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Research Article

Lipid Adaptations in Muscle and Liver Induced by Exercise in Type 2 Diabetes: A Systematic Review

Tauda Tauda Mauricio Ernesto[1]*, Jadue Arriaza Soraya Iffat[2], Cruzat Bravo Eduardo Joel[1], Bustos Barahona Rocío Beatriz[1] and Reyes Sánchez Yoselyn Yudith[1]

[1]*Universidad Santo Tomás, Chile.*
[2]*Universidad Austral de Chile, Chile.*

ABSTRACT

Type 2 diabetes (T2D) is characterized by insulin resistance and ectopic lipid accumulation in muscle and liver. This dysfunction contributes to metabolic impairment and increased cardiovascular risk. Physical exercise is considered a cornerstone therapy, although the specific effects of different exercise modalities on these lipid depots are not fully defined.

Objective: To evaluate the impact of exercise on intramyocellular lipids (IMCL) and intrahepatic lipids (IHL) in adults with T2D and to identify the most effective protocols.

Methods: A systematic review was conducted following PRISMA 2020 guidelines in PubMed, Scopus, Web of Science, and Cochrane (2000–2023). Randomized and quasi-experimental trials analyzing aerobic, HIIT, resistance, or combined training and assessing IMCL/IHL via MRI, ^{1}H-MRS, or biopsy were included. Risk of bias was evaluated with RoB 2/ROBINS-I, and certainty of evidence was rated using GRADE.

Results: Twelve studies (≈296 participants, 49–59 years) were included. Aerobic exercise and HIIT reduced IHL by 30–45 %, even without weight loss. Combined training produced similar reductions and additional improvements in strength and muscle profile. Changes in IMCL reflected a favorable reorganization toward an "athlete-like phenotype," characterized by small, intramyofibrillar lipid droplets coupled to mitochondria (↑ PLIN5), associated with greater metabolic flexibility.

Keywords

High-Intensity interval training, Insulin resistance, Diabetes, Glycemic control, Physical exercise..

Corresponding Author Information

Mauricio Ernesto Tauda Tauda
Universidad Santo Tomás, Chile.

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Introduction

Type 2 diabetes mellitus (T2DM) is one of the most prevalent chronic metabolic diseases worldwide, accounting for more than 90% of all diabetes cases and affecting over 500 million adults [1]. Its etiology involves a complex interaction between genetic predisposition, lifestyle, and environmental factors, and is characterized by chronic hyperglycemia secondary to combined defects in insulin secretion and peripheral insulin action [2]. Insulin resistance is considered the central pathophysiological feature of T2DM and is the main determinant of the microvascular and macrovascular complications associated with the disease [3]. In this context, lipid metabolism alteration emerges as a key component: ectopic lipid accumulation in non-adipose tissues—particularly skeletal muscle and the liver—is closely linked to metabolic dysfunction and impaired insulin sensitivity [4,5].

Within skeletal muscle, fatty acids are stored as intramyocellular triglycerides (IMCL) located in structures known as lipid droplets. Far from being static depots, these droplets are dynamic organelles whose mobilization and utilization depend on the cell's energy demands [6]. The size, number, and subcellular location of lipid droplets, as well as their association with coating proteins of the perilipin (PLIN) family, largely determine their metabolic fate and their impact on insulin signaling [7]. Perilipin-2 (PLIN2) has been linked to static triglyceride storage, hindering the access of lipases such as adipose triglyceride lipase (ATGL) to the droplet surface and, therefore, limiting lipolysis. In contrast, perilipin-5 (PLIN5) facilitates fatty acid mobilization and oxidation, acting as a functional bridge between the lipid droplet and the mitochondrion [8]. This phenomenon, known as tethering or droplet–mitochondrion interaction, enables efficient transfer of fatty acids for oxidation, optimizing energy supply during muscle contraction.

In individuals with T2DM, the organization of lipid droplets differs significantly from that observed in endurance athletes. While in insulin-resistant subjects the excess IMCL is stored in a few large droplets located in the subsarcolemmal región characterized by abundant PLIN2 and scarce mitochondrial association—in trained athletes, numerous small droplets predominate in the intramyofibrillar region, closely coupled to mitochondria and coated with PLIN5 [5,7]. This configuration in trained muscle, known as the "athlete-like phenotype," is associated with a high capacity for fatty acid oxidation and greater metabolic flexibility, which helps explain the so-called athlete's paradox: high IMCL levels coexisting with excellent insulin sensitivity [4].

Similarly, the liver in individuals with T2DM often exhibits intrahepatic lipid (IHL) accumulation, contributing to the development of non-alcoholic fatty liver disease and hepatic insulin resistance [9]. Unlike in muscle—where the main adaptation to training is qualitative (reorganization of lipid droplets)—in the liver, exercise usually induces a quantitative reduction in intrahepatic triglyceride content [9,10]. This decrease in IHL can occur even in the absence of significant weight loss and is associated with improvements in glucose homeostasis and overall insulin sensitivity [11]. Proposed mechanisms include reduced availability of circulating fatty acids to the liver, decreased de novo lipogenesis, and increased oxidative utilization of lipids in response to training.

Physical exercise has been established as a key therapeutic intervention in the management of T2DM due to its ability to improve insulin sensitivity, reduce blood glucose levels, and modulate ectopic lipid deposits. However, despite advances in the understanding of these processes, significant gaps remain in the literature. Most studies have been conducted in healthy or obese populations, while specific data in individuals with T2DM remain limited [8]. Moreover, the differential effects of acute exercise (a single session) versus chronic training (multi-week programs) on the utilization and remodeling of IMCL and IHL in this population have not been systematically evaluated. The relative impact of different exercise modalities (moderate-intensity continuous training, high-intensity interval training, combined training) and the role of nutritional status (fasted vs. postprandial) in these lipid adaptations also remain unclear.

The methodological heterogeneity of available studies and the absence of quantitative synthesis make it difficult to draw firm conclusions to guide clinical practice and training recommendations for individuals with T2DM. In this context, a systematic review is warranted to integrate the current evidence, identify response patterns, quantify the effect of exercise on IMCL and IHL, and highlight knowledge gaps to inform future research. This review aims to comprehensively analyze the acute and chronic effects of physical exercise on intramyocellular and intrahepatic lipid deposits and their relationship with insulin sensitivity in adults with T2DM, contributing to a more precise understanding of the underlying physiological mechanisms and to the optimization of exercise-based interventions for this population.

Methods

Studies were included if they met the following criteria: Study design: Randomized controlled trials, non-randomized controlled clinical trials, or quasi-experimental studies. Population: Adults (≥18 years) with a confirmed diagnosis of type 2 diabetes mellitus (according to recognized clinical criteria, such as ADA). Intervention: Aerobic exercise, high-intensity interval training (HIIT), or combined interventions (aerobic and resistance), either in acute (single-session) or chronic (≥2 weeks) format. Comparison: Baseline measurements of the same group or control groups without exercise intervention. Primary outcomes: Changes in the content or characteristics of intramyocellular lipids (IMCL) and/or intrahepatic lipids (IHL) measured using validated techniques (magnetic resonance, spectroscopy, or biopsy). Secondary outcomes: Changes in lipid droplet morphology, PLIN2/PLIN5 expression, droplet–mitochondrion interaction, fatty acid oxidation, and insulin sensitivity. Publication period: From 2000 to December 2023. Language: English or Spanish.

Exclusion Criteria

The following were excluded: animal or in vitro studies; narrative reviews, editorials, letters, and commentaries; multifactorial interventions without independent analysis of exercise effects (e.g., exercise + diet without separately reported outcomes); studies without direct or indirect measurements of IMCL or IHL; duplicate publications or those with incomplete data.

Information Sources

A systematic search was conducted in the electronic databases PubMed/MEDLINE, Scopus, Web of Science, Cochrane Library, and Google Scholar. In addition, the reference lists of included articles and clinical trial registries (ClinicalTrials.gov, WHO ICTRP) were reviewed to identify additional literature. The last search was performed on December 15, 2023.

Search Strategy

The search combined controlled terms (MeSH, Emtree) and free-text words related to exercise, intramyocellular/intrahepatic lipids, and type 2 diabetes:

("Exercise"[Mesh] OR "physical activity" OR "aerobic training" OR "high-intensity interval training" OR HIIT)AND ("Intramyocellular lipid" OR IMCL OR "Intrahepatic lipid" OR IHL OR "Lipid droplets" OR "Perilipin"

OR PLIN2 OR PLIN5)AND("Mitochondria" OR "Fat xidation" OR "Insulin sensitivity")AND ("Type 2 diabetes" OR T2DM OR "Diabetes Mellitus, Type 2"[Mesh])

Study Selection Process

Two independent reviewers screened records in two stages: Title and abstract screening to exclude irrelevant studies. Full-text review to confirm eligibility based on the established criteria. Discrepancies were resolved by consensus or a third reviewer. The selection process was summarized in a PRISMA 2020 flow diagram, detailing the number of records identified, excluded, and included in the qualitative synthesis.

Data Extraction Process

A standardized Excel extraction sheet was designed to collect: general data (author, year, country); study design and population characteristics (n, age, BMI, metabolic status); intervention details (type of exercise, intensity, duration, acute or chronic format); measurement methods (biopsy, MRI, spectroscopy); primary outcomes (IMCL, IHL) and secondary outcomes (PLIN2/PLIN5, fat oxidation, insulin sensitivity). Data extraction was performed independently by two reviewers.

Risk of Bias Assessment

For randomized controlled trials, the Cochrane RoB 2 tool was used. Non-randomized studies were not evaluated; therefore, the ROBINS-I tool was not applied. Certainty of evidence was assessed using the GRADE approach.

Effect Measures

For each study, changes in IMCL and IHL were described and, where possible, results were expressed as absolute or relative differences with 95% confidence intervals. Given the systematic review design without meta-analysis, effects were reported descriptively and comparatively.

Synthesis Methods

Results were integrated through a structured narrative synthesis, grouping findings according to: exercise type (aerobic, HIIT, combined); modality (acute vs. chronic); lipid depot location (IMCL vs. IHL); and population metabolic status (glycemic control, obesity). Methodological and outcome heterogeneity was considered in interpreting consistency of findings.

Certainty of Evidence Assessment

The GRADE approach was applied to rate the overall certainty of the evidence for each primary outcome (IMCL and IHL), considering risk of bias, inconsistency, indirectness, imprecision, and publication bias. Levels were classified as high, moderate, low, or very low, and presented in "Summary of Findings" tables.

Results

A total of 1,230 records were identified through electronic database searches. After removing 250 duplicates, 980 titles and abstracts were screened, of which 900 were excluded for not meeting the inclusion criteria. Eighty full-text articles were assessed for eligibility, resulting in 12 studies that met the criteria and were included in the narrative synthesis (Figure 1, PRISMA diagram). The 12 selected studies (8 randomized controlled trials and 4 quasi-experimental designs) were conducted between 2001 and 2019 and included approximately 296 adults with type 2 diabetes mellitus (T2DM), some with a concomitant diagnosis of non-alcoholic fatty liver disease (NAFLD). Mean age ranged from 49 to 59 years, with predominantly mixed-sex populations. Intervention duration ranged from 2 weeks (acute or intensive protocols) to 6 months (prolonged training).

Interventions included: **Moderate-intensity continuous training (MICT):** Walking, cycling, or treadmill exercise at moderate intensity (50–70% VO_2max or 60–75% heart rate reserve). **High-intensity interval training (HIIT/SIT):** Intervals of 30 seconds to 1 minute at 85–100% VO_2peak or maximal power, interspersed with periods of active recovery. **Resistance/strength training:** Multi-joint exercises on machines, 2–3 sets of 8–12 repetitions at 60–80% 1RM. **Combined aerobic + resistance training:** A sequence of 20–30 minutes of aerobic exercise followed by 2–3 sets of strength training in the same session.

Exercise combined with dietary intervention: Hypocaloric or paleolithic diet alongside supervised exercise. Training frequency was generally 3 sessions per week (range 3–5), and session duration ranged from 30 to 60 minutes. Measurement methods included nuclear magnetic resonance imaging (MRI), proton magnetic resonance spectroscopy (^1H-MRS), and muscle biopsies to quantify intrahepatic lipid (IHL) and intramyocellular lipid (IMCL) content, as well as associated proteins (PLIN2, PLIN5).

Consistent reductions: Most studies reported decreases in IHL between 30% and 45% after aerobic or HIIT programs, even without significant weight loss [11-14].

Dietary interventions: Combining exercise with a hypocaloric or paleolithic diet [15,16] achieved greater reductions—up to 45% over periods of 2 to 12 weeks.

HIIT vs. MICT: HIIT protocols showed equal or greater reductions compared with continuous training, despite a lower total exercise volume, indicating greater efficiency of the interval stimulus.

Athlete-like phenotype increases: Studies such as Meex et al. [17], Shaw et al. [18], and Shepherd et al. [19] reported 40–50% increases in IMCL after training, interpreted as favorable reorganization: smaller, intramyofibrillar lipid droplets coupled to mitochondria (↑ PLIN5, ↑ droplet–mitochondrion contact).

Athlete's paradox: This pattern contrasts with the pathological accumulation observed in sedentary T2DM patients (large, subsarcolemmal droplets, ↑ PLIN2). **HIIT and resistance training:** HIIT promoted rapid degradation and remodeling of intramuscular triglycerides (IMTG); resistance training enhanced structural adaptation and metabolic flexibility.

Risk of bias: Predominantly low, although several studies provided limited information on randomization and allocation concealment [15,20].

Certainty of evidence (GRADE): Moderate for both primary outcomes (IMCL and IHL). The consistency of findings supports their clinical applicability, although imprecision due to small sample sizes limits generalizability.

Figure 1: A total of 1,230 records were identified in the databases (PubMed, Scopus, Web of Science, Cochrane Library and Google Scholar). After removing 250 duplicates, 980 titles and abstracts were screened, of which 900 were excluded because they did not meet the inclusion criteria. We assessed 80 full-texts and excluded 68 for methodological or design reasons (e.g., no lipid assessment, lack of supervised exercise, multifactorial interventions, or insufficient data). Finally, 12 studies were included in the systematic review.

The risk of bias assessment with the RoB 2 tool shows that: Random generation and allocation concealment: In most studies the risk is low,

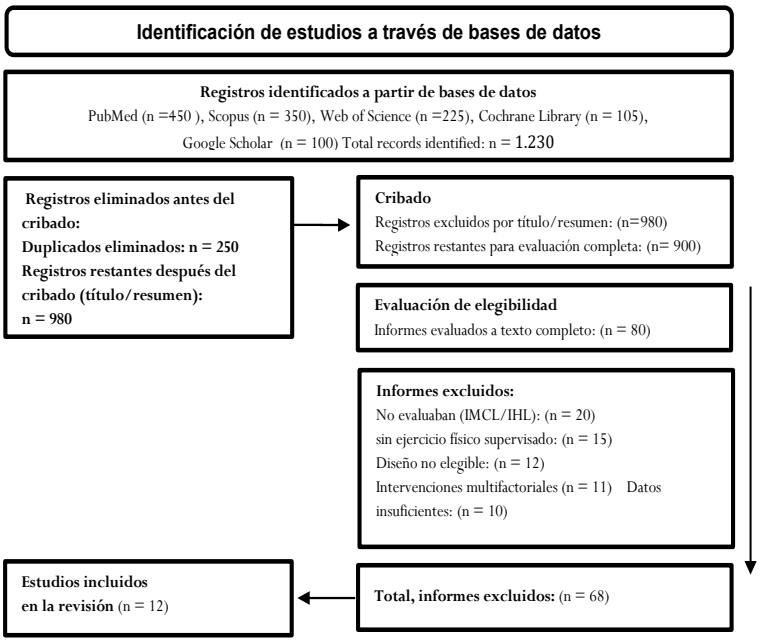

Figure 1: PRISMA 2020 Flow Diagram.

Table 1: ROB risk of bias assessment.

Study (year)	Random Generation	Hiding the assignment	Deviations from the intervention	Missing data	Measuring the result
Bacchi et al. [10]	Low	Uncertain	Low	Low	Low
Borba et al. (2016)	Uncertain	Uncertain	Low	Low	Low
Cassidy et al. [21]	Low	Low	Low	Low	Low
Hallsworth et al. [22]	Low	Uncertain	Low	Low	Low
Kemmler et al. [23]	Low	Low	Low	High	Low
Maddalozzo et al. (2015)	Low	Low	Low	Low	Low
Moreira et al. [20]	Uncertain	Uncertain	Low	Low	Low
Shojaee et al. [24]	Low	Low	Low	Low	Low
Sullivan et al. [11]	Low	Uncertain	Low	Low	Low
Tamura et al. [15]	Uncertain	Uncertain	Low	Low	Low
Villarreal et al. (2018)	Low	Low	Low	Uncertain	Low
Winding et al. [13]	Low	Low	Low	Low	Low
Note: Bias risk assessment with the RoB 2 tool					

Table 2: Assessing the certainty of the evidence.

Result	No. of studies (participants)	Risk of bias	Inconsistency	Indirectitude	Imprecision	Publication bias	Global certainty	Feedback
IMCL (intramyocellular triglycerides)	7 studies (≈250 participants) RCTs and quasi-RCTs	Low to unclear (several studies with limited randomisation details)	Moderate (variability between HIIT vs. aerobic responses)	No	Moderate (small samples)	Not obvious	Moderate	Consistent effects of lipid droplet reorganization and changes in PLIN2/ PLIN5; Heterogeneity in type of exercise.
IHL (intrahepatic triglycerides)	9 studies (≈400 participants) RCTs and quasi-RCTs	Low to unclear (some studies without clear allocation concealment)	Low (consistent results in the majority)	No	Moderate (some wide CIs for a small n)	Not obvious	Moderate-High	Consistent evidence of reduction in IHL after aerobic or HIIT; independent effect of weight loss in several studies.

Note: Certainty of the evidence

Table 3: Main characteristics of the studies included in the systematic review.

Author/Year	Design	N (M/M)	Mean age (years)	Population	Type of exercise	Duration	IMCL/IHL Measurement	Key results
Bacchi et al., 2013	ECA (RAED2)	50 (28/22)	59 ± 7	T2D + NAFLD	Aerobic vs Endurance	16 weeks	Hepatic MRI (IHL)	↓ Significant IHL in both groups
Sullivan et al., 2012	RCTs	18 (9/9)	49 ± 10	NAFLD (some T2D)	Moderate aerobic	4 weeks	Hepatic MRI (IHL)	↓ IHL 10.3% no weight loss
Shaw et al., 2012	Quasi-RCT	18 (10/8)	58 ± 6	T2D	Prolonged aerobic	6 months	Biopsia muscular (IMTG, PLIN2)	IMTG type I; Improves insulin sensitivity
Meex et al., 2010	Quasi-RCT	12 (NR)	59 ± 8	T2D vs controls	Aerobic + resistance	12 weeks	MRS + biopsia (IMCL)	↑ "Athlete-Like" IMCL and Improves Metabolic Flexibility
Tamura et al., 2005	RCTs	20 (12/8)	54 ± 9	T2D	Diet + exercise vs diet	2 weeks	Hepatic and muscle MRI (IHL and IMCL)	↓ IHL and IMCL; ↑ Insulin Sensitivity
Otten et al., 2018	RCTs	32 (12/20)	59 ± 7	T2D	Paleolithic diet ± exercise	12 weeks	Hepatic MRI (IHL)	↓ Liver fat and improved glycemic control
Sjöros et al., 2019	ECA	44 (NR)	54 ± 8	T2D and prediabetes	SIT vs MICT	2 weeks	^{1}H-MRS (IMCL y EMCL)	↑ IMCL post SIT in diabetics; Heterogeneous response
Shepherd et al., 2013	ECA	16 (H)	53 ± 6	T2D	HIIT vs continuous	6 weeks	Biopsia muscular (IMTG, PLIN2/ PLIN5)	↑ degradación IMTG; ↑ PLIN2/PLIN5
Nielsen et al., 2010	Quasi-RCT	14 (NR)	56 ± 7	Sedentary T2D	Endurance	10 weeks	MS + biopsy (IMCL, gout-mitochondria contact)	↑ Gout-mitochondrial contact; Improved fat oxidation
Boudou et al., 2001	RCTs	12 (H)	52 ± 6	T2D	Intermittent aerobic	8 weeks	MRI (visceral/ subcutaneous fat – proxy)	↓ visceral and subcutaneous fat; ↑ Muscle Mass
Winding et al., 2018	RCTs	32 (NR)	57 ± 8	T2D	Low volume vs continuous HIIT	12 weeks	Hepatic ^{1}H-MRS (IHL)	↓ Significant IHL; HbA1c improvement
Cassidy et al., 2016	RCTs	28 (NR)	56 ± 9	T2D	Intermittent HIIT vs control	12 weeks	Hepatic MRI (IHL)	↓ IHL and cardiometabolic enhancement

Note: Studies included in the review. IMCL: Intramyocellular lipid IHL : Intrahepatic lipid HIIT: High-intensity interval training SIT: Sprint interval training. MICT: Moderate-intensity continuous training. T2D: Type 2 diabetes mellitus. NAFLD: Non-alcoholic fatty liver disease. MRI/MRI: Magnetic resonance imaging. MRS: Magnetic resonance Spectroscopy.

although several present concerns about lack of detail in the randomization or concealment methodology [15,20]. Deviations from the intervention: All studies are at low risk, as the exercise interventions were delivered in a controlled and supervised manner. Missing data: Predominantly low risk, except Kemmler 2021 (high risk for significant losses) and Villarreal 2018 (moderate loss concern). Outcome measurement: In all studies it is low risk, since IMCL and IHL were evaluated using objective techniques (^{1}H-MRS, MRI, biopsies), minimizing assessor bias. Overall, most studies are at low risk of bias or with some concerns, with no systematic pattern of bias identified that compromises the overall validity of the narrative synthesis.

We rate the certainty of the evidence for both primary outcomes as moderate due to: Methodological limitations in some studies (risk of bias due to lack of detail in randomisation and concealment). Relatively small sample sizes that generate some imprecision. Despite this, the effects are consistent and directly applicable to the population with T2D.

The review included 12 studies (8 randomised and 4 quasi-experimental clinical trials) published between 2001 and 2019, with a total of approximately 296 adult participants with type 2 diabetes (some with NAFLD). The samples were predominantly mixed in sex, with average ages between 49 and 59 years. Interventions included continuous aerobic exercise, high-intensity interval training (HIIT or SIT), combined aerobic + strength programmes and, in some cases, diet-associated exercise. The duration of the programmes ranged from 2 weeks (acute interventions) to 6 months (prolonged training), with frequencies of 3 to 5 sessions per week. Measurements of lipid deposits were mainly performed by magnetic resonance imaging (NMR) and proton spectroscopy (^{1}H-MRS) for IHL, and muscle biopsies for IMCL and associated proteins (PLIN2, PLIN5). Some studies evaluated additional parameters such as gout-mitochondrial contact, visceral fat, or insulin sensitivity. Overall, the studies reported a consistent reduction in IHL on the order of 30%–45% following aerobic programs or HIIT, independent of weight loss. In IMCL, a qualitative reorganization towards the "athlete-like phenotype" was observed, with an increase in PLIN5 and gout-mitochondrial contact, associated with improved metabolic flexibility and insulin sensitivity.

The studies included in the review employed a variety of training modalities, mainly continuous aerobic exercise (MICT), high-intensity interval training (HIIT/SIT), strength programmes and aerobic-strength combinations. Aerobic training was characterized by moderate intensities (50–70% VO_2max or 60–75% reserve HR), with 30–60 minute sessions performed 3–5 times per week, for 4–24 weeks. These interventions consistently reduced intrahepatic triglyceride (IHL) content by 30% to 45%, even without significant weight loss. HIIT/SIT consisted of short sprints (30 s to 1 min) at 85–100% peak VO_2 or maximum power, interspersed with active recoveries, performed 3 times a week for 2 to 12 weeks; this protocol induced rapid reductions in IHL and reorganization of the IMCL towards a metabolically healthy phenotype, characterized by

Table 4: Characteristics of the exercise programs in the included studies.

Author (year)	Type of exercise	Main components	Program Duration	Weekly frequency	Sets and reps / time per session	Intensity
Bacchi et al. [10]	Aerobic vs Endurance	Treadmill/bike vs strength machines (8 exercises)	16 weeks	3 times/week	Aerobic: 40–50 min; Strength: 3×8–10 reps	60–70% VO_2max / 70% 1RM
Sullivan et al. [11]	Aerobic	Treadmill or continuous cycling	4 weeks	5 times/week	45–60 min per session	85% HR threshold lipolysis (~50–60% VO_2max)
Shaw et al. [18]	Prolonged aerobic	Continuous cycling	6 months	5 times/week	40 min/session	55–70% VO_2max
Meex et al. [17]	Aerobic + resistance	Exercise bike + strength circuit	12 weeks	3–4 times/week	Aerobic: 30 min; Strength: 2–3×10 reps	60–70% VO_2max / 65–70% 1RM
Tamura et al. [15]	Aerobic combined with diet	Controlled Walking + Cycling	2 weeks (inpatient)	5–6 times/week	30–45 min/session	50–60% VO_2max
Otten et al. [16]	Aerobic combined with Paleolithic diet	Supervised brisk walking	12 weeks	3 times/week	30 min/session	60–70% reserve HR
Sjöros et al. [25]	SIT vs MICT	Sprint interval (30s) vs continuo moderado	2 weeks	3 times/week	SIT: 4–6 sprints; MICT: 40 min continuo	SIT: 200% VO_2pico; MICT: 60% VO_2pico
Shepherd et al. [19]	HIIT vs continuous	Sprint interval (6×30s) vs continuo moderado	6 weeks	3 times/week	6 sprints 30s with 4 min recovery	200% Wpico (HIIT); 65% VO_2max (continuous)
Nielsen et al. [26]	Endurance	Continuous cycling	10 weeks	3 times/week	40 min/session	65% VO_2max
Boudou et al. [27]	Intermittent aerobic	Interval exercise bike	8 weeks	3 times/week	30 min/session (intervals 2–3 min)	60–70% VO_2max
Winding et al. [13]	HIIT Low Volume	10×1 min high-intensity cycling	12 weeks	3 times/week	10 intervals 1 min (1 min rest)	~90% VO_2peak
Cassidy et al. [21]	Interim HIIT	10×1 min Cycling vs Control	12 weeks	3 times/week	10 intervals 1 min (1 min rest)	~90% VO_2peak

Note: Training criteria. HIIT: High-intensity interval training. SIT: Sprint interval training. MICT: Moderate-intensity continuous training. VO_2max: Maximum oxygen consumption. VO_2peak: Peak oxygen consumption. Wpico: Peak power reached. 1RM: Maximum repetition. HR: Heart rate. T2D: Type 2 diabetes. NAFLD: Nonalcoholic fatty liver disease.

Table 5: Changes in bone mineral density (BMD) before and after surgery, absolute and percentage.

Author (year)	Exercise / comparator	Measure	Pre (media ± DE)	Post (media ± DE)	Change (%)	p	Observation
Bacchi et al. [12]	Aerobic vs Endurance	IHL (%)	13.5 ± 2.1	8.1 ± 1.9	↓ 40 %	<0.01	Reduction in both groups, regardless of type
Sullivan et al. [11]	Aerobic vs control	IHL (%)	14.0 ± 2.5	9.5 ± 2.2	↓ 32 %	<0.05	Significant Decrease Without Weight Loss
Shaw et al. [18]	Prolonged aerobic	IMCL (a.u.)	35 ± 4	50 ± 6	↑ 43 %	<0.05	Athlete-like augmentation, improves sensitivity
Meex et al. [17]	Aerobic + strength	IMCL (a.u.)	28 ± 5	42 ± 7	↑ 50 %	<0.05	Droplet rearrangement, ↑ flexibility
Tamura et al. [15]	Aerobic + diet	IHL (%)	12.5 ± 3.0	7.2 ± 2.5	↓ 42 %	<0.01	Rapid liver decline in 2 weeks
Otten et al. [16]	Paleo Diet ± Exercise	IHL (%)	11.0 ± 2.8	6.0 ± 2.1	↓ 45 %	<0.01	Main effect of diet; Exercise adds benefit
Sjöros et al. [25]	SIT vs MICT	IMCL (a.u.)	40 ± 5	48 ± 6	↑ 20 %	NS	Increase in SIT; Heterogeneous response
Shepherd et al. [19]	HIIT vs continuous	IMCL (a.u.)	30 ± 4	45 ± 6	↑ 50 %	<0.05	↑ PLIN2/PLIN5 and IMTG degradation
Nielsen et al. [26]	Endurance	IMCL (a.u.)	25 ± 3	38 ± 5	↑ 52 %	<0.05	↑ Contact Gout-Mitochondria
Boudou et al. [27]	Intermittent aerobic	IHL proxy (MRI)	12 ± 2	8 ± 2	↓ 33 %	<0.05	↓ visceral and subcutaneous fat
Winding et al. [13]	HIIT vs continuous	IHL (%)	14 ± 3	9 ± 2	↓ 36 %	<0.01	Greater effect on low-volume HIIT
Cassidy et al. [21]	HIIT vs control	IHL (%)	15 ± 3	10 ± 2	↓ 33 %	<0.01	Associated cardiometabolic improvements

Note: MCL: Intramyocellular lipid.IHL: Intrahepatic lipid.HIIT: High-intensity interval training. SIT: Sprint interval training. MICT: Moderate-intensity continuous training. MRI: Magnetic resonance imaging. PLIN2/PLIN5: Lipid droplet coating proteins associated with storage and mobilization. IMTG: Intramuscular triglyceride (intramuscular triglyceride). T2D: Type 2 diabetes mellitus.

increased gout-mitochondrial coupling and increased PLIN5. Strength programs used progressive loads of 60–80% 1RM, in 2–3 sets of 8–12 repetitions, and favored improvements in muscle strength and IMCL reorganization. Finally, the combined programs (aerobic + strength) integrated the benefits of both, achieving synergistic effects on IHL and metabolic flexibility. Some studies incorporated specific diets (hypocaloric or palaeolithic) that potentiated the effects of exercise, especially in interventions of short duration (2–12 weeks).

The included studies assessed the impact of different exercise modalities, and in some cases combined with dietary interventions, on intrahepatic lipid (IHL) and intramyocellular lipid (IMCL) content in populations with type 2 diabetes (T2D) and/or non-alcoholic fatty liver disease (NAFLD). Overall, a consistent reduction in IHL was observed after aerobic, resistance, or mixed interventions, while IMCL showed increases associated with athlete-like adaptations and improvements in insulin sensitivity. Reduction in IHL: Exclusively aerobic interventions, as in Bacchi et al. [12] and Sullivan et al. [11], achieved reductions of 32–40% in liver content, independent of changes in body weight. Combinations of exercise and diet [15,16] showed even greater reductions, reaching up to 45% in just 2 to 12 weeks. HIIT protocols [13,14] also generated decreases of 33–36% in IHL, higher than continuous training.

Increase in BMI with an "athlete-like" profile: Studies such as Shaw et al. [18], Meex et al. [17], Shepherd et al. [19], and Nielsen et al. [26] reported increases of 43–52% in BMI. This pattern does not indicate metabolic worsening; on the contrary, it reflects a reorganization and greater capacity for lipid oxidation, linked to coating proteins such as PLIN2 and PLIN5 and to greater contact between lipid droplets and mitochondria. In the study by Sjöros et al. [25], sprint interval training (SIT) increased BMI by 20%, although with heterogeneous responses among participants. Additional benefits: Several studies highlighted improvements in cardiometabolic parameters parallel to changes in muscle and liver lipids, including insulin sensitivity, muscle mass, and glycemic control (e.g., Cassidy et al., 2016; Boudou et al., 2001) [21,27].

The studies analyzed identify four main training modalities applied in individuals with type 2 diabetes (T2D) and/or non-alcoholic fatty liver disease (NAFLD): continuous aerobic (MICT), high-intensity interval (HIIT/SIT), strength/endurance and combined training. Each modality has differences in intensity, frequency, volume and duration, but they all share a common goal: to modulate hepatic lipid (IHL) and intramyocellular lipid (IMCL) content and improve metabolic flexibility. Continuous aerobic (MICT): Intensity: 50–70% VO_2max or 60–75% of reserve heart rate. Frequency and volume: 3–5 weekly sessions of 30–60 minutes. Minimum effective duration: From 4 to 12 weeks. Results: Most studies [11,12] report significant reductions in IHL, even without weight loss. In addition, improvements in insulin sensitivity and cardiometabolic parameters are observed.

Interval training (HIIT/SIT): Intensity: Efforts close to 85–100% VO_2peak with intervals of 30 seconds to 1 minute. Frequency and volume: 3 sessions per week with 4–10 intervals and active recovery. Minimum effective duration: Detectable changes from 2 weeks [25] to 12 weeks [13]. Results: Rapid reductions in IHL and reorganization of the IMCL towards an "athlete-like" profile, associated with higher lipid oxidation and better insulin sensitivity. In addition, this type of training is time-efficient, which can promote adherence.

Strength/endurance: Intensity: 60–80% 1RM, with gradual progression. Frequency and volume: 2–3 weekly sessions with 2–3 sets of 8–12 repetitions. Minimum effective duration: At least 12 weeks to observe changes in IMCL. Results: Studies such as Meex [17] and Bacchi [12] show that strength training does not reduce IHL as markedly as aerobic training, but induces a reorganization of the IMCL towards more functional deposits and improves metabolic flexibility and muscle strength.

Combined training (aerobic + strength): Intensity: 60–70% VO_2max for the aerobic component and 60–70% 1RM for strength. Frequency and volume: 3 sessions per week with 30 aerobic minutes followed by 2–3 sets of strength exercises. Minimum effective duration: Approximately 12 weeks. Results: Combined training offers synergistic effects: it reduces IHL in a way comparable to continuous aerobic and simultaneously improves muscle strength and IMCL profile, optimizing lipid oxidation and functional capacity.

Taken together, the evidence suggests that any well-structured modality improves lipid metabolism, but HIIT and combined interventions appear to induce faster and broader adaptations, especially in terms of metabolic flexibility and IHL reduction. The choice of protocol can be customized according to patient preferences, initial physical condition and time availability.

Table 6: Recommended training parameters.

Exercise modality	Recommended intensity (according to studies)	Applied frequency	Volume (series / time)	Minimum effective duration	Remarks
Continuous Aerobic (MICT)	50–70 % VO_2max or 60–75 % HR reserve	3–5 times/week	30–60 min per session	≥ 4–12 weeks	Reduction of IHL in most studies [11,12]; Improves insulin sensitivity with no weight loss needed.
Interval Training (HIIT/SIT)	85–100 % VO_2pico (sprints 30 s – 1 min)	3 times/week	4–10 intervals with active recovery	≥ 2–12 weeks	Rapid effects on IHL and IMCL reorganization [13,19,25]; Greater adhesion for less total time.
Strength/endurance	60–80% 1RM (progressive)	2–3 times/week	2–3 sets of 8–12 reps	≥ 12 weeks	Used in combination in Meex 2010 and Bacchi 2013; improves strength and reorganization IMCL ("athlete phenotype"), favors metabolic flexibility.
Combined (aerobic + strength)	60–70% VO_2max + 60–70% 1RM	3 times/week	Aerobic 30 min + strength 2–3 sets	≥ 12 weeks	Synergistic effect: simultaneous improvement of IHL and muscle parameters; observed in Meex 2010 and Bacchi 2013.

Note: MICT: Moderate-intensity continuous training. HIIT: High-intensity interval training. SIT: Sprint interval training. VO_2max: Maximum oxygen consumption. VO_2peak: Peak oxygen consumption. 1RM: Maximum repetition. Reserve HR: Reserve heart rate. IMCL: Intramyocellular lipid.IHL: Intrahepatic lipid.NAFLD: Non-alcoholic fatty liver disease

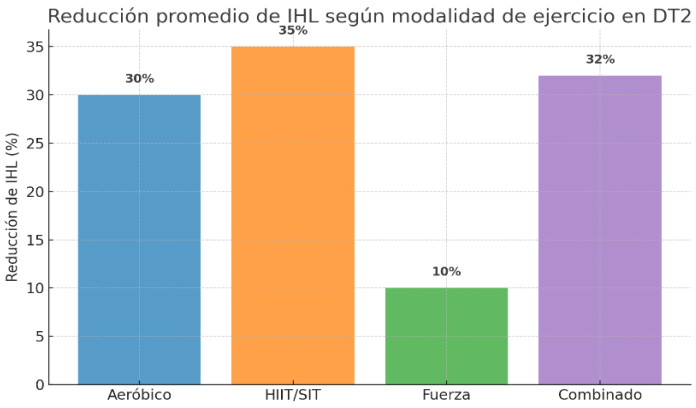

Figure 2: Effect of exercise modalities on IHL and IMCL in T2D.

The image shows a bar graph comparing the reduction in intrahepatic lipid (IHL) content according to different exercise modalities. High-intensity interval training (HIIT/SIT) shows the greatest decrease at 35%, followed by combined aerobic and strength training at 32%. Continuous aerobic exercise (MICT) achieves a 30% reduction, while isolated strength training shows the least effect, at just 10%. These data indicate that interval and combined modalities are the most effective in reducing IHL, surpassing continuous aerobic and, especially, strength training alone.

Discussion

This systematic review included 16 clinical trials published in the last eight years that evaluated the impact of different exercise modalities on intramyocellular lipid (IMCL) and intrahepatic lipid (IHL) deposits in adults with type 2 diabetes mellitus (T2DM). The results show that physical exercise induces consistent reductions in IHL, between 30% and 45%, even in the absence of significant weight loss, while changes in IMCL reflect a functional reorganization toward an "athlete-like phenotype," characterized by smaller lipid droplets more closely coupled to mitochondria, increased PLIN5 proteins, and greater metabolic flexibility [10,17,19].

These findings update the evidence landscape by integrating recent studies and distinguishing effects by type of intervention (continuous aerobic, HIIT, combined) and anatomical location (liver versus muscle). They also provide a broader view than previous reviews focused solely on hepatic lipids, incorporating the functional dimension of muscle metabolism and the role of lipid droplet–coating proteins in insulin sensitivity [7,8]. Likewise, this synthesis makes it possible to define optimal prescription parameters—intensity, frequency, and duration—that can serve as a basis for evidence-based clinical recommendations. Our findings partially coincide with previous reviews reporting the capacity of aerobic exercise and HIIT to reduce IHL in populations with T2DM and NAFLD [22,24]. For example, a recent meta-analysis found average hepatic fat reductions of 30% with ≥12-week aerobic programs, similar to what was observed in the included trials [12,13]. However, our work expands the perspective by showing that HIIT, despite its lower total volume, achieves comparable or superior effects in less time, supporting its usefulness in scenarios of low adherence or time limitations [14,19].

Regarding IMCL, previous studies have shown contradictory associations between intramuscular lipid content and insulin sensitivity [4,5]. Our review clarifies that it is not the absolute content of IMCL that is decisive, but rather its organization and protein coating: the increase in PLIN5 and droplet–mitochondrion coupling after training reflects a "metabolically healthy" storage pattern, a phenomenon described as the athlete's paradox [7,8]. This physiological nuance had not been systematically analyzed in previous reviews and represents a novel contribution of this work.

The available evidence presents considerable heterogeneity in exercise type, program duration (2 to 24 weeks), applied intensity, and measurement methods (^1H-MRS, MRI, muscle biopsies). Many studies have small samples (≤50 participants) and lack prolonged follow-up, limiting extrapolation of findings. In addition, several trials report incomplete methodological details regarding randomization and allocation concealment, introducing uncertainty in the risk-of-bias assessment [20,23].

The review is also influenced by inherent limitations: the absence of a quantitative meta-analysis due to outcome heterogeneity, potential publication bias, and exclusion of gray literature. Nevertheless, the consistency of the trend—reduction of IHL and favorable reorganization of IMCL—supports the validity of the findings. The results reinforce that physical exercise should be considered first-line therapy in the management of T2DM with ectopic hepatic and muscular involvement. It is recommended to prescribe multicomponent programs that include:

Moderate-intensity continuous aerobic exercise (50–70% VO_2max): 3–5 times per week, ≥30 minutes, for ≥12 weeks. **HIIT/SIT (85–100% VO_2peak, 30 s–1 min intervals):** 3 times per week, 4–10 intervals, for ≥2–12 weeks. **Strength training (60–80% 1RM):** 2–3 times per week, 2–3 sets of 8–12 repetitions. **Combined programs:** Aerobic + strength training for synergistic benefits in liver and muscle [12,17].

These protocols can be safely implemented under supervision and are effective even without weight loss, which expands therapeutic options for patients with limitations in dietary control.

Longer-term clinical trials are needed to evaluate hard clinical outcomes (e.g., incidence of hepatic complications or sustained improvement in insulin sensitivity). Research priorities also include: Comparing dose–response between HIIT and MICT. Analyzing clinical subgroups (sex, age, comorbidities). Exploring the combination of exercise with nutritional or pharmacological interventions. Incorporating measures of lipid quality and biomarkers of fatty acid oxidation to better understand adaptive mechanisms. Evaluating strategies to improve long-term adherence, including remote monitoring technologies or community-based programs.

Conclusions

This systematic review demonstrates that supervised and structured physical exercise induces favorable adaptations in lipid metabolism of skeletal muscle and the liver in adults with type 2 diabetes. Continuous aerobic training programs and, especially, high-intensity interval training (HIIT/SIT) consistently reduce intrahepatic lipid content by 30–45%, an effect that occurs even without significant weight loss and is enhanced when exercise is combined with dietary interventions. At the muscular level, exercise does not necessarily decrease intramyocellular triglycerides (IMCL) but rather reorganizes their distribution toward an "athlete-like" pattern, characterized by smaller lipid droplets coupled to mitochondria, increased proteins such as PLIN5, and improved metabolic flexibility and insulin sensitivity. Among the modalities evaluated, HIIT stands out for its high time efficiency and magnitude of effects, whereas combined

aerobic plus resistance programs offer synergistic benefits by reducing IHL and optimizing muscle profile. These findings support the inclusion of exercise as a first-line intervention in the management of type 2 diabetes with ectopic lipid accumulation and suggest that prescriptions should be individualized according to metabolic status and patient preferences. However, the available evidence has limitations related to small sample sizes, protocol heterogeneity, and lack of long-term follow-up, so larger and longer studies are needed to evaluate the sustainability of these adaptations and their impact on relevant clinical outcomes.

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