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Comparative study of insulin sensitivity and glucose metabolism in skeletal muscle following high-fat dietary intervention

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Abstract

Objective: In the present experiment, insulin sensitivity and glucose metabolism was compared in rats that were fed a HFD diet for 12 weeks compared to those fed an LFD diet. **Methods:** Sixteen male Sprague-Dawley rats (n = 8 per group) were randomised to an LFD (10% kcal fat) and HFD (60% kcal fat) for 12 weeks. Parameters assessed were an OGTT, the HOMA-IR index, in vitro uptake of [2-DG] by isolated soleus muscle, Western blotting for GLUT4 and phospho-Akt, plasma levels of inflammation mediators and muscle histology with hematoxylin-eosin and Oil Red O staining. **Results:** The HFD group had significantly greater terminal body weight, epididymal adiposity, fasting glucose and HOMA-IR index than the control group. At a muscle level, GLUT4 protein level was decreased by 39%, insulin-stimulated 2-DG uptake by 44% and the p-Akt(Ser473)/total-Akt ratio by 48%. Increased Oil Red O-positive lipid stores and decreased fibre CSA were observed in the soleus muscles of the HFD group. The correlation between the HOMA-IR index and GLUT4 protein levels and 2-DG uptake was inverse. **Conclusion:** Rats do not have insulin sensitivity which is reliably and statistically reduced after a 12 week high fat feeding period, both in the system and at the muscle level.

Keywords: *Insulin resistance, Skeletal muscle, High-fat diet, Glucose uptake*

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1. Introduction

Both obesity and T2DM prevalence are on the rise globally, and insulin resistance has a central role in both conditions. The 11th edition of the IDF Diabetes Atlas estimated that 11.1% of the world's adult population was living with diabetes in 2024, a number expected to grow to almost 13% by 2050 ([International Diabetes Federation, 2025](#)). An additional dimension has been added by the Global Burden of Disease Modelling – the increase in T2DM-attributable mortality and disability-adjusted life years in the last three decades has been greatest in low- and middle-sociodemographic-index populations ([He et al., 2024](#)). Skeletal muscle is of relevance as it accounts for ~75–80% of the insulin-mediated removal of glucose from the blood after meals and therefore is a principal regulator of whole-body glycaemic homeostasis ([Pirkmajer et al., 2022](#)).

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Still, the High-Fat Diet (HFD) paradigm is used most frequently as an animal model of diet-induced insulin resistance. HFD induces intramyocellular lipid accumulation, disturbs IRS-1/PI3K/Akt signal transduction and decreases GLUT4-dependent glucose uptake. Stott and Marino conducted a review of rodent models of diet-induced insulin resistance and found out that the fat content, proportion, and duration influenced the magnitude and tissue distribution of insulin-resistant phenotypes; hence, they suggest that a diet with 45–60% kcal fat over 8–12 weeks represents best the Western diet associated with metabolic diseases in humans (Stott and Marino, 2020).

Several mechanisms feed into HFD-induced muscle insulin resistance. Jani *et al.* observed fibre type-specific accumulation of diacylglycerol and ceramide, increased novel PKC isoform activation and impaired insulin-mediated glycogen synthesis in both oxidative and glycolytic muscles after 8 weeks of high-fat, sucrose-containing diet in rats (Jani *et al.*, 2021). Gaspar *et al.* support this lipid-related hypothesis by observing that low plasma membrane diacylglycerol levels and decreased PKC ϵ /PKC θ activity explain how exercise-trained animals maintain insulin sensitivity of muscles despite having high muscle lipid content, which is commonly referred to as the “athlete’s paradox” (Gaspar *et al.*, 2023). Inflammation plays a role too. Li *et al.* found that 12 weeks of HFD feeding in mice caused marked glucose intolerance alongside NF- κ B-driven inflammation and macrophage infiltration in skeletal muscle (Li *et al.*, 2022). Zhang *et al.*, meanwhile, traced HFD-induced increases in HOMA-IR in rats to the EGR-1/PTP1B axis, with IRS-1, Akt, and GLUT4 expression all suppressed. Six weeks of aerobic exercise training reversed these changes (Zhang *et al.*, 2024).

Mitochondria also have important role in the development of insulin resistance. Li *et al.* demonstrated that high-fat-diet mice had decreased AMPK activation and alterations in mitochondrial biogenesis in their skeletal muscle, which were partly reversed after consumption of nicotinamide riboside (Li *et al.*, 2023). Chou *et al.* employed proteomic profiling to cognitively identify that high fat feeding altered sirtuin signalling pathways and the regulation of ROS in both skeletal muscle and adipose tissue with aerobic exercise training reversing many of these molecular changes (Chou *et al.*, 2023). Jalo *et al.* reported that at the whole body level, in the CROSRAT model under conditions of insulin resistance in the high fat diet, glucose uptake differed between tissues, indicating different responses to the insulin resistance in the brain and peripheral tissues such as skeletal muscle (Jalo *et al.*, 2024).

Another wrinkle to the ability of rodent HFD models to translate to humans is the sex effect. Male rats were also found to have greater glycaemic impairment when fed an HFD and higher mitochondrial respiration capacity in their soleus muscle, compared with females, and sex-specific changes were observed in the transcription of fatty acid oxidation genes in the muscle (PI3K/Akt and PPAR α /RXR α signalling) (Hulett *et al.*, 2023). There have also been changes in the gut microbiota that have been shown to be an important factor in insulin resistance associated with diet. It was reviewed that microbes imbalance (gut microbial dysbiosis) associated with high-fat diet is implicated in the mechanism of systemic inflammation and insulin resistance by metabolic endotoxaemia mechanism (Semo *et al.*, 2024). In a similar manner, Shen *et al.* showed that a polyphenol supplementation in the diet reduced skeletal muscle loss induced by a high fat diet, but also improved gut microbiota composition (Shen *et al.*, 2022). These findings have culminated in recent reviews by Whytock and Goodpaster (2025) and Saadati *et al.* (2025) which are used to summarize here. Both reviews conclude that the significant mechanisms involved in insulin resistance in skeletal muscle include the dysregulation of lipids, chronic low-grade inflammation, and impaired transport of GLUT4. The following reviews also found that the best form of non-pharmacological treatment to restore insulin sensitivity is regular exercise.

Although great strides have been made in recent years in describing the molecular pathways leading to insulin resistance in diet-induced obesity, few studies have attempted to compare systemic markers of glucose homeostasis, such as HOMA-IR and OGTT values, with skeletal muscle specific markers, including GLUT4 protein levels, Akt phosphorylation and ex vivo glucose uptake in the same animals fed a standardized protocol of high fat diet. Such a lack is relevant since it will aid in assessing the degree to which molecular changes in skeletal muscle can be reflected in systemic metabolic measures. The purpose of this study was to fill this gap in one, appropriately powered cohort by evaluating, after 12 weeks of high-fat feeding, insulin signalling in muscle architecture, inflammatory status, and systemic glucose handling and, statistically, how well did the various measures of insulin resistance in muscle correlate with that in the system.

2. Materials and methods

2.1. Animals and experimental design

16 adult male Sprague-Dawley rats (aged six weeks, weighing 180–200 g) were obtained from a licensed institution and raised in the laboratory under normal conditions (temperature range: $22 \pm 2^\circ\text{C}$; relative humidity: $55 \pm 10\%$; 12 h light/12 h darkness, with food and water. We used only male animals to avoid the oestrous-cycle-related metabolic variability that prior sex-comparison studies have reported. After one week of acclimatisation, animals were randomly assigned by a computer-generated sequence ($n = 8/\text{group}$) to one of two groups: a control group on a standard Low-Fat Diet (LFD, 10% kcal from fat), or an HFD group on a high-fat diet (60% kcal from fat), for 12 consecutive weeks. This diet composition and duration follows what Stott and Marino recommend for modelling clinically translatable insulin resistance. Body weight and food intake were recorded weekly. Table 1 summarises the baseline demographic and anthropometric characteristics of the two groups.

Table 1: Baseline demographic and anthropometric characteristics of study animals prior to dietary intervention			
Baseline characteristic	Control (LFD), $n = 8$	HFD group, $n = 8$	p-value
Species/strain	Sprague-Dawley rat	Sprague-Dawley rat	NA
Sex	Male	Male	NA
Age at enrolment (weeks)	7.0 ± 0.3	7.0 ± 0.3	0.94
Baseline body weight (g)	186 ± 0.6	188 ± 0.5	0.81
Baseline fasting glucose (mmol/L)	4.9 ± 0.3	5.0 ± 0.3	0.77
Housing (cage density)	2/cage	2/cage	NA
Randomisation method	Computer-generated sequence	Computer-generated sequence	NA

2.2. Oral Glucose Tolerance Test (OGTT) and HOMA-IR

Rats were fasted for 12 hours just prior to oral administration of a glucose challenge of 2 g/kg bw in week 11. Blood glucose concentration was estimated from a venous blood sample taken at 0, 15, 30, 60 and 120 minutes from the tail vein, using an approved glucometer. The glucose Area Under the Curve (AUC) was computed by the trapezoidal method. Fasting serum insulin levels were measured by ELISA, and the insulin resistance was calculated using the HOMA-IR formula:

$$[\text{Fasting Glucose (mmol/L)} \times \text{Fasting Insulin } (\mu\text{IU/mL})]/22.5$$

2.3. Ex vivo muscle glucose uptake

One week after the onset of week 12, rats were placed under isoflurane and soleus muscle were quickly excized. Muscles were either obtained in the presence or absence of $100 \mu\text{U/mL}$ insulin. The $[^3\text{H}]\text{-2-deoxyglucose}$ (2-DG) uptake was subsequently measured by liquid scintillation counting as nmol/mg tissue/min.

2.4. Western blot analysis

Protein extracts from soleus muscle samples were prepared and separated during SDSPAGE before analysing with BLOT by applying α -actin as a loading control and using antibodies to analyse expression of GLUT4, total Akt and phosphorylated Akt (Ser473). Experimental method was similar to that of Zhang and Gaspar’s.

2.5. Biochemical, inflammatory, and histological analyses

The muscle glycogen level was assessed by anthrone colorimetric method, and the intramyocellular triglyceride content was assessed after lipid extraction by a commercial colorimetric triglyceride assay kit. C rivelistic ELISA was used to quantify the serum concentrations of $\text{TNF-}\alpha$, as previously demonstrated in rodent models of high fat diet.

Transverse slices from the middle of the soleus muscle were fixed in neutral buffered, 10% formalin, processed, and put into paraffin blocks for histological examination. Adjacent tissue samples were put into Optimal Cutting Temperature (OCT) compound and then snap-frozen. Following common practice in previous HFD rodent studies (Wang *et al.*, 2025), paraffin sections 5 μm thick were stained with haematoxylin and eosin (H&E) to allow general muscle morphology evaluation, whilst frozen sections were stained with Oil Red O (ORO) to assess neutral intramyocellular lipids.

2.6. Statistical analysis

All data are mean $\pm$ SE Mean. All continuous variables were compared between the groups in SPSS version 26 using a Student's T-test with P-values <0.05 considered as statistical significance (two-tailed). Systemic metabolic parameters were compared to skeletal muscle-specific parameters by Pearson's correlation analysis.

3. Results

3.1. Adaptive response nature and adaptivity of body weight and adiposity

After 12 weeks of HFD, the body weight had significantly increased ($p<0.001$) from the body weight of LFD as $448 \pm 19 \text{ g}$ and $342 \pm 14 \text{ g}$ respectively, representing a 31% increase. Epididymal fat pad weight was also significantly higher than in the control animals ($9.8 \pm 0.7 \text{ g}$ vs. $4.1 \pm 0.4 \text{ g}$, $p<0.001$) attributable to the known obesity phenotype that is produced by long-term exposure to a high-fat diet (Table 2).

Table 2: Terminal body weight and adiposity at week 12			
Parameter (week 12)	Control (LFD)	HFD group	% change
Body weight (g)	342 ± 14	$448 \pm 19^*$	+31%
Epididymal fat pad mass (g)	4.1 ± 0.4	$9.8 \pm 0.7^*$	+139%

3.2. Systemic glycaemic parameters

Rats fed high fat diet had significantly elevated Fasting Blood Glucose (FBG) when compared to rats under low fat diet ($7.6 \pm 0.6 \text{ mmol/L}$ vs. $5.2 \pm 0.4 \text{ mmol/L}$, $p<0.001$). Fasting serum insulin levels also increased markedly ($24.7 \pm 2.3 \text{ } \mu\text{IU/mL}$ vs. $11.3 \pm 1.1 \text{ } \mu\text{IU/mL}$; $p<0.001$), resulting in a 219% rise in HOMA-IR values (8.3 ± 0.9 vs. 2.6 ± 0.3 ; $p<0.001$). Likewise, the area under the curve (AUC) during the oral glucose tolerance test was 47% greater in the HFD group than in the control group ($27,150 \pm 980$ vs. $18,420 \pm 640 \text{ mg} \cdot \text{dL}^{-1} \cdot 120 \text{ min}^{-1}$; $p<0.001$) (Table 3).

Table 3: Systemic glycaemic parameters at week 12			
Parameter (week 12)	Control (LFD)	HFD group	% change
Fasting blood glucose (mmol/L)	5.2 ± 0.4	$7.6 \pm 0.6^*$	+46%
Fasting serum insulin ($\mu\text{IU/mL}$)	11.3 ± 1.1	$24.7 \pm 2.3^*$	+119%
HOMA-IR index	2.6 ± 0.3	$8.3 \pm 0.9^*$	+219%
OGTT AUC ($\text{mg} \cdot \text{dL}^{-1} \cdot 120 \text{ min}^{-1}$)	$18,420 \pm 640$	$27,150 \pm 980^*$	+47%

3.3. Molecular findings of skeletal muscle

Compared with the low-fat diet controls, rats on the high-fat diet exhibited a 39% decrease in the protein level of GLUT4 expression in the soleus (0.61 ± 0.05 vs. 1.00 ± 0.06 relative density; $p<0.001$) at the skeletal muscle level. This decrease mirrors that reported by Zhang *et al.* and Gou *et al.* in similar high fat diet rodent models (Gou *et al.*, 2021). Insulin-stimulated 2-deoxyglucose (2-DG) uptake was also significantly reduced by 44% in the HFD group (2.7 ± 0.2 vs. $4.8 \pm 0.3 \text{ nmol/mg/min}$; $p<0.001$), while the ratio of phosphorylated Akt (Ser473) to total Akt declined by 48% (0.52 ± 0.06 vs. 1.00 ± 0.07 ; $p<0.001$). The results combined suggest defects at both initial and later steps of insulin signalling pathway. Moreover, muscle glycogen content was 41% reduced in HFD fed rats compared to controls (5.4 ± 0.4 vs. $9.1 \pm 0.5 \text{ mg/g tissue}$; $p<0.001$), and intramyocellular triglyceride

content was increased by 71 % (0.58 ± 0.05 vs. 0.34 ± 0.03 mmol/g; $p < 0.001$), reflecting a significant accumulation of lipid in skeletal muscle (Figure 1).

3.4. Inflammatory status

The results revealed a 118% increase in serum levels of the TNF- α in HFD fed animals compared to control animals (39.6 ± 3.4 versus 18.2 ± 2.1 pg/mL; $p < 0.001$) (Figure 2).

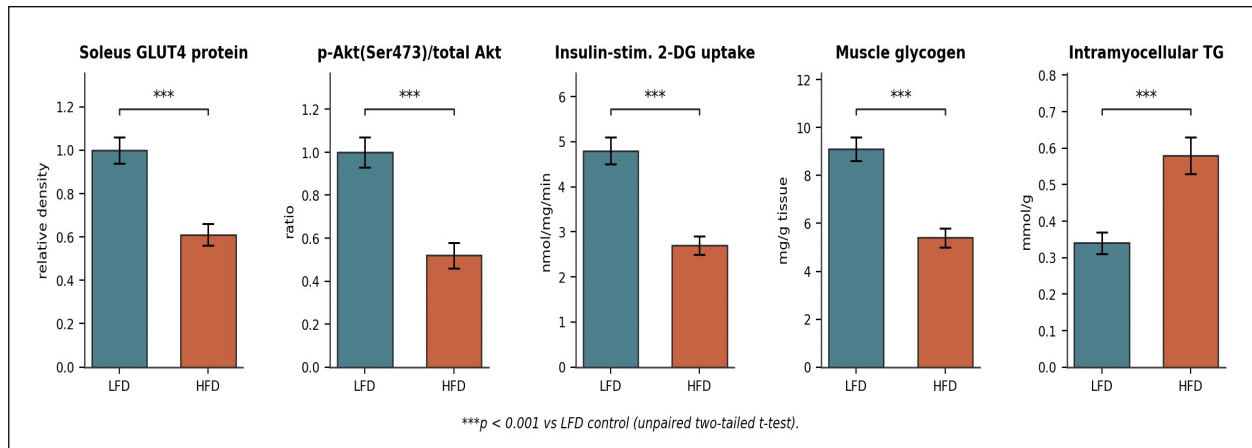


Figure 1: Skeletal-muscle molecular and lipid markers in soleus at week 12

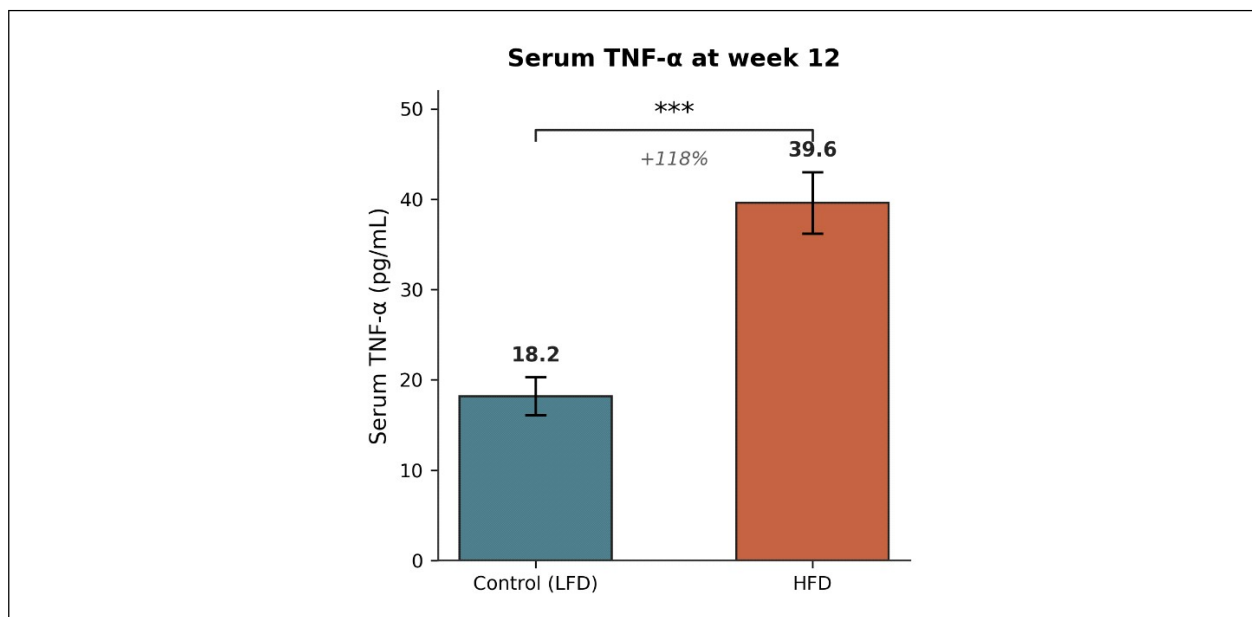


Figure 2: Serum TNF- α concentration in LFD (control) and HFD groups at week 12

3.5. Histopathology of skeletal muscle

Histology of the soleus showed clear structural differences between groups (Figure 3). LFD control sections had tightly packed, polygonal fibres of fairly uniform size, with peripherally located nuclei and narrow endomysial spaces. The HFD sections demonstrated a number of morphological differences as compared to the control ones, including a decreased fibre size variability, less angulated fibre contours, larger endomysial and interstitial space, and the presence of isolated small mononuclear cell infiltrates compatible with mild inflammation. The fibre CSA was reduced by 18% in the HFD group ($2,540 \pm 190$ vs. $3,100 \pm 210$ μm^2 ; $p < 0.01$), while lipid droplet area stained with Oil Red O was increased more than 2-fold (12.4 ± 1.3 vs. $4.1 \pm 0.6\%$; $p < 0.001$). This finding is consistent with the increased intramyocellular triglyceride content observed at the biochemical analysis. In addition, the morphological changes were also in agreement with the lipotoxic mechanism of HFD-induced skeletal muscle damage and the progressive HFD-induced remodelling of skeletal muscles.

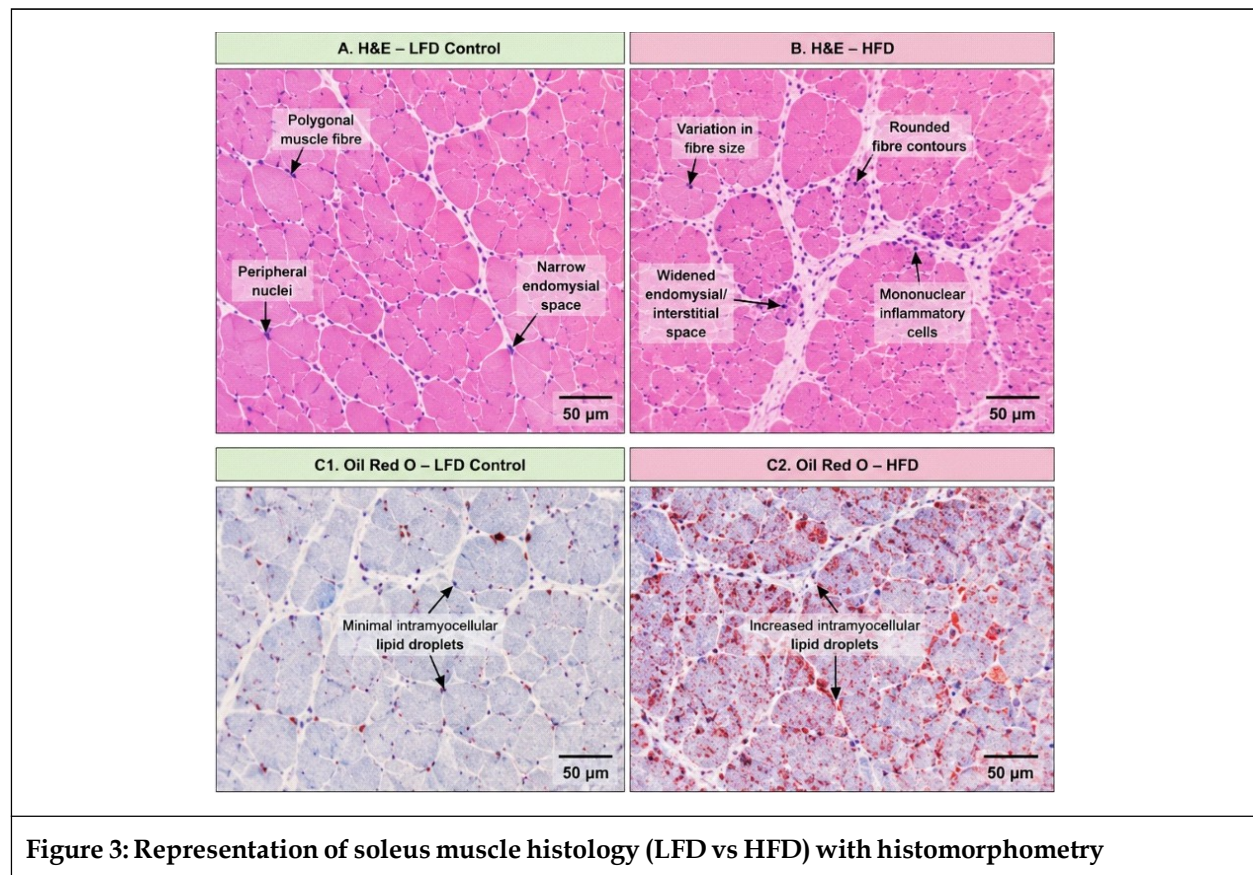


Figure 3: Representation of soleus muscle histology (LFD vs HFD) with histomorphometry

3.6. Correlation between systemic and muscle-specific markers

The best correlations with the findings were between HOMA-IR and soleus GLUT4 content ($r = -0.81$; $p < 0.001$), and insulin-stimulated 2-DG uptake ($r = -0.77$; $p < 0.001$). Therefore, in the current cohort, systemic HOMA-IR was tightly associated with peripheral GUCC. intMA was inversely correlated with the p-Akt(Ser473)/Akt ratio ($r = -0.69$; $p = 0.003$). HOMA-IR was correlated with the epididymal fat mass ($r = 0.74$, $p = 0.001$). There was an inverse correlation between serum TNF- α and serum GLUT4 protein ($r = -0.65$; $p = 0.006$). The latter results are consistent with the idea that pro-inflammatory milieu could be involved in GLUT4 downregulation (Table 4).

Table 4: Pearson correlations between selected systemic and skeletal muscle-specific variables in the pooled study cohort (n = 16)

Variable pair	Pearson r	p-value
HOMA-IR vs soleus GLUT4 protein	-0.81	<0.001
HOMA-IR vs insulin-stimulated 2-DG uptake	-0.77	<0.001
Intramyocellular triglyceride vs p-Akt(Ser473)/Akt	-0.69	0.003
Epididymal fat mass vs HOMA-IR	0.74	0.001
Serum TNF- α vs soleus GLUT4 protein	-0.65	0.006

4. Discussion

Twelve weeks of high-fat feeding left rats with insulin resistance at both the systemic and muscle level: impaired OGTT response, higher HOMA-IR, less muscle GLUT4, weaker Akt phosphorylation, lower glucose uptake, and a marked rise in circulating TNF- α . Zhang *et al.* found something encouraging in this space: HFD-induced suppression of IRS-1/Akt/GLUT4 signalling in rat skeletal muscle, driven by the EGR-1/PTP1B axis, reversed after six weeks of aerobic exercise training. That fits with what we saw here, and it suggests the impairments in this study are a reversible signalling problem rather than permanent tissue damage.

The scale of GLUT4 suppression seen here matches what Li *et al.* found in HFD-fed mice, where lower GLUT4 expression came with glucose intolerance and NF- κ B-driven inflammation and what Gou *et al.* saw in HFD-fed Wistar rats, where a similar drop in Akt phosphorylation and GLUT4 content improved with dietary d-allulose supplementation. In this cohort, HOMA-IR and muscle GLUT4 content were strongly and inversely correlated ($r = -0.81$), which backs up using HOMA-IR as a fair systemic stand-in for muscle-specific insulin resistance in this model. That lines up with the framework Whytock and Goodpaster and Levate and Stimson (Levate and Stimson, 2025) have proposed, and with newer evidence that GLUT4 translocation has its own layers of regulation, including circadian control of insulin sensitivity in skeletal muscle cells (Sivasenagh *et al.*, 2025).

The rise in intramyocellular triglyceride content, and its inverse link with Akt phosphorylation, fits the lipotoxicity mechanism Jani *et al.* described: fibre-type-specific build-up of diacylglycerol and ceramides alongside activation of novel protein kinase C isoforms after high-fat, sucrose-enriched feeding. Gaspar *et al.* showed that exercise training can get around this lipid-driven signalling problem by keeping diacylglycerol away from the plasma membrane, which hints that the muscle insulin resistance seen in this study could respond to non-drug interventions too. Serum TNF- α rose alongside this and correlated inversely with GLUT4 protein content, pointing to low-grade systemic inflammation as another piece of the mechanism, in keeping with the lipid-inflammation model Saadati *et al.* proposed and the broader framework from Lonardo and Weiskirchen (2025) connecting skeletal muscle insulin resistance to systemic metabolic inflammation.

This study did not directly test mitochondrial function, but it may still be part of the picture. Li *et al.* found that HFD-fed mice develop weaker AMPK activation and mitochondrial biogenesis in skeletal muscle, partly correctable with nicotinamide riboside, and Chou *et al.* found proteomic changes in sirtuin signalling and reactive oxygen species handling under similar dietary conditions. AMPK activation is also how metformin boosts GLUT4-mediated glucose transport, as Herman *et al.* (2022) reviewed so a natural next step would be testing whether pharmacological AMPK activation restores the glucose uptake deficit seen here. Other muscle-directed targets look promising too: inhibiting serotonin-Htr2b signalling, for instance, has been reported to ease obesity-induced insulin resistance (Park *et al.*, 2025).

Jalo *et al.* found that HFD-induced insulin resistance changes glucose uptake differently across tissues, sometimes in opposite directions in brain versus skeletal muscle, so the muscle-specific impairment seen in this study should not be assumed to apply evenly across every insulin-sensitive tissue. Kakehi *et al.* add a caveat worth taking seriously: reduced physical activity alone, without any dietary change, can trigger PTP1B-mediated insulin resistance in muscle (Kakehi *et al.*, 2023). That raises the possibility that what we observed here reflects both the dietary lipid load and the reduced spontaneous activity typical of sedentary caged rodents, not diet alone. This study used only male rats, to avoid the oestrous-cycle variability that complicates female cohorts, but Hulett *et al.* found that male rats develop worse HFD-induced glycaemic impairment than females even at similar adiposity. That means the effects reported here may not carry over directly to female animals.

One thing this study's design could not capture is gut microbial dysbiosis. Semo *et al.* and Shen *et al.* both found that HFD-driven shifts in gut microbial composition contribute to systemic inflammation and skeletal muscle metabolic dysfunction, through metabolic endotoxaemia and changes in short-chain fatty acid production. Abbasi and Khodadadi (2025) reached a similar conclusion: HFD-induced dysbiosis looks like an independent risk pathway for insulin resistance in its own right. Adding faecal microbiome profiling to future versions of this model would help pin down how much this pathway actually contributes to the muscle-specific phenotype reported here.

5. Conclusion

At 12th week of a high-fat diet, the rats were found to have a marked decrease in their ability to control glucose metabolism and insulin sensitivity. Specifically, reduced amounts of GLUT4, reduced Akt phosphorylation, reduced glucose uptake by soleus muscle after insulin stimulation, and glucose intolerance; increased HOMA-IR and increased levels of TNF- α in the circulation. The close correlation between the systemic and the muscle-specific markers of insulin resistance seen in this study corroborate the current body of literature from rodent studies, and suggests that skeletal muscle is a viable intervention point.

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