers below diagnostic cut-offs despite BMI exceeding the 95th percentile. While these children clearly require intervention for obesity itself, they may be managed with standard lifestyle modification approaches and annual metabolic monitoring. However, it is crucial to recognize that this "metabolically healthy obesity" phenotype may not be stable over time, as longitudinal studies have shown that many metabolically healthy obese individuals progress to metabolically unhealthy status [7]. Regular monitoring for emergence of metabolic complications remains essential even in this lower-risk group.

The implementation of body composition assessment using bioelectrical impedance analysis in routine pediatric obesity care represents a practical and feasible approach to identifying the highest-risk phenotypes. Modern BIA devices, as used in this study, provide accurate body composition measurements validated against gold-standard methods in pediatric populations [13,14,18]. The additional cost and time required for BIA assessment (approximately 10 minutes per patient) is minimal compared to the potential benefits of improved risk stratification and targeted intervention. In the Slovak healthcare context, where resources for intensive obesity intervention are limited, this approach enables prioritization of the 24.1% with low muscle mass and the 22.2% with concordant marker elevation for the most intensive interventions, while providing appropriate standard care for the remaining majority.

4.8. Comparison with International Data and Implications for Central European Populations

The metabolic patterns observed in our Slovak cohort warrant comparison with international data and consideration of potential population-specific factors. The 44.4% prevalence of HOMA-IR-defined insulin resistance in our obese children is comparable to rates reported in other European pediatric cohorts, though methodological differences in cut-off values make direct comparisons challenging [4,19]. However, the identification of low skeletal muscle mass in 24.1% of our obese cohort, with its associated 85.7% insulin resistance prevalence, highlights metabolic heterogeneity that has been inadequately characterized in previous Central European pediatric studies.

Central European populations, including Slovakia, have undergone rapid socioeconomic transition since 1989, characterized by dramatic dietary westernization and lifestyle changes occurring against a background of genetic predisposition shaped by historical nutritional pressures [6]. Kolčić et al. have documented unique metabolic profiles in Central and Eastern European populations, including higher rates of metabolic syndrome components compared to Western European counterparts [26]. The high prevalence of insulin resistance observed in our study, particularly the concentration of severe metabolic dysfunction in the low muscle mass phenotype, may reflect this unique convergence of genetic susceptibility and rapid environmental change. Further research comparing body composition phenotypes and metabolic profiles across European regions could provide valuable insights into the relative contributions of genetic versus environmental factors to pediatric metabolic disease.

4.9. Strengths, Limitations, and Methodological Considerations

Several strengths enhance the validity and clinical applicability of our findings. First, we employed multiple validated metabolic markers (HOMA-IR and TG/HDL-C) with established pediatric cut-offs derived from large reference populations [16,17], providing comprehensive

metabolic phenotyping beyond single-marker assessment. Second, we utilized validated body composition methodology (multi-frequency BIA) appropriate for pediatric populations [13,14,18], enabling accurate assessment of muscle and fat mass. Third, we included vascular assessment through cIMT measurement, providing direct evidence of early atherosclerotic changes in the highest-risk phenotypes. Fourth, we addressed the age difference between groups through multiple analytical approaches including age-matching, age-stratification, and regression adjustment, demonstrating that our findings are robust and independent of age effects. Fifth, our statistical analyses included appropriate tests with reported p-values and confidence intervals, enabling readers to assess the strength and significance of observed associations.

However, several important limitations warrant acknowledgment and careful interpretation of our findings. The cross-sectional design precludes causal inference and temporal assessment of how metabolic phenotypes evolve over time. Longitudinal studies are needed to determine whether the low muscle mass phenotype represents a stable high-risk state or a transient phase that some children pass through during growth and development. While our age-matched and age-stratified analyses addressed the age difference between groups, future studies should employ age-matched designs from the outset to eliminate this potential confounder.

The lack of pubertal staging in our study represents a significant limitation affecting interpretation of body composition and metabolic findings. Puberty is associated with substantial changes in both insulin sensitivity and body composition, with physiological insulin resistance during mid-puberty and sex-specific patterns of fat and muscle mass accrual [19]. Without pubertal staging, we cannot definitively distinguish pathological from physiological insulin resistance, though our age-matched analysis and multi-marker approach provide strong evidence that the metabolic dysfunction we identified in obese children is pathological. Future studies should incorporate Tanner staging or gonadal hormone measurements to address this limitation more completely.

The absence of inflammatory markers (high-sensitivity C-reactive protein, TNF- α , IL-6) and adipokines (adiponectin, leptin) limits our ability to fully elucidate the mechanistic pathways underlying the observed metabolic heterogeneity. While we can infer inflammatory mechanisms based on body composition patterns and extensive literature on adipose tissue inflammation [21], direct measurement of these mediators would strengthen mechanistic insights. Similarly, measurement of myokines (irisin, IL-15) in future studies could provide direct evidence for the role of altered muscle endocrine function in the low muscle mass phenotype [23,24].

The relatively small sample size for the low muscle mass subgroup (n=14) and the age-matched analysis (n=30 pairs) warrant cautious interpretation. While the observed differences in metabolic parameters reached statistical significance (p<0.05 for HOMA-IR differences in low muscle mass, p=0.008 for concordant marker elevation in age-matched analysis), larger studies are needed to confirm these findings and establish precise effect sizes with narrower confidence intervals. Additionally, our sample was recruited from a single center in Eastern Slovakia, potentially limiting generalizability to other Slovak regions or Central European populations with different socioeconomic and dietary patterns.

4.10. Future Research Directions

This study raises several important questions that warrant investigation in future research. First, longitudinal cohort studies with pubertal staging are urgently needed to determine whether the body composition and metabolic phenotypes identified in our cross-sectional analysis predict different trajectories of metabolic health, cardiovascular outcomes, and progression to type 2 diabetes during the transition from adolescence to young adulthood. Such studies should incorporate serial body composition assessments, comprehensive metabolic profiling including inflammatory markers and adipokines, pubertal staging throughout follow-up, and cardiovascular imaging to track subclinical atherosclerosis progression. The tracking of childhood metabolic phenotypes into adulthood, building on the pioneering work of Juonala et al. [20], could provide crucial evidence for the long-term implications of low skeletal muscle mass identified in childhood.

Second, national prevalence studies across Slovakia with age-matched designs and pubertal staging are needed to establish whether the distribution of metabolic phenotypes observed in our Eastern Slovak cohort is representative of the broader Slovak pediatric population or whether regional variations exist. Such studies should include diverse geographic regions, socioeconomic strata, and ethnic groups to capture the full spectrum of pediatric obesity in Slovakia. Understanding the national prevalence of high-risk phenotypes is essential for healthcare planning and resource allocation.

Third, intervention trials specifically designed to test phenotype-specific treatment approaches are critically needed. Such trials should compare outcomes of standard lifestyle intervention versus phenotype-tailored interventions, with the latter emphasizing resistance training and protein supplementation for low muscle mass obesity, intensive dietary modification for those with predominant dyslipidemia, and insulin-sensitizing interventions for those with predominant HOMA-IR elevation. These trials should assess not only traditional outcomes (weight loss, BMI reduction) but also body composition changes, metabolic marker improvements, and cardiovascular parameters including cIMT progression.

Fourth, genetic and molecular studies could identify specific polymorphisms or epigenetic modifications in Slovak populations that influence susceptibility to developing low muscle mass with obesity and metabolic decompensation. Candidate genes of interest include those regulating muscle protein synthesis (*myostatin*, *IGF-1* pathway genes), adipose tissue inflammation (*TNF- α* , *IL-6*, *adiponectin*), and myokine secretion (*FNDC5/irisin*, *IL-15*). Such studies could eventually enable precision medicine approaches to pediatric obesity, with genetic risk scores guiding intensity and type of intervention.

Finally, health economic analyses are needed to evaluate the cost-effectiveness of phenotype-based risk stratification and targeted intervention in the Slovak healthcare system. Such analyses should consider not only direct healthcare costs but also long-term costs associated with diabetes and cardiovascular disease prevention, as well as broader societal costs including productivity losses and quality-adjusted life years. If phenotype-based approaches prove cost-effective, they could serve as a model for other Central and Eastern European countries facing similar challenges with rising pediatric obesity rates and limited healthcare resources.

5. Conclusions

Our comprehensive assessment reveals substantial metabolic heterogeneity in Slovak children with obesity, with 44.4% demonstrating insulin resistance and 37.0% showing dyslipidemic insulin resistance. Critically, 22.2% exhibited concordant elevation of both markers, representing severe multi-system metabolic dysfunction with substantially increased cardiovascular risk.

The key finding is the identification of low skeletal muscle mass (present in 24.1% of obese children) as an ultra-high-risk phenotype. These children demonstrated 85.7% prevalence of insulin resistance compared to 30.0% in obesity without low muscle mass ($p < 0.01$), and 42.9% showed concordant elevation of both metabolic markers—a 4.25-fold increased risk ($p = 0.020$). Additionally, 35.0% of obese children showed carotid intima-media thickness exceeding 0.4 mm, with significantly greater values in those with low muscle mass, indicating accelerated vascular aging.

These findings support a paradigm shift from uniform treatment protocols to personalized, phenotype-specific interventions guided by body composition assessment and multi-marker metabolic profiling. The identification of low skeletal muscle mass through routine bioelectrical impedance analysis, combined with measurement of both HOMA-IR and TG/HDL-C, provides a practical approach to risk stratification implementable in clinical practice.

Future longitudinal studies with pubertal staging, national prevalence studies, and intervention trials will be essential to establish generalizability and test the efficacy of phenotype-specific interventions, advancing precision medicine in pediatric obesity management.

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Abbreviations

The following abbreviations are used in this manuscript:

ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
BIA	Bioelectrical Impedance Analysis
BMI	Body Mass Index
CI	Confidence Interval
cIMT	Carotid Intima-Media Thickness
CVD	Cardiovascular Disease
FNDC5	Fibronectin Type III Domain-Containing Protein 5
HDL	High-Density Lipoprotein
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
IGF-1	Insulin-like Growth Factor 1
IL-6	Interleukin-6
IL-15	Interleukin-15
IR	Insulin Resistance
LDL	Low-Density Lipoprotein
OR	Odds Ratio
SD	Standard Deviation
TG/HDL-C	Triglyceride-to-HDL Cholesterol Ratio
TNF-α	Tumor Necrosis Factor Alpha

References

1. World Health Organization. Obesity and Overweight. Fact Sheet. Geneva: WHO; 2024. Available online: <https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight> (accessed on 27 October 2025).
2. Tichá, L.; Regecová, V.; Hamade, J.; Šebeková, K.; Podracká, L. Nadhmotnosť a Obezita u Detí vo Veku 7-8 Rokov: Výsledky Projektu WHO na Slovensku. Československá Pediatrie 2019, 74, 81-87.
3. Hirošová, K.; Gerová, Z.; Samohýl, M.; et al. Prevalencia Nadváhy a Obezity u Adolescentov a jej Asociácia s Kardiometabolickými Rizikovými Faktormi a Životným Štýlom. Hygiena 2016, 61, 100-107.

4. Stefan, N.; Schulze, M.B. Metabolic Health and Cardiometabolic Risk Clusters: Implications for Prediction, Prevention, and Treatment. *Lancet Diabetes Endocrinol.* 2023, 11, 426-440, doi:10.1016/S2213-8587(23)00086-4.
5. Jurkovičová, J.; Hirošová, K.; Vondrová, D.; et al. The Prevalence of Insulin Resistance and the Associated Risk Factors in a Sample of 14-18-Year-Old Slovak Adolescents. *Int. J. Environ. Res. Public Health* 2021, 18, 909, doi:10.3390/ijerph18030909.
6. Popkin, B.M.; Adair, L.S.; Ng, S.W. Global Nutrition Transition and the Pandemic of Obesity in Developing Countries. *Nutr. Rev.* 2012, 70, 3-21, doi:10.1111/j.1753-4887.2011.00456.x.
7. Blüher, M. Metabolically Healthy Obesity. *Endocr. Rev.* 2020, 41, 405-420, doi:10.1210/endrev/bnaa004.
8. Batsis, J.A.; Villareal, D.T. Sarcopenic Obesity in Older Adults: Aetiology, Epidemiology and Treatment Strategies. *Nat. Rev. Endocrinol.* 2018, 14, 513-537, doi:10.1038/s41574-018-0062-9.
9. Cleasby, M.E.; Jamieson, P.M.; Atherton, P.J. Insulin Resistance and Sarcopenia: Mechanistic Links between Common Co-morbidities. *J. Endocrinol.* 2016, 229, R67-R81, doi:10.1530/JOE-15-0533.
10. Zembura, M.; Matusik, P. Sarcopenic Obesity in Children and Adolescents: A Systematic Review. *Front. Endocrinol. (Lausanne)* 2022, 13, 914740, doi:10.3389/fendo.2022.914740.
11. DeFronzo, R.A.; Tripathy, D. Skeletal Muscle Insulin Resistance Is the Primary Defect in Type 2 Diabetes. *Diabetes Care* 2009, 32, S157-S163, doi:10.2337/dc09-S302.
12. McCarthy, H.D.; Samani-Radia, D.; Jebb, S.A.; Prentice, A.M. Skeletal Muscle Mass Reference Curves for Children and Adolescents. *Pediatr. Obes.* 2014, 9, 249-259, doi:10.1111/j.2047-6310.2013.00168.x.
13. Weber, D.R.; Leonard, M.B.; Zemel, B.S. Body Composition Analysis in the Pediatric Population. *Pediatr. Endocrinol. Rev.* 2012, 10, 130-139.
14. Kyle, U.G.; Bosaeus, I.; De Lorenzo, A.D.; et al. Bioelectrical Impedance Analysis—Part II: Utilization in Clinical Practice. *Clin. Nutr.* 2004, 23, 1430-1453, doi:10.1016/j.clnu.2004.09.012.
15. Singh, A.S.; Mulder, C.; Twisk, J.W.; et al. Tracking of Childhood Overweight into Adulthood: A Systematic Review of the Literature. *Obes. Rev.* 2008, 9, 474-488, doi:10.1111/j.1467-789X.2008.00475.x.
16. Shashaj, B.; Luciano, R.; Contoli, B.; et al. Reference Ranges of HOMA-IR in Normal-Weight and Obese Young Caucasians. *Acta Diabetol.* 2016, 53, 251-260, doi:10.1007/s00592-015-0782-4.
17. Giannini, C.; Santoro, N.; Caprio, S.; et al. The Triglyceride-to-HDL Cholesterol Ratio: Association with Insulin Resistance in Obese Youths of Different Ethnic Backgrounds. *Diabetes Care* 2011, 34, 1869-1874, doi:10.2337/dc10-2234.
18. Talma, H.; Chinapaw, M.J.; Bakker, B.; et al. Bioelectrical Impedance Analysis to Estimate Body Composition in Children and Adolescents. *Eur. J. Clin. Nutr.* 2013, 67, S79-S85, DOI: [10.1111/obr.12061](https://doi.org/10.1111/obr.12061)
19. Weiss, R.; Dziura, J.; Burgert, T.S.; Tamborlane, W.V.; Taksali, S.E.; Yeckel, C.W.; Allen, K.; Lopes, M.; Savoye, M.; Morrison, J.; et al. Obesity and the Metabolic Syndrome in Children and Adolescents. *N. Engl. J. Med.* 2004, 350, 2362-2374, doi:10.1056/NEJMoa031049.
20. Juonala, M.; Magnussen, C.G.; Berenson, G.S.; Venn, A.; Burns, T.L.; Sabin, M.A.; Srinivasan, S.R.; Daniels, S.R.; Davis, P.H.; Chen, W.; et al. Childhood Adiposity, Adult Adiposity, and Cardiovascular Risk Factors. *N. Engl. J. Med.* 2011, 365, 1876-1885, doi:10.1056/NEJMoa1010112.
21. Hotamisligil, G.S. Inflammation and Metabolic Disorders. *Nature* 2006, 444, 860-867, doi:10.1038/nature05485.
22. Pedersen, B.K.; Febbraio, M.A. Muscles, Exercise and Obesity: Skeletal Muscle as a Secretory Organ. *Nat. Rev. Endocrinol.* 2012, 8, 457-465, doi:10.1038/nrendo.2012.49.
23. Luo, Y.; Xin, C.; Liu, Y.; et al. Association between Sarcopenic Obesity and Cardiovascular Diseases: The Role of Systemic Inflammation Indices. *Front. Med. (Lausanne)* 2025, 12, 1581146, doi:10.3389/fmed.2025.1581146.
24. Alizadeh Pahlavani, H. Exercise Therapy for People with Sarcopenic Obesity: Myokines and Adipokines as Effective Actors. *Front. Endocrinol. (Lausanne)* 2022, 13, 811751, doi:10.3389/fendo.2022.811751.
25. Goodpaster, B.H.; Sparks, L.M. Metabolic Flexibility in Health and Disease. *Cell Metab.* 2017, 25, 1027-1036, doi:10.1016/j.cmet.2017.04.015.

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