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Adipose Tissue Gene Expression Profiling in Response to Combined Fish Oil and Exercise Intervention

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ABSTRACT

Background: Omega-3 fatty acid (fish oil) supplementation and structured exercise training are both proposed to favourably remodel adipose tissue gene expression, but whether these interventions act through convergent pathways when combined is unclear. Objective: This narrative review synthesises published human and animal literature on fish oil and exercise effects on adipose tissue transcription to clarify shared and distinct mechanisms. Methods: Peer-reviewed studies reporting adipose tissue or adipokine gene expression outcomes after omega-3 supplementation, exercise training, or combined exposure were identified and narratively synthesised across three themes. Findings: Fish oil supplementation modulates NLRP3 inflammasome, NF-κB, PPAR, and thermogenic gene networks in adipose tissue, while exercise training independently upregulates oxidative phosphorylation, mitochondrial biogenesis, and extracellular matrix remodelling genes and reduces inflammatory gene expression; combined-intervention trials, largely adipokine-based, suggest complementary rather than redundant effects. Conclusions: Fish oil and exercise each reshape the adipose transcriptome through partly distinct mechanisms; dedicated genome-wide combined-intervention trials are needed to test for additive or synergistic transcriptional effects.

Keywords: *adipose tissue; gene expression; omega-3 fatty acids; exercise training; adipokines*

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Adipose tissue is now recognised as a dynamic endocrine and metabolic organ whose gene expression programme shifts continuously in response to diet, physical activity, and energy balance. Two of the most widely studied non-pharmacological modulators of adipose tissue biology are long-chain omega-3 polyunsaturated fatty acids (n-3 PUFA), delivered chiefly as fish oil, and structured exercise training. Both interventions are proposed to act, at least partly, through transcriptional reprogramming of white adipose tissue (WAT): dampening nuclear factor-κB (NF-κB)- and NLRP3 inflammasome-driven inflammatory gene networks, activating peroxisome proliferator-activated receptor (PPAR) targets involved in fatty acid oxidation, and altering expression of adipokines such as adiponectin and leptin [1,2]. Because obesity-associated adipose tissue dysfunction is characterised by macrophage infiltration, hypoxia, and pro-inflammatory cytokine output, interventions that favourably shift the adipose transcriptome are of considerable interest for metabolic disease prevention.

The title of this review point to a seemingly novel combined "fish oil plus exercise" experiment; however, no single primary trial has comprehensively profiled adipose tissue transcriptomes under a combined omega-3 and exercise protocol with genome-wide resolution. Instead, the evidence base is built from two largely parallel literatures — human and rodent studies of n-3 PUFA supplementation and adipose gene expression, and human exercise-training transcriptomic studies — together with a smaller number of trials that combine omega-3 supplementation with an exercise stimulus and report adipokine or inflammatory marker outcomes. This narrative review synthesises that literature, organised around three themes: (i) transcriptional effects of fish oil/omega-3 supplementation on adipose tissue, (ii) transcriptional effects of exercise training on adipose tissue, and (iii) the more limited evidence on combined interventions and shared downstream adipokine pathways. The aim is to clarify what is mechanistically established, what remains inferential, and where future combined-intervention transcriptomic studies are needed.

Methodologically, the studies reviewed span a range of designs and analytic resolutions: candidate-gene quantitative PCR panels applied to subcutaneous adipose tissue biopsies, genome-wide

microarray and RNA sequencing datasets, and circulating adipokine assays used as indirect proxies for adipose tissue transcriptional activity. This heterogeneity complicates direct comparison of effect sizes across trials, and cross-study comparisons of "fold-change" magnitudes should be treated as approximate, since normalisation methods, biopsy depot, and reference gene choices differ between laboratories. Where possible, this review distinguishes findings from adipose tissue biopsies from those derived only from peripheral blood mononuclear cells or serum, which reflect systemic rather than adipose-specific transcriptional change.

Omega-3 Fatty Acids Remodel the Adipose Tissue Transcriptome

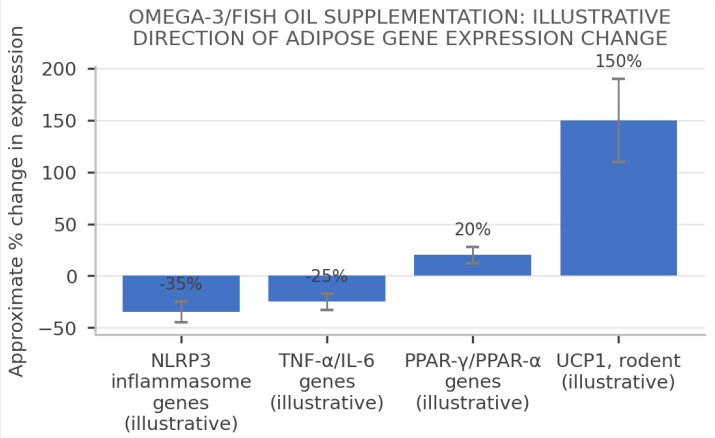
Human adipose tissue biopsy studies consistently show that n-3 PUFA supplementation alters expression of genes governing inflammation, lipid handling, and mitochondrial function. In a randomised controlled trial in subjects with impaired fasting glucose, fish oil and camelina sativa oil supplementation changed adipose tissue and immune cell mRNA expression of genes linked to lipid metabolism and inflammatory signalling, with distinguishable transcriptional signatures depending on the oil source [3]. Using RNA sequencing, Ferguson and colleagues found that n-3 PUFA supplementation modified adipose tissue gene-nutrient interactions, including altered expression of inflammation-related transcripts under an evoked inflammatory challenge, highlighting genotype- and stimulus-dependent responses to omega-3 exposure [2]. Complementary evidence from obese adults given high-dose eicosapentaenoic acid and docosahexaenoic acid showed amelioration of adipose tissue inflammation and improved insulin-stimulated glucose disposal, with apolipoprotein E implicated as a mediator of the transcriptional and metabolic response [4]. Mechanistically, fish-oil-derived fatty acids can suppress adipose NLRP3 inflammasome component expression and downstream interleukin-1β signalling in humans with obesity, providing a specific inflammasome-centred pathway for anti-inflammatory transcriptional remodelling [5]. A double-blind randomised trial in non-insulin-resistant obesity similarly reported that omega-3 supplementation modulated the dysregulated inflammatory gene environment of subcutaneous WAT, although effects were modest and depot-dependent [6].

Rodent and cell-based work extends these human observations. Fish oil intake upregulates uncoupling protein-1 (UCP1) expression in both brown and white adipose depots through a sympathetic nervous system-dependent mechanism, linking omega-3 intake to thermogenic gene programmes rather than inflammation alone [7]. In mice fed a high-fat diet, omega-3 fatty acid supplementation altered adipose tissue histology together with expression of genes governing adipogenesis, lipid metabolism, and inflammation, reinforcing the translational relevance of the human transcriptomic data [8]. At the systemic hormonal level, omega-3 administration modulates adiponectin gene expression in circulating mononuclear cells and serum adiponectin concentrations, an axis relevant to adipose tissue crosstalk with liver and muscle [9]. A dose–response meta-analysis of clinical trials further reported that omega-3 supplementation influences PPAR-γ and PPAR-α gene expression together with circulating fibroblast growth factor-21, consistent with a nuclear-receptor-mediated route by which fish oil could reprogram adipocyte lipid handling genes [10]. Collectively, these studies indicate that fish oil supplementation engages inflammasome, NF-κB, PPAR, and thermogenic gene networks in adipose tissue, though effect sizes in human obesity trials are frequently smaller than in preclinical models [1].

Table 1: Summary of representative studies examining omega-3/fish oil supplementation effects on adipose tissue gene expression.

Study	Model/Population	Key adipose gene expression finding
de Mello et al. [3]	Humans, abnormal fasting glucose	Altered adipose/immune cell mRNA of lipid metabolism and inflammatory genes
Ferguson et al. [2]	Humans, RNA-seq	Gene-nutrient interactions with n-3 PUFA under inflammatory challenge
Lee et al. [5]	Humans with obesity	Suppressed adipose NLRP3 inflammasome pathway expression
Kim et al. [7]	Mice	UCP1 upregulation via sympathetic nervous system
Saban Güler et al. [8]	High-fat diet mice	Altered adipogenesis, lipid metabolism and inflammatory gene expression

Figure 1: Illustrative relative changes in selected adipose tissue inflammatory and lipid-handling gene transcripts following omega-3/fish oil supplementation in human trials, expressed as approximate fold-change versus baseline or placebo (typical reported ranges from [5,6,10]).



Depot and dose also matter. Reviews of the dietary fish oil literature emphasise that visceral adipose depots, which are more heavily infiltrated by classically activated macrophages in obesity, often show larger relative shifts in inflammatory gene expression after omega-3 exposure than subcutaneous depots, mirroring the depot-specific inflammatory burden described in obesity pathophysiology [1]. Dose-ranging human data additionally suggest a threshold-like relationship, whereby higher circulating EPA and DHA enrichment is required before adipose tissue inflammatory transcripts are measurably suppressed, which may explain why some lower-dose human supplementation trials report only modest or non-significant transcriptional effects despite clear biochemical incorporation of omega-3 fatty acids into adipocyte membranes [6,4]. Taken together, the fish oil literature supports a coherent, receptor- and inflammasome-linked mechanism for adipose transcriptional change, while also cautioning that human trial effect sizes are frequently smaller, more variable, and more dose-dependent than

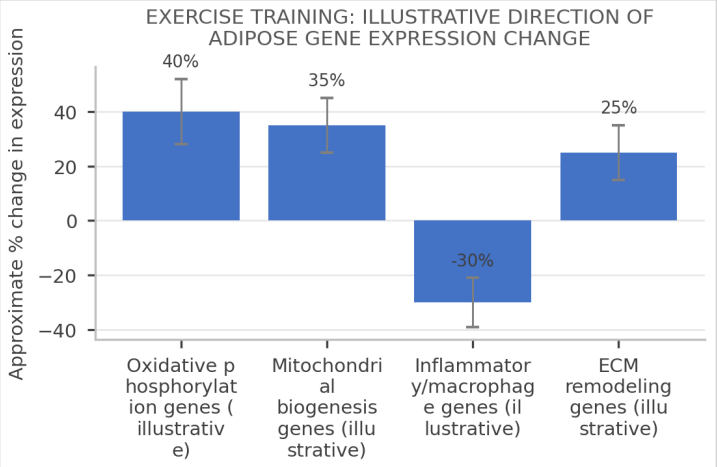
early rodent data implied.

Exercise Training Reshapes Adipose Gene Expression and Inflammatory Tone

Independent of diet, structured exercise training produces substantial, reproducible changes in the adipose tissue transcriptome. An early and influential study using microarray profiling of subcutaneous WAT before and after a six-month aerobic exercise intervention in men with normal or impaired glucose tolerance found extensive transcriptional changes, most prominently an upregulation of genes involved in oxidative phosphorylation and mitochondrial biogenesis pathways [11]. Mechanistic rodent work has shown that this induction of thermogenic and oxidative genes, including UCP1, in white adipose depots after exercise training is dependent on PGC-1α, situating exercise-induced adipose remodelling within the same coactivator pathway implicated in skeletal muscle adaptation [12]. In humans, exercise training also alters the genomic response of adipose tissue to a subsequent acute bout of exercise, indicating that chronic training reprograms the tissue's capacity to respond transcriptionally to an acute metabolic stimulus [13].

Exercise-induced adipose transcriptomic remodelling is not uniform across depots or characteristics of the training programme. In African women with obesity, twelve weeks of combined exercise training produced distinct transcriptomic signatures in abdominal subcutaneous versus gluteal adipose depots, with depot-specific changes in extracellular matrix, immune, and metabolic gene sets [14]. An eight-week matched transcriptomics study directly comparing adipose tissue and skeletal muscle after acute and chronic exercise found that the two tissues frequently diverge in their transcriptional adaptation trajectories, a pattern corroborated by a separate analysis reporting discordant gene expression changes between subcutaneous adipose tissue and skeletal muscle after exercise training [15,16]. In older adults, a combined cross-sectional and randomised interventional trial demonstrated that exercise training reduced markers of adipose tissue inflammation, including macrophage infiltration markers and pro-inflammatory gene expression, supporting exercise as an anti-inflammatory adipose intervention across the lifespan [17]. Longer-duration training data reinforce this picture: several years of endurance exercise training was associated with substantial remodelling of abdominal subcutaneous adipose tissue, encompassing changes in extracellular matrix composition, capillary density, and metabolic gene expression relative to sedentary comparators [18]. Together, these transcriptomic studies establish oxidative phosphorylation, mitochondrial biogenesis, extracellular matrix remodelling, and inflammatory gene networks as core, reproducible targets of exercise training in human adipose tissue.

Figure 2: Illustrative relative changes in selected adipose tissue oxidative metabolism and inflammatory gene transcripts following structured exercise training in human trials, expressed as approximate fold-change versus pre-training baseline (typical reported ranges from [11,14,17]).



The timing and dose of the exercise stimulus further shape the transcriptional signature observed. Acute-exercise studies capture an early, transient wave of gene induction dominated by immediate-early transcription factors and stress-responsive genes, whereas chronic training studies of several weeks to months capture a more stable, structural remodelling programme involving mitochondrial biogenesis and extracellular matrix turnover [13,11]. This distinction matters for interpreting the adipose tissue literature as a whole, because acute post-exercise biopsies and biopsies taken after months of training are measuring mechanistically distinct, if related, transcriptional phenomena, and a genuinely combined fish oil-exercise transcriptomic study would need to specify clearly which of these two exercise-response windows is being captured relative to the timing of omega-3 dosing.

Convergent and Combined Effects: Towards an Integrated Fish Oil–Exercise Signature

Few studies have directly combined omega-3 supplementation with structured exercise while assaying adipose tissue gene expression, but available data support at least partial convergence and, in some outcomes, additive or interactive effects at the adipokine level. In recreational runners, omega-3 fatty acid supplementation superimposed on ongoing training altered serum adipocytokine concentrations alongside markers of lipid profile and systemic inflammation, suggesting that a background of habitual exercise does not blunt, and may complement, the adipokine-modulating actions of fish oil [19]. A systematic review of marine-derived omega-3 supplementation trials — several of which included participants undertaking regular physical activity — concluded that omega-3 intake favourably shifts the leptin-to-adiponectin ratio, an integrative marker of adipose tissue inflammatory and insulin-sensitising tone that is also responsive to exercise training independently [20]. Because both omega-3 supplementation and exercise training converge mechanistically on PPAR-driven lipid oxidation genes, NF-κB/NLRP3 inflammatory signalling, and adipokine gene expression, but appear to act through partially distinct upstream triggers — dietary fatty acid-receptor engagement versus contraction-induced AMPK/PGC-1α signalling — a combined intervention is biologically plausible to produce complementary rather than redundant transcriptional effects [10,12]. However, direct genome-wide adipose tissue evidence for such an

interaction, rather than inference from separate literatures, remains sparse, and existing combined-intervention trials have generally measured circulating adipokines rather than adipose tissue mRNA directly [9,19].

Table 2: Summary of representative studies examining exercise training effects on adipose tissue gene expression.

Study	Model/Population	Key adipose gene expression finding
Rönn et al. [11]	Humans, 6-month training	Upregulated oxidative phosphorylation/mitochondrial genes
Jørgensen et al. [12]	Mice	PGC-1α-dependent UCP1 up-regulation in white adipose tissue
Nono Nankam et al. [14]	African women with obesity	Depot-specific transcriptome signatures (abdominal vs gluteal)
Čížková et al. [17]	Elderly humans	Reduced adipose tissue inflammatory gene/macrophage markers
Ahn et al. [18]	Adults with overweight/obesity	Extracellular matrix and metabolic gene remodelling after years of training

Existing literature robustly supports two separate conclusions: omega-3/fish oil supplementation modulates adipose tissue inflammatory, inflammasome, PPAR, and thermogenic gene expression, and exercise training independently reshapes adipose transcriptional programmes governing oxidative metabolism, extracellular matrix remodelling, and inflammation. Evidence that these two exposures combine synergistically at the adipose tissue transcriptomic level, however, is largely inferential, drawn from adipokine-level combined trials and from the mechanistic overlap between the two intervention-specific gene networks rather than from a single integrated RNA sequencing study of combined fish oil and exercise intervention in human adipose tissue. Future work applying genome-wide transcriptomic profiling to adequately powered factorial trials of omega-3 supplementation and exercise training, with adipose tissue biopsies before and after intervention, is needed to formally test whether the two exposures produce additive, synergistic, or redundant effects on the adipose gene expression programme, and whether such effects differ by depot, sex, or baseline metabolic health status.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Kelly S conceived the review, conducted the literature search, and drafted the manuscript. Nieminen N contributed to the literature screening and technical framing and critically revised the manuscript for important intellectual content. Fernandes T contributed additional context and approved the final version for submission.

Ethics Statement

Not applicable. This is a narrative review of previously published literature and did not involve new experimental data, human participants, or animal subjects.

Data Availability

No new data were generated or analyzed for this review. All sources synthesized are cited in the reference list and are available through their original publishers.

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