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Exploring molecular links between obesity and osteoporosis: insights from in-silico analysis and mannose supplementation

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D-mannose, a plant-derived monosaccharide used as a dietary supplement, has shown potential in alleviating obesity symptoms and improving bone loss in mice. Obesity, a known risk factor for osteoporosis (OP), suggests shared molecular pathways between these conditions. This study explores the molecular mechanisms of obesity-induced OP and the potential therapeutic role of mannose supplementation. Using in-silico analysis, GEO2R was applied to dataset GSE110796 to identify differentially expressed genes (DEGs) under high-fat diet-induced obesity and mannose supplementation. Enrichment analysis via Enrichr and ClueGO revealed significant molecular pathways altered by high-fat diets and reversed by mannose. Similarly, pathways for OP were identified using the GEO dataset GSE56815 and DisGeNET-associated genes. Forty-four overlapping pathways were identified between obesity and OP, with key immune and inflammatory pathways modulated by mannose. Notably, genes upregulated in osteoclast differentiation during obesity were downregulated with mannose. These findings suggest that mannose modulates shared pathways in obesity and OP, offering a cost-effective therapeutic approach. This study enhances understanding of obesity-induced OP and provides a foundation for innovative medical interventions.

Keywords D-mannose, Osteoporosis, Obesity-induced osteoporosis, Molecular pathways, Mannose supplementation, Inflammation, Osteoclast differentiation, In-silico analysis

Abbreviations

OP	Osteoporosis
PMOP	Post-menopausal OP
MIF	Macrophage migration inhibitory factor
ECM	Extracellular matrix
MSigDB	Molecular signatures database
BMD	Bone mineral density
GO	Gene ontology
IL	Interleukin
KEGG	Kyoto Encyclopedia of genes and genomes
PPI	Protein-protein interaction

One in three women worldwide suffers from osteoporosis (OP), a debilitating metabolic disorder characterised by fragile bones prone to sudden fractures, leading to significant morbidity and mortality[1]. The primary symptom of OP is often a fracture, although chronic pain, particularly back pain, may precede it. This condition predominantly affects postmenopausal women and the ageing population[2,3]. Premature ovarian failure, which reduces estrogen levels, can lead to the early onset of OP[4]. Peak bone mass attained during early life plays a

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critical role in determining the risk of OP in older age. In 2018, an estimated 10 million people in the U.S. were affected by OP[5]. Among elderly women in India, deteriorating bone density often results in a stooped posture and increased susceptibility to hip fractures[6,7]. Various risk factors, including age, lifestyle, diet, vitamin D status, and drug use, contribute to OP. A study in Japan also highlighted Helicobacter pylori infection as a potential risk factor[8].

The prevalence of obesity continues to rise globally, affecting both the elderly and an increasing number of young individuals. Obesity is characterised by excess body fat, which predisposes individuals to cardiometabolic diseases[9]. Obesity has doubled in prevalence among adults and children in recent years. In Kerala, India, a 2016 study reported a 17.25% prevalence of OP, further linking metabolic disorders to lifestyle changes[10]. The obesity rate among adolescents has increased threefold. Some consider obesity a disease rather than just a condition[11].

Adipose tissue plays a crucial role in linking obesity and OP, as its accumulation increases in both conditions[12–14]. Expanding adipose tissue triggers inflammatory responses, recruits immune cells to the site, and further amplifies the production of inflammatory factors[15]. In OP, bone marrow adipose tissue (MAT) increases, acting as an endocrine organ and contributing to elevated levels of cytokines and adipokines[16]. Inflamm-ageing is closely linked to OP[17,18]. The adipose tissue factor can also connect OP to diabetes[19]. Interestingly, increasing body fat mass is inversely associated with bone mass, positioning adipose tissue as a critical link between obesity and OP[20,21].

D-mannose, a natural monosaccharide derived from the breakdown of plant polysaccharides, offers various health benefits and is used as a dietary supplement[22,23]. Obesity and certain inflammatory diseases, which are the result of disordered metabolism, are connected to the imbalances in the microbiota of the gut[24]. Mannose can positively influence the gut microbiome, which in turn alters metabolism to alleviate several adverse metabolic conditions. Studies in mice show that, anti-inflammatory effects of an altered gut microbiome via mannose supplementation can reduce bone loss[25]. Long-term mannose supplementation has shown no adverse effects in mice and has been reported to improve bone architecture[26]. Dipsacus asper polysaccharide, which contains mannose, has demonstrated anti-osteoporotic effects in ovariectomised rat models[27].

Animal models, particularly mice and rats, are widely used to investigate metabolic diseases such as diabetes, obesity and cardiovascular disorders[28]. They serve to test the efficacy of various treatments and to investigate the genetic, environmental, physiologic and molecular factors underlying the development of various disorders[29,30].

To date, no transcriptomic studies in humans have been conducted under the experimental conditions of mannose supplementation in the context of a high-fat diet. This lack of data makes it challenging to elucidate the molecular pathways involved in humans under such conditions. Consequently, the GEO dataset GSE110796, which includes microarray data from mouse models, was selected to explore the molecular mechanisms underlying high-fat diets and mannose supplementation.

In obesity as well as in OP, mannose is visibly altering the gut microbiota, which in turn alters the metabolism of the body[25,31]. Obesity and OP, both metabolic disorders, are intricately linked[32]. Yet the molecular genetic connection between them remains obscure. Although obesity is inversely related to bone mass, this study investigates whether this inverse relationship leads to OP through metabolic shifts in the body. These shifts may result from altered regulation of molecular pathways influenced by obesity.

This study utilised various computational tools, including GEO2R, STRING, the Cytoscape plugin ClueGO, Enrichr and a multiple-list comparator, to identify molecular pathways influenced by high-fat diets in mice (Fig. 1.). The analysis also examined how mannose supplementation might mitigate obesity induced by a high-fat diet. Additionally, the study explored the molecular mechanisms linking obesity and OP, identifying common disrupted pathways that could contribute to their coexistence. Finally, the potential of mannose supplementation in alleviating OP was investigated. Understanding the molecular mechanisms of mannose action could pave the way for developing more effective and affordable treatment strategies for OP.

Methodology

Identification of molecular pathways deregulated in obesity using the GEO dataset GSE110796

To identify molecular pathways deregulated during a high-fat diet in mice, the GEO dataset GSE110796 was selected from Gene Expression Omnibus. According to the study associated with this dataset, obesity was induced in mice through a high-fat diet, and mannose supplementation prevented weight gain[31]. Pathways enriched during mannose supplementation during HFD were identified using the same dataset.

GEO dataset GSE110796 for obesity

GEO2R analysis was performed on the dataset GSE110796 to identify differentially expressed genes in the epididymal fat tissue. The dataset GSE110796, retrieved from the NCBI-GEO database, comprises gene expression profiles from Mus musculus (house mouse) subjected to various dietary interventions—normal diet, high-fat diet and high-fat diet supplemented with mannose for 16 weeks. In the study associated with the dataset, total RNA was extracted from epididymal fat tissue using the Qiagen RNeasy Lipid Tissue mini kit. Biotin-labelled cDNA was hybridised to MouseWG-6 expression bead chips, and scanning was performed using an Illumina BeadArray Reader. Processed data were analysed using GenomeStudio software.

Differential gene expression analysis using GEO2R

Expression data from the GSE110796 dataset (platform GPL6887) were analysed using GEO2R[33] to identify DEGs in mice fed an HFD or HFD with mannose supplementation. DEGs were filtered based on fold change and a p-value threshold of ≤ 0.05, separately identifying upregulated and downregulated genes.

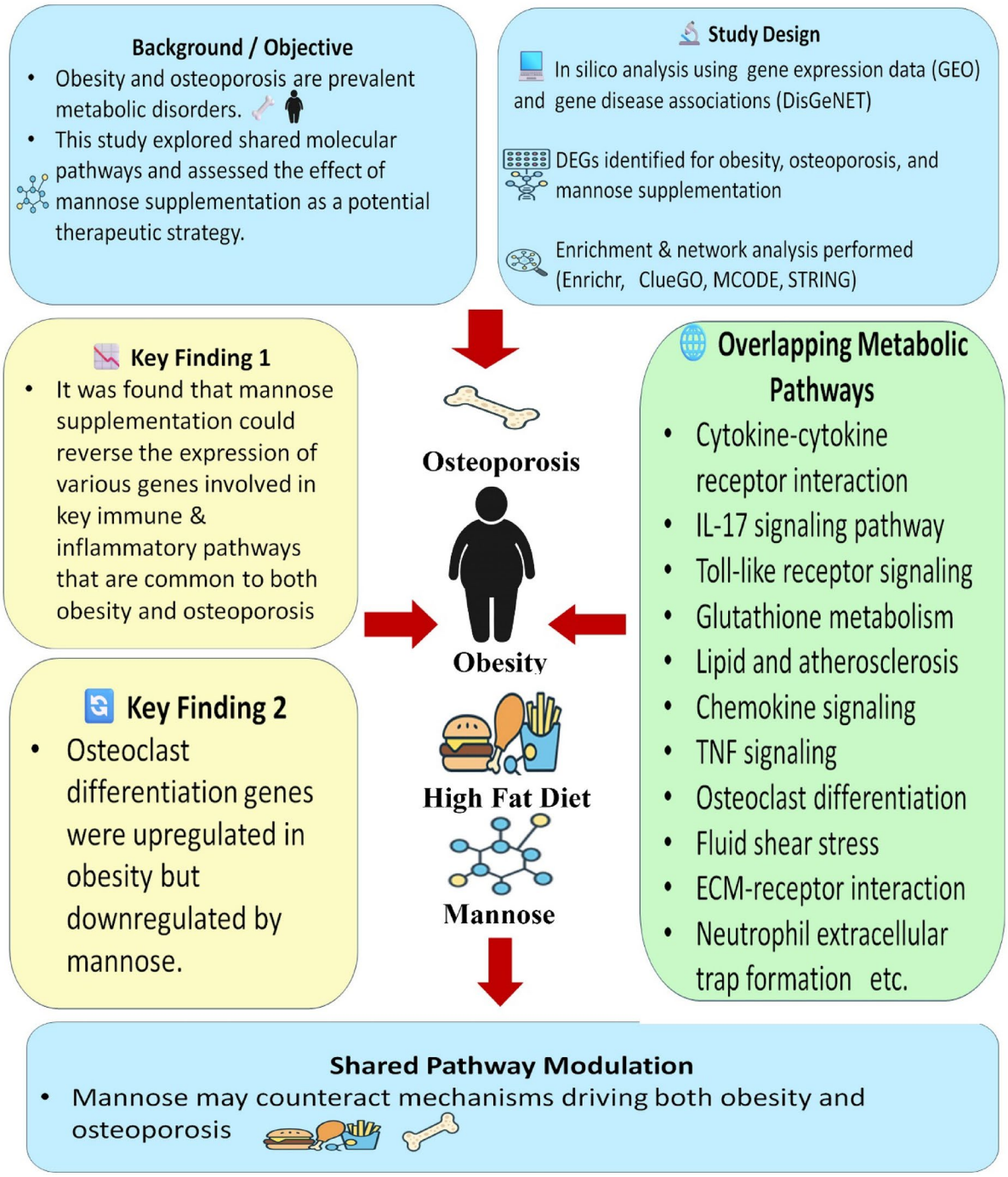


Fig. 1. Computational identification of shared molecular pathways in obesity and OP, highlighting the influence of mannose supplementation.

Pathway enrichment analysis of GSE110796

Identified DEGs were subjected to pathway enrichment analysis using Enrichr[34–36] and ClueGO[37]. Enrichr provided KEGG pathway annotations by converting gene lists into Entrez IDs, while ClueGO in Cytoscape[38] enabled visualisation of molecular interaction networks and assigned DEGs to specific pathways.

Construction of PPI network using Cytoscape

A protein–protein interaction (PPI) network was constructed using DEGs inserted into the Cytoscape STRING app[39]. Pathway enrichment analysis was performed on this network using ClueGO, and the identified pathways, along with assigned genes, were exported for further analysis.

Multiple testing correction was applied using the Benjamini–Hochberg false discovery rate (FDR) method in GEO2R to control for potential false positives arising from multiple comparisons. Similarly, for pathway

enrichment analysis using ClueGO, p-values were corrected using the Bonferroni step-down method to ensure statistical rigour.

MCODE enrichment analysis for highly interconnected pathways

MCODE analysis was performed on the GO network created in Cytoscape to identify clusters of highly interconnected pathways. These clusters represent key functional areas in the pathway enrichment network.

Assessing the effectiveness of mannose supplementation in obesity

Data from GEO2R and pathway enrichment analyses were combined to evaluate the impact of mannose supplementation on alleviating obesity. Shared pathways between HFD and mannose supplementation were analysed, and the expression trends of associated genes (upregulated or downregulated) were manually marked. Pathways common to obesity and mannose supplementation were listed, and their expression trends were evaluated.

Identification of molecular pathways in OP using the GEO Dataset GSE56815

For the identification of molecular pathways deregulated during the development of OP, another GEO dataset, which provides expression profiles from postmenopausal women with OP, was selected from Gene Expression Omnibus.

GEO dataset GSE56815 for post-menopausal osteoporosis (PMOP):

To investigate deregulated pathways in OP, the GEO dataset GSE56815 was selected. This dataset contains microarray data from monocytes of Caucasian females with high and low bone mineral density (BMD). DEGs were identified via GEO2R analysis and subjected to enrichment analysis using Enrichr and ClueGO in Cytoscape. The resulting KEGG pathways were compiled for further analysis.

Pathway enrichment analysis of osteoporosis-associated genes from DisGeNET

Genes associated with OP were downloaded from the DisGeNET database, a comprehensive resource of gene-disease associations. These genes were analysed for pathway enrichment using Enrichr and Cytoscape to identify key pathways linked to OP.

Overlap analysis of pathways to uncover crosstalk between obesity and osteoporosis

To identify shared pathways between obesity and OP, an overlap analysis was performed. KEGG pathways enriched in obesity and OP were pooled and compared using molbiotools.com (https://www.molbiotools.com/listcompare.html) and Venny 2.1. (https://bioinfogp.cnb.csic.es/tools/venny/) Venn diagrams were created to visualise overlapping and unique pathways. Literature mining was conducted to explore the role of overlapping pathways in the progression of both metabolic disorders.

Evaluating mannose supplementation for addressing osteoporosis

If overlapping pathways were identified between obesity and OP, and if genes in these pathways exhibited inverse expression patterns during mannose supplementation, this would suggest the potential of mannose supplementation in alleviating OP.

Correlation analysis between obesity- and osteoporosis-related gene sets from the molecular signatures database

Gene sets related to obesity and OP were obtained from the Molecular Signatures Database[40] (MSigDB) (Supplementary File). Z-scores were calculated to quantify pathway activation, representing the relative activity of each gene set across individual samples[41]. Hierarchical clustering was performed using dChip software[42] to group gene sets and genes with similar activation profiles. This analysis facilitated the identification of co-activated gene sets and their relationships across sample subsets. The activation patterns and clustering results were visualized using heatmaps. To examine the relationships between obesity- and OP-related gene sets, Pearson's correlation analysis was conducted on the Z-scores. Correlation coefficients quantified the strength and direction of these associations, with statistical significance determined at a threshold of $p < 0.05$. The results were visualized as heatmaps generated in R version 4.2.1 (https://www.r-project.org/). Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were conducted to identify biologically enriched pathways and processes. Separate analyses were performed for obesity and OP gene sets using the clusterProfiler package in R. GO analysis categorized genes into three domains: biological processes (BP), molecular functions (MF), and cellular components (CC). KEGG analysis identified relevant metabolic and signaling pathways. Enrichment significance was determined using an adjusted p-value threshold of < 0.05. The enriched terms and pathways were subsequently compared to uncover shared mechanisms underlying the pathophysiology of obesity and OP.

Results

GEO2R analysis and differential gene expression under high-fat diet conditions and mannose supplementation in mice

GEO2R analysis of GEO dataset GSE110796 was performed using Gene Expression Omnibus. After filtering DEGs based on fold change and a p-value threshold of ≤ 0.05, significant differential expression was identified in 357 genes from the expression profile of epididymal fat of HFD mice. Among these, 259 genes were upregulated, while 98 were downregulated. In obese mice (HFD) supplemented with mannose, 263 DEGs were identified,

with 68 genes upregulated and 195 downregulated. The volcano plot and mean-difference plot illustrating the differential expression data obtained from the GEO2R analysis is presented in Fig. 2.

Pathway enrichment analysis of DEGs from GSE110796—functional molecular pathways in obesity and mannose supplementation

Enrichment analysis of DEGs from the GEO dataset GSE110796 was conducted using the bioinformatics tools Enrichr and Cytoscape ClueGO, revealing a predominance of Inflammatory pathways among the enriched results. In the analysis of KEGG pathways for the HFD-induced obese phenotype using Enrichr, four pathways were significantly enriched (Fig. 3)—Fluid shear stress and atherosclerosis, IL-17 signaling pathway, Drug Metabolism and TNF signaling pathway. The pathway for osteoclast differentiation was also enriched with a p-value of 0.0035. For mannose-supplemented HFD mice, Enrichr identified eleven significantly enriched pathways (adjusted p-value ≤ 0.05), including Viral protein interaction with cytokine and cytokine receptor, Fluid shear stress and atherosclerosis, Cytokine-cytokine receptor interaction, Toll-like receptor signaling pathway, TNF signaling pathway, Rheumatoid arthritis, IL-17 signaling pathway, Chemokine signaling pathway,

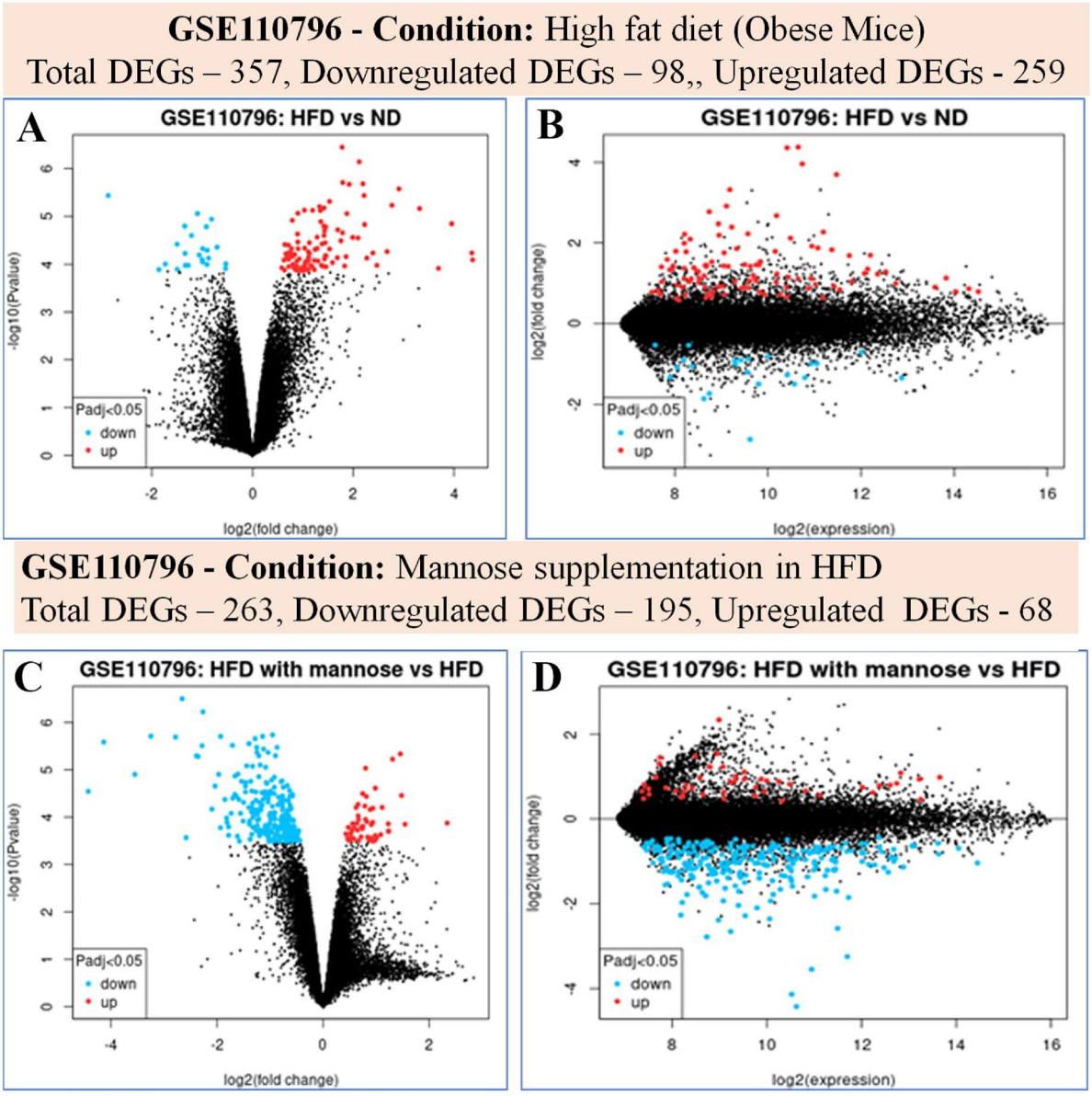
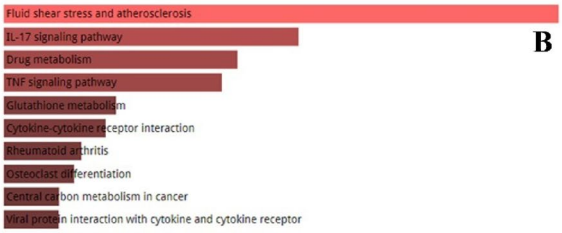


Fig. 2. Volcano and mean-difference plots depicting the differential gene expression in epididymal fat tissue under high-fat diet conditions and following mannose supplementation. (**A**) Volcano plot of differential expression in High fat diet (HFD) Vs Normal diet (ND). (**B**) Mean-difference plot of differential expression in High-fat diet (HFD) Vs Normal diet (ND). (**C**) Volcano plot of differential expression in High-fat diet supplemented with mannose Vs High-fat diet. (**D**) Mean-difference plot of differential expression in High-fat diet supplemented with mannose Vs High-fat diet.

A Terms	P-value	Adjusted P-value
Fluid shear stress and atherosclerosis	1.62E-06	4.02E-04
IL-17 signaling pathway	9.98E-05	0.012374
Drug metabolism	2.62E-04	0.02084
TNF signaling pathway	3.36E-04	0.02084



C Terms	Genes
Fluid shear stress and atherosclerosis	THBD↓;GSTA4↓;GSTA3↓;GPC1↑;HMOX1↑;CCL2↑;CYBA↑;GSTT1↓;PIK3R1↓;FOS↑;MMP9↓;ASS1↑
IL-17 signaling pathway	CXCL10↑;CCL7↑;MMP3↑;CCL2↑;CXCL1↑;FOS↑;MMP9↓;S100A8↑
Drug metabolism	MAOB↓;GSTA4↓;NME7↓;GSTA3↓;FMO1↓;GSTT1↓;CYP2E1↓;TK1↑
TNF signaling pathway	CXCL10↑;MMP3↑;CCL2↑;CXCL1↑;PIK3R1↓;FOS↑;JUNB↑;MMP9↓

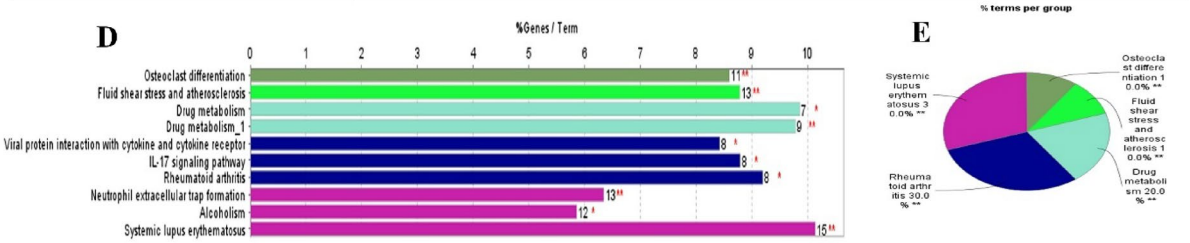


Fig. 3. KEGG pathway enrichment analysis of high-fat diet impact using Enrichr and ClueGO. (**A**) Significant molecular pathways enriched in high-fat diet (obese mice). (**B**) Bar graph showing KEGG pathways enriched in high-fat diet (obese mice) from analysis in Enrichr. Pathways are sorted by p-value ranking. (**C**) DEGs binned into pathways enriched in high-fat diet (upregulation and downregulation of genes shown. Green—downregulated, Red—upregulated). (**D**) ClueGO results (HFD) —Specific Clusters. (**E**) ClueGO results (HFD) —Overview: Specific Cluster.

Glutathione metabolism, Osteoclast differentiation and Lipid and atherosclerosis (Fig. 4). ClueGO analysis of the same DEGs identified nine significant pathways (p-value ≤ 0.05) in the HFD condition and eighteen in the mannose supplementation condition (Tables 1 and 2). KEGG pathway enrichment network for HFD and mannose supplementation from ClueGO analysis is shown in Fig. 5. The expression pattern of genes associated with the pathways enriched in high-fat diet obese phenotype and mannose supplementation is shown in Tables 1 and 2. An inverse expression trend was observed for genes in overlapping pathways between the HFD and mannose supplementation groups. For instance, the FOS transcription factor, which was upregulated in obese mice, exhibited a reversed expression pattern under mannose supplementation.

Pathway-based clustering via MCODE enrichment analysis

Highly interconnected regions within the GO enrichment network were identified using MCODE. In obese mice following a high-fat diet (HFD) without mannose supplementation, a single pathway cluster was detected, with a score of 3, three nodes and three edges, using a node score cutoff of 0.2. This cluster included the pathways Alcoholism, Systemic lupus erythematosus and Neutrophil extracellular trap formation. In HFD mice supplemented with mannose, three distinct pathway clusters were retrieved (Fig. 6) using the same node score cutoff of 0.2. These clusters were associated with biodegradation, inflammation and immune response. Most of the genes assigned to cluster 1 were upregulated, whereas those in clusters 2 and 3 were predominantly downregulated.

Pathway enrichment analysis of the GEO dataset GSE56815 and DisGeNET genes for osteoporosis

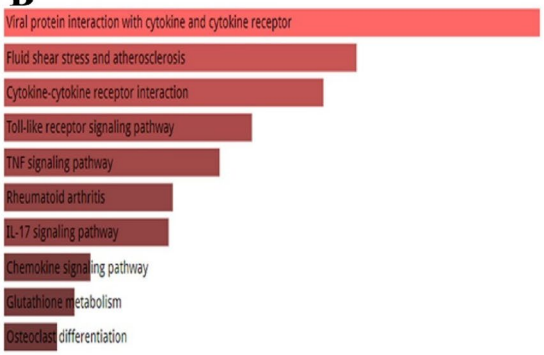
To identify potential molecular pathways underlying the metabolic disorder OP, a GEO dataset of post-menopausal OP and OP-associated genes from the DisGeNET database was utilised. Differentially expressed genes (DEGs) identified through GEO2R analysis of GSE56815 were subjected to pathway enrichment analysis using Enrichr and ClueGO. The pathways showing statistically significant p-values were consolidated for overlap analysis. Similarly, OP-associated genes retrieved from DisGeNET underwent pathway enrichment analysis using the same tools.

Key pathways enriched in these analyses included Growth hormone synthesis, secretion and action, Neurotrophin signaling pathway, MAPK signaling pathway, Osteoclast differentiation, Ras signaling pathway, Type II diabetes mellitus and Insulin signaling pathway. Kinase-mediated pathways such as MAPK signaling pathway, PI3K-Akt signaling pathway, AMPK signaling pathway and cGMP-PKG signaling pathway were prominently enriched. Immune system-related pathways identified included B cell receptor signaling pathway,

A

Term	P-value	Adjusted P-value
Viral protein interaction with cytokine and cytokine receptor	2.07E-07	4.27E-05
Fluid shear stress and atherosclerosis	4.32E-06	4.48E-04
Cytokine-cytokine receptor interaction	7.52E-06	5.19E-04
Toll-like receptor signaling pathway	2.46E-05	0.001273
TNF signaling pathway	4.20E-05	0.00174
Rheumatoid arthritis	9.16E-05	0.002898
IL-17 signaling pathway	9.80E-05	0.002898
Chemokine signaling pathway	3.58E-04	0.009268
Glutathione metabolism	4.67E-04	0.010737
Osteoclast differentiation	6.24E-04	0.012924
Lipid and atherosclerosis	8.09E-04	0.015233

B



C

Term	Genes
Viral protein interaction with cytokine and cytokine receptor	CXCL10↓;CXCL12↓;CCL8↓;CCL7↓;CCL5↓;IL20RB↓;CCL2↓;CXCL1↓;CCL19↓;CCR5↓
Fluid shear stress and atherosclerosis	THBD↑;GSTA4↑;GSTA3↑;HMOX1↓;CCL2↓;GSTT1↑;FOS↓;MAP2K7↑;ASS1↓;GSTM5↑
Cytokine-cytokine receptor interaction	IL1RN↓;IL20RB↓;CXCL1↓;GDF3↓;CXCL10↓;CXCL12↓;CCL8↓;CCL7↓;CCL5↓;CCL2↓;CCL19↓;CCR5↓;IL7R↓;TNFRSF21↓
Toll-like receptor signaling pathway	CXCL10↓;CTSK↓;CCL5↓;SPP1↓;IRF5↓;LBP↓;FOS↓;MAP2K7↑
TNF signaling pathway	CXCL10↓;CCL5↓;MMP3↓;CCL2↓;CXCL1↓;FOS↓;MAP2K7↑;JUNB↓
Rheumatoid arthritis	CXCL12↓;CTSK↓;CCL5↓;MMP3↓;CCL2↓;CXCL1↓;FOS↓
IL-17 signaling pathway	CXCL10↓;CCL7↓;MMP3↓;CCL2↓;CXCL1↓;FOS↓;S100A8↓
Chemokine signaling pathway	CXCL10↓;CXCL12↓;CCL8↓;CCL7↓;CCL5↓;CCL2↓;CXCL1↓;CCL19↓;CCR5↓
Glutathione metabolism	GSTA4↑;GPX3↑;GSTA3↑;GSTT1↑;GSTM5↑
Osteoclast differentiation	TYROBP↓;CTSK↓;NCF4↓;TREM2↓;FOS↓;MAP2K7↑;JUNB↓
Lipid and atherosclerosis	CCL5↓;NCF4↓;MMP3↓;CCL2↓;CXCL1↓;FOS↓;HSPA2↑;LBP↓;MAP2K7↑

Fig. 4. KEGG pathway enrichment analysis of high-fat diet supplemented with mannose using Enrichr. (**A**) Significant pathways enriched from the enrichment analysis of DEGs in high-fat diet supplemented with mannose. (**B**) Bar graph depicting KEGG pathways enriched using Enrichr for high-fat diet supplemented with mannose, with pathways ranked by p-value. (**C**) DEGs associated with pathways enriched in high-fat diet with mannose supplementation, highlighting upregulated and downregulated genes.

Term	Term P value corrected with Bonferroni step down	Associated genes found
Osteoclast differentiation	1.6 E-3	CTSK↑, CYBA↑, FCGR3↑, FCGR4↑, FOS↑, JUNB↑, LILRB4A↑, PIK3R1↓, SIRPB1A↑, TREM2↑, TYROBP↑
Fluid shear stress and atherosclerosis	2.3 E-4	ASS1↑, CCL2↑, CYBA↑, FOS↑, GPC1↑, GSTA3↓, GSTA4↓, GSTT1↓, GSTT3↓, HMOX1↑, MMP9↓, PIK3R1↓, THBD↓
Drug metabolism	1.9 E-2	CYP2E1↓, FMO1↓, GSTA3↓, GSTA4↓, GSTT1↓, GSTT3↓, MAOB↓
Viral protein interaction with cytokine and cytokine receptor	2.1 E-2	CCL19↑, CCL2↑, CCL6↑, CCL7↑, CCL8↑, CCL9↑, CXCL1↑, CXCL10↑
IL-17 signaling pathway	1.6 E-2	CCL2↑, CCL7↑, CXCL1↑, CXCL10↑, FOS↑, MMP3↑, MMP9↓, S100A8↑
Rheumatoid arthritis	1.2 E-2	ATP6V0A1↑, CCL2↑, CTSK↑, CXCL1↑, FOS↑, H2-DMB1↑, H2-DMB2↑, MMP3↑
Neutrophil extracellular trap formation	7.1 E-3	CYBA↑, FCGR4↑, H2AC10↑, H2AC12↑, H2AC13↑, H2AC15↑, H2AC22↑, H2AC7↑, H2BC12↑, H2BC14↑, H2BC7↑, H2BC9↑, PIK3R1↓
Alcoholism	2.4 E-2	GNGT2↑, H2AC10↑, H2AC12↑, H2AC13↑, H2AC15↑, H2AC22↑, H2AC7↑, H2BC12↑, H2BC14↑, H2BC7↑, H2BC9↑, MAOB↓
Systemic lupus erythematosus	6.3 E-6	C2↓, C7↓, FCGR4↑, H2-DMB1↑, H2-DMB2↑, H2AC10↑, H2AC12↑, H2AC13↑, H2AC15↑, H2AC22↑, H2AC7↑, H2BC12↑, H2BC14↑, H2BC7↑, H2BC9↑

Table 1. ClueGO result table for KEGG pathways in HFD (obesity). ↑—upregulated, ↓—downregulated.

C-type lectin receptor signaling pathway, Fc gamma R-mediated phagocytosis, Chemokine signaling pathway, T cell receptor signaling pathway, Fc epsilon RI signaling pathway, Leukocyte transendothelial migration, Rheumatoid arthritis, Toll-like receptor signaling pathway, Th17 cell differentiation, IL-17 signaling pathway, Th1 and Th2 cell differentiation, Hematopoietic cell lineage, RIG-I-like receptor signaling pathway, Natural killer cell mediated cytotoxicity and Complement and coagulation cascades. Notably, several immune signaling pathways, including Chemokine signaling pathway, Rheumatoid arthritis, Toll-like receptor signaling pathway, IL-17 signaling pathway and Complement and coagulation cascades, were also enriched in high-fat diet.

Furthermore, several immune system pathways, along with pathways such as Cytokine-cytokine receptor interaction, TNF signaling pathway, Fluid shear stress and atherosclerosis and Inflammatory mediator regulation

Term	Term P value corrected with Bonferroni step down	Associated genes found
Leishmaniasis	4.1 E-2	FCGR4↓, FOS↓, H2-DMB1↓, H2-DMB2↓, NCF4↓
NF-kappa B signaling pathway	1.9 E-3	BCL2A1B↓, BCL2A1D↓, CCL19↓, CCL21A↑, CXCL1↓, CXCL12↓, GADD45B↓, LBP↓
Osteoclast differentiation	2.2 E-4	CTSK↓, FCGR4↓, FOS↓, JUNB↓, LILRB4A↓, MAP2K7↑, NCF4↓, SIRPB1A↓, TREM2↓, TYROBP↓
Neutrophil extracellular trap formation	3.3 E-2	CLEC7A↓, FCGR4↓, H2AC10↓, H2AC12↓, H2AC13↓, H2AC15↓, H2AC22↓, H2AC7↓, NCF4↓
Systemic lupus erythematosus	3.6 E-3	FCGR4↓, H2-DMB1↓, H2-DMB2↓, H2AC10↓, H2AC12↓, H2AC13↓, H2AC15↓, H2AC22↓, H2AC7↓
Cytokine-cytokine receptor interaction	5.0 E-5	CCL19↓, CCL2↓, CCL21A↑, CCL5↓, CCL7↓, CCL8↓, CCL9↓, CCR5↓, CXCL1↓, CXCL10↓, CXCL12↓, GDF3↓, IL1RN↓, IL20RB↓, IL7R↓, TNFRSF21↓
Viral protein interaction with cytokine and cytokine receptor	1.3 E-7	CCL19↓, CCL2↓, CCL21A↑, CCL5↓, CCL7↓, CCL8↓, CCL9↓, CCR5↓, CXCL1↓, CXCL10↓, CXCL12↓, IL20RB↓
Chemokine signaling pathway	1.3 E-3	CCL19↓, CCL2↓, CCL21A↑, CCL5↓, CCL7↓, CCL8↓, CCL9↓, CCR5↓, CXCL1↓, CXCL10↓, CXCL12↓
Toll-like receptor signaling pathway	1.4 E-3	CCL5↓, CTSK↓, CXCL10↓, FOS↓, IRF5↓, LBP↓, MAP2K7↑, SPP1↓
IL-17 signaling pathway	4.5 E-3	CCL2↓, CCL7↓, CXCL1↓, CXCL10↓, FOS↓, MMP3↓, S100A8↓
TNF signaling pathway	3.1 E-3	CCL2↓, CCL5↓, CXCL1↓, CXCL10↓, FOS↓, JUNB↓, MAP2K7↑, MMP3↓
Rheumatoid arthritis	6.6 E-5	CCL2↓, CCL5↓, CTSK↓, CXCL1↓, CXCL12↓, FOS↓, H2-DMB1↓, H2-DMB2↓, MMP3↓
Lipid and atherosclerosis	4.0 E-2	CCL2↓, CCL5↓, CXCL1↓, FOS↓, HSPA2↑, LBP↓, MAP2K7↑, MMP3↓, NCF4↓
Glutathione metabolism	3.9 E-2	GPX3↑, GSTA3↑, GSTA4↑, GSTM5↑, GSTT1↑
Metabolism of xenobiotics by cytochrome P450	4.1 E-2	CYP2F2↑, GSTA3↑, GSTA4↑, GSTM5↑, GSTT1↑
Drug metabolism	4.6 E-3	CES1D↑, CES1F↑, GSTA3↑, GSTA4↑, GSTM5↑, GSTT1↑, TK1↓
Chemical carcinogenesis	4.2 E-2	CYP2C23↓, CYP2C70↓, GSTA3↑, GSTA4↑, GSTM5↑, GSTT1↑
Fluid shear stress and atherosclerosis	7.7 E-4	ASS1↓, CCL2↓, FOS↓, GSTA3↑, GSTA4↑, GSTM5↑, GSTT1↑, HMOX1↓, MAP2K7↑, THBD↑

Table 2. ClueGO result table for KEGG pathways during HFD supplemented with mannose. ↑—upregulated, ↓—downregulated.

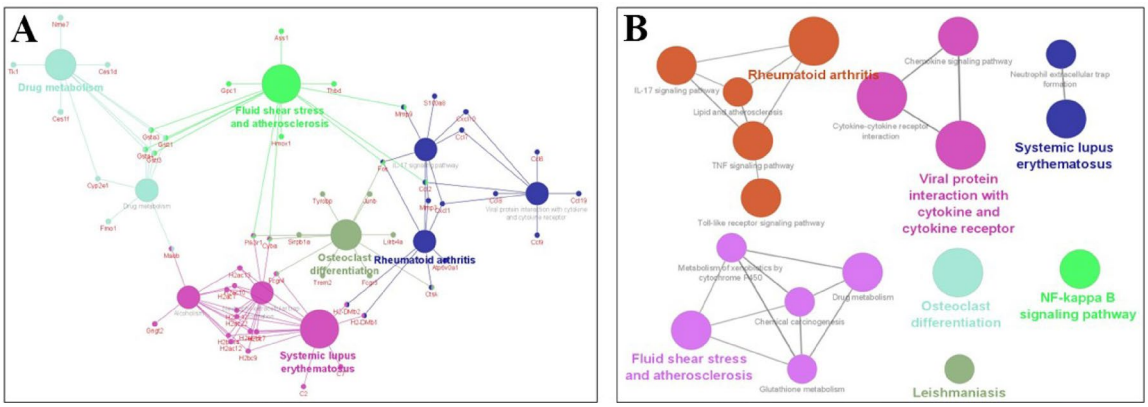


Fig. 5. KEGG pathway enrichment network for HFD and mannose supplementation (ClueGO analysis). (**A**) KEGG pathways enriched for HFD in ClueGO analysis. (**B**) KEGG pathways enriched for Mannose supplementation in HFD (Analysis in ClueGO).

of TRP channels play crucial roles in driving chronic inflammatory response in the body, a key feature in the pathophysiology of metabolic disorders.

Overlap analysis: key pathways linking obesity and osteoporosis

Overlap analysis of molecular pathways enriched for obesity and OP revealed shared elements between the two conditions. A Venn diagram constructed using Venny 2.1 identified 23 overlapping KEGG pathways between HFD and PMOP datasets (Fig. 6). This analysis utilised pathways enriched from DEGs in the GEO datasets GSE110796 and GSE56815. Additionally, pathways derived from enrichment analysis of OP-associated genes retrieved from DisGeNET revealed 44 molecular pathways common to high-fat diet-induced obesity and OP. Notably, the IL-17 signaling pathway, which plays a crucial role in chronic inflammation, was enriched in both conditions. Similarly, the osteoclast differentiation pathway, integral to bone remodeling and BMD, was found in both analyses. These findings highlight a significant overlap between pathways associated with obesity and those linked to OP. The primary functions of key overlapping pathways are summarised in Table 3. The roles and functions of molecular pathways may vary based on specific conditions such as cell or tissue type, disease state,

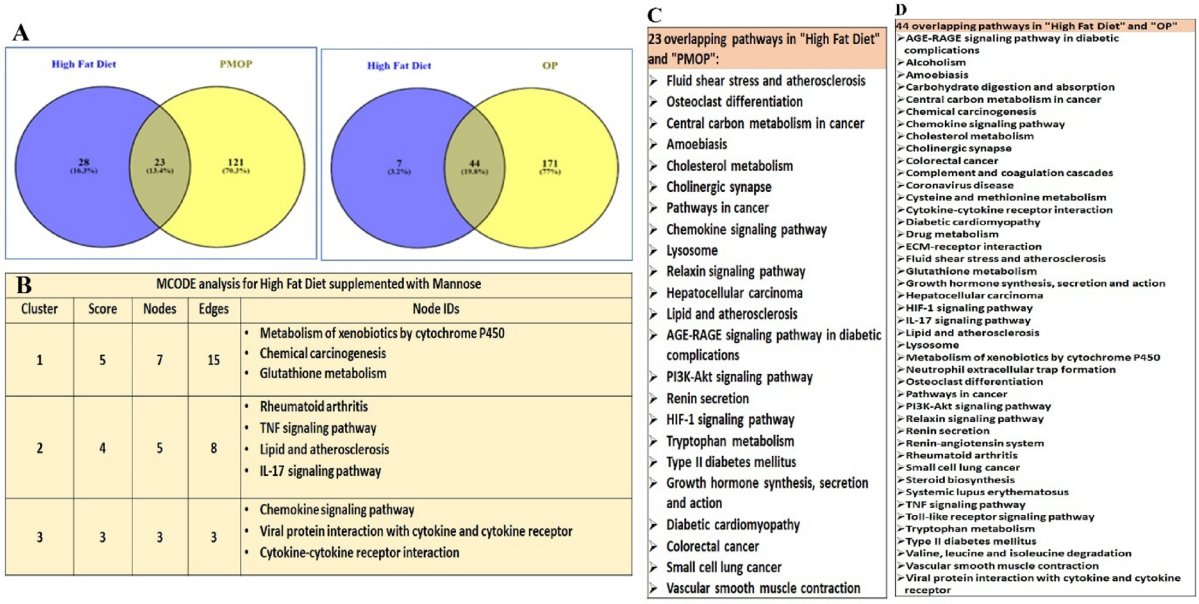


Fig. 6. Overlap analysis of KEGG molecular pathways enriched in high-fat diet (obesity) and post-menopausal osteoporosis. (**A**) Venn diagrams of overlap analyses between obesity (HFD) and osteoporosis. (**B**) MCODE analysis for high-fat diet supplemented with mannose. (**C**) Overlapping pathways in obesity (HFD) and post-menopausal osteoporosis. (**D**) Overlapping pathways in obesity (HFD) and osteoporosis.

external stimuli or metabolic status. Furthermore, genes involved in several immune, inflammatory and signaling pathways common to both conditions showed inverse expression patterns following mannose supplementation.

Correlation patterns between obesity- and osteoporosis-related gene sets from MSigDB

Gene set analysis revealed distinct activation patterns for obesity- and OP-related pathways across the cohort. Z-scores were computed to assess pathway activity, with 47.5% of the total samples exhibiting low BMD and 17.5% showing high BMD. Stratification by menopausal status highlighted that 20% of pre-menopausal individuals and 45% of post-menopausal individuals exhibited high expression of obesity- and OP-related gene sets, suggesting a stronger molecular interplay in post-menopausal individuals. Correlation analysis between the obesity-related NADLER_Obesity_Up gene set and the OP-related HP_Osteoporosis gene set showed a significant positive correlation. The heatmap (Fig. 7A) shows Z-scores across 80 samples, categorised by BMD status (low or high) and menopausal status (pre- or post-menopausal). Hierarchical clustering reveals co-activation patterns of gene sets. Heatmap showing the positive correlation between the HP_Osteoporosis gene set and the NADLER_Obesity_Up gene set, based on Z-score analysis, is shown in Fig. 7B. Among shared genes, macrophage migration inhibitory factor (MIF) was identified, indicating its role as a shared regulatory factor. Enrichment analysis identified key biological processes associated with each condition (Fig. 8). For OP, processes included ossification and bone remodeling, while for obesity, pathways related to adipogenesis and inflammatory regulation were enriched. Shared mechanisms, such as extracellular matrix (ECM) remodeling and chronic inflammation, were prominent, with the proteoglycans in the cancer pathway emerging as a common link. This pathway plays a role in ECM dynamics, inflammation and metabolic regulation, underlining its importance in the pathophysiology of both conditions.

Discussion

The computational analysis done in this study provides insights into the molecular crosstalk between metabolic disorders, obesity and OP. This study reveals that there is a substantial number of overlapping functional molecular pathways common to the pathophysiology of both conditions. Notably, inflammatory pathways, immune signaling pathways, pathways concerned with endothelial function and angiogenesis, and multiple pathways associated with cell cycle/cell survival were identified. These pathways appear to play an important role in the complex relationship between obesity and OP, with each condition potentially contributing to the development of the other. Furthermore, these functional pathways shed light on the underlying mechanisms of obesity-induced OP.

Inflammatory pathways were identified in two MCODE clusters, and most of the associated genes in these pathways were downregulated following mannose supplementation. Genes associated with the pathway, Fluid shear stress and atherosclerosis, exhibited inverse expression patterns in response to HFD and mannose supplementation. The DEGs that were upregulated in HFD were downregulated when HFD was supplemented with mannose. This indicates that mannose supplementation can modulate the activity of this pathway. This is reflected in the physiological improvements in the mice, specifically preventing weight gain and alleviating obesity.

Molecular pathway	Functions	KEGG class
Fluid shear stress and atherosclerosis	Endothelial dysfunction, leading to inflammatory states	Cardiovascular disease
Osteoclast differentiation	Bone resorption	Development and regeneration
Cholesterol metabolism	Cardiovascular disease	Digestive system
Cholinergic synapse	Neuroinflammation	Nervous system
Chemokine signaling pathway	Inflammatory immune response	Immune system
Lysosome	Endocytosis, phagocytosis, and autophagy	Transport and catabolism
Relaxin signaling pathway	Vasodilatory, anti-fibrotic and angiogenic effects	Endocrine system
Lipid and atherosclerosis	Inflammation, endothelial dysfunction	Cardiovascular disease
AGE-RAGE signaling pathway in diabetic complications	Inflammation, vascular dysfunction, angiogenesis	Endocrine and metabolic disease
PI3K-Akt signaling pathway	Angiogenesis	Signal transduction
Renin secretion	Blood pressure homeostasis	Endocrine system
HIF-1 signaling pathway	Angiogenesis	Signal transduction
Tryptophan metabolism	Glycolysis	Amino acid metabolism
Type II diabetes mellitus	Obesity is a causative factor	Endocrine and metabolic disease
Growth hormone synthesis, secretion and action	Cell growth and metabolism	Endocrine system
Diabetic cardiomyopathy	Reactive oxygen species (ROS) generation, contractile dysfunction, fibrosis	Cardiovascular disease
Vascular smooth muscle contraction	Vasoconstriction and vasodilation	Circulatory system
Cytokine-cytokine receptor interaction	Inflammatory host defences, cell growth, differentiation, cell death, angiogenesis, and development and repair processes	Signaling molecules and interaction
ECM-receptor interaction	Adhesion, migration, differentiation, proliferation, and apoptosis	Signaling molecules and interaction
IL-17 signaling pathway	Acute and chronic inflammatory responses	Immune system
Rheumatoid arthritis	Inflammation, osteoclast differentiation	Immune disease
TNF signaling pathway	Cell survival, inflammation	Signal transduction
Viral protein interaction with Cytokine and cytokine receptor	Immunity, inflammation	Signaling molecules and interaction
Alcoholism	Regulation of states of addiction, neuroadaptation (to food leading to obesity)	Human Diseases
Carbohydrate digestion and absorption	Glycolysis, energy production	Digestive Systems
Complement and coagulation cascades	Inflammation, vasodilation, phagocytosis, and cell lysis	Immune system
Cysteine and methionine metabolism	Production of cysteine from homocysteine, atherogenicity	Amino acid metabolism
Drug metabolism	Xenobiotic degradation	Metabolism
Glutathione metabolism	Xenobiotic degradation	Metabolism
Metabolism of xenobiotics by cytochrome P450	Xenobiotic degradation	Xenobiotics biodegradation and metabolism
Neutrophil extracellular trap formation	Immune response	Immune system
Renin-angiotensin system	Vasodilation, vasoconstriction, aldosterone secretion, and inflammation	Endocrine system
Rheumatoid arthritis	Angiogenesis, inflammation, joint destruction, bone resorption, osteoclast differentiation	
Steroid biosynthesis	Formation of calcitriol, the active form of Vitamin D	Lipid metabolism
Systemic lupus erythematosus	Impaired endothelial function	Immune disease
Toll-like receptor signaling pathway	Production of pro-inflammatory cytokines, proinflammatory effects	Immune system
Valine, leucine and isoleucine degradation	Serum level of valine, leucine and isoleucine	Amino acid metabolism

Table 3. Functions of significant overlapping molecular pathways between obesity and OP (KEGG GenomeNet).

The DEGs associated with the IL-17 signaling pathway were predominantly upregulated, except for MMP9, during HFD. A total of eight DEGs were mapped to this pathway, which appears to be downregulated with mannose supplementation. Several studies have shown that IL-17 expression is elevated in obese patients, and it contributes to the inflammation in adipose tissue through the upregulation of inflammatory cytokines[43,44]. Anti-IL-17 treatments have been found to inhibit inflammation and increase adipokine levels[45]. Additionally, pro-osteoclastogenic cytokine production is promoted by IL-17, which directly induces bone loss. Estrogen can act as a functional block to IL-17, leading to a reduction in bone loss, which is particularly relevant in the development of post-menopausal OP[46]. In this study, HFD was observed to upregulate genes in the IL-17 signaling pathway suggesting that HFD-induced increase in IL-17 could contribute to both obesity and OP.

The DEGs in the TNF signaling pathway were primarily upregulated in obese mice, except for PIK3R1 and MMP9. This pathway exhibited an overall trend of upregulation in response to HFD. However, mannose supplementation was found to reverse the expression of DEGs in this pathway, leading to its downregulation. In ClueGO analysis, the pathway was not significantly enriched in HFD alone but became prominent with downregulated DEGS during mannose supplementation. TNF-α has been shown to contribute to the development of OP through RANK-L-mediated osteoclastogenesis. TNF-α levels were found to be elevated in

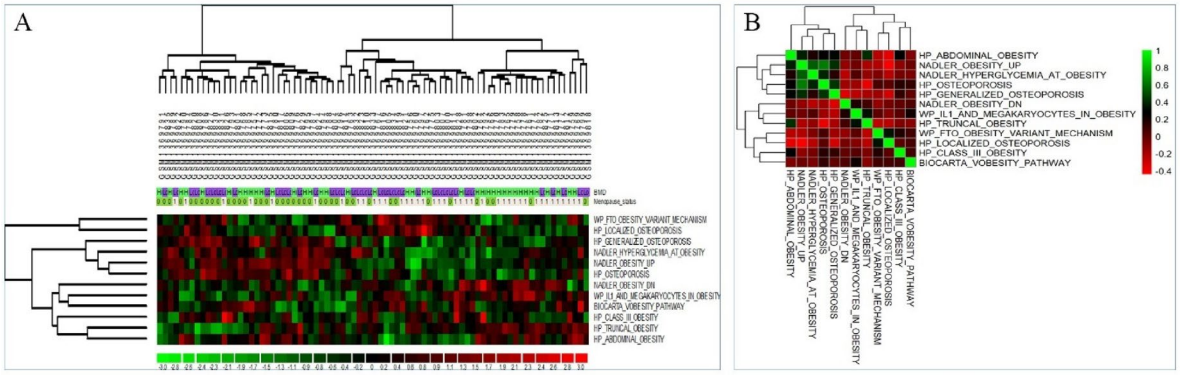


Fig. 7. Heatmaps from correlation analysis between obesity- and osteoporosis-related gene sets from MSigDB. (**A**) Heatmap of pathway activation Z-scores for obesity- and osteoporosis-related gene sets. (**B**) Heatmap showing the positive correlation between the HP_Osteoporosis gene set and the NADLER_Obesity_Up gene set, based on Z-score analysis.

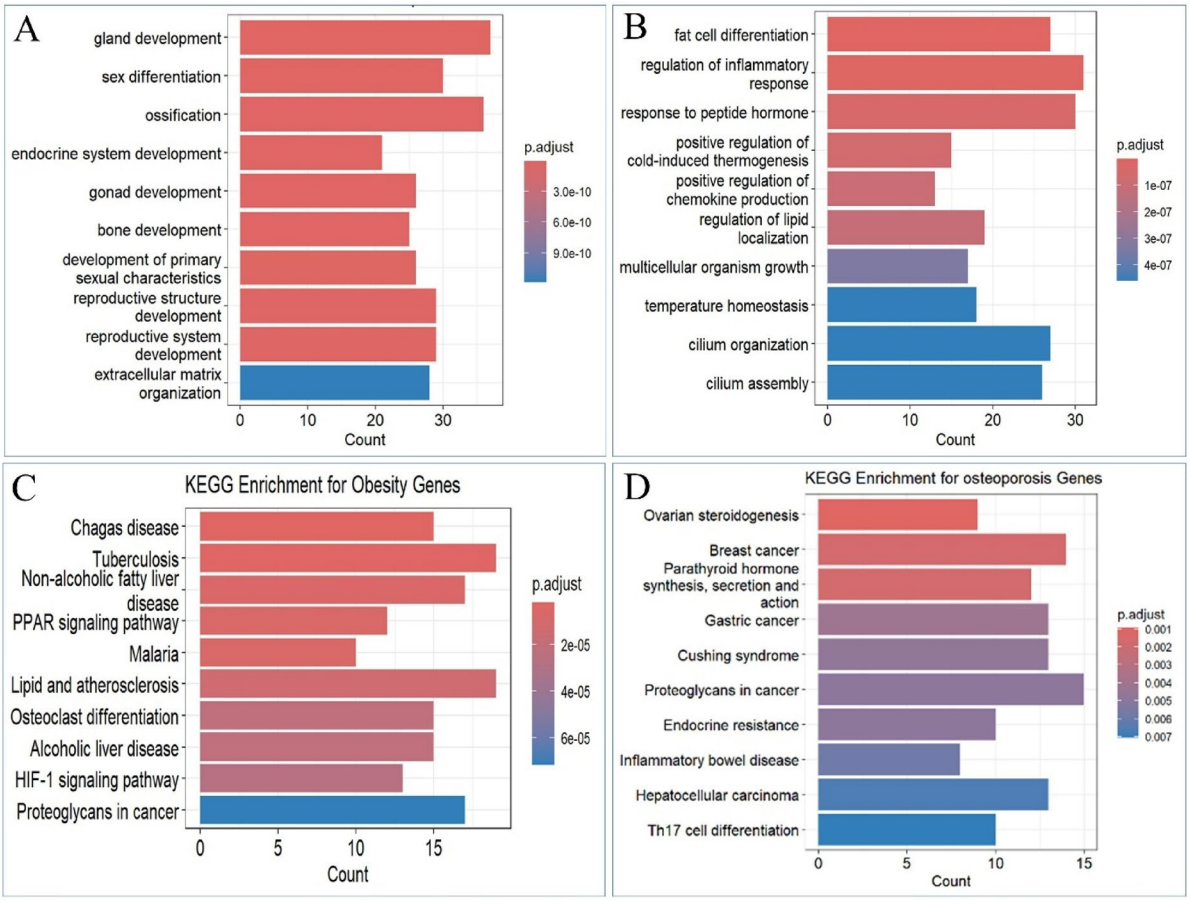


Fig. 8. (**A** & **B**) GO and (**C** & **D**) KEGG pathways enriched under correlation analyses of obesity- and osteoporosis-related gene sets from MSigDB. Bar plots showing significantly enriched Gene Ontology (GO) terms for Biological Processes (BP) alongside Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways.

postmenopausal women[47]. Postmenopausal women with obesity also show a higher risk of OP[48], suggesting a link between obesity and OP in this population through these pathways. Additionally, it is found that TNF-α increases the expression of sclerostin, which decreases bone mass in HFD-induced obese mice[49].

The DEGs in the inflammatory signaling pathway, Viral protein interaction with cytokine and cytokine receptor, were downregulated with mannose supplementation but upregulated with HFD. Enrichment of this

molecular pathway is attributed to the presence of chemokines, interleukins and TNF family members, whose levels and activity are altered in both obesity and OP[50–53]. Chronic low-grade inflammatory environment resulting from viral infections contributes to obesity, while the distinct chemokine profile established in obese individuals increases the susceptibility to viral infections[54,55]. White adipose tissue, a source of inflammatory interleukins, drives inflammation in obesity and is linked to conditions such as diabetes, hypertension and OP[56–58]. Studies have shown that pro-inflammatory cytokines accelerate bone loss in menopause[59] and inflammation profoundly impacts bone turnover[52,60,61]. If mannose supplementation can downregulate this pathway, it may help stabilise the body's inflammatory state, offering a protective effect against obesity and related metabolic disorders. Additionally, this pathway is enriched in gene set enrichment analysis of genes associated with OP.

Mannose supplementation also downregulates DEGs in several other inflammatory pathways, including cytokine-cytokine receptor interaction pathway, toll-like receptor signaling pathway, rheumatoid arthritis and chemokine signaling pathway. Inflammatory pathways that trigger an inflammatory response in the hypothalamus can lead to leptin resistance, a condition linked to obesity[62], and leptin resistance is also associated with reduced bone density[63]. The toll-like receptor pathway plays a key role in initiating obesity-induced inflammatory responses via various cytokines[64], many of which, as previously noted, contribute to bone loss and the development of OP. This connection highlights the link between obesity and OP, especially in post-menopausal and elderly populations. Bone marrow adipose tissue function is crucial in bone remodeling[65,66]. As the body shifts from a lean to an obese state due to a high-fat diet, obesity-associated inflammation is established through the production of inflammatory factors such as TNF-α, IL-6, IL-1β and MCP-1, which promote adipocyte generation. This process also involves CC Chemokine receptors CCR2 and CCR5[67,68]. Chemokines play a significant role in the pathogenesis of bone density reduction and OP. For instance, the chemokine CCL11 binds with high affinity to CCR3, which is overexpressed during osteoclast differentiation, thereby promoting bone resorption[69,70]. Based on enrichment analysis, mannose supplementation can downregulate genes within inflammatory pathways linked to the development of obesity and OP, and alter the expression of these pathways. Thus, mannose may serve as a promising therapeutic agent for the treatment of obesity, OP and associated conditions.

DEGs in the pathways Drug metabolism and Glutathione metabolism were upregulated with mannose supplementation. The KEGG Drug metabolism pathway is involved in the biodegradation of xenobiotics. Drug metabolism, which primarily occurs in the liver, directly affects the plasma concentrations of various drugs and depends on the presence and activity of liver enzymes, particularly cytochrome P450 and monoamine oxidase[71]. The activity of different Cytochrome P450 enzymes varies differently in the obese condition[72]. DEGs in the Drug metabolism pathway were downregulated in HFD-fed mice.

The KEGG pathway of osteoclast differentiation showed upregulated DEGs in HFD conditions and downregulated DEGs with mannose supplementation. This finding suggests that diet-induced obesity can disrupt bone remodeling, potentially leading to OP, while mannose supplementation may help address underlying factors associated with OP. Osteoclast differentiation is influenced by various cytokines, including follicle-stimulating hormone[73], several microRNAs—miRNA-133a[74], miRNA-483-5p[16], miRNA-338-3p[27], activated macrophages[75], estrogen deficiency[76] and many other factors. Additionally, DEGs associated with the inflammatory pathway, lipid and atherosclerosis, were downregulated during mannose supplementation, except HSPA2 and MAP2K7.

The pathways within the first MCODE cluster (Fig. 6) are primarily involved in the metabolism of drugs and xenobiotics, with most genes in these pathways upregulated by mannose supplementation. Pathways in the second and third MCODE clusters, identified as common to both obesity and OP through commonality analysis, are primarily immune pathways that contribute to the development of both conditions. Genes enriched in these pathways were generally downregulated with mannose supplementation. Many pathways involved in the pathophysiology of obesity and OP play functional roles in inflammation, immunity, endothelial dysfunction and angiogenesis[77] (Table 3).

The study identified significant enrichment of infectious pathways and cancer pathways (Table 3), likely due to various interconnected biological processes. Low-grade chronic inflammation is a common feature of metabolic diseases[78,79], which can increase the susceptibility to infectious diseases[80]. This chronic inflammatory state is also associated with various infectious diseases ([81–83] and cancers[84–86], which may explain the enrichment of infectious and cancer pathways in the analysis. These findings suggest that metabolic disorders heighten vulnerability to frequent infections and may predispose the body to cancer. Many immune system pathways are dysregulated in both obesity and OP. This shows that these metabolic disorders can lead to impaired immune function and vice versa. Altered immune responses in obesity, such as macrophage polarisation[87] and T-cell dysfunction[88] can increase the susceptibility to infectious diseases[89] and elevate cancer risk[90,91]. Additionally, many of the dysregulated pathways detected in high-fat diet-induced obesity are also associated with impaired bone remodeling, as indicated by previous in-silico studies[77]. Oxidative stress, a common feature of metabolic disorders, can further contribute to cancer initiation and progression over time[92]. Infections, in turn, may increase susceptibility to various metabolic disorders[93–95]. Chronic inflammation, oxidative stress and persistent viral infections contribute to immunosenescence, accelerating ageing[96] and raising the incidence of age-related metabolic disorders, including OP. Metabolic reprogramming observed during various infections and cancer[97,98] can further alter immune responses. Moreover, obesity and other metabolic disorders can disrupt the gut microbiome, which plays an important role in immunity[99]. Changes in the gut microbiome can increase susceptibility to infections and cancer[100,101].

Uncontrolled eating, a behaviour common among obese individuals, is comparable to the uncontrollable intake of ethanol[102] and may explain the enrichment of the pathway Alcoholism. This molecular pathway was found to be a shared element in the study. Carbohydrate craving, a characteristic seen in some forms of obesity, is linked to brain neurotransmitter serotonin and serum tryptophan levels[103]. The enrichment of the carbohydrate

digestion and absorption pathway as a shared element suggests that a diet high in carbohydrates may gradually contribute to the development of obesity-induced OP. In obesity, adipose tissue secretes complement proteins that influence lipid and glucose metabolism and promote low-grade chronic inflammation in the body[104]. Additionally, cysteine and methionine metabolism is closely associated with BMD and osteoclast activation[105]. Elevated plasma homocysteine levels are linked to atherogenesis[106] and subsequently to endothelial dysfunction. Since OP can develop secondary to endothelial dysfunction, this association is significant. Homocysteine is metabolised to cysteine, which is then incorporated into structural proteins and collagen[105].

Further, serum levels of amino acid metabolites of valine, leucine and isoleucine (branched-chain amino acids—BCAAs) have been found to have an inverse relationship with OP[107]. Biological processes such as the formation of immune complexes, the membrane attack complex, leukocyte trans endothelial migration, tissue injury and damage, that are integral to the disease pathway, Systemic lupus erythematosus, may contribute to endothelial dysfunction as well[108].

The correlation analysis using gene sets from the Molecular Signatures Database (MSigDB) highlights a significant prevalence of obesity- and OP-related gene activation in post-menopausal individuals, suggesting that hormonal changes during menopause amplify the molecular interplay between the two conditions. The higher proportion of individuals with low BMD showing elevated gene expression underscores the potential role of these pathways in bone health deterioration. A notable positive correlation between the HP_Osteoporosis and NADLER_Obesity_Up gene sets, with Macrophage Migration Inhibitory Factor (MIF) as a shared factor, indicates a crucial molecular link. MIF, known to regulate inflammation and metabolism, may play a dual role in both diseases, reflecting how chronic low-grade inflammation, characteristic of obesity, contributes to bone resorption in OP.

Enrichment analyses reveal distinct yet interconnected biological processes driving OP and obesity. For OP, processes such as ossification, bone development and extracellular matrix (ECM) organisation[109] underscore the importance of bone formation, remodeling and structural integrity in disease pathology. Hormonal regulation, particularly influenced by post-menopausal changes, significantly impacts bone health[110], as evidenced by enriched terms like sex differentiation, gonad development and endocrine system development.

Conversely, obesity-related processes such as fat cell differentiation and regulation of lipid localisation[111] emphasize the role of adipose tissue dysfunction in obesity's pathophysiology. Enriched pathways associated with inflammatory response regulation and chemokine production highlight the chronic low-grade inflammation characteristic of obesity[111,112]. Additionally, processes like cilium organisation point to the involvement of primary cilia as signaling hubs in metabolic pathways[113,114].

Shared mechanisms, including chronic inflammation, ECM remodeling, and hormonal dysregulation, provide insights into the molecular link between obesity and OP. The ECM serves as a scaffold for bone and adipose tissues, with proteoglycans mediating structural integrity and signal transduction[115,116]. In obesity, ECM remodeling is associated with adipogenesis and inflammation[116], while in OP, disruptions in ECM composition contribute to reduced BMD[117]. The shared role of proteoglycans in these processes highlights their potential as therapeutic targets.

The findings underscore proteoglycans and MIF as potential molecular bridges linking obesity and OP. Their involvement in adipogenesis, inflammation and bone degradation underscores the need for targeted therapeutic strategies. Osteoglycin, a proteoglycan primarily found in bone matrix, plays a critical role in linking bone health to energy metabolism by coordinating bone remodeling with changes in body fat levels and energy balance[118]. Research indicates that obesity can alter osteoglycin levels in mice. A negative association between bone mass and decreased level of circulating osteoglycin was reported in obese mice fed a high-fat diet[119]. The role of osteoglycin in bone health is not yet fully understood, with existing studies presenting conflicting evidence regarding its influence[120]. Beyond bone, osteoglycin is expressed in various tissues, including muscle and adipose tissue[118], underscoring its multifaceted role in metabolic and skeletal regulation.

Exploring the role of primary cilia in metabolic signaling and their contribution to the molecular interplay between these conditions could also yield valuable insights. Future research should focus on the detailed molecular underpinnings of these shared pathways, enabling the development of dual-targeted interventions to mitigate the impact of obesity-induced OP. In this in-silico analysis, we identified several pathways that link obesity and OP, reinforcing that obesity-related mechanisms may also contribute to OP risk. These findings suggest that strategies aimed at alleviating obesity, such as mannose supplementation, could potentially benefit OP management as well.

While cross-species analyses are commonly used to explore shared biological mechanisms, it is important to recognise that mice and humans have differences in gene expression, metabolism and bone biology. While our study provides valuable insights into the molecular interplay between obesity and osteoporosis, it is important to recognise the inherent limitations of cross-species comparisons. Transcriptomic data for obesity and mannose supplementation were derived from murine models (GSE110796), while osteoporosis-related gene expression profiles were sourced from human samples (GSE56815). Therefore, findings from mouse models need to be interpreted carefully when applied to human osteoporosis. Species-specific differences in gene expression and metabolic regulation can influence translational interpretation. Focusing on pathways conserved across species can help reduce the potential discrepancies. To address this, our analysis prioritised conserved inflammatory and metabolic pathways, such as IL-17 signaling, TNF signaling, osteoclast differentiation, and chemokine signaling[121–123], which are well-established to be functionally conserved across mice and humans. Furthermore, studies have shown that critical metabolic signaling pathways, such as the insulin/IGF-I pathway, are evolutionarily conserved from yeast to humans, supporting the validity of cross-species inferences in metabolic and ageing-related research[123]. Importantly, conserved features of inflammatory and matrix remodeling pathways, such as the expression of matrix metalloproteinases and the SASP factor CXCL-1, have been demonstrated in both human and murine cells under physiological conditions, further supporting the validity of cross-species

pathway analyses in metabolic and inflammatory research[124]. The focus on pathway-level, rather than single-gene correlations, minimises the impact of interspecies variation and enhances the biological relevance of the findings. Thus, despite the differences between species, our pathway-level approach strengthens the translational value of the findings. Nevertheless, we recognise that clinical studies and human validation models will be necessary to confirm the therapeutic potential of mannose supplementation in obesity-induced osteoporosis. While our study highlights the promising effects of mannose based on preclinical data, it is important to note that these findings have not yet been confirmed in human studies. Clinical evidence supporting the therapeutic utility of mannose exists in other contexts, such as urinary tract infections, where a pilot study demonstrated its potential to reduce UTI recurrence in women through anti-adhesive and immunomodulatory effects[125]. Dietary mannose supplementation is used in cases such as phosphomannomutase 2 deficiency[126]. Clinical trials will be crucial to understand whether mannose can offer similar benefits in people with obesity-related bone loss. To date, no clinical trials have examined the role of mannose in obesity or osteoporosis, highlighting a valuable opportunity for future human studies to validate its therapeutic potential.

While our analysis suggests that mannose may exert part of its effects through modulation of the gut microbiome, direct microbiome profiling or integration of metagenomic datasets was not performed in this study. The observed effects were inferred from host transcriptomic responses and existing literature. Future studies involving microbiome sequencing and functional validation will be critical to elucidate the precise gut microbiome changes underlying mannose-mediated protection against obesity-induced osteoporosis. D-mannose, the monosaccharide naturally present in fruits such as cranberries, grapes and apples[22], is generally regarded as safe and is commonly used as a dietary supplement, especially in urinary tract infections in women[127]. However, occasional reports of gastrointestinal discomfort[128], particularly at high doses or in sensitive individuals, highlights the need for careful consideration of dosage in future translational research focused on metabolic and bone health. Long-term supplementation of D-mannose has been explored in preclinical models with generally favourable outcomes. A five-month study in mice administering 20% D-mannose via drinking water reported no adverse effects on body weight, organ function, metabolism, or reproductive parameters, suggesting good tolerance even at high doses[26]. The study observed elevated blood and milk mannose levels without accompanying toxicity. However, more recent evidence indicates that chronic high-dose D-mannose intake may lead to behavioural changes, such as anxiety-like symptoms and memory impairments, potentially via hippocampal signaling pathways[129]. These findings emphasise the importance of carefully optimising mannose dosage and duration in future translational studies and clinical applications.

Conclusion

This study highlights significant pathways through which obesity and OP are interconnected, revealing potential shared mechanisms and therapeutic targets. Our study found a predominance of inflammatory pathways in the etiology of both obesity and OP, with the two conditions sharing 44 overlapping molecular pathways. The pathway, osteoclast differentiation, a key process in bone remodeling, was significantly enriched in both conditions. These findings reinforce the hypothesis that obesity and OP are interlinked through shared molecular mechanisms. Mannose supplementation in obese mice was observed to alter the expression of multiple genes involved in pathways associated with both conditions, particularly those related to inflammation. Additionally, genes involved in xenobiotic metabolism were upregulated with mannose supplementation. The study identified enrichment in infectious and cancer pathways, likely driven by low-grade chronic inflammation, a common feature of metabolic diseases. The pathways enriched in the study suggest that immune system dysregulation may play a role in both obesity and OP. This suggests that mannose could be a potential therapeutic strategy for alleviating both obesity and OP, especially in cases of obesity-induced OP. Mannose may also influence the gut microbiome, which plays a critical role in overall metabolism. However, further investigation is needed to determine whether the observed gene expression changes are directly mediated by mannose or indirectly through microbiome modulation. Together, these findings suggest that obesity-related mechanisms contribute to OP risk and underscore the importance of targeting shared pathways to alleviate both conditions. The study's findings indicate that therapeutic strategies for obesity, such as mannose supplementation, may offer potential benefits for managing OP as well, providing a promising avenue for future research and intervention. Correlation patterns between obesity- and OP-related gene sets from MSigDB highlight potential molecular targets, including MIF and ECM-related pathways, for therapeutic intervention in obesity-induced OP.

Data availability

Data is provided within the manuscript or supplementary information files.

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Author contributions

RJ & SKS designed the research framework and defined the objectives of the study. VK contributed to the development of the study's conceptual framework of the study. RJ & FP collected and curated the genomic data used in the study. RJ & APE performed the statistical analysis and interpretation of the genomic data. KNS, VS, FP & VK assisted in analysing the data and interpreting the results. APE and VK refined the methodology and ensured its alignment with the study objectives. SKS supervised the overall research project and guided the team. SKS ensured the availability of tools and software required for data analysis. RJ, VK & APE created visual representations of the data and results. RJ, VK & APE designed the figures and tables for the manuscript. RJ wrote the original draft. VK, VS, APE & FP contributed sections to the draft and provided critical input. All the authors reviewed and edited the manuscript for clarity and scientific rigor.

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