KMANPUB | Health Nexus Vol. 4 No. 4 (2026): 1-12

Article history:
Received 10 April 2026
Revised 07 July 2026
Accepted 15 July 2026
Initial Publication 26 July 2026
Final Publication 01 October 2026

Independent and Interactive Effects of Combined Aerobic–Resistance Training and Coenzyme Q10 Supplementation on Amyloidogenic Pathway Markers and IDE-Dependent Amyloid Clearance in the Hippocampus of Male Wistar Rats With Amyloid-β-Induced Alzheimer-Like Pathology

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A r t i c l e I n f o

Article type:
Original Research

How to cite this article:
Soleimani Naeini, P., Banaei Borojeni, J., & Sarrami, L. (2026). Independent and Interactive Effects of Combined Aerobic–Resistance Training and Coenzyme Q10 Supplementation on Amyloidogenic Pathway Markers and IDE-Dependent Amyloid Clearance in the Hippocampus of Male Wistar Rats With Amyloid-β-Induced Alzheimer-Like Pathology. *Health Nexus, 4*(4), 1-12.
https://doi.org/10.61838/kman.hn.5837

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A B S T R A C T

Alzheimer-like pathology is associated with increased amyloid-β production and impaired peptide clearance. This study investigated the independent and interactive effects of combined aerobic-resistance training and coenzyme Q10 supplementation on hippocampal markers of amyloidogenic processing and insulin-degrading enzyme (IDE)-dependent clearance. Forty-eight male Wistar rats were allocated to six groups (n = 8): healthy control, sham, Alzheimer-like pathology, Alzheimer-like pathology plus combined training, Alzheimer-like pathology plus coenzyme Q10, and Alzheimer-like pathology plus combined training and coenzyme Q10. Alzheimer-like pathology was induced by intracerebroventricular Aβ1-42 administration. The combined training protocol and a diet containing 0.4% coenzyme Q10 were applied for 12 weeks. Hippocampal APP, BACE1, PSEN1, and IDE gene expression was measured by real-time PCR; Aβ42 concentration was measured by ELISA; and IDE activity was determined enzymatically. One-way ANOVA with Tukey testing and 2 × 2 two-way ANOVA were used. Model induction significantly increased APP, BACE1, PSEN1, and Aβ42 and reduced IDE expression and activity. Training and coenzyme Q10 each significantly attenuated all alterations. The combined-intervention group showed the most favorable means across all outcomes. Significant training-by-supplementation interactions were observed for BACE1 and Aβ42, but not for APP, PSEN1, IDE expression, or IDE activity. Combined aerobic-resistance training and coenzyme Q10 supplementation improved the balance between markers related to amyloid production and IDE-dependent clearance in this rat model. The findings are limited to hippocampal molecular outcomes in an experimentally induced Alzheimer-like condition and require confirmation using protein-level, histological, cognitive, and translational assessments.

Keywords: *Alzheimer-like pathology; amyloid-β; combined training; coenzyme Q10; hippocampus; insulin-degrading enzyme*

1. Introduction

Alzheimer's disease is a progressive neurodegenerative disorder and the most common cause of dementia. Its clinical course is characterized by deterioration in memory and other cognitive domains, while its neuropathology includes extracellular amyloid-β deposition, intracellular tau pathology, synaptic dysfunction, neuroinflammation, and progressive neuronal loss. The hippocampus is particularly relevant because it supports the encoding, organization, and consolidation of episodic and spatial information and is among the earliest regions to exhibit structural and functional disruption during Alzheimer's disease (1, 2). Although the disorder is biologically heterogeneous, altered amyloid metabolism remains an important component of the pathological cascade and a major target of mechanistic investigation (3).

Amyloid-β peptides are generated from amyloid precursor protein (APP) through sequential proteolytic processing. In the amyloidogenic pathway, β-site APP-cleaving enzyme 1 (BACE1) performs the initial β-secretase cleavage, generating a membrane-associated fragment that is subsequently processed by the γ-secretase complex. Presenilin 1, encoded by PSEN1, contributes the catalytic core of γ-secretase. This sequence produces amyloid-β peptides of different lengths, including Aβ42, which has a high tendency to aggregate and is strongly linked to amyloid plaque formation and oligomer-mediated synaptic toxicity (4, 5). Expression of APP, BACE1, or PSEN1 does not by itself prove increased enzymatic activity or complete pathway flux; however, simultaneous evaluation of these transcripts together with a downstream peptide such as Aβ42 provides a broader indication of the direction of amyloidogenic change.

Brain amyloid burden is determined not only by production but also by degradation and removal. Insulin-degrading enzyme is a zinc metalloprotease capable of degrading several short peptides, including amyloid-β. Experimental reduction or deletion of IDE impairs amyloid-β degradation and increases cerebral peptide accumulation, whereas enhanced IDE availability may support extracellular and intracellular clearance pathways (6, 7). Because IDE also participates in insulin metabolism, its role is especially relevant to the intersection between metabolic dysfunction and Alzheimer-related pathology. Nevertheless, IDE represents only one component of amyloid clearance; neprilysin activity, autophagic-lysosomal processing, microglial uptake, vascular transport, and glymphatic exchange also contribute. Therefore, concurrent measurement of IDE expression, IDE enzymatic activity, and Aβ42 offers useful but not exhaustive information about amyloid clearance.

Regular exercise is a non-pharmacological intervention with broad effects on metabolic regulation, cerebral perfusion, neurotrophic signaling, oxidative balance, inflammation, synaptic plasticity, and mitochondrial function. In transgenic animal models, voluntary or structured exercise has been associated with lower amyloid burden and improved cognitive performance (8, 9). Aerobic and resistance exercise do not produce identical adaptations. Aerobic activity strongly challenges cardiorespiratory and oxidative metabolism, whereas resistance exercise provides mechanical and neuromuscular stimuli that can influence insulin sensitivity, growth-factor signaling, and tissue remodeling. Experimental evidence indicates that both modalities may support memory through partially distinct molecular pathways (10). A combined aerobic-resistance protocol may therefore engage a wider range of protective adaptations than either modality alone, although the molecular response depends on training intensity, duration, progression, recovery, and disease model.

Coenzyme Q10 is an endogenous lipid-soluble quinone that participates in mitochondrial electron transfer and exists in oxidized and reduced forms. It supports oxidative phosphorylation and contributes to antioxidant protection of cellular membranes and lipoproteins. Coenzyme Q10 status and redox cycling are therefore relevant to tissues with high energy demand, including the brain (11, 12). Mitochondrial dysfunction and oxidative stress can amplify amyloidogenic processing, impair proteostasis, and weaken synaptic resilience. Supplementation with coenzyme Q10 may partly counter these disturbances by supporting electron transport and limiting oxidative damage. However, its effects are influenced by formulation, bioavailability, dose, duration, tissue distribution, and the biological model, and antioxidant activity should not be assumed to normalize every component of Alzheimer-like pathology.

Exercise and coenzyme Q10 may act through complementary mechanisms. Exercise can improve

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E-ISSN: 2981-2569

systemic and neural metabolic regulation, activate endogenous antioxidant defenses, and induce neurotrophic and vascular adaptations. Coenzyme Q10 can directly support mitochondrial electron transfer and membrane-associated antioxidant capacity. Their combination might consequently produce additive or interactive effects on amyloid production and clearance. An interaction is statistically distinct from simple numerical superiority: a combined group may have the most favorable mean because the two main effects accumulate, whereas a significant interaction indicates that the effect of one intervention depends on the presence of the other. This distinction is important when evaluating combined interventions.

Previous studies have commonly examined exercise or coenzyme Q10 separately or have focused on oxidative stress, neurotrophic factors, histological amyloid burden, or behavioral outcomes. Less information is available regarding the independent and interactive effects of combined aerobic-resistance training and dietary coenzyme Q10 on a coordinated set of hippocampal markers that includes APP, BACE1, PSEN1, Aβ42, and both the expression and activity of IDE. The present study therefore evaluated these outcomes in male Wistar rats with intracerebroventricular Aβ1-42-induced Alzheimer-like pathology. It was hypothesized that training and coenzyme Q10 would each reduce markers related to amyloidogenic processing, increase IDE expression and activity, and that the simultaneous intervention would produce the most favorable pattern. Training-by-supplementation interactions were tested separately for each outcome.

2. Methods and Materials

3. Study design

This quantitative, controlled laboratory experiment used a six-group posttest design. The independent variables were combined aerobic-resistance training and coenzyme Q10 supplementation. The dependent variables were hippocampal APP, BACE1, PSEN1, and IDE gene expression, IDE enzymatic activity, and Aβ42 concentration. Sample size was determined with reference to the six-group design, comparable animal studies, an expected effect size, a two-sided alpha level of .05, and statistical power of at least 80%.

3.1. Animals and housing

Forty-eight male Wistar rats, 8–10 weeks old and initially weighing 220–280 g, were obtained from an accredited breeding center. Animals were acclimatized to the laboratory for seven days and housed at 22 ± 2 °C, 45%–65% relative humidity, and a 12:12-hour light-dark cycle, with free access to water and standard laboratory chow. General health, body mass, food intake, and signs of stress or illness were monitored throughout the study. Healthy animals without motor impairment were eligible. Severe illness, infection, surgical injury, abnormal weight loss, persistent inability to perform training, or an unsuitable tissue sample constituted exclusion criteria.

3.2. Group allocation

After acclimatization, rats were randomly allocated, with initial body mass considered during allocation, to six groups of eight: healthy control (HC), sham, Alzheimer-like pathology (AD), Alzheimer-like pathology plus combined training (AD+CT), Alzheimer-like pathology plus coenzyme Q10 (AD+Q10), and Alzheimer-like pathology plus combined training and coenzyme Q10 (AD+CT+Q10). The healthy control group received neither surgery nor intervention. The sham group underwent anesthesia, surgery, and intracerebroventricular administration of the peptide vehicle. The AD group underwent model induction without subsequent training or supplementation. The three intervention groups received combined training, coenzyme Q10, or both after model induction. Base diet, housing, routine handling, and tissue-collection timing were standardized across groups.

3.3. Induction of Alzheimer-like pathology

Oligomeric Aβ1-42 was prepared in the specified vehicle and incubated under controlled conditions according to the manufacturer's instructions and the approved laboratory protocol. Rats were anesthetized with ketamine and xylazine and fixed in a stereotaxic apparatus. The lateral-ventricle injection site was determined relative to bregma using a rat-brain atlas. Aβ1-42 was administered intracerebroventricularly at a fixed volume, concentration, and rate defined by the approved protocol. The needle remained in position briefly after administration to reduce

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backflow. Sham animals received the same volume of vehicle without peptide. Animals were monitored until complete recovery, and interventions began after stabilization. The procedure was treated as an amyloid-β-induced Alzheimer-like injury model rather than as a model reproducing the full chronic human disease.

3.4. *Combined training protocol*

Combined training was conducted for 12 weeks and included three weekly aerobic swimming sessions and two weekly resistance ladder-climbing sessions on separate days at a consistent time within the light cycle. At least one rest day was provided each week. Swimming was performed in water maintained at 30–33 °C. Duration progressed from 5–15 minutes during week 1 to 20, 30, and 45 minutes during weeks 2–4, respectively, and reached 60 minutes during weeks 5–9. During weeks 10–12, volume overload was introduced by progressively increasing the number of swimming bouts while allowing recovery. Rats were dried after each session, and tolerance and signs of excessive fatigue were monitored.

3.5. *Resistance training*

Resistance exercise used an approximately 1-m ladder with 26 rungs positioned at an 85° incline. Following one week of familiarization without external load, training load progressed from 30% of body mass in week 2 to 70%–90% during weeks 3–5, 100%–110% during weeks 6–8, 120%–130% during weeks 9–10, and 140%–150% during the final two weeks. Each session consisted of three sets of four climbs. Rest intervals were 30–60 seconds between climbs and 120–150 seconds between sets. Body mass was measured weekly and the load was adjusted accordingly. Sessions were stopped when persistent inability or severe fatigue was observed.

3.6. *Coenzyme Q10 supplementation*

Coenzyme Q10 of laboratory-grade purity was uniformly incorporated into standard chow at 0.4% by weight. The supplemented feed was prepared at regular intervals and stored in opaque containers under dry, temperature-controlled conditions. The amount offered and remaining was recorded to estimate food consumption. Supplemented groups received the coenzyme Q10-containing diet daily from the beginning of the intervention through the end of week 12. The nonsupplemented groups received a diet with a comparable base composition and energy content.

3.7. *Tissue collection*

Forty-eight hours after the final training session, all animals were sampled at the same time of day after standardized fasting. Rats were anesthetized with ketamine and xylazine, and the brain was rapidly removed. The hippocampi from both hemispheres were dissected on a cold surface. Comparable tissue portions were allocated to gene-expression analysis, Aβ42 measurement, and IDE activity assessment, immediately frozen in liquid nitrogen, and stored at −80 °C until analysis. Tissue collection and laboratory assays were performed using coded samples.

3.8. *Gene-expression analysis*

Total RNA was extracted from hippocampal tissue. Concentration and purity were evaluated by spectrophotometry using 260/280 and 260/230 absorbance ratios. Complementary DNA was synthesized, and APP, BACE1, PSEN1, and IDE expression was quantified by real-time PCR using SYBR Green master mix, gene-specific primers, and a validated reference gene. Amplification specificity was evaluated by melting-curve analysis and no-template controls. Relative expression was calculated using the $2^{-\Delta\Delta Ct}$ method with the healthy control group as calibrator. ΔCt values were used for statistical analysis, whereas relative fold-change values were used for biological presentation.

3.9. *Aβ42 and IDE activity*

A fixed amount of hippocampal tissue was homogenized in cold buffer containing a protease inhibitor. After centrifugation, Aβ42 in the supernatant was quantified using a rat-specific ELISA, calculated from a standard curve, and normalized to total protein. IDE activity was measured in hippocampal homogenate using a specific fluorogenic-substrate assay and was expressed relative to total protein as nmol/min/mg protein. Samples were distributed randomly across assay plates and analyzed with consistent technical replication using calibrated equipment. The investigator

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E-ISSN: 2981-2569

conducting the assays was unaware of group assignment, and the animal was the independent statistical unit.

3.10. Statistical analysis

Data were analyzed in SPSS version 27 and are reported as mean ± standard deviation. Normality was examined using the Shapiro-Wilk test and homogeneity of variance using Levene's test. One-way analysis of variance followed by Tukey's post hoc test compared the six groups. The four Alzheimer-like groups were then entered into a 2 × 2 two-way ANOVA to evaluate the main effect of training, the main effect of coenzyme Q10, and the training × supplementation interaction for each outcome. When an interaction was significant, simple effects were examined with adjustment for multiple comparisons. Partial eta squared was reported as the effect-size measure, 95% confidence intervals were considered in interpretation, and $P < .05$ was defined as statistically significant.

4. Findings and Results

The Shapiro-Wilk test confirmed normal distributions and Levene's test confirmed homogeneity of variance. One-way ANOVA with Tukey's post hoc test was therefore used to compare the six groups. Main effects of training and coenzyme Q10 and the training × supplementation interaction were examined in the four Alzheimer-like groups using 2 × 2 two-way ANOVA. Data from all eight animals in each group were included in the final analysis.

One-way ANOVA showed significant between-group differences in APP, BACE1, and PSEN1 gene expression and Aβ42 concentration. As presented in Table 1, APP, BACE1, PSEN1, and Aβ42 were significantly higher in the AD group than in the healthy control and sham groups. Both combined training and coenzyme Q10 reduced these outcomes, and the lowest values among the Alzheimer-like groups were observed in the AD+CT+Q10 group.

Table 1

Comparison of APP, BACE1, and PSEN1 gene expression and Aβ42 concentration among the study groups

Group	APP, relative expression	BACE1, relative expression	PSEN1, relative expression	Aβ42, pg/mg protein
Healthy control	1.00 ± 0.12^{a}	1.00 ± 0.13^{a}	1.00 ± 0.11^{a}	44.3 ± 5.1^{a}
Sham	1.04 ± 0.14^{a}	1.03 ± 0.12^{a}	1.02 ± 0.13^{a}	45.7 ± 5.4^{a}
Alzheimer-like control	2.45 ± 0.28^{d}	2.72 ± 0.31^{d}	2.25 ± 0.27^{d}	108.6 ± 10.8^{d}
Alzheimer-like + training	1.68 ± 0.22^{c}	1.79 ± 0.24^{c}	1.58 ± 0.21^{c}	72.4 ± 8.2^{c}
Alzheimer-like + Q10	1.82 ± 0.24^{c}	1.93 ± 0.25^{c}	1.69 ± 0.22^{c}	79.1 ± 8.7^{c}
Alzheimer-like + training + Q10	1.28 ± 0.18^{b}	1.37 ± 0.19^{b}	1.24 ± 0.17^{b}	56.8 ± 6.5^{b}
F	58.76	72.02	49.22	80.01
P	< .001	< .001	< .001	< .001
Partial eta squared	.875	.896	.854	.905

Note. Values are mean ± standard deviation. Different superscript letters within a column indicate a significant difference based on Tukey's post hoc test at $P < .05$.

Figure 1 displays the mean and standard error for APP, BACE1, PSEN1, and Aβ42. The Alzheimer-like condition increased all four outcomes, whereas training and coenzyme Q10, particularly when administered together, reduced them.

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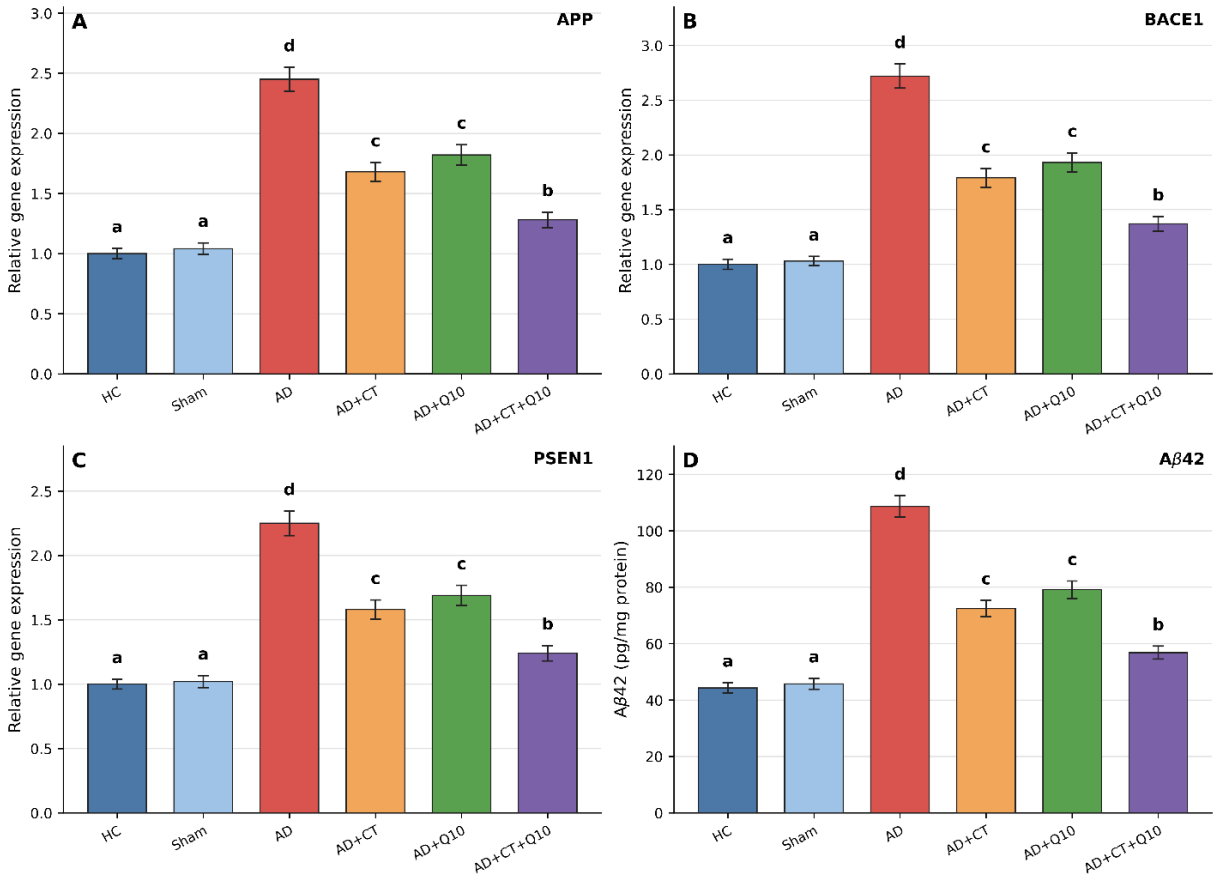
Figure 1

Changes in APP, BACE1, and PSEN1 gene expression and Aβ42 concentration across the six study groups.



Bars represent means and error bars represent standard errors. Bars with different letters differ significantly at P < .05. HC, healthy control; AD, Alzheimer-like pathology; CT, combined training.

One-way ANOVA also showed significant differences in IDE gene expression and IDE enzymatic activity. As shown in Table 2, induction of the Alzheimer-like model significantly decreased both IDE expression and activity. Training and coenzyme Q10 increased both outcomes, and the highest IDE expression and activity among the Alzheimer-like groups occurred in the combined-intervention group.

Table 2

Comparison of IDE gene expression and enzymatic activity among the study groups

Group	IDE, relative gene expression	IDE activity, nmol/min/mg protein
Healthy control	1.00 ± 0.11^{d}	6.80 ± 0.62^{d}
Sham	0.98 ± 0.12^{d}	6.70 ± 0.66^{d}
Alzheimer-like control	0.48 ± 0.08^{a}	3.10 ± 0.44^{a}
Alzheimer-like + training	0.75 ± 0.10^{c}	5.20 ± 0.55^{c}
Alzheimer-like + Q10	0.68 ± 0.09^{bc}	4.70 ± 0.51^{b}
Alzheimer-like + training + Q10	0.91 ± 0.12^{d}	6.10 ± 0.60^{d}
F	29.92	49.35
P	< .001	< .001
Partial eta squared	.781	.855

Note. Values are mean ± standard deviation. Different superscript letters within a column indicate a significant difference based on Tukey's post hoc test at P < .05.

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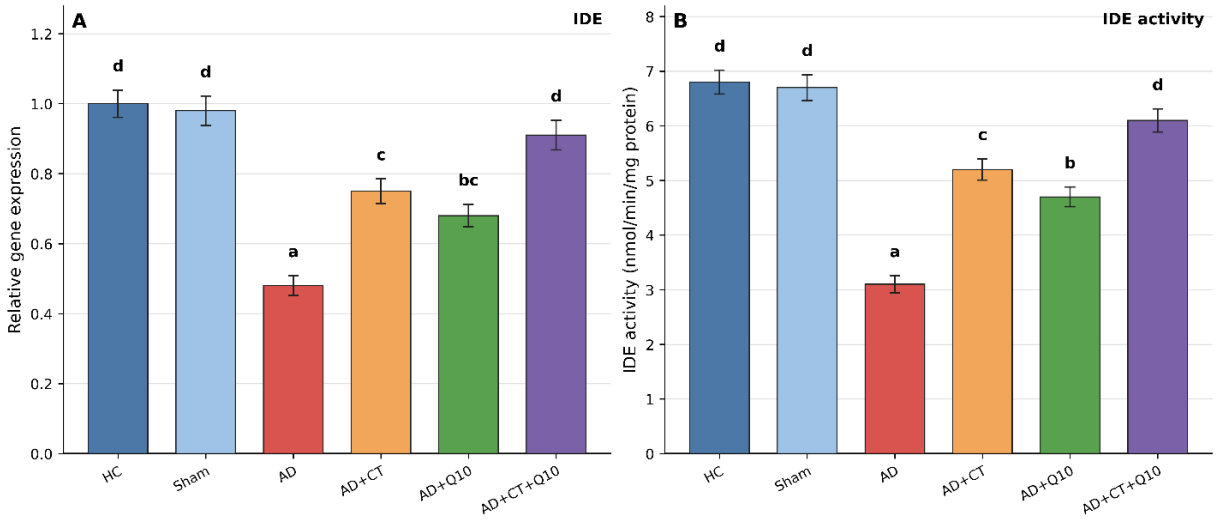
Figure 2 illustrates the mean and standard error for IDE gene expression and enzymatic activity. Both outcomes were reduced in the AD group and improved following training and coenzyme Q10, with the greatest improvement in the AD+CT+Q10 group.

Figure 2

Changes in IDE gene expression and IDE enzymatic activity across the six study groups.



Bars represent means and error bars represent standard errors. Bars with different letters differ significantly at P < .05. HC, healthy control; AD, Alzheimer-like pathology; CT, combined training.

The four Alzheimer-like groups were entered into two-way ANOVA to test the main effect of training, the main effect of coenzyme Q10, and the training × supplementation interaction. As presented in Table 3, the main effects of training and coenzyme Q10 were significant for every outcome. The interaction was significant only for BACE1 and Aβ42 and did not reach significance for APP, PSEN1, IDE expression, or IDE activity.

Table 3

Two-way analysis of variance for the effects of combined training and coenzyme Q10

Outcome	Effect	F	P	Partial eta squared
APP	Training	63.32	< .001	.693
	Q10	39.15	< .001	.583
	Training × Q10	1.95	.174	.065
BACE1	Training	70.40	< .001	.715
	Q10	46.42	< .001	.624
	Training × Q10	4.34	.047	.134
PSEN1	Training	51.65	< .001	.648
	Q10	33.35	< .001	.544
	Training × Q10	1.99	.169	.066
Aβ42	Training	90.71	< .001	.764
	Q10	53.91	< .001	.658
	Training × Q10	5.12	.032	.155
IDE expression	Training	51.41	< .001	.647
	Q10	26.65	< .001	.488
	Training × Q10	0.33	.570	.012
IDE activity	Training	87.80	< .001	.758
	Q10	44.79	< .001	.615
	Training × Q10	3.51	.071	.111

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Because the interaction was significant for BACE1 and Aβ42, simple effects were examined with adjustment for multiple comparisons (Table 4). Training and coenzyme Q10 each reduced BACE1 and Aβ42 relative to the AD group. The difference between the two single interventions was not significant; however, simultaneous training and coenzyme Q10 produced lower values than either intervention alone.

Table 4

Simple-effect comparisons for BACE1 and Aβ42

Comparison	BACE1 mean difference	BACE1 P	Aβ42 mean difference	Aβ42 P
AD vs AD + training	0.93	< .001	36.2	< .001
AD vs AD + Q10	0.79	< .001	29.5	< .001
AD vs AD + training + Q10	1.35	< .001	51.8	< .001
AD + training vs AD + Q10	−0.14	.378	−6.7	.214
AD + training vs AD + training + Q10	0.42	.004	15.6	.002
AD + Q10 vs AD + training + Q10	0.56	< .001	22.3	< .001

Note. Positive values indicate a higher mean in the first group, and negative values indicate a lower mean in the first group. P values were adjusted for multiple comparisons. AD, Alzheimer-like pathology.

Overall, induction of Alzheimer-like pathology increased markers associated with amyloidogenic processing and reduced IDE expression and activity. Combined training and coenzyme Q10 independently attenuated these alterations, and the most favorable pattern was observed when the interventions were administered together.

5. Discussion

The present study examined the independent and interactive effects of 12 weeks of combined aerobic-resistance training and dietary coenzyme Q10 on hippocampal markers related to amyloid production and IDE-dependent degradation in male Wistar rats with Aβ1-42-induced Alzheimer-like pathology. Model induction increased APP, BACE1, PSEN1, and Aβ42 while reducing IDE gene expression and enzymatic activity. Each intervention significantly shifted all outcomes toward the healthy pattern, and the combined-intervention group showed the most favorable mean for every measured variable. Two-way analysis, however, identified significant interactions only for BACE1 and Aβ42. Thus, the results support independent effects of training and coenzyme Q10 across all outcomes and an interaction specifically at a key β-secretase-related marker and its downstream amyloid peptide.

The molecular pattern observed after Aβ1-42 administration is consistent with disruption of the balance between amyloid production and clearance. APP provides the substrate for amyloidogenic processing, BACE1 initiates the β-secretase pathway, and PSEN1 contributes to γ-secretase-mediated cleavage. The simultaneous elevation of these transcripts, together with the large increase in hippocampal Aβ42, indicates coordinated movement in an amyloidogenic direction. This interpretation remains appropriately limited because messenger-RNA expression is not equivalent to protein abundance, enzyme activity, substrate accessibility, or complete APP-processing flux. Nevertheless, agreement between transcript-level changes and the downstream Aβ42 measurement strengthens the biological coherence of the result. The absence of meaningful differences between the healthy control and sham groups further suggests that anesthesia, stereotaxic surgery, and vehicle injection were not sufficient to reproduce the changes caused by Aβ1-42.

Combined training independently reduced APP, BACE1, PSEN1, and Aβ42. These findings agree with the broader preclinical literature in which regular exercise attenuates amyloid accumulation and supports hippocampal function. Adlard et al. (2005) reported reduced amyloid burden following voluntary exercise in a transgenic Alzheimer model (8), and subsequent reviews have described potential roles for exercise-induced changes in neurotrophic signaling, synaptic plasticity, vascular function, mitochondrial regulation, inflammation, and amyloid handling (9). The current findings extend that framework by showing concurrent reductions in three gene-expression

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markers along the amyloidogenic pathway and in Aβ42 after a program combining aerobic swimming and progressive resistance ladder climbing.

The combined exercise format may be relevant to the magnitude of the response. Aerobic exercise imposes sustained energetic demand and can promote oxidative capacity, vascular adaptation, and systemic insulin sensitivity. Resistance exercise produces a distinct mechanical and metabolic stimulus and can activate signaling associated with growth, neuromuscular adaptation, and glucose utilization. Cassilhas et al. (2012) demonstrated that aerobic and resistance exercise can improve memory through divergent molecular mechanisms, supporting the possibility that a combined protocol recruits a broader set of adaptations (10). The present experiment did not compare aerobic and resistance exercise separately, so their individual contributions cannot be identified. It also did not measure cardiorespiratory fitness, muscle adaptation, circulating metabolic markers, or neurotrophic factors. Consequently, the proposed mechanisms remain plausible explanations rather than measured mediators.

Exercise may influence amyloidogenic markers through several interconnected processes. Improved mitochondrial function can reduce excessive reactive oxygen species that otherwise promote stress-sensitive APP processing. Better insulin action and cerebral metabolic regulation may reduce competition between insulin and amyloid-β for degradation and may support IDE function. Exercise-related neurotrophic and vascular changes may increase neuronal resilience and proteostatic capacity, while anti-inflammatory effects may modify microglial handling of amyloid. These pathways are not mutually exclusive. Importantly, none was directly assessed in this study; the evidence demonstrates changes in APP, BACE1, PSEN1, Aβ42, and IDE, not the intermediate pathways presumed to link exercise to these outcomes.

Coenzyme Q10 independently reduced the amyloidogenic markers and increased IDE expression and activity. This pattern is biologically compatible with the dual role of coenzyme Q10 in mitochondrial electron transfer and antioxidant defense. The reduced form of coenzyme Q can limit lipid peroxidation and regenerate other antioxidants, while the quinone pool supports electron flow through the respiratory chain (11). Reviews of supplementation in aging and disease describe potential benefits when endogenous synthesis, redox balance, or mitochondrial function is compromised, although tissue uptake and clinical efficacy are variable (12). In the present model, dietary coenzyme Q10 may have reduced an oxidative and bioenergetic environment favorable to amyloidogenic processing. Because oxidative damage, mitochondrial respiration, ATP, lipid peroxidation, and antioxidant enzymes were not measured, this mechanism cannot be confirmed directly.

The IDE findings are a central contribution of the experiment. Alzheimer-like pathology reduced both IDE gene expression and measured enzymatic activity, whereas training and coenzyme Q10 increased both. Concordance between transcriptional and functional measures is informative because it shows that the intervention-related change was not confined to messenger RNA. IDE has a demonstrated capacity to degrade amyloid-β, and experimental loss of IDE increases cerebral amyloid accumulation (6). Earlier work also showed that IDE can regulate extracellular amyloid-β levels through degradation (7). The inverse pattern between IDE and Aβ42 in the present data is therefore consistent with improved IDE-dependent degradation. It does not establish that IDE alone caused the reduction in Aβ42, because other proteases and clearance systems were not measured and because lower amyloid production could itself reduce the peptide burden presented to clearance pathways.

The combined intervention produced the most favorable numerical values for all six outcomes. For APP and PSEN1, IDE expression, and IDE activity, however, the training × coenzyme Q10 interaction was not statistically significant. The correct interpretation is that training and supplementation each had significant main effects and that their combined administration yielded a larger overall shift, without evidence that the effect of one intervention depended statistically on the other. This distinction prevents overuse of the term synergy. For these outcomes, the combined pattern may reflect additive or parallel effects that converge on the same biological system.

In contrast, significant interactions were found for BACE1 and Aβ42. Simple-effects comparisons showed that training and coenzyme Q10 each lowered both outcomes relative to untreated Alzheimer-like rats; the single interventions did not differ significantly from each other;

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and the combined intervention produced lower values than either alone. BACE1 is the initiating β-secretase in amyloidogenic APP processing, and Aβ42 is a major aggregation-prone product of that pathway. An interaction at these two levels suggests that the interventions may converge on processes governing pathway initiation and net peptide accumulation. Exercise-related metabolic and proteostatic adaptations could complement the mitochondrial and redox support provided by coenzyme Q10, thereby producing a response greater than expected from a simple uniform shift. The experiment did not measure BACE1 protein or activity, γ-secretase activity, oxidative status, or mitochondrial endpoints, so the molecular basis of the interaction remains unresolved.

The effect sizes for one-way group comparisons and for the main effects of training and supplementation were large. These values indicate substantial separation under the tightly controlled experimental conditions. They should not be interpreted as direct estimates of expected effects in humans. Animal experiments minimize environmental variability, use genetically and physiologically similar subjects, and can employ invasive induction procedures and precisely standardized exposures. These features can generate clearer between-group contrasts than are typically observed in clinical populations. Moreover, intracerebroventricular Aβ1-42 administration models selected aspects of amyloid-related injury rather than the age-dependent, genetically and metabolically heterogeneous human disease. It does not reproduce the full development of tau pathology, vascular contributions, long prodromal progression, or interactions with comorbidities.

Several limitations define the scope of the conclusions. First, the study measured APP, BACE1, and PSEN1 at the gene-expression level but did not quantify the corresponding proteins, β-secretase activity, γ-secretase activity, or intermediate APP fragments. Second, only Aβ42 was assessed; Aβ40, the Aβ42/Aβ40 ratio, soluble and insoluble fractions, oligomeric species, and plaque histology were not measured. Third, although IDE was evaluated at both expression and activity levels, other clearance mechanisms such as neprilysin, autophagy, microglial uptake, blood-brain barrier transport, and glymphatic function were not examined. Fourth, no behavioral test of learning or memory was included, so molecular improvement cannot be equated with cognitive recovery. Fifth, the use of only male rats, eight animals per group, one coenzyme Q10 concentration, one training design, and one sampling time limits generalizability and prevents evaluation of sex, dose, intensity, or temporal dependence.

Future studies should integrate gene expression with protein quantification and direct enzyme assays for BACE1 and γ-secretase. Measuring Aβ40, Aβ42/Aβ40, oligomers, soluble and insoluble pools, and histological plaque burden would provide a more complete account of amyloid processing. Additional clearance markers, oxidative and inflammatory indices, mitochondrial respiration, ATP production, neurotrophic signaling, and synaptic proteins should be included to test mediation. Behavioral outcomes such as spatial learning, recognition memory, and anxiety-related behavior are needed to determine whether molecular changes have functional significance. Factorial studies comparing aerobic training, resistance training, combined training, multiple coenzyme Q10 doses, and both sexes would clarify which components are necessary and whether the interaction is reproducible. Longer follow-up after intervention withdrawal would also establish persistence.

Despite these limitations, the study provides a coherent dataset linking the two sides of amyloid balance. The Alzheimer-like condition was associated with higher markers of amyloidogenic processing and lower IDE-dependent degradation. Training and coenzyme Q10 each moved both domains in a favorable direction, and simultaneous treatment generated the strongest overall pattern. The selective interaction for BACE1 and Aβ42 is especially informative because it identifies outcomes at which the combined response cannot be summarized solely by independent main effects. These findings justify more detailed mechanistic work but do not support direct clinical recommendations regarding coenzyme Q10 supplementation or exercise treatment for Alzheimer's disease.

6. Conclusion

Twelve weeks of combined aerobic-resistance training and 0.4% dietary coenzyme Q10 independently reduced hippocampal APP, BACE1, PSEN1, and Aβ42 and increased IDE expression and activity in male Wistar rats with Aβ1-42-induced Alzheimer-like pathology. The

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E-ISSN: 2981-2569

simultaneous intervention produced the most favorable means, with significant training-by-supplementation interactions for BACE1 and Aβ42. The results indicate improved balance between amyloidogenic markers and IDE-dependent degradation in this experimental model. Confirmation requires protein-level, histological, cognitive, dose-response, sex-comparative, and human studies.

Authors' Contributions

The authors acknowledge the laboratory personnel who assisted with animal care, training supervision, and biochemical analyses.

Declaration

The authors declare that artificial intelligence tools were used only to assist with language editing, translation, and improvement of the manuscript's readability. All conceptualization, study design, data collection, data analysis, interpretation of findings, and final approval of the manuscript were performed by the authors. The authors take full responsibility for the accuracy, integrity, and originality of the content.

Transparency Statement

Data are available for research purposes upon reasonable request to the corresponding author.

Acknowledgments

The authors thank the participating centers, clinicians, adolescents, and guardians who made the study possible.

Declaration of Interest

The authors report no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethics Considerations

The study was conducted in accordance with institutional standards for the care and use of laboratory animals and the ARRIVE reporting principles. The protocol was reviewed and approved by the Research Ethics Committee of Islamic Azad University, Najafabad Branch (Ethics Code: IR.IAU.NAJAFABAD.REC.1405.051). Animal numbers and experimental procedures were planned to obtain the required scientific information while minimizing unnecessary use, pain, and distress. Anesthesia was used for stereotaxic procedures and terminal tissue collection, animals were monitored throughout the study, and predefined humane exclusion criteria were applied.

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E-ISSN: 2981-2569