International Journal of General Medicine

Dovepress
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ORIGINAL RESEARCH

The Role of *ADIPOQ* and AMPK Signaling Pathway in Sarcopenia

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Objective: To identify the hub genes involved in sarcopenia and analyze their correlation with lipid metabolism.

Methods: Differentially expressed genes (DEGs) from sarcopenia/non-sarcopenia cohorts in *GSE111006* and *GSE111010* datasets were cross-analyzed with diabetes-related genes (GeneCards). Key genes underwent functional enrichment and protein-protein interaction (PPI) network analysis. The expression and receiver operating characteristic (ROC) curve of the hub gene was analyzed in both datasets. Enzyme-linked immunosorbent assay (ELISA) was utilized to quantify hub gene levels in sarcopenia, type 2 diabetes (T2DM), and healthy samples.

Results: Twenty key genes were identified through differential expression and diabetes-related gene screening. Functional enrichment analysis revealed their involvement in external stimulus response, inflammatory regulation, extracellular processes, adenosine monophosphate-activated protein kinase (AMPK) signaling pathway, and insulin signaling pathways ($p<0.05$). Adiponectin (*ADIPOQ*) emerged as the hub gene via PPI network analysis, showing significant overexpression in sarcopenia (GSE111006: $p<0.01$; GSE111010: $p<0.05$) with diagnostic AUCs of 0.944 (0.869–1.000) and 0.696 (0.471–0.920) respectively. Ultimately, 60 sarcopenia, 10 type 2 diabetes, 10 healthy samples were collected. Seventy percent of the samples exhibited abnormal lipid metabolism. Adiponectin *(ADIPOQ)* and AMPK were overexpressed in sarcopenia samples ($p < 0.01$). However, *ADIPOQ* and AMPK were no difference in the expression levels between individuals with T2DM and healthy individuals ($p>0.05$). This study identified a significant correlation between *ADIPOQ*, AMPK, and blood lipids in sarcopenia (*ADIPOQ* vs AMPK, $p < 0.0001$, $r = 0.736$; *ADIPOQ* vs HDL-C, $p = 0.0003$, $r = -0.448$; AMPK vs HDL-C, $p = 0.001$, $r = -0.415$).

Conclusion: The present study confirms that glycolipid metabolism is a risk factor for sarcopenia. Both ADIPOQ and AMPK are overexpressed in sarcopenia and demonstrate a significant positive correlation. This study hypothesizes that *ADIPOQ* may regulate AMPK activity, affect lipid metabolism, and accelerate the occurrence and development of sarcopenia.

Keywords: sarcopenia, glycolipid metabolism, adiponectin, adenosine 5'-monophosphate-activated protein kinase, lipid metabolism

Introduction

Sarcopenia, a term coined by Rosenberg in 1989, refers to the reduction or loss of muscle mass.[1] In 2010, the International Working Group on Sarcopenia defined sarcopenia as "age-related reduction in overall muscle mass and/or decrease in muscle strength or physiological muscle function".[2] Currently, about 50 million people worldwide suffer from sarcopenia, and it is estimated to reach 500 million by 2050.[3–5] The incidence of sarcopenia increases with age, with a global prevalence of 6% to 20% among people aged 65 and above and up to 50% among people aged 80 and above.[6] In China, the prevalence of sarcopenia is about 16% (approaching 25 million) among elderly people aged 60 and above.[7] Apart from age, various other factors such as inflammatory response, nutrient absorption and utilization disorders, lack of exercise, endocrine disorders, changes in gut microbiota, and genetics can all contribute to sarcopenia.[8–10] Sarcopenia predisposes aging populations to heightened fracture susceptibility and functional decline. This musculoskeletal deterioration cascade culminates in multidimensional morbidity burdens, including compromised independence, accelerated frailty progression, and 1.7-fold increased all-cause mortality risk compared to non-sarcopenic peers.[11,12] Several regions worldwide have established expert consensus for assessing and diagnosing sarcopenia based

Received: 8 January 2025
Accepted: 3 July 2025
Published: 12 August 2025

on the regional population, including Asian Working Group for Sarcopenia (AWGS) 2014, AWGS 2019, European Working Group on Sarcopenia in Older People (EWGSOP) 1, EWGSOP 2, International Working Group for Sarcopenia (IWGS), and the Foundation for the National Institutes of Health (FNIH) in the United States.[13,14]

Sarcopenia as a comorbidity of diabetes has attracted much attention in recent years.[15] S Emerging evidence links sarcopenia development in diabetic populations to compromised insulin signaling and elevated oxidative stress,[15] triggering progressive musculoskeletal deterioration through atrophic pathways.[15,16] Epidemiologic data reveal a tripled sarcopenia prevalence among those with diabetes versus non-diabetic counterparts, with this metabolic comorbidity correlating strongly with adverse clinical trajectories.[9,15,16] The interplay between diabetes and sarcopenia in their pathogenic mechanisms involves complex interactions, with dysregulation of gene expression serving as a critical bridge linking these two comorbidities.[17] Aberrant diabetes-associated genes can directly or indirectly exacerbate muscle loss by regulating pathways such as insulin signaling, inflammatory responses, mitochondrial function, glycolipid metabolism, and muscle regeneration.[18,19] To identify key genes that connect diabetes and sarcopenia, a dual approach integrating bioinformatics analysis (utilizing Gene Expression Omnibus (GEO) datasets) and clinical validation (such as ELISA or lipid profiling) may serve as a novel integrated strategy.

This investigation disclosed transcriptomic disparities through comparative analysis of sarcopenic versus control cohorts in two independent GEO datasets (GSE111006/111,010), and the DEGs and DM-related genes were screened to determine the key genes. Through systematic interrogation of PPI clusters, essential network mediators were delineated using maximal clique centrality metrics. Finally, the study collected serum samples of patients with DM and sarcopenia for verification.

Methods and Materials

Data Collection and Workflow

The mitochondrial ribonucleic acid (mRNA) transcriptome profiles were derived from Gene Expression Omnibus (GEO, https://www.ncbi.nlm.nih.gov/geo/) accessions *GSE111006* (36 controls vs 4 sarcopenia) and *GSE111010* (30 controls vs 9 cases), accessible through the NCBI repository. T2DM-associated genetic targets were curated from GeneCards (v5.12, https://www.genecards.org) using "type 2 diabetes mellitus" as the primary search term. Analytical procedures are schematically summarized in Figure 1.

DEGs and Intersection Gene Screening

Transcriptomic datasets underwent processing with R v4.0.2's (http://www.r-project.org/) clusterProfiler package for functional annotation. Differential expression analysis was conducted via limma v3.40.6 (Bioconductor) with stringent thresholds (FDR<0.01, |log2FC|≥1.5). Consensus candidates emerged from comparative visualization of DEG subsets across cohorts using Venn diagrammatic analysis.

Functional Enrichment Analysis: Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) Pathway

Gene Ontology (GO) tripartite functional characterization encompassed biological processes (BP), molecular functions (MF), and cellular components (CC), while Kyoto Encyclopedia of Genes and Genomes (KEGG) interrogation focused on systems biology pathways. Critical genomic elements underwent pathway annotation via DAVID v6.8 (https://david.ncifcrf.gov), with subsequent visualization of enriched terms (ggplot2 v3.3.5 in R v4.0.2) meeting stringent significance thresholds (Benjamini-Hochberg adjusted $p<0.05$, FDR<0.25).

PPI Network Identification and Receiver Operating Characteristic (ROC) Curves of Hub Genes

Protein interaction networks were reconstructed using STRING-DB v11.5 (http://string-db.org/), with subsequent topological interrogation in Cytoscape v3.6.1(http://www.cytoscape.org/) employing betweenness centrality metrics to pinpoint pivotal regulators. Graph theoretical analysis quantified node connectivity through degree centrality algorithms. Diagnostic performance validation incorporated pROC v1.18.0 and ggplot2 v3.3.6 in R v4.0.2, calculating receiver operating characteristics (AUC, 95% CI) and operational efficiency parameters (sensitivity/specificity) across both transcriptomic cohorts.

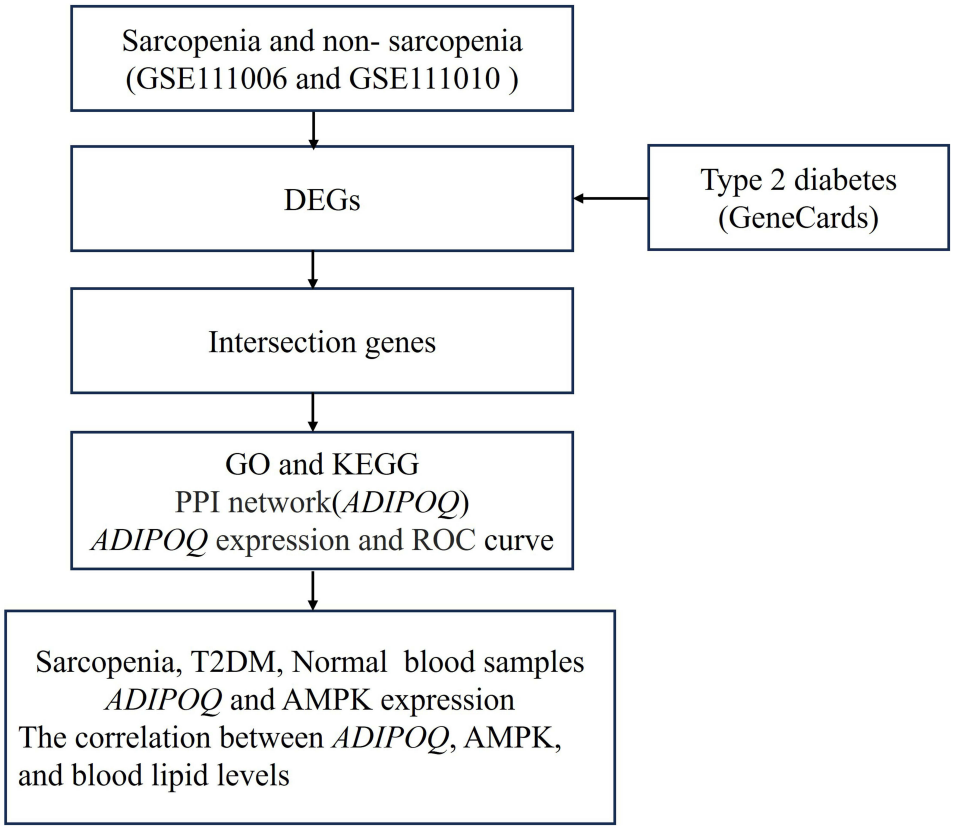

Figure 1 Workflow of the present study.

Clinical Data Collection

The study obtained clinical data from patients diagnosed with sarcopenia in Zhuzhou Central Hospital from January 2021 to June 2024. The inclusion criteria were: 1. Age > 60 years; 2. Other diseases in the stable phase; 3. Informed consent provided by the patient (personally signed or if < 18 years, then signed by the guardian) to join this study. The exclusion criteria were: 1. Other comorbidities in the active phase; 2. Oral medications that affect blood lipid metabolism; 3. No consent for this study. All tissue collection protocols received approval from the Institutional Review Board at Zhuzhou Central Hospital (Ethics No. 20231072), and documented informed consent was secured from all enrolled study participants.

Blood Lipid Profile Detection

Following an 8–12 hour fasting protocol, venous blood samples (4mL) were collected from fasting participants for lipidomic profiling. Serum lipid quantification was performed using a Hitachi 7600 automated analyzer (Tokyo, Japan) with Wako diagnostic reagents, measuring total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). Dyslipidemia diagnostic thresholds were defined as: TC ≥5.18 mmol/L, TG ≥1.7 mmol/L, LDL-C ≥3.37 mmol/L, and HDL-C <1.04 mmol/L.[20]

Enzyme-Linked Immunosorbent Assay (ELISA) Detection of Adiponectin, C1Q and Collagen Domain Containing (ADIPOQ) and Adenosine Monophosphate-Activated Protein Kinase (AMPK)

Human adiponectin ELISA kit (EH2593) and human AMPK ELISA kit (EH2622) were purchased from Wuhan Fine Biotech Co, Ltd (Wuhan, China). The plasma concentrations of *ADIPOQ* and AMPK were detected according to the instructions of the reagent kit. The optical density (OD) measurements were recorded by reading the absorbance at 450 nm in the microplate. The relative OD_{450} was calculated as follows:

Relative OD_{450} = OD_{450} of each well) – OD_{450} of blank well

The standard curve was constructed by plotting the relative OD_{450} of each standard solution (y-axis) against the respective concentration of the standard solution (x-axis).

Statistical Analysis

Comparative analyses employed Student's *t*-test (R v4.0.2) to assess inter-group differences between experimental and control cohorts, with statistical significance thresholded at p<0.05p<0.05. Graphical representations were generated using ggplot2 (v3.3.6) within the R computational environment.

Results

DEGs and Key Genes in Sarcopenia and DM Were Identified

The DEGs of the sarcopenia and non-sarcopenia samples in the *GSE111006* and *GSE111010* datasets were screened. The *GSE111006* dataset comprised 694 upregulated and 862 downregulated genes. The *GSE111010* dataset contained 33 upregulated and 371 downregulated genes (Figure 2A–D). The study obtained data on 19,079 genes related to DM from the GeneCards dataset. Twenty key genes were screened by constructing a Venn diagram containing the DEGs and DM-related genes (Figure 2E and Supplementary Table 1).

Functional Enrichment Analyses of Key Genes

The 20 key genes were studied by conducting functional enrichment analysis (GO and KEGG). The GO functions included regulating the response to external stimulus, inflammatory response, extracellular region, oxidoreductase activity, CH-OH donor group activity, with nicotinamide adenine dinucleotide (NAD) or nicotinamide adenine dinucleotide phosphate (NADP) as the acceptor, (p < 0.05; Figure 3A–C). The KEGG analysis included the AMPK signaling pathway, neuroactive ligand-receptor interaction, and insulin signaling pathway (p < 0.05; Figure 3D).

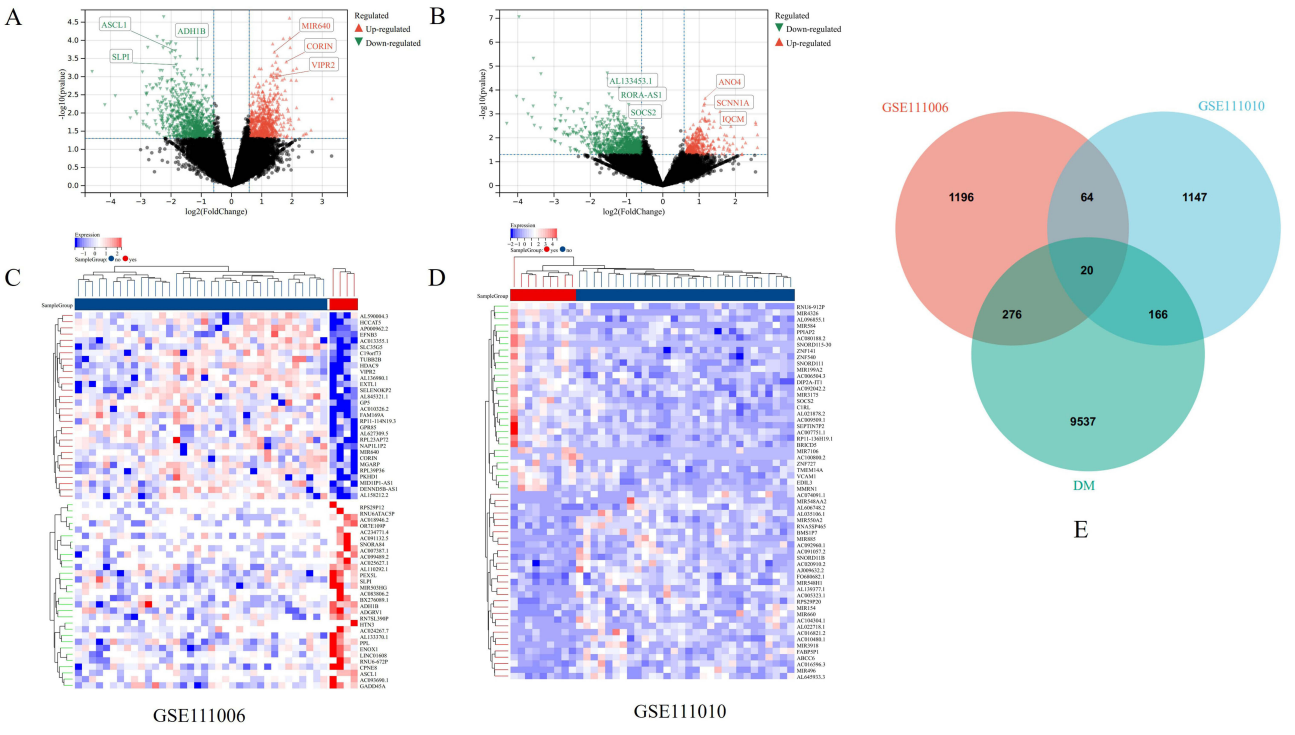

Figure 2 Screening process for DEGs and key genes in the *GSE111006* dataset, *GSE111010* dataset, and diabetes-related genes. (**A** and **B**) Volcano plot of DEGs in sarcopenia and non-sarcopenia samples obtained from the *GSE179285* dataset. (**C** and **D**) Heatmap of the DEGs and the top 30 genes. (**E**) Venn diagram depicting the key genes between DEGs and diabetes -related genes.

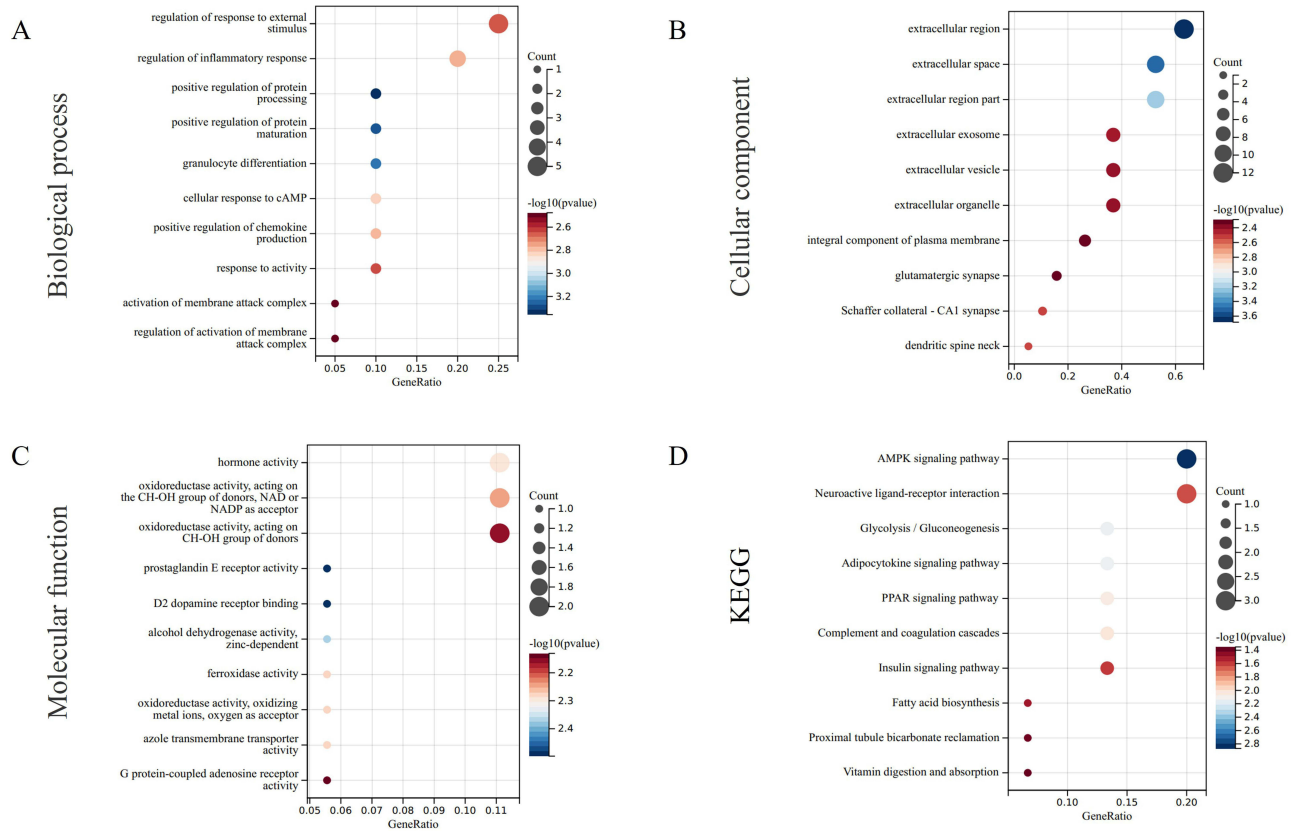

Figure 3 Functional enrichment analysis. (**A–C**) GO functional enrichment analysis (GO includes biological processes, cellular components, and molecular functions). (**D**) KEGG pathway.

Hub Gene Expression and ROC Curves in Sarcopenia

The hub genes were screened using the PPI network, and *ADIPOQ* was identified as the hub gene (Figure 4A). *ADIPOQ* was significantly overexpressed in sarcopenia samples in the *GSE111006* and *GSE111010* datasets ($p<0.001$, Figure 4B and C). In addition, *ADIPOQ* demonstrated good predictability for sarcopenia and non-sarcopenia, as confirmed through the ROC curves for the two datasets. The specificity was 1 and 0.944, respectively, and the sensitivity was 0.625 and 0.733, respectively. The accuracy rate was 94.872% and 71.053%, and the AUCs were 0.944 (95% CI = 0.869–1.000) and 0.696 (95% CI = 0.471–0.920), respectively (Figure 4D and E, Table 1).

ADPOQ and AMPK Affect Lipid Metabolism in Sarcopenia

The study obtained blood samples from 60 patients with sarcopenia, 10 people with T2DM, and 10 healthy individuals (Table 2). *ADIPOQ* and AMPK were overexpressed in sarcopenia ($p<0.01$, Figure 5A and B). However, the study observed no difference in the expression levels between individuals with T2DM and healthy individuals ($p>0.05$, Figure 5A and B). Subsequently, all 80 blood samples were tested for lipids, and 70% of the samples of patients with sarcopenia exhibited elevated blood lipids (Table 2). This highlights a significant correlation between *ADIPOQ*, AMPK, and blood lipid levels in sarcopenia (*ADIPOQ* vs AMPK, $p<0.0001$, $r = 0.736$; *ADIPOQ* vs HDL-C, $p = 0.0003$, $r = -0.448$; AMPK vs HDL-C, $p = 0.001$, $r = -0.415$) (Figure 5C–E).

Discussion

Sarcopenia is prevalent in the elderly population and can also occur in middle age.[21] Apart from age, various other factors such as inflammatory response, nutrient absorption and utilization disorders, lack of exercise, endocrine disorders, changes in gut microbiota, and genetics can all lead to the occurrence of sarcopenia.[8–10] Sarcopenia has been

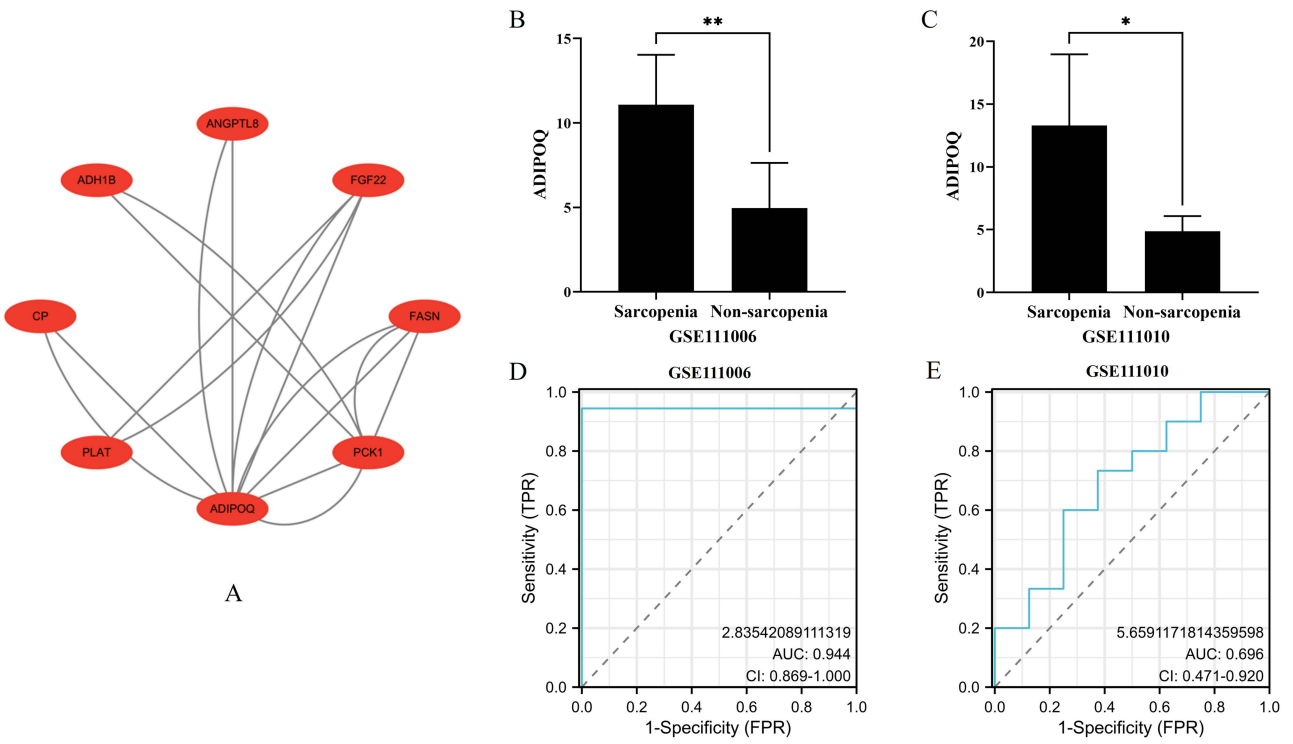

Figure 4 Screening, expression, and ROC curves of hub genes in the *GSE111006* and *GSE111010* datasets. (**A**) PPI network that helped identify *ADIPOQ* as a hub gene. (**B** and **C**) Expression of *ADIPOQ* in the *GSE111006* and *GSE111010* datasets. (**D** and **E**) Specificity and sensitivity of *ADIPOQ*, as analyzed by ROC curves in sarcopenia and non-sarcopenia samples obtained from *GSE111006* and *GSE111010* datasets. (*p<0.05; **p<0.01).

demonstrated to be related to the risk of DM, metabolic syndrome, non-alcoholic liver disease, cardiovascular disease, renal insufficiency, respiratory disease, malignant tumor, cognitive impairment, Parkinson's syndrome, depression, dysphagia, and it has also been correlated to the prognosis of certain diseases.[10–12] Emerging research highlights sarcopenia's role as a diabetic comorbidity, with pooled prevalence rates reaching 18% in affected populations and demonstrating male predominance.[9,22]

The present study identified *ADIPOQ* as the hub gene in sarcopenia, non-sarcopenia, and DM samples. Importantly, *ADIPOQ* was significantly upregulated in sarcopenia samples and can help effectively predict its occurrence. *ADIPOQ* is a cytokine secreted by adipose tissue involved in biological processes related to lipid and energy metabolism and insulin sensitivity regulation.[23] Emerging evidence identifies adiponectin as a pivotal regulator of lipid homeostasis in animal models, mediated through AdipoR1/R2 receptor activation. This endocrine mechanism enhances mitochondrial β-oxidation, suppresses lipogenic pathways, and maintains metabolic equilibrium, as evidenced by recent investigations.[24,25] In addition to promoting fatty acid oxidation, *ADIPOQ* can also lower TG or cholesterol levels in the blood by inhibiting lipid synthesis.[26] Injecting *ADIPOQ* into mice reduced the TG or cholesterol plasma levels.[27] Therefore, this study hypothesizes that *ADIPOQ* is closely related to lipid metabolism.

Table 1 The Specificity, Sensitivity, and Accuracy of the Adiponectin (ADIPOQ) Were Evaluated Using Receiver Operating Characteristic Curves in GSE111006 and GSE111010 Datasets

Datasets	Gene	Cut-Off	Specificity	Sensitivity	Accuracy
GSE111006	*ADIPOQ*	10.372	1	0.944	0.949
GSE111010	*ADIPOQ*	4.4253	0.625	0.733	0.711

Table 2 Clinical Characteristics of 80 Samples

	Sarcopenia (n=60)	T2DM (n=10)	Normal (n=10)	p
Age(y)	56.40±12.37	59.20±9.58	41.50±13.80	>0.05
Sex				>0.05
Man	38	6	4	
Female	22	4	6	
Blood lipid (mmol/L)				
TC	3.75±1.30	3.28±0.97	4.26±0.90	>0.05
TG	1.54±0.85	1.35±0.47	1.39±0.50	>0.05
LDL-C	1.07±0.27	1.70±0.80	1.44±0.86	>0.05
HDL-C	2.05±0.95*	0.87±0.33	0.90±0.40	<0.001
Lipids metabolism (n)				
Normal	18 (30%) *	8(80%)	9 (90%)	<0.001
Abnormal	42 (70%) *	2 (20%)	1 (10%)	

Note: *There is a difference compared to the other two groups.
Abbreviations: T2DM, Type 2 Diabetes Mellitus; TC, Total cholesterol; TG, Triglyceride; LDL-C, Low-Density Lipoprotein Cholesterol; HDL-C, High density lipoprotein cholesterol.

This study also obtained clinical data from 60 patients with sarcopenia, and 70% of them exhibited abnormal blood lipid metabolism, underscoring its association with sarcopenia. Emerging evidence from multi-ethnic cohorts demonstrates pathogenic lipidomic signatures in sarcopenic populations. Chinese sarcopenia patients (n=151) exhibited

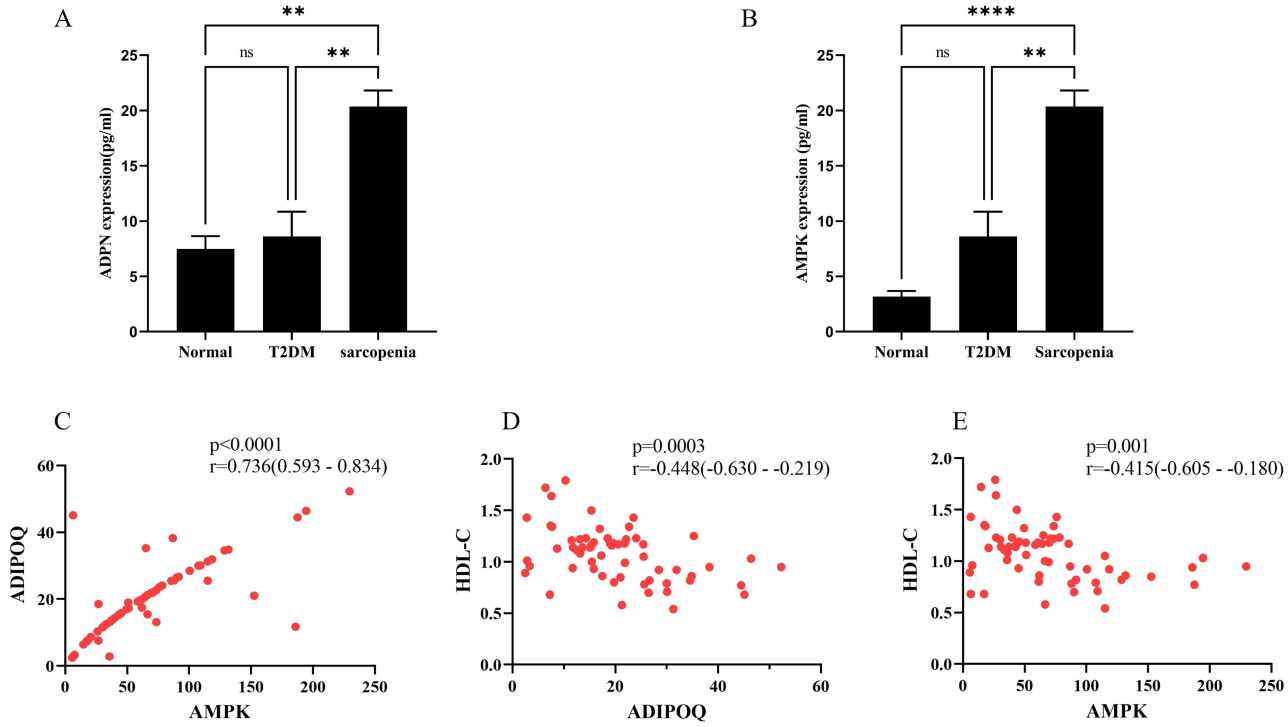

Figure 5 Expressions of *ADIPOQ* and AMPK and their correlation with blood lipids in sarcopenia. (**A** and **B**) Expression of *ADIPOQ* and AMPK in normal, T2DM, and sarcopenia samples. (**C**–**E**) Correlation between *ADIPOQ*, AMPK, and blood lipids (high-density lipoprotein cholesterol (HDL-C). (ns, $p>0.05$; **$p<0.01$; ****$p<0.0001$).

https://doi.org/10.2147/IJGM.S516414

hypocholesterolemic profiles (↓TC/TG) with elevated LDL concentrations,[28] paralleling findings in elderly Berliners showing hypertriglyceridemia.[29] Notably, longitudinal data from Korean midlife women identified circulating triglycerides as independent predictors of age-associated myosteatosis (β=0.43, p=0.008).[30] This tri-continental consensus confirms aberrant lipid homeostasis as a conserved metabolic risk marker for muscle wasting disorders, aligning with our pathophysiological observations.

In recent years, diseases related to glucose and lipid metabolism have emerged as global chronic diseases, with glucose and lipid metabolisms demonstrating a strong correlation, which can easily contribute to the occurrence of various chronic diseases and impact human health.[31,32] Accumulating evidence delineates sarcopenia's pathophysiological interplay with dysregulated adipokine signaling, impaired insulin sensitivity, and aberrant carbohydrate processing.[33–36] AMPK, known as the "energy receptor", is extensively involved in regulating cellular metabolism.[37] AMPK activation can affect glucose uptake, utilization, and fatty acid oxidation, and it can inhibit pathways such as gluconeogenesis, lipid synthesis, and glycogen synthesis.[38,39]

The present study found that AMPK was highly expressed in patients with sarcopenia and positively correlated to *ADIPOQ* and blood lipids (positively correlated). Ye et al[40] summarized the research on sarcopenia and frailty over the past 30 years and identified the pathogenesis and endocrine metabolic regulation pathways involved in them, including AMPK, cellular aging, and hormone resistance pathways. AMPK not only regulates lipid metabolism and directly leads to sarcopenia, but it also contributes to the onset of sarcopenia through other mechanisms. Akabane et al[41] identified that reduced AMPK signal transduction can accelerate skeletal muscle sarcopenia and decrease autophagy.

Studies suggest that *ADIPOQ* activates AMPK through AdipoR1 and AdipoR2 receptors, inducing acetyl coenzyme A carboxylase (ACC) phosphorylation and ultimately promoting fatty acid oxidation.[42–44] In addition, *ADIPOQ* can activate the AMPK-ACC signaling pathway in various tissues and cells.[37,45] In vitro and in vivo experiments have demonstrated that *ADIPOQ* can rapidly (within one hour) activate AMPK and significantly increase ACC phosphorylation levels in C2C12 cells, cardiomyocytes, extensor digitorum longus muscles, and gastrocnemius muscles, thereby promoting fatty acid oxidation.[46] Based on previous research and our results, we hypothesize that abnormal lipid metabolism is a risk factor for sarcopenia, and *ADIPOQ* and AMPK are key factors affecting glycolipid metabolism in sarcopenia.

Conclusion

The present study confirms that glycolipid metabolism is a risk factor for sarcopenia. As a key gene regulating glycolipid metabolism, *ADIPOQ* was significantly overexpressed in sarcopenia samples. Moreover, AMPK was found to be overexpressed in sarcopenia samples and demonstrated a significant positive correlation with *ADIPOQ*. Therefore, this study hypothesizes that *ADIPOQ* may regulate AMPK activity, affect lipid metabolism, and accelerate the occurrence and development of sarcopenia.

Data Sharing Statement

Research datasets are accessible through correspondence with the principal investigator, Feike Yang, at yangfk2019wz@163.com.

Ethics Approval and Consent to Participate

This research was performed in accordance with the Declaration of Helsinki. Ethical approval, including for biospecimen collection, was granted by Zhuzhou Central Hospital's Institutional Review Board (IRB #20231072).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the Natural Science Foundation of Hunan Province (Grant No. 2024JJ9500).

Disclosure

The authors have no competing interests to declare.

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