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REVIEW

Unlocking liver health: Can tackling myosteatosis spark remission in metabolic dysfunction-associated steatotic liver disease?

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Abstract

Myosteatosis is highly prevalent in metabolic dysfunction-associated steatotic liver disease (MASLD) and could reciprocally impact liver function. Decreasing muscle fat could be indirectly hepatoprotective in MASLD. We conducted a review to identify interventions reducing myosteatosis and their impact on liver function. Non-pharmacological interventions included diet (caloric restriction or lipid enrichment), bariatric surgery and physical activity. Caloric restriction in humans achieving a mean weight loss of 3% only reduces muscle fat. Lipid-enriched diet increases liver fat in human with no impact on muscle fat, except sphingomyelin-enriched diet which reduces both lipid contents exclusively in pre-clinical studies. Bariatric surgery, hybrid training (resistance exercise and electric stimulation) or whole-body vibration in human decrease both liver and muscle fat. Physical activity impacts both phenotypes by reducing local and systemic inflammation, enhancing insulin sensitivity and modulating the expression of key mediators of the muscle-liver-adipose tissue axis. The combination of diet and physical activity acts synergistically in liver, muscle and white adipose tissue, and further decrease muscle and liver fat. Several pharmacological interventions (patchouli alcohol, KBP-089, 2,4-dinitrophenol methyl ether, adipoRon and atglistatin) and food supplementation (vitamin D or resveratrol) improve liver and muscle phenotypes in pre-clinical studies by increasing fatty acid oxidation and anti-inflammatory properties. These interventions are effective in reducing myosteatosis in MASLD while addressing the liver disease itself. This review supports that disturbances in inter-organ crosstalk are key pathophysiological mechanisms involved in MASLD and myosteatosis pathogenesis. Focusing on the skeletal muscle might offer new therapeutic strategies to treat MASLD by modulating the interactions between liver and muscles.

Abbreviations: ^{1}H-MRS, proton magnetic resonance spectroscopy; ATG, atglistatin; C15:0, pentadecanoic acid; CAP, controlled attenuation parameter; CGF, canagliflozin; CT, computed tomography; EGF, empagliflozin; EMLC, extramyocellular lipid content; FAO, fatty acid oxidation; GLUT, glucose transporter; IMLC, intramyocellular lipid content; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MRI, magnetic resonance imaging; PPAR, peroxisome proliferator-activated receptor; SGLT-2, sodium-glucose cotransporter 2; SIRT, sirtuin; SM, sphingomyelin; TE, transient elastography; WAT, white adipose tissue.

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KEYWORDS
diet, liver, MASLD, myosteatosis, physical activity, skeletal muscle

1 | BACKGROUND

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most prevalent chronic liver disease worldwide and is strongly linked to obesity epidemic.[1] MASLD is a spectrum spanning from isolated steatosis, metabolic-associated steatohepatitis (MASH) leading to the onset of liver fibrosis to cirrhosis and hepatocellular carcinoma in a metabolic context (overweight, insulin resistance, metabolic syndrome).[1–3]

Besides hepatic complications, MASLD leads to numerous extra-hepatic complications including muscle changes. In particular, myosteatosis, defined by an excessive muscle lipid content, is highly prevalent already at non-cirrhotic stages of MASLD and is associated with poor clinical outcomes, including all-cause mortality, and cardiovascular events.[4,5] Muscle fat is also correlated to insulin resistance[6,7] and muscle function decay[4,8] in MASLD but these observations are more controversial and further data in humans are needed. Myosteatosis is even more prevalent in cirrhosis of any origin with a reported prevalence of more than 50% and is associated with its complications such as hepatic encephalopathy.[5,9–12] It is also likely that myosteatosis in cirrhosis contributes to the peripheral insulin resistance frequently observed in this situation.[12,13] Myosteatosis is defined by an excessive muscle lipid content though a consensus on the threshold is lacking.[10,14] Ectopic lipids are stored in the cytoplasm of myocytes (intramyocellular lipid content or IMLC) or in the interstitium (extramyocellular lipid content or EMLC).[15] Ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) are imaging techniques allowing non-invasive and quantitative assessment of muscle fat content.[16] However, only proton magnetic resonance spectroscopy (^{1}H-MRS) can determine the location of lipids in skeletal muscles non-invasively. Indeed, the resonance frequency of IMLC and EMLC slightly differs due to differences in micro-environmental interactions and variations in methylene group content.[17] Therefore, the best assessment tool to accurately assess muscle phenotype is ^{1}H-MRS.

The pathophysiology of myosteatosis in MASLD as well as its related metabolic consequences have been previously reviewed.[16] Among those pathophysiological mechanisms, liver disease activity and systemic inflammation play a key role in the onset of myosteatosis. Indeed, muscle lipid content assessed by CT in morbidly obese subjects is correlated to histological features of MASH and serum levels of inflammation biomarkers.[18–21]

Diet and physical exercise are currently the only effective treatment options for histological regression of MASLD.[22–25] However, although the results of the first molecules in this field were disappointing,[23,26] emerging drug therapies still investigated in phase 2 and 3 trials showed promising results in terms of MASH histological remission,[27] sometimes even combined with regression of fibrosis.[28,29] The pathophysiological mechanisms by which physical exercise improves liver function remain poorly known. There are two main hypotheses: physical activity modulates liver and muscle metabolisms independently or synergistically modulates the muscle-liver crosstalk. Physical activity could hypothetically firstly decrease muscle fat and modify the muscle secretome. Those mediators could secondarily modulate liver metabolism resulting in decreasing liver fat.

Hence, we propose to review the available data on interventions against myosteatosis in the context of MASLD and its reported effects on liver phenotype.

The results of this review are summarized according to intervention modalities as follows: non-pharmacological interventions, including diet, bariatric surgery and physical activity, followed by food supplements and pharmacological interventions targeting muscle and liver fat in MASLD.

Key points

- Decreasing muscle lipid content might positively impact liver function in metabolic dysfunction-associated steatotic liver disease.
- Physical activity improves both liver and muscle phenotype by anti-inflammatory properties, improving insulin sensitivity and modulating the muscle-liver-adipose tissue axis.
- Food supplementation in resveratrol and vitamin D decreases liver and muscle fat content in mice but needs further investigations in humans.
- Several non-muscle targeting pharmacological interventions are reported to improve liver and muscle phenotype exclusively in pre-clinical studies.
- Targeting lipid content to enhance skeletal muscle health appears as a promising therapeutic strategy to treat metabolic-dysfunction-associated steatotic liver disease.

2 | NON-PHARMACOLOGICAL INTERVENTIONS

As mentioned above, no medical treatment approved by regulatory agency is currently available for MASLD subjects.[26] Therefore, therapeutic options for MASLD subjects are limited in clinical practice to two types of non-pharmacological interventions: diet changes and physical exercise. However, although independently effective

to induce a histological remission of MASH and liver fibrosis reversal through weight loss, their respective mechanisms of action on liver and skeletal muscle are not entirely known. Here, we summarize the studies that investigated the impact of diet and physical exercise on liver and muscle fat content in pre-clinical and clinical models of MASLD.

2.1 | Diet

Weight loss dietary regimens have demonstrated to reduce liver steatosis and MASLD progression from a 7% weight loss[30] though few studies focused simultaneously on both liver and skeletal muscles. Two main types of interventions have been investigated on that topic: caloric restriction, by diet or bariatric surgery, and lipid-enriched diet (Figure 1).

2.1.1 | Caloric restriction

One pre-clinical study investigated the impact of a 20-week low-fat diet (9%) on a 30-week high-fat diet-induced mouse model of MASH[31] compared to 50-week high-fat diet. Low-fat diet decreased total body weight (−18%), insulin resistance and dyslipidaemia. This weight loss was correlated to a decrease in liver macrovesicular steatosis (−57%) and histological features of MASH with a drop in lobular inflammation (−94%) and fibrosis (−42%). A decrease in quadriceps lipid content (−34%) was also observed as well as muscle strength improvement assessed by grip strength (+18%). Interestingly, low-fat diet also reduced systemic and white adipose tissue (WAT) inflammation as shown by a decrease in TNF-α plasma level and adipose infiltration of macrophages. This observation was confirmed by transcriptomics profiling of liver, quadriceps and WAT highlighting a diet-related multi-systemic downregulation of several inflammatory pathways.[31]

In humans, a mean weight loss of 3% of the mean total body weight induced a decrease in subcutaneous adipose tissue and IMLC, but not EMLC, in tibialis anterior assessed by MRI and ^{1}H-MRS in 10 overweight patients following a 500 kcal-restricted diet for a period of 6 months.[32] However, liver lipid content assessed by MRI did not decrease while an improvement in aspartate aminotransferase serum levels was reported.[32] There was no change in muscles other than tibialis anterior. In particular, IMLC was not reduced in soleus, rich in oxidative muscle fibres. This observation argues against an increase in oxidative metabolism induced by the intervention.

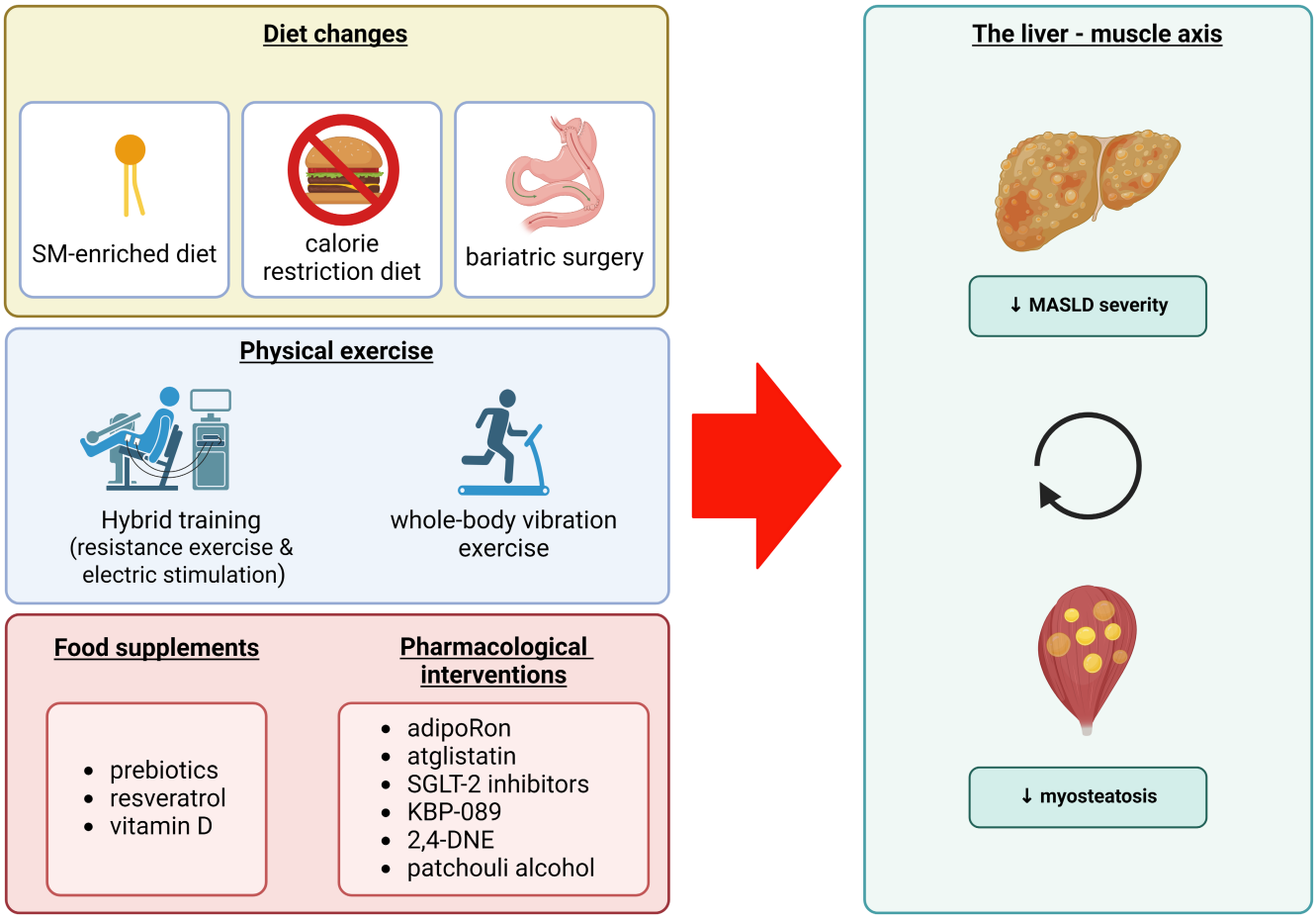

FIGURE 1 Graphical summary of interventions potentially decreasing muscle and liver fat contents in MASLD. DNE, dinitrophenol-methyl ether; MASLD, metabolic dysfunction-associated steatotic liver disease; SGLT-2, sodium/glucose cotransporter 2; SM, sphingomyelin.

Eventually, It is important to note that although the beneficial effect of calorie restriction is well described in MASLD, compliance remains a major problem.[22]

2.1.2 | Lipid-enriched diet

Sphingolipids are reported to improve both liver and muscle lipid content in MASLD. Among those sphingolipids, sphingomyelin (SM) is found in animal products such as eggs or dairy.[33] Previous data highlighted that SM from eggs reduces in a dose-dependent way cholesterol, fatty acid and triglyceride intestinal absorption in a mouse model of MASLD[34] (Figure 1).

Decreased lipid absorption is associated with a decreased storage in adipose and in ectopic tissues such as muscle and liver, the latter being linked to a reduced expression of peroxisome proliferator-activated receptor (PPAR) γ2.[35] Lower adipose storage induced by SM is associated with a decrease in WAT infiltration by macrophages and improvement of adipose insulin sensitivity and fatty acid oxidation (FAO).[35] Hence, increasing SM oral intake in the context of a high-fat diet might decrease liver and muscle fat content by reducing lipid absorption, but also probably by a positive impact on WAT.

Another study focused on the impact on both liver and skeletal muscles of the quantity as well as the quality of fatty acids orally supplemented.[36] Irrespective of the type of fat (animal saturated lipid, polyunsaturated lipids rich in n-3 fatty acids, and mixed lipid diets at 300 g lipid/kg), fat-rich diets increase liver lipid content.[36] In contrast, none of those diets impact muscle lipid content.[36] It was shown that lipid-enriched diets promoted the intramyocellular uptake of fatty acids by increasing the expression of cluster of differentiation 36 (CD36).[36] In addition, they also enhance mitochondrial FAO in muscles by increasing the expression of the peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α) and the mitochondrial transporter carnitine palmitoyltransferase 1 (CPT1).[36] Therefore, muscle lipid content histologically assessed remains unchanged, with increased lipid uptake being compensated by greater lipid combustion.[36] Furthermore, only the diet enriched in animal saturated lipids was reported to promote obesity and insulin resistance independently of muscle lipid content.[36] The type of enriched lipids has an impact on liver and skeletal muscle lipid metabolism independently of the quantity.

2.1.3 | Combined caloric restriction and lipid-enriched diet

Pentadecanoic acid (C15:0), an odd-chain saturated fatty acid from milk, has been investigated in combination with a restricted calorie Mediterranean-like diet in a cohort of Chinese females with MASLD and compared with diet without supplementation or habitual diet.[37] Body weight and total adiposity assessed by MRI and bioelectrical impedance equally decreased in all three groups.[37] Liver fat content assessed exclusively by PDFF similarly decreased but there was no difference between the C15:0 substituted group and the Mediterranean-like diet group.[37] No impact on muscle fat assessed by ^{1}H-MRS was observed in all three groups.[37]

Therefore, none of these fat-rich diets is recommended on its own or in combination with calorie restriction in MASLD.

2.1.4 | Other types of diet

Previous studies focusing on the impact of intermittent fasting or ketogenic diet on MASLD subjects reported a decrease in body weight and liver fat.[22,38] Though intermittent fasting is reported to decrease muscle mass,[39] its impact on muscle lipid content has not been previously investigated. Similarly, studies evaluating the effect of a ketogenic diet on myosteatosis in MASLD subjects are missing.

2.2 | Bariatric surgery

Duodenal-jejunal bypass in obese mice demonstrated an early decrease in liver and muscle lipid content independently of weight loss by promoting lysosomal lipolysis in both tissues[40] via the degradation of perilipin 2 triggered by lysosomal associated membrane protein 2.[40,41] In parallel, insulin sensitivity is increased in liver and muscles.[40] This observation has been confirmed in a cohort of 24 morbidly obese subjects undergoing gastric bypass using histology to assess liver steatosis and CT for psoas lipid content before and 14 months after bariatric surgery.[18] A simultaneous decrease in liver and muscle lipid contents was observed.[18] As in rodents, the decrease in muscle lipid content was not positively correlated to weight loss.[18] By contrast, the decrease in muscle lipid content was highly correlated to the histological remission of MASH.[18]

2.3 | Physical exercise

Physical activity has many health benefits notably by improving metabolic disturbances through interactions between skeletal muscle and multiple organs such as liver, adipose tissue or even bones. Indeed, physical activity reduces liver steatosis independently of weight loss.[24,42–44]

However, the mechanisms involved and the type of exercise (aerobic versus resistance) to be preferred remain unclear. Aerobic exercise is associated with a higher energy consumption in comparison to resistance exercise and thereby aerobic exercise counteracts some metabolic syndrome features such as serum cholesterol or glucose levels in humans.[45] Aerobic exercise also requires efficient cardiorespiratory reserves. Importantly, moderate-intensity activity is not contraindicated under supervision and after medical clearance in case of cardiovascular comorbidities[45,46] (Figure 2).

Resistance exercise is based on muscle contractions against external resistance. It is also correlated to the improvement of metabolic syndrome features[42,47] although at the cost of a lower energy

expenditure.[48] Hence, resistance exercise might be a good alternative to aerobic exercise, especially in case of poorer cardiorespiratory capacity. However, the cost-benefit ratio is less in favour of resistance exercise because it requires a bit more equipment compared to aerobic exercise (Figure 2).

Both aerobic and resistance exercises reduce transaminase levels or intrahepatic lipids in MASLD without reported differences between these two types of exercise in humans.[48]

However, resistance exercise might have a deeper impact on lipid metabolism by specifically increasing skeletal muscle expression of irisin,[49,50] a myokine that promotes browning in subcutaneous adipose tissue and thermogenesis[51] and whose serum level decreases in MASLD[52] (Figure 2). Hence, resistance exercise should be preferred due to a better impact on lipid profiles and greater cardiovascular safety.[48] However, effects of irisin on muscle lipid content are not known.

Physical activity increases the rate of MASLD remission non-invasively assessed and independently of weight loss,[24,43] but data on the impact of exercise alone on liver histology are scarce. Yet, the mechanisms linking physical activity and liver phenotype improvement are poorly described. The following section firstly focuses on the impact of physical activity on liver and muscle phenotypes in MASLD, and secondly on the highlighted mechanisms of action linking these two.

Many trials studied the impact of physical exercise on MASLD subjects and the mechanisms involved. However, the recognition of myosteatosis and its potential role in MASLD being recent,[18] only a few published studies investigated the impact of physical activity on muscle lipid content in MASLD.

2.3.1 | Physical exercise, muscle and liver fat in rodents

Chronic aerobic exercise during 20 weeks simultaneously decreased liver and muscle lipid contents in high-fat diet-fed animals.[31] It decreased body weight (−18%), plasma cholesterol (−18%), microvesicular steatosis (−42%) and hepatic cholesterol esters (−13%). It also decreased triglycerides in quadriceps (−38%) although this was not a consistent finding across studies.[31,53] Conversely to dietary measure, physical activity had no impact on liver macrovesicular steatosis.[31] This might be explained by the fact that exercise and diet do not decrease the same lipid species in the liver. Exercise decreased hepatic cholesterol esters and enhanced FAO by promoting the expression of AMPK and ACOX1 while diet reduces hepatic triglycerides, hepatic free cholesterol and cholesterol esters.[31] Four weeks of rotarod training in a rat model of MASLD also decreased liver lipid content but gastrocnemius and hamstring fat content histologically assessed remained unchanged.[54]

2.3.2 | Physical exercise, muscle and liver fat in MASLD subjects

Two types of physical exercise have been investigated in human subjects and are discussed in the following section: one form of hybrid training combining resistance exercise with electric stimulation and whole-body vibration exercise.

The form of hybrid training investigated in this topic combined spontaneous skeletal muscle contractions against resistance and

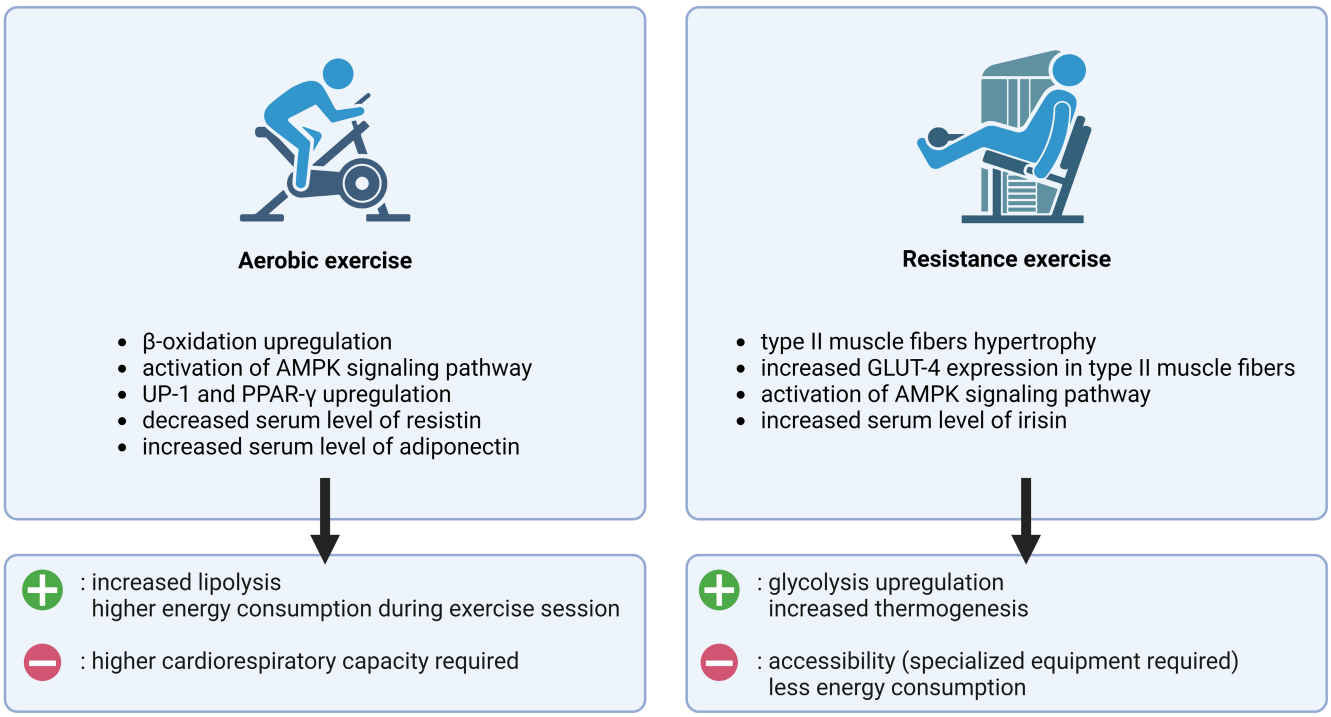

FIGURE 2 Comparison of advantages and disadvantages of aerobic and resistance exercises. AMPK, adenosine monophosphate kinase; GLUT, glucose transporter; PPAR, peroxisome proliferator-activated receptor; UP, ubiquitin pathway.

simultaneous electrical stimulation in the antagonist muscles leading to a greater exercise load. This form of hybrid training was firstly developed for astronauts to prevent muscle atrophy secondary to space weightlessness.[55] It can be performed when seated which is especially convenient for obese patients frequently suffering from joint pain. In a cohort of 15 obese women with MASLD, a 19-minute session of this hybrid exercise on thigh muscles, twice a week for 24 weeks, decreased serum liver transaminases and liver steatosis assessed by ultrasound. ^{1}H-MRS demonstrated a decrease in quadriceps IMLC but not in hamstrings. Quadriceps strength was also improved.[56] No other type of hybrid training (e.g. aerobic with resistance exercise) has been investigated in this topic.

Whole-body vibration induces passive exercise via intense vibratory stimulation producing dynamic changes in muscle fibre length through oscillations. Two studies investigated whole-body vibration exercise in overweight MASLD subjects.[57,58] Eighteen obese and 25 overweight subjects were enrolled in 3 or 6-month supervised programs of whole-body vibration exercise respectively.[57,58] All patients experienced a decrease in visceral adiposity, in liver steatosis, assessed by CAP and ^{1}H-MRS, and in transaminases.[57,58] Quadriceps lean mass and strength assessed by isokinetic dynamometer and bioelectrical impedance increased.[57,58] Surprisingly, the 3-month program in obese subjects but not the 6-month program in overweight participants decreased IMLC exclusively in quadriceps. In both trials, the intervention had no effect on systemic insulin resistance assessed by the homeostasis model of insulin resistance and liver stiffness assessed by transient elastography (TE).[57,58] Hence, vibration seems to benefit more to obese MASLD subjects than hybrid training.[57,58] This might be related to the passive nature of whole-body vibration in comparison with hybrid training, for example, and the secondary lack of myocyte lipid catabolism enhancement. Unfortunately, energy expenditure was not assessed in this clinical trial.

Data on the effects of resistance exercise on muscle lipid content in non-obese subjects with MASLD are not available.

Interestingly, a single 45-min session of aerobic exercise on an elliptical trainer in 12 young, lean and insulin-resistant subjects already decreases liver lipid content assessed by ^{1}H-MRS because it increases substrate consumption and insulin sensitivity.[59]

A key issue of physical activity in MASLD is motivation and compliance. Aerobic exercise is accessible to everyone and does not require assistance or special equipment or infrastructure. This is not the case for resistance exercise. There are many obstacles limiting long-term physical activity including psychological disorders such as depression, anxiety or fatigue that are highly prevalent in MASLD.[60–62]

The question was addressed by comparing the effects of supervised aerobic exercise and lifestyle counselling on liver and muscle lipid contents in 69 obese subjects with MASLD (38 in the supervised exercise group vs 31 in the counselling group).[53] The aerobic exercise program consisted of exercises of moderate intensity including treadmill and bike ergometer for 16 weeks.[53] A higher weight loss was observed in the supervised exercise group. Liver lipid content assessed by ^{1}H-MRS further decreased in that group as well.[53] Liver disease severity at baseline and effects of the intervention on it were not investigated.[53] Supervised exercise improved insulin sensitivity in parallel with weight loss but no correlation with reduced liver lipid content was reported.[53] Interestingly, there was no change in soleus and tibialis anterior lipid contents in either group as assessed by ^{1}H-MRS.[53]

Consequently, supervision of physical activity in patients with MASLD, particularly if they are obese, should be encouraged rather than simple counselling, since this seems to counteract the psychological limitations.

2.3.3 | Exercise promotes MASLD remission by counteracting insulin resistance

The benefits of physical activity on insulin resistance in MASLD patients have been repeatedly described. However, the mechanisms involved are poorly understood. Recently, researchers focused on skeletal muscle insulin resistance with the hypothesis that muscle fat itself might contribute to peripheral insulin resistance. Indeed, pre-clinical studies on MASLD mouse models highlighted that insulin resistance sequentially appears in the steatotic liver, WAT and then eventually skeletal muscle.[22,63–66]

Skeletal muscle plays a central role in glucose homeostasis by taking up to 90% of serum glucose in response to insulin stimulation.[67] One key mechanism of muscle glucose uptake is the membrane expression of glucose transporter 4 (GLUT4).[68] Indeed, GLUT4 exocytosis from cytosolic storage vesicles is suppressed in vitro and in insulin-resistant mouse models.[69–71] When insulin resistance occurs in skeletal muscle, glucose is hypothetically redirected from myocyte mitochondrial aerobic respiration for energy expenditure or glycogen synthesis to hepatic lipogenesis, eventually leading to increased triglyceride serum level and metabolic syndrome-related complications.[72] Hence, targeting skeletal muscle insulin resistance might decrease hepatic lipogenesis and so liver lipid content and MASLD.

However, the data on the impact of myosteatosis reduction on insulin resistance are contradictory and vary according to the type of physical exercise assessed. Four weeks of aerobic exercise protects against metabolic consequences of high-fat diet in a mouse model of MASLD. Systemic insulin resistance is assessed by glucose and insulin tolerance tests and improves by decreasing lipid content in the liver and in hamstring muscles and quadriceps.[54] Highlighted pathophysiological mechanisms included a downregulation of hepatic lipogenic genes (PPARα, ChREBP, Fsp27, LXR) and an enhanced muscle insulin sensitivity by decreasing the expression of TRIM72, a lipid raft protein antagonizing IRS-1,[73] and activating the PI3K/Akt/mTOR, resulting in the upregulation of GLUT4 expression.[54]

Interestingly, a single short exercise session of aerobic exercise increased more than threefold postprandial muscle glycogen synthesis in young, lean and insulin-resistant subjects but it did not change muscle fat.[59] Hepatic lipogenesis and triglyceride synthesis

also decreased though glycogen content assessed by carbon magnetic resonance spectroscopy remained unchanged.[59] Therefore, the benefit of exercise on insulin resistance could be mediated primarily by the improvement of skeletal muscle insulin sensitivity, independently of changes in muscle lipid content; the improved insulin sensitivity secondarily reduces hepatic lipogenesis.

2.3.4 | Exercise promotes MASLD remission by decreasing local and systemic inflammation

Systemic inflammation plays a key role in MASLD and related complications, including myosteatosis. Several circulating inflammatory mediators are involved in its pathogenesis including TNFα, IL6, IL15, INFα2.[16]

The anti-inflammatory properties of physical exercise have been demonstrated in pre-clinical and clinical MASLD studies. In MASLD mouse models, exercise decreases muscle expression of TNF-α and IL-6 by downregulating the NF-κB signalling pathway,[54] though to a lower extent compared to the effect of low-fat diet.[31] TNF-α circulating level was also decreased.[31] While low-fat diet had a more pronounced effect on reducing inflammation in the liver and in the adipose tissue, exercise significantly inhibited the activation of hepatic stellate cells, thereby reducing fibrosis.[31]

In clinical studies, circulating levels of TNF-α and IL-6 were decreased by both resistance and aerobic exercises.[56–58]

Therefore, physical exercise has multi-systemic anti-inflammatory properties eventually decreasing systemic and local inflammation as demonstrated by a lower level of circulating and local inflammatory biomarkers.

2.3.5 | Exercise modulates the expression of tissue-specific mediators involved in the liver-muscle-adipose tissue axis

As mentioned above, pre-clinical data highlighted the impact of physical activity on all organs involved in the liver-muscle-adipose tissue axis at the transcription level.[31] However, circulating mediators linking this inter-organ crosstalk are poorly known.[16] Among those mediators, physical activity particularly impacts adipokine serum levels in pre-clinical and clinical models.[31,56–58] Indeed, aerobic exercise increases adiponectin[57,58] while aerobic and resistance exercises decrease leptin serum levels.[56,57] Increased serum adiponectin, found to be low in MASLD, promotes β and ω FAO in skeletal muscle by recruiting AMPK and PPARα signalling pathways.[74,75] The improved muscle mitochondrial function is in fact the main impact of physical exercise on muscle transcriptomic profile in MASH mice.[31] On the contrary, the decrease in leptin serum level, found to be high in MASLD,[76,77] is associated with lower hepatic lipogenesis and improved insulin sensitivity. In summary, the effects of physical activity on liver and muscle lipid content are notably mediated by resolving disturbances in the liver-muscle-adipose tissue axis occurring in MASLD. Although many other tissue-specific mediators involved in this axis have been previously highlighted,[78] no other was reported as modulated by physical activity and to impact myosteatosis in MASLD. Of note, high-intensity interval training has not been investigated in this topic but could also have an impact on muscle fat content notably by increasing the muscle expression of irisin, a myokine-promoting WAT browning.[79,80]

2.4 | Combining physical exercise and diet: the winning combo?

Only one study investigated the separate and combined effects of low-fat chow diet and physical exercise for 20 weeks in a mouse model of MASLD-fed high-fat diet for 30 weeks.[31] Combination therapy further decreased body weight (−32%) and liver steatosis compared to diet or physical exercise alone by simultaneously impacting micro- (−77%) and macrovesicular steatosis (−79%). Lobular inflammation was also further decreased (−95%). However, combining diet and exercise had no further impact in terms of fibrosis regression compared to diet alone. Concerning skeletal muscle lipid content, combination therapy further decreased quadriceps lipid content (−59%) as shown by histology and tissue lipid extraction. Interestingly, transcriptomics analysis of liver, quadriceps and WAT from a mouse model of MASLD demonstrated that the combined therapy impacts its own pathways not equivalent to the sum of those respectively expressed by physical exercise and diet.[31] Therefore, combination therapy appears more efficient in decreasing both liver and muscle lipid content compared to diet and physical activity alone by specific mechanisms of action. In humans, we know that weight loss achieved by dietary measures combined with physical activity advice of 200 min of walking a week is effective against MASH (on histology).[25] Additional studies are needed to evaluate the effect of combination therapy on human MASH, liver fibrosis and myosteatosis.[31]

2.5 | Food supplements

Despite the fact that MASLD is the most common chronic liver disease worldwide, there is currently no pharmacological treatment approved by the Food and Drug Administration and the European Medicines Agency to treat MASLD besides experimental treatments in pharmacological clinical trials.[23] We summarize here the very few studies investigating the impact of food supplements, including vitamin D, prebiotics and resveratrol on both muscle and liver lipid contents in pre-clinical models of MASLD (Figure 3). This topic has not been investigated in humans yet (Table 1).

2.5.1 | Vitamin D

A strong correlation between low serum level of 25-hydrocholecalciferol, high body mass index, insulin resistance and β-cell dysfunction has been previously reported in MASLD patients.[81]

This observation is related to the decreased bioavailability of vitamin D sequestrated within the body fat.[82] Oral supplementation in 1.25-dihydroxycholecalciferol improves metabolic parameters including body weight, insulin resistance and liver steatosis in obese mice.[83] Vitamin D supplementation also induces a drop in muscle lipid content histologically assessed and therefore counteracts the major negative consequences related to high-fat diet in mice.[83] This might be related to insulin signalling improvement as supported by a reduction in Ser^{307} phosphorylation of IRS-1, but also by reduced skeletal muscle inflammation as supported by the lower activation of NF-κB[83] (Figure 3). No study investigated the impact of vitamin D supplementation on muscle lipid content and liver histology in MASLD subjects.

2.5.2 | Prebiotics

Prebiotics are nutrients selectively metabolized by gut microorganisms.[84] Inulin-type fructans are dietary fibres highly concentrated in some vegetables.[85] A 3-month oral supplementation with inulin-type fructans combined with caloric restriction induced a greater weight loss in a cohort of 150 obese subjects compared to caloric restriction alone.[86] Liver and muscle lipid contents were assessed in a subgroup of 35 obese patients and no effect on liver and muscle lipid contents was observed as assessed by CAP and CT respectively.[87] An additional analysis was carried out on participants in the cohort who completed the long form of international physical activity questionnaire.[88] Liver enzymes (aspartate aminotransferase and gamma-glutamyl transferase) and liver stiffness assessed by TE further decreased in participants treated with inulin who voluntarily increased their level of physical activity during the study. These synergistic effects were confirmed in obese mice. Exercise decreases circulating lipids and hepatic steatosis, and tends to reduce the degree of intramuscular fat. The combination of exercise and inulin improved glucose tolerance notably by increasing the expression of GLUT4 in skeletal muscle.[88]

2.5.3 | Resveratrol

Resveratrol is a natural antioxidant present in grape seeds and pips. It activates sirtuin-1 (SIRT-1), a cytosolic nicotinamide

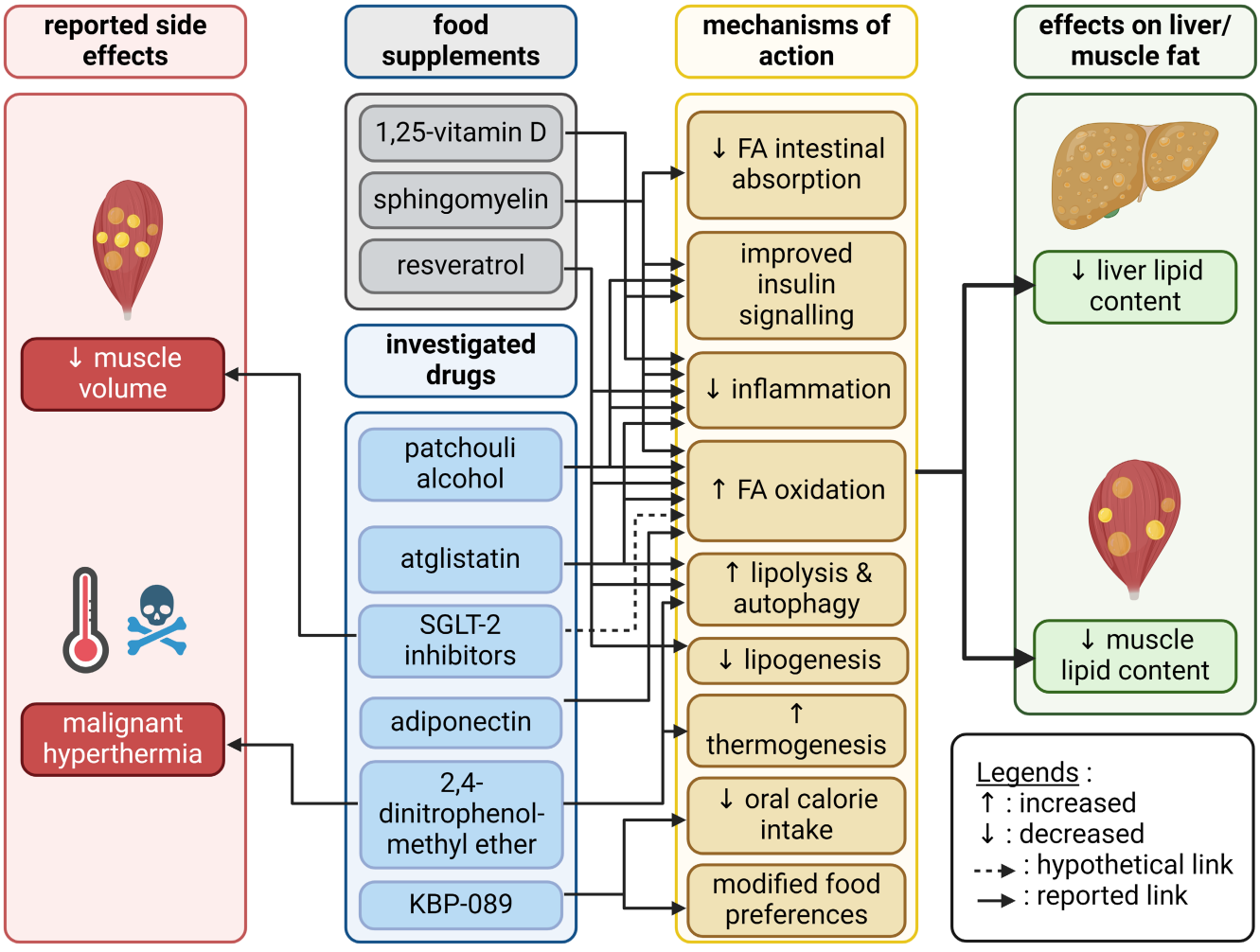

FIGURE 3 Pharmacological interventions and food supplements potentially decreasing muscle and liver fat contents and related mechanisms of action in MASLD. FA, fatty acids; SGLT-2, sodium/glucose cotransporter 2.

TABLE 1 Original articles on pre-clinical models included in this systematic review listed in alphabetical order by first authors.

Original manuscript references	Pre-clinical models of MASLD	Diet/treatment groups compared	Investigated muscles	Investigation technique of liver and muscle lipid content	Liver/muscle fat changes induced by intervention
Angelini et al.[40]	Wistar rats	*N* = 20 Duodenal-jejunal bypass on HFD (*N* = 10) Sham operation on HFD (*N* = 10)	Not available	Liver: optical microscopy Muscle: optical microscopy	Liver: ↓ Muscle: ↓
Benetti et al.[83]	C57BL/6J mice	*N* = 40 control group on ND (*N* = 10) ND & vitamin D (*N* = 6) HFHS diet (*N* = 10) HFHS diet & vitamin D (*N* = 14)	Gastrocnemius	Liver: optical microscopy Muscle: optical microscopy	Liver: ↓ Muscle: ↓
Feillet Coudray et al.[36]	Wistar rats	*N* = 48 Mixed diet with 5% (*N* = 8) or 30% lipids (*N* = 8) Lard diet with 5% (*N* = 8) or 30% lipids (*N* = 8) Fish oil diet with 5% (*N* = 8) or 30% lipids (*N* = 8)	Gastrocnemius	Liver: tissue lipid extraction Muscle: tissue lipid extraction	Liver: ↓ Muscle: ↔
Gydesen et al.[99]	Male SD rats ZDF rats	*N* = 39 ND rats on KBP-089 (*N* = 9) or vehicle (*N* = 10) and HFD ZDF rats on KBP-089 (*N* = 10) or vehicle (*N* = 10) and ND	Gastrocnemius	Liver: optical microscopy Muscle: optical microscopy	Liver: ↓ Muscle: ↓
Liu et al.[93]	C57BL/6J mice	*N* = 32 Control group on ND (*N* = 5) MASH group on HF-MCD (*N* = 9) MASH-resv group on HF-MCD & resv (*N* = 9) MASH-resv & EX527 group on HF-MCD & resv & EX527 (*N* = 9)	Gastrocnemius	Liver: optical microscopy Muscle: optical microscopy	Liver: ↓ Muscle: ↓
Norris et al.[35]	C57BL/6J mice	*N* = 52 Low-fat diet (*N* = 10) High-fat high-cholesterol diet (*N* = 14) High-fat and milk sphingomyelin diet (*N* = 14) High-fat and egg sphingomyelin diet (*N* = 14)	Quadriceps	Liver: tissue lipid extraction Muscle: tissue lipid extraction	Liver: ↓ Muscle: ↓
Perry et al.[105]	C57BL/6J mice	*N* = 4–8 per group HFD & DNPME HFD & vehicle	Quadriceps	Liver: tissue lipid extraction Muscle: tissue lipid extraction	Liver: ↓ Muscle: ↓
Selvais et al.[107]	C57BL/6J mice	(*N* per group not available) Old mice (62 weeks) on ND Old mice on HFD Old mice on HFD and adipoRon Young mice (12 weeks) on ND	Paravertebral muscles, soleus, extensor digitorum longus	Liver: optical microscopy Muscle: micro-CT & electronic microscopy	Liver: ↓ Muscle: ↓

(Continues)

TABLE 1 (Continued)

Original manuscript references	Pre-clinical models of MASLD	Diet/treatment groups compared	Investigated muscles	Investigation technique of liver and muscle lipid content	Liver/muscle fat changes induced by intervention
Van den Hoek et al.[31]	Ldlr −/−.leiden mice	N = 99 ND for 30 weeks (N = 19) HFD for 30 weeks (N = 10) HFD for 50 weeks (N = 17) HFD for 50 weeks and exercise (N = 17) HFD for 30 weeks followed by low-fat diet for 20 weeks (N = 18) HFD for 30 weeks followed by low-fat diet for 20 weeks and exercise (N = 18)	Gastrocnemius, quadriceps	Liver: optical microscopy Muscle: optical microscopy	Liver: ↓ Muscle: ↓
Yu et al.[54]	Female SD rats	N = 6–9 per group ND ND & exercise HFD HFD & exercise	Hamstrings, gastrocnemius	Liver: optical microscopy Muscle: optical microscopy	Liver: ↓ Muscle: ↓

Abbreviations: ↓, decreased; ↔, unchanged; CT, computed-tomography; DNPME, 2,4-dinitrophenol-methyl ether; HFD, high-fat diet; HFHS, high fat high sugar; HF-MCD, high-fat methionine and choline-deficient diet; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; NASH, non-alcoholic steatohepatitis ND, normal diet; resv, resveratrol; SD, Sprague Dawley; ZDF, Zucker diabetic fatty.[31,35,36,40,54,83,93,99,105,107]

adenine dinucleotide-sensitive deacetylase expressed in liver, adipose tissue and skeletal muscle.[89] SIRT-1 modulates the transcriptional activity and gene expression of key transcription factors involved in lipid and energy metabolism.[89] SIRT-1 limits excessive lipid storage by decreasing lipogenesis, increasing FAO, decreasing oxidative stress as well as local and systemic inflammation.[89] Of interest, SIRT-1 liver expression is downregulated in MASH mice.[90] Beneficial effects of SIRT-1 have been reported in pre-clinical models with SIRT-1 deletion promoting MASLD[91] and MASLD progression, contrarily to SIRT-1 overexpression, which protects from MASLD.[92] A recent study investigated the impact of resveratrol on both liver and skeletal muscle in a mouse model of MASLD. A decrease in liver and gastrocnemius lipid content was observed in histology.[93] In parallel, insulin sensitivity and muscle function assessed by grip strength test and running distance were improved.[93] The decrease in triglyceride muscle content resulted from increased lipolysis, restored autophagy and decreased oxidative stress specifically mediated by SIRT-1 activation as shown in vivo and in vitro on palmitate-treated C2C12 myocytes[93] (Figure 3).

2.6 | Pharmacological interventions

2.6.1 | Patchouli alcohol

Patchouli alcohol is a tricyclic sesquiterpene with anti-inflammatory properties notably by suppressing NF-κB signalling pathway in cultured mouse macrophages and human monocytes.[94,95] This anti-inflammatory property was reported in MASLD. Indeed, in vitro, patchouli alcohol increases insulin sensitivity in palmitate-treated C2C12 myocytes and protects HepG2 cells from palmitate-induced fat accumulation.[96] Patchouli alcohol dampens inflammation in vitro and in vivo in a MASLD mouse model in a dose-dependent manner by activating the AMPK/SIRT-1 signalling pathway in liver and skeletal muscles eventually lowering pro-inflammatory markers (NF-κB and IκB)[96,97] (Figure 3). Besides this anti-inflammatory property, patchouli alcohol reduces liver steatosis and myosteatosis by increasing FAO in both myocytes and hepatocytes via the same signalling pathway[97] (Figure 3).

2.6.2 | KBP-089

KBP-089 is a dual amylin and calcitonin receptor agonist. Compounds of this therapeutic class reduce food intake and change food preferences in monkeys and rats leading to weight reduction and glucagon serum level suppression.[98,99] After 8 weeks of treatment, KBP-089 also decreases global adiposity as well as liver and gastrocnemius lipid contents as confirmed by histology. Furthermore, increases in glucose tolerance and even lean mass are reported.[99] Hence, its effects appear to be mediated by several mechanisms including reducing food intake, increasing lean mass and changing food preferences[99] (Figure 3). This drug family is currently studied in association with a glucagon-like peptide 1 receptor agonist to pharmacologically reduce food intake in animal models of type 2 diabetes.[100] However, KBP-089 has not yet been studied in human subjects (Table 2).

TABLE 2 Original articles on human subjects included in this systematic review listed in alphabetical order by first authors.

Original manuscript references	Clinical Models of MASLD	Diet/treatment groups compared	Investigated muscles	Investigation technique of liver/muscle lipid content	Liver/muscle fat changes induced by intervention
Chooi et al.[37]	Overweight Chinese females	*N* = 88 12-week high fibre, USFA diet & C15:0 supplements (*N* = 31) High fibre, USFA diet (*N* = 28) Nutritional counselling (*N* = 29)	Soleus	Liver: MRI Muscle: ^{1}H-MRS	Liver: ↓ Muscle: ↔
Cuthbertson et al.[53]	Non-diabetic and sedentary obese subjects	*N* = 69 16-week supervised exercise (*N* = 38) Exercise counselling (*N* = 31)	Soleus, tibialis anterior	Liver: ^{1}H-MRS muscle: ^{1}H-MRS	Liver: ↓ Muscle: ↔
Hiruma et al.[102]	Type 2 diabetes subjects	*N* = 44 12-week sitagliptin 100 mg/day (*N* = 19) Empagliflozin 10 mg/day (*N* = 23)	Tibialis anterior	Liver: optical microscopy and ^{1}H-MRS muscle: ^{1}H-MRS	Liver: ↓ (empagliflozin alone) Muscle: ↔
Nachit & Kwanten et al.[18]	Obese subjects	*N* = 39 Diet counselling (*N* = 15) Bariatric surgery (*N* = 24)	Psoas	Liver: optical microscopy Muscle: cross-sectional CT (L3)	Liver: ↓ Muscle: ↓
Nachit & Lanthier et al.[87]	Obese subjects	*N* = 48	Paravertebral and abdominal muscles	Liver: CAP Muscle: CT	Liver: ↓ Muscle: ↓
Nishimiya et al.[101]	Type 2 diabetes subjects	*N* = 9 6-month canagliflozin 100 mg daily	Paravertebral and abdominal muscles	Liver: MRI, CT & CAP Muscle: cross-sectional CT (L3)	Liver: ↓ Muscle: ↔
Oh et al.[57]	Obese subjects and lifestyle counselling failure	*N* = 18 12-week acceleration training program	Bilateral quadriceps	Liver: CAP & ^{1}H-MRS Muscle: ^{1}H-MRS	Liver: ↓ Muscle: ↓
Oh et al.[56]	Obese women and lifestyle counselling failure	*N* = 15 24-week hybrid training program	Hamstrings, quadriceps	Liver: US Muscle: ^{1}H-MRS	Liver: ↔ Muscle: ↓
Oh et al.[58]	Overweight subjects and lifestyle counselling failure	*N* = 45 6-month whole-body vibration program (*N* = 25) Control group (*N* = 20)	Quadriceps	Liver: CAP & ^{1}H-MRS Muscle: ^{1}H-MRS	Liver: ↓ Muscle: ↔
Rabol et al.[59]	Lean insulin-resistant subjects	*N* = 12 One 45-min session of aerobic exercise	Soleus, vastus lateralis	Liver: ^{1}H-MRS Muscle: ^{1}H-MRS	Liver: ↓ Muscle: ↔
Thomas et al.[32]	Overweight subjects	*N* = 10 6-month 500 kcal restricted diet	Soleus, tibialis anterior	Liver: ^{1}H-MRS Muscle: ^{1}H-MRS	Liver: ↔ Muscle: ↓

Abbreviations: ↓, decreased; ↔, unchanged; ^{1}H-MRS, hydrogen-magnetic resonance spectroscopy; C15:0, pentadecanoic acid; CAP, controlled attenuation parameter; CT, computed tomography; L3, third lumbar vertebra; MASLD, metabolic dysfunction-associated steatotic liver disease; MRI, magnetic resonance imaging; NASH, non-alcoholic steatohepatitis; TE, transient elastography; US, ultrasound; USFA, unsaturated fatty acids.[18,32,37,53,56–59,87,101,102]

2.6.3 | Sodium-glucose co-transporter 2 inhibitors

Canagliflozin (CGF), a sodium-glucose cotransporter 2 (SGLT-2) inhibitor, was investigated in a cohort of nine overweight patients with MASLD and type 2 diabetes for a period of 6 months at the dose of 100 mg daily.[101] CGF decreased body weight and total adiposity resulting in an enhanced insulin sensitivity.[101] Liver lipid content assessed by MRI and CAP decreased but with no impact on liver stiffness assessed by transient and magnetic resonance elastography at study completion.[101] Interestingly, CGF had no impact on muscle density of paravertebral and abdominal muscles at the third lumbar level assessed by CT.[101] Unfortunately, intra- and extramyocellular lipid content were not assessed. Empagliflozin (EGF), another SGLT-2 inhibitor, was also investigated in a cohort of 23 overweight patients with MASLD and type 2 diabetes at the dose of 10 mg/day for a period of 3 months.[102] EGF also decreased total adiposity, liver fat assessed by ^{1}H-MRS and hepatic insulin resistance specifically measured by hyperinsulinaemic-euglycaemic clamp.[102] No impact on IMCL and EMCL of tibialis anterior measured by ^{1}H-MRS was reported.[102] Interestingly, both SGLT-2 inhibitors decreased lean muscle mass measured by CT (CGF)[101] and dual-energy X-ray absorptiometry (EGF)[102] (Figure 3). Further large cohort studies investigating the impact of SGLT-2 inhibitors on muscle fat are needed considering the potential indirect decrease in IMCL. Indeed, SGLT-2 inhibitors promote FAO by decreasing glucose bioavailability through urinary excretion (Figure 3). Interestingly, EGF was compared to sitagliptin, a dipeptidyl peptidase-4 inhibitor, at the daily dose of 100 mg/day for 12 weeks also.[102] No changes in body mass index, total adiposity assessed by dual-energy X-ray absorptiometry and liver and muscle lipid content assessed by ^{1}H-MRS were reported.[102]

2.6.4 | 2,4-dinitrophenol-methyl ether

Mitochondrial uncoupling is defined by an induced reduction in proton fluxes in the mitochondrial electron transport chain resulting in decreased oxidative phosphorylation and ATP production.[103] The resulting decrease in mitochondrial oxidative capacity promotes a shift in energy metabolism and notably increases thermogenesis, lipolysis and lipophagy through activation of the AMPK signalling pathway and suppression of the PI3K-Akt-mTOR axis.[103] On the contrary, impairment of adaptive thermogenesis to high-fat dietary load in response to cold in a mouse model of MASLD promotes liver steatosis.[104] This uncoupling process can occur under physiological circumstances in skeletal muscle and brown adipose tissue such as physical activity through mediators called uncoupling proteins or be pharmacologically induced.[103] Mitochondrial uncouplers were used in the 30s as a treatment for obesity but were rapidly taken off the market by the FDA due to their lethal systemic side effects including malignant hyperthermia.[105] One of them, the 2,4-dinitrophenol-methyl ether, a liver-specific mitochondrial uncoupler, improved in a mouse model both liver and peripheral insulin sensitivity through a drastic reduction in liver and muscle diacyl and triacylglycerol content by over 40%. This decrease in liver and muscle lipid content secondarily induced a drop in protein kinase Cε and θ translocations in both tissues[105] (Figure 3).

2.6.5 | AdipoRon

Given the low levels of adiponectin in obesity and MASLD, as well as the beneficial effect of adiponectin on liver and skeletal muscle,[74,106] an orally active synthetic adiponectin analogue called adipoRon has been recently investigated in a mouse model of MASLD.[107] AdipoRon oral administration for 1 year induced a reduction in both liver and dorsal muscle lipid content assessed histologically and by CT, and an enhancement in skeletal muscle function assessed by a treadmill exhaustion test.[107] Electron microscopy confirmed reduction in IMLC.[107] AdipoRon promoted MASH remission by decreasing all histological features of liver disease activity. Those effects are mediated by restoring mitochondrial oxidative capacities through an increased AMPK pathway activation with no effect on liver or skeletal muscle mitochondrial biogenesis[107] (Figure 3).

2.6.6 | Atglistatin

Atglistatin (ATG) is a hydrophobic synthetic inhibitor of the adipose triglyceride lipase, key hydrolase involved in the triglyceride lipolysis of WAT. This inhibitor was orally administered for 140 days in mice with MASLD. It decreased total adiposity including liver and quadriceps lipid contents, resolved liver disease activity and corrected insulin resistance.[108] ATG also positively impacts WAT quality and not only its mass. Indeed, WAT-related inflammation is decreased by ATG administration as highlighted by a decrease in macrophage infiltration and a normalization of the expression profiles of adipokines. ATG increases adiponectin and decreases leptin serum levels fighting against global excessive lipid storage by promoting FAO (Figure 3). Although mechanisms of action were not investigated in skeletal muscle, its impact on liver and muscle lipid content is exclusively indirect. Indeed, ATG concentration was extremely low in skeletal muscle and hepatocyte lipolysis was not sufficiently inhibited to promote liver steatosis despite a higher liver concentration. Therefore, ATG probably decreased liver and muscle content by reducing fatty acids release from WAT.[108] This observation reinforced the important contribution of triglyceride lipolysis of WAT in MASLD pathogenesis.

3 | CONCLUSION

Myosteatosis in MASLD is highly prevalent and linked to the onset of peripheral insulin resistance, decay in muscle function and MASH. Liver and muscle phenotypes improvement are associated with pharmacological in rodents and non-pharmacological interventions

in humans and rodents. This review argues in favour of the multisystemic pathophysiology of MASLD and its complications mediated by complex disturbances in the muscle-liver-adipose tissue axis and related mediators. Consequently, re-establishing this interorgan dialogue by supplementing the mediators involved, such as adiponectin, or combating the main disruptors of this axis, such as systemic inflammation, are efficient and potentially promising therapies against MASLD. For the time being, physical activity and dietary intervention have been mainly explored as tools to intervene on the muscle-adipose-liver axis.

Although sphingomyelin has interesting effects in mice, the current dietary guidelines in humans are not in favour of lipid supplements in MASLD. Concerning physical activity, its beneficial effects in MASLD are well known and have recently been reviewed in a meta-analysis.[24] However, the mechanisms of action linking physical activity to MASLD remission are currently poorly known and clearly need further mechanistic clinical studies.

In terms of medications, some drugs have the potential to simultaneously decrease liver and muscle lipid contents as well as liver disease activity through several mechanisms of action. In this context, it is important to note that the effect of PPAR agonists on liver and muscle lipid content was not reviewed in this work despite their potential impact on both phenotypes. Besides the impact on liver fat content, it is important to notice that the only intervention linking a decrease in myosteatosis and MASH resolution in human is bariatric surgery.[18]

To conclude, reducing the lipid content to enhance skeletal muscle quality emerges as a noteworthy clinical outcome warranting further investigation, given the observed remission rate of MASLD. To this end, clarifications are needed in order to insure cross-study consistency. In particular, which muscle to assess and which imaging cut-off to use must be defined. MRI and ^{1}H-MRS are by far the most accurate techniques to follow the impact of an intervention on muscle lipid content and, at this stage, must be preferred to other less accurate imaging techniques. Therefore, further clinical trials on real-life cohorts of patients in whom liver and muscle lipid contents are simultaneously and properly monitored are required to disentangle the contribution of the liver-muscle-adipose tissue axis in the onset and the progression of MASLD and other steatotic liver diseases such as alcohol-related liver disease.

AUTHOR CONTRIBUTIONS

GH and NL conceived and designed the analysis; GH collected the data, performed the analysis and wrote the first draft of the manuscript; AL, IAL, LD and NL contributed to intellectual content, revised and edited the manuscript; IAL, LD and NL obtained funding; NL supervised the work; all authors revised and accepted the final version.

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CONFLICT OF INTEREST STATEMENT

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