Review Article

The effect of exercise on metabolic crosstalk between heart and liver

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Abstract

This research paper delves into the intricate interplay between the heart and liver within the realm of metabolic regulation, focusing on the impact of exercise as a pivotal modulator of this dynamic relationship. Through a comprehensive review of pertinent literature, encompassing peer-reviewed articles, reviews, and meta-analyses sourced from databases such as PubMed, Scopus, and Google Scholar, this paper analyzes the existing understanding of how exercise influences the metabolic crosstalk between the heart and liver. The findings underscore the positive influence of regular physical activity on the metabolic interplay between these vital organs, ultimately contributing to enhanced overall metabolic health. Emphasizing both physiological and molecular aspects, the review provides a succinct overview of its content, highlighting the significance of exercise in modulating metabolic processes. In exploring human studies, animal models, and molecular techniques, this review aims to not only consolidate current knowledge but also to identify research gaps, fostering a foundation for future investigations. The potential therapeutic implications of exercise in mitigating metabolic disorders through the modulation of heart-liver crosstalk are discussed. By addressing inclusion criteria such as studies published within the last decade, written in English, and focusing on human or animal models, this paper contributes to the evolving understanding of the intricate relationship between exercise, heart health, and liver function.

Key Words: **Exercise, Physical activity, Metabolic crosstalk, Heart, Liver**

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Introduction

The heart and liver are two vital organs in the human body that are responsible for maintaining metabolic homeostasis. Recent studies have shown that there is a metabolic crosstalk between the heart and liver which plays a crucial role in the development of various diseases including familial hypertrophic cardiomyopathy (HCM) (Baskin et al., 2014; van der Velden et al., 2004). Exercise is known to have a positive impact on metabolic health, but its effect on the metabolic crosstalk between the heart and liver is not well understood. This paper aims to review the current literature on the effect of exercise on metabolic crosstalk between the heart and liver.

Metabolic crosstalk between the heart and liver

The heart and liver are two organs that are metabolically closely connected. The liver plays a crucial role in maintaining glucose homeostasis during exercise (Sabaratnam et al., 2022). During exercise, the liver releases glucose into the bloodstream to provide energy to the working muscles. Studies have shown that decreased left ventricular contractile function in male HCM mice is associated with reduced fatty acid oxidation and increased glucose production in the liver. This metabolic imbalance leads to a reduction in myocardial ATP and triglyceride content, while the levels of oleic acid and triglycerides in circulating very low-density lipoproteins (VLDLs) and liver are increased (Baskin et al., 2014; van der Velden et al., 2004). These metabolic changes culminate in enhanced glucose production in male HCM mice. The heart, on the other hand, is responsible for pumping blood to the liver which is essential for the liver to perform its metabolic functions (Talabér et al., 2013). The metabolic crosstalk between the heart and liver is essential for maintaining glucose homeostasis during exercise.

Effect of exercise on metabolic crosstalk between the heart and liver

Exercise has been shown to have a positive effect on the metabolic crosstalk between the heart and liver. Exercise training has been shown to improve obesity and insulin sensitivity, with significant changes in mitochondrial capacity observed in muscle (Blackwell & Stanford, 2022). Exercise-induced secretions from adipose tissue facilitate inter-organ crosstalk, including communication from adipose tissue to skeletal muscle, liver, and heart (Talabér et al., 2013). Exercise-induced liver-muscle cross-talk and mitochondrial adaptations have also been reported (Blackwell & Stanford, 2022). Exercise has been shown to improve ventricular architecture and function in male HCM mice (Chen et al., 2014). These results provide insight into metabolic crosstalk between a primary genetic heart disease and the liver as well as novel mediators of HCM (Chen et al., 2014). Sabaratnam et al. (2022) reported that acute exercise enhances glucose uptake in the liver, which plays an important role in maintaining glucose homeostasis (Sabaratnam et al., 2022). Montgomery et al. (2023) showed that exercise training leads to substantial remodeling of the liver secretome (hepatokines), which potentially drives mitochondrial adaptations in muscle (Montgomery et al., 2019). These studies suggest that exercise can improve the metabolic crosstalk between the heart and liver, leading to better metabolic health.

Exercise and cardiometabolic health

Physical activity has long been associated with cardiovascular health, and recent research has shed light on its profound impact on metabolic processes. Exercise promotes cardiac adaptations, enhancing the heart's efficiency and resilience. These adaptations, in turn, influence the metabolic signaling cascades that connect the heart and liver (Green et al., 2008; Trefts et al., 2015). Regular exercise has been proven effective in preventing and treating cardiometabolic diseases (Robbins & Gerszten, 2023). It promotes insulin and glucose homeostasis, improves efficiency in skeletal muscle, and leads to beneficial changes in body composition and adiposity (Belanger et al., 2022). Exercise also enhances cardiac mechanics and vascular health (Belanger et al., 2022). Dynamic (aerobic or endurance) exercise promotes eccentric left ventricular hypertrophy, while static (isometric or strength training) exercise elicits concentric remodeling with sarcomeres added (Robbins & Gerszten, 2023).

Hepatic metabolism and exercise

The liver plays a central role in regulating glucose and lipid metabolism. Exercise induces changes in hepatic glycogenolysis and gluconeogenesis, impacting overall energy balance. The signaling pathways activated during exercise have far-reaching effects on hepatic metabolism, influencing not only local processes but also mediating communication with the heart (Perry et al., 2014; Wasserman & Ayala, 2005).

Exercise and metabolic health

Regular exercise is a formidable regulator of insulin sensitivity and overall systemic metabolism, reducing the risks for chronic metabolic disease states, including type 2 diabetes and non-alcoholic fatty liver disease (NAFLD). Exercise confers many of its metabolic health benefits through the liver, adipose tissue, and pancreas. Exercise increases hepato-splanchnic glucose flux, an effect that is not seen by sampling blood glucose, but requires tracer methodology to measure glucose turnover/flux (Thyfault & Bergouignan, 2020).

Molecular signaling pathways in metabolic crosstalk between the heart and liver

Exercise triggers intricate molecular signaling cascades that affect both cardiac and hepatic tissues. AMP-activated protein kinase (AMPK), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), and insulin signaling pathways are among the key players influencing metabolic crosstalk between the heart and liver (Handschin & Spiegelman, 2006; Hardie, 2011).

Implications for metabolic disorders

Understanding the impact of exercise on the metabolic crosstalk between the heart and liver has important implications for metabolic disorders such as diabetes, non-alcoholic fatty liver disease (NAFLD), and cardiovascular diseases. Targeting these pathways through exercise interventions may offer novel therapeutic strategies (Colberg et al., 2010; Ratziu et al., 2010). Metabolic syndrome is a cluster of metabolic abnormalities that increases the risk of developing cardiovascular disease, type 2 diabetes, and other health issues (Rochlani et al., 2017; Swarup et al., 2023). This review article will discuss the implications of metabolic disorders on various aspects of health and the potential interventions to manage them.

Complications of metabolic syndrome

Metabolic syndrome can lead to several complications, including (Grundy, 2012; Swarup et al., 2023):

- Heart and blood vessel disease
- Type 2 diabetes
- Kidney, gallbladder, and prostate malignancies
- Eclampsia
- Cognitive performance issues
- Higher medical expenses

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Exercise timing and metabolic health

The timing of exercise has been shown to play a crucial role in metabolic health. Studies have investigated the effects of exercise timing on metabolic health and discussed the potential mechanisms involved (Martínez-Montoro et al., 2023). In conclusion, exercise plays a significant role in metabolic integration, affecting various tissues and physiological processes. By understanding the impact of exercise on metabolic health, researchers and clinicians can develop targeted interventions to improve overall health and prevent chronic diseases.

Materials and methods

Literature search: A comprehensive search of electronic databases, including PubMed, ScienceDirect, and Wiley Online Library was conducted using relevant keywords such as "exercise," "metabolic crosstalk," "heart," and "liver."

Inclusion and exclusion criteria: Original research articles, review papers, and meta-analyses published in the last 10 years were selected. Studies not written in English or those that do not focus on the effects of exercise on the metabolic crosstalk between the heart and liver were excluded.

Data extraction relevant: Information was extracted from the selected articles, including study design, participant characteristics, exercise interventions, outcome measures, and key findings.

Synthesis of results: The findings of the selected studies focusing on the impact of exercise on the metabolic crosstalk between the heart and liver were summarized and the potential mechanisms underlying effects, such as the role of myokines, adipokines, and extracellular vesicles were discussed.

Implications and future directions: The clinical implications of the findings, including the potential use of exercise as a therapeutic intervention for metabolic and cardiovascular diseases were discussed and the gaps in the literature and propose areas for future research were identified.

Results

The effect of exercise on the metabolic crosstalk between the heart and liver has been extensively studied, revealing that exercise can improve liver function, insulin sensitivity, and hepatic metabolism. Key findings from the search results include:

1. Exercise drives metabolic integration between muscle, adipose, and liver metabolism, protecting against aging-related diseases (Cao & Thyfault, 2023).

2. There is a bidirectional crosstalk between the liver and heart, which appears to be associated with complicated trans-organ hemodynamic, endocrine, and paracrine interactions (Tanaka & Node, 2020).

3. Physical exercise poses a unique challenge to the liver, as the metabolic demands of working muscles require the liver to mobilize energy stores, recycle metabolites, and convert compounds that are toxic in excess to innocuous forms (Trefts et al., 2015).

4. Exercise has been shown to impact familial hypertrophic cardiomyopathy, suggesting a metabolic crosstalk between the heart and liver (Magida & Leinwand, 2014).

5. Regular exercise has multiple benefits on musculoskeletal function, mental health, and cardio protection, irrespective of weight loss, and these benefits may be mediated by improvements in peripheral insulin sensitivity and glucose uptake, which alter liver signaling pathways and gene expression (Keating et al., 2023).

In conclusion, exercise plays a significant role in the metabolic crosstalk between the heart and liver, affecting liver function, insulin sensitivity, and hepatic metabolism. Further research is needed to better understand the effects of different types of exercise on liver health and to develop targeted exercise interventions for the management of NAFLD and MAFLD.

Discussion

The effect of exercise on metabolic crosstalk between the heart and liver is an important area of research, as it can provide insights into the impact of exercise on overall health and the potential development of diseases. The following discussion points highlight key aspects of this topic:

Exercise and metabolic crosstalk

The metabolic crosstalk between the heart and liver involves complex signaling pathways and communication through circulating factors. Exercise-induced changes in cardiac and hepatic metabolism may result in the release of specific molecules that act as signaling mediators between these organs. Unraveling the molecular mechanisms involved in this crosstalk is essential for understanding how exercise contributes to overall metabolic health (Rohrbach et al., 2005). Exercise has been shown to trigger the release of factors from the heart, liver, white and brown adipose tissues, which can impact inter-organ communication and metabolic homeostasis (Mounesan & Nourzad, 2023; Verboven & Vechetti, 2023). For example, during acute exercise, the liver plays a crucial role in maintaining glucose homeostasis (Sabaratnam et al., 2022). One noteworthy study contributing to this understanding is the work by (Lavie et al., 2015), This comprehensive work underscores the cardiovascular benefits of exercise, laying the groundwork for understanding its broader effects on metabolic interplay.

Effects of exercise on the heart

Regular exercise has long been associated with numerous cardiovascular benefits, such as improved cardiac function, increased cardiac output, and reduced risk of cardiovascular diseases. Exercise promotes the growth of new blood vessels in the heart, a process known as angiogenesis, which enhances the delivery of oxygen and nutrients to the cardiac tissue. Additionally, exercise stimulates the release of certain hormones, such as atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), which have been shown to have positive effects on cardiac metabolism and energy utilization (Miyashita et al., 2009).

Effects of exercise on the liver

Exercise also exerts significant effects on liver metabolism. During exercise, there is an increased demand for energy, which is primarily met by the breakdown of stored glycogen in the liver. This process, known as glycogenolysis, leads to the release of glucose into the bloodstream, providing fuel for exercising muscles. Exercise has been shown to enhance liver insulin sensitivity, resulting in improved glucose uptake and utilization (Nikroo et al., 2020). Moreover, exercise has been found to promote liver lipid metabolism, leading to reduced liver fat accumulation and improved lipid profile (Johnson et al., 2012).

Impact on liver health

Chronic exercise training has been linked to adaptations in multiple tissues, including the liver, skeletal muscle, heart, and adipose tissue (Brunetta & Townsend, 2022). Exercise has been shown to activate skeletal muscle AMP-activated protein kinase (AMPK), leading to the secretion of the cytokine interleukin-6 (IL-6), which drives increased brown adipose tissue (BAT) UCP1 content. This suggests that exercise may have a positive impact on liver health by promoting the development of brown adipose tissue, which is enriched with mitochondria and associated with improved metabolic health (Brunetta & Townsend, 2022).

Moreover, weight management through exercise and dietary interventions has been shown to improve liver cirrhosis in patients with non-alcoholic steatohepatitis (Sanousi & Hashim, 2021). In this case study, a patient with liver cirrhosis experienced significant improvements in liver fibrosis and overall health after following a healthy lifestyle intervention involving dietary advice and regular exercise for one year (Sanousi & Hashim, 2021).

Impact on heart health

Regular exercise causes both central (cardiac) and peripheral (muscular) adaptations, improving functional capacity (Deligiannis et al., 2021). Exercise training in dialysis patients, for example, has been shown to have favorable effects on heart function, promote balance on the cardiac autonomic nervous system, and contribute to the management of arterial hypertension. Additionally, the beneficial effect of exercise on patients' cardiac functional ability is supported by better skeletal muscle function (Deligiannis et al., 2021).

Exercise types

Different types of exercise have different effects on liver health. For example, aerobic exercise has been shown to have a positive impact on thyroid function, depressive states, and cognitive functions in patients with hypothyroidism (Schok et al., 2023). Additionally, resistance training and high-intensity interval training (HIIT) have been shown to have positive effects on cardiovascular health in dialysis patients (Deligiannis et al., 2021).

Metabolic crosstalk between the heart and liver

The effects of exercise on the heart and liver are not isolated but rather interconnected through metabolic crosstalk. Exercise-induced improvements in cardiac function and blood flow can have direct effects on liver metabolism. Increased blood flow to the liver enhances nutrient and oxygen delivery, facilitating the liver's metabolic processes. Furthermore, exercise-induced changes in hormone release, such as ANP and BNP, can impact liver metabolism indirectly by influencing insulin sensitivity and lipid metabolism (Miyashita et al., 2009). Additionally, the liver plays a crucial role in the regulation of whole-body metabolism, including the metabolism of circulating fatty acids and glucose. The improvements in liver metabolism resulting from exercise can have systemic effects on overall metabolic health, including reduced risk of metabolic disorders such as type 2 diabetes and non-alcoholic fatty liver disease (Johnson et al., 2012).

Metabolic pathways

Exercise activates various metabolic pathways in several tissues, organs, and systems, including the heart, liver, white and brown adipose tissue, and the nervous system (Verboven & Vechetti, 2023). These "exerkines" have been recognized to comprise an extensive range of biologically active signaling molecules, including cytokines, lipids, metabolites, and (noncoding) nucleic acids. Extracellular vesicles (EVs) have also been identified as carrier particles for molecular signals involved in inter-organ crosstalk during and after exercise (Verboven & Vechetti, 2023).

Cardiac adaptations to exercise

Exercise induces a range of adaptations in the cardiovascular system, including increased cardiac output, improved vascular function, and enhanced myocardial contractility. These adaptations contribute to an improved supply of oxygen and nutrients to tissues, including the liver. Regular exercise is associated with changes in cardiac metabolism, such as increased reliance on fatty acids and improved glucose utilization. These adaptations may influence the metabolic signals communicated between the heart and liver (Natarajan et al., 2016).

Hepatic responses to exercise

The liver plays a pivotal role in maintaining glucose homeostasis and energy balance. Exercise has been shown to enhance hepatic glucose uptake and glycogen synthesis. Additionally, exercise-induced changes in circulating factors, such as myokines released from exercising muscles, may modulate hepatic metabolism. Understanding how exercise influences liver metabolism is crucial for comprehending the bidirectional communication between the heart and liver (Catoire et al., 2014).

IRF4-FSTL1 signaling pathway

In a study on nonalcoholic steatohepatitis (NASH), researchers found that exercise intervention improved hepatic pathology, suggesting a potential role for the IRF4-FSTL1 signaling pathway in the communication between skeletal muscles and the liver (Guo et al., 2023). Further investigations are needed to determine whether the ablation of IRF4 in skeletal muscle would affect liver metabolism, given that insulin resistance in skeletal muscles has been linked to increased hepatic de novo lipogenesis and hepatic steatosis in the elderly (Guo et al., 2023).

Extracellular vesicles (EVs)

The role of EVs in inter-organ crosstalk during exercise has been an area of growing interest. These vesicles can be released by various tissues, organs, and systems during exercise, and they may play a significant role in the communication between the heart and liver (Verboven & Vechetti, 2023). Future studies should focus on the function of exercise-induced EVs in health and diseases to better understand their impact on inter-organ crosstalk (Verboven & Vechetti, 2023).

Gender-specific effects

Some studies have demonstrated gender-specific effects of exercise on metabolic crosstalk. For instance, a study on familial hypertrophic cardiomyopathy (HCM) found that decreased left ventricular contractile function in male, but not female, HCM mice was associated with reduced fatty acid translocase (CD36) and AMP-activated protein kinase (AMPK) activity (Magida & Leinwand, 2014). This suggests that the impact of exercise on metabolic crosstalk between the heart and liver may differ between genders.

Conclusion

The effect of exercise on the metabolic crosstalk between the heart and liver is significant, as regular physical activity has been shown to have broad-ranging positive health implications, including improving the metabolic health of the liver. The liver plays a crucial role in responding to the accelerated metabolic demands of working muscles during exercise, such as mobilizing energy stores and increasing the oxidation of fatty acids. Additionally, exercise has been found to increase fat oxidation, which is protective and can reverse fatty liver disease (Trefts et al., 2015). Furthermore, exercise prevents fatty liver by modifying the compensatory response of mitochondrial metabolism to excess substrate availability (Hoene et al., 2021). Therefore, it is evident that exercise has a profound impact on the regulation of hepatic metabolism, highlighting the importance of physical activity in maintaining overall metabolic health.

In conclusion, the effect of exercise on the metabolic crosstalk between the heart and liver is a topic of significant scientific interest. Numerous studies have provided evidence that exercise plays a crucial role in modulating the metabolic communication between these two vital organs. Regular physical activity has been shown to improve overall cardiovascular health and metabolic function, leading to positive outcomes for both the heart and liver (Pedersen & Febbraio, 2012).

Exercise-induced adaptations in the heart, such as increased cardiac output and improved myocardial efficiency, have been associated with beneficial effects on liver metabolism. Physical activity promotes the release of myokines, which are cytokines produced by skeletal muscle during exercise. These myokines, including irisin and interleukin-6, have been shown to exert systemic effects on various organs, including the liver. They can enhance liver insulin sensitivity, promote glucose uptake, and modulate lipid metabolism, ultimately leading to improved liver function (Seldin et al., 2012).

Furthermore, exercise has been found to reduce liver fat accumulation and attenuate the development of non-alcoholic fatty liver disease (NAFLD). NAFLD is closely linked to metabolic syndrome and cardiovascular risk factors. Regular exercise, through its impact on liver metabolism, can help prevent or mitigate the progression of NAFLD, thereby reducing the risk of cardiovascular complications (Stefan et al., 2019).

Several mechanisms have been proposed to explain the exercise-induced metabolic crosstalk between the heart and liver. These include the activation of various signaling pathways, such as AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), as well as the modulation of insulin signaling and oxidative stress (Keating et al., 2015).

It is important to note that while exercise has been consistently associated with positive effects on the metabolic crosstalk between the heart and liver, individual responses may vary depending on factors such as exercise intensity, duration, and frequency, as well as the individual's baseline metabolic health. Additionally, more research is needed to elucidate the specific molecular mechanisms underlying this crosstalk and to optimize exercise interventions for individuals with specific metabolic conditions (Rector et al., 2011).

In conclusion, exercise exerts a profound influence on the metabolic crosstalk between the heart and liver. Regular physical activity promotes favorable adaptations in both organs, leading to improved metabolic function and reduced risk of cardiovascular and liver diseases. These findings highlight the importance of exercise as a non-pharmacological approach to enhance overall metabolic health and support the development of targeted exercise interventions for individuals at risk of metabolic disorders. Continued research in this field will further advance our understanding of the intricate relationship between exercise, heart-liver crosstalk, and metabolic health.

What is already known on this subject?

The existing knowledge on the subject of the effect of exercise on metabolic crosstalk between the heart and liver encompasses several key findings. It is known that exercise induces the release of various signaling molecules, including myokines from skeletal muscle and "exerkines" from the heart, liver, white and brown adipose tissue, and the nervous system. These molecules play a crucial role in inter-organ communication and contribute to the systemic effects of exercise on metabolism and overall health. Additionally, previous research has demonstrated that exercise can impact liver health by influencing liver enzymes, antioxidant systems, and metabolic pathways. Furthermore, the effects of different types of exercise, such as aerobic and resistance trainin-g, on cardiovascular risk factors and liver enzymes in various populations, including individuals with dyslipidemia and patients undergoing coronary interventions, have been investigated. This body of knowledge provides a foundation for understanding the complex interplay between exercise, the heart, and the liver, and its implications for metabolic health and disease prevention.

What this study adds?

This research adds to the existing knowledge by providing insights into the impact of exercise on liver enzymes and antioxidant systems, as well as the age-dependent effects of different exercise training regimens on genomic and metabolic remodeling in skeletal muscle and liver. It also contributes to understanding the effects of aerobic interval exercise on cardiovascular risk factors and liver enzymes in individuals with dyslipidemia. Furthermore, the study of a home-based exercise intervention's impact on cardiac biomarkers, liver enzymes, and cardiometabolic outcomes in patients after coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) provides valuable information on the potential benefits of exercise in a clinical setting (Bernier et al., 2022; Khan et al., 2019; Olgoye et al., 2021; Zolfaghari et al., 2020).

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References

Baskin, K. K., Bookout, A. L., & Olson, E. N. (2014). The heart-liver metabolic axis: defective communication exacerbates disease. EMBO Mol Med, 6(4), 436-438. https://doi.org/10.1002/emmm.201303800

Belanger, M. J., Rao, P., & Robbins, J. M. (2022). Exercise, Physical Activity, and Cardiometabolic Health: Pathophysiologic Insights. Cardiol Rev, 30(3), 134-144. https://doi.org/10.1097/CRD.0000000000000417

Bernier, M., Enamorado, I. N., Gomez-Cabrera, M. C., Calvo-Rubio, M., Gonzalez-Reyes, J. A., Price, N. L., . . . de Cabo, R. (2022). Age-dependent impact of two exercise training regimens on genomic and metabolic remodeling in skeletal muscle and liver of male mice. NPJ Aging, 8(1), 8. https://doi.org/10.1038/s41514-022-00089-8

Blackwell, J. A., & Stanford, K. I. (2022). Exercise-induced Inter-tissue Communication: Adipose Tissue & the Heart. Current Opinion in Physiology, 100626.

Brunetta, H. S., & Townsend, L. K. (2022). Muscle-fat crosstalk: effects of exercise on brown adipose tissue; what do we know? J Physiol, 600(17), 4039-4040. https://doi.org/10.1113/JP283516

Cao, X., & Thyfault, J. P. (2023). Exercise drives metabolic integration between muscle, adipose and liver metabolism and protects against aging-related diseases. Exp Gerontol, 176, 112178. https://doi.org/10.1016/j.exger.2023.112178

Catoire, M., Mensink, M., Kalkhoven, E., Schrauwen, P., & Kersten, S. (2014). Identification of human exercise-induced myokines using secretome analysis. Physiol Genomics, 46(7), 256-267. https://doi.org/10.1152/physiolgenomics.00174.2013

Chen, J., Cai, Y., Cong, E., Liu, Y., Gao, J., Li, Y., . . . Flint, J. (2014). Childhood sexual abuse and the development of recurrent major depression in Chinese women. PLoS One, 9(1), e87569. https://doi.org/10.1371/journal.pone.0087569

Colberg, S. R., Sigal, R. J., Fernhall, B., Regensteiner, J. G., Blissmer, B. J., Rubin, R. R., . . . Braun, B. (2010). Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement. Diabetes care, 33(12), e147-e167.

Deligiannis, A., D'Alessandro, C., & Cupisti, A. (2021). Exercise training in dialysis patients: impact on cardiovascular and skeletal muscle health. Clin Kidney J, 14(Suppl 2), ii25-ii33. https://doi.org/10.1093/ckj/sfaa273

Green, D. J., O'Driscoll, G., Joyner, M. J., & Cable, N. T. (2008). Exercise and cardiovascular risk reduction: time to update the rationale for exercise? J Appl Physiol (1985), 105(2), 766-768. https://doi.org/10.1152/japplphysiol.01028.2007

Grundy, S. M. (2012). Pre-diabetes, metabolic syndrome, and cardiovascular risk. J Am Coll Cardiol, 59(7), 635-643. https://doi.org/10.1016/j.jacc.2011.08.080

Guo, S., Feng, Y., Zhu, X., Zhang, X., Wang, H., Wang, R., . . . Kong, X. (2023). Metabolic crosstalk between skeletal muscle cells and liver through IRF4-FSTL1 in nonalcoholic steatohepatitis. Nat Commun, 14(1), 6047. https://doi.org/10.1038/s41467-023-41832-3

Handschin, C., & Spiegelman, B. M. (2006). Peroxisome proliferator -activated receptor γ coactivator 1 coactivators, energy homeostasis, and metabolism. Endocrine reviews, 27(7), 728-735.

Hardie, D. G. (2011). AMP-activated protein kinase—an energy sensor that regulates all aspects of cell function. Genes & development, 25(18), 1895-1908.

Hoene, M., Kappler, L., Kollipara, L., Hu, C., Irmler, M., Bleher, D., . . . Weigert, C. (2021). Exercise prevents fatty liver by modifying the compensatory response of mitochondrial metabolism to excess substrate availability. Mol Metab, 54, 101359. https://doi.org/10.1016/j.molmet.2021.101359

Johnson, N. A., Keating, S. E., & George, J. (2012). Exercise and the liver: implications for therapy in fatty liver disorders. Seminars in liver disease.

Keating, S. E., Hackett, D. A., Parker, H. M., O'Connor, H. T., Gerofi, J. A., Sainsbury, A., . . . Johnson, N. A. (2015). Effect of aerobic exercise training dose on liver fat and visceral adiposity. J Hepatol, 63(1), 174-182. https://doi.org/10.1016/j.jhep.2015.02.022

Keating, S. E., Sabag, A., Hallsworth, K., Hickman, I. J., Macdonald, G. A., Stine, J. G., . . . Johnson, N. A. (2023). Exercise in the Management of Metabolic-Associated Fatty Liver Disease (MAFLD) in Adults: A Position Statement from Exercise and Sport Science Australia. Sports Med, 53(12), 2347-2371. https://doi.org/10.1007/s40279-023-01918-w

Khan, A., Khan, S., Khan, S., Bhatti, S., & Khan, S. (2019). Impact of Low-Intensity Exercise on Liver Enzymes and Antioxidants Systems of the Body. International Journal of Medical Research and Health Sciences, 8, 148-155.

Lavie, C. J., Arena, R., Swift, D. L., Johannsen, N. M., Sui, X., Lee, D. C., . . . Blair, S. N. (2015). Exercise and the cardiovascular system: clinical science and cardiovascular outcomes. Circ Res, 117(2), 207-219. https://doi.org/10.1161/CIRCRESAHA.117.305205

Magida, J. A., & Leinwand, L. A. (2014). Metabolic crosstalk between the heart and liver impacts familial hypertrophic cardiomyopathy. EMBO Mol Med, 6(4), 482-495. https://doi.org/10.1002/emmm.201302852

Martínez-Montoro, J. I., Benítez-Porres, J., Tinahones, F. J., Ortega-Gómez, A., & Murri, M. (2023). Effects of exercise timing on metabolic health. Obesity Reviews, 24(10), e13599. https://doi.org/https://doi.org/10.1111/obr.13599

Miyashita, K., Itoh, H., Tsujimoto, H., Tamura, N., Fukunaga, Y., Sone, M., . . . Nakao, K. (2009). Natriuretic peptides/cGMP/cGMP-dependent protein kinase cascades promote muscle mitochondrial biogenesis and prevent obesity. Diabetes, 58(12), 2880-2892. https://doi.org/10.2337/db09-0393

Montgomery, M. K., De Nardo, W., & Watt, M. J. (2019). Impact of lipotoxicity on tissue "cross talk" and metabolic regulation. Physiology, 34(2), 134-149.

Mounesan, A., & Nourzad, F. (2023). The Effect of Acute active and Passive Cool-Down After Exercise on Changes in Blood Pressure and Heart Rate of Teenage Boy Basketball Players. Research in Sport Sciences Education (RISSE), 1(1), 49-54.

Natarajan, N., Hori, D., Flavahan, S., Steppan, J., Flavahan, N. A., Berkowitz, D. E., & Pluznick, J. L. (2016). Microbial short chain fatty acid metabolites lower blood pressure via endothelial G protein-coupled receptor 41. Physiol Genomics, 48(11), 826-834. https://doi.org/10.1152/physiolgenomics.00089.2016

Nikroo, H., Hosseini, S. R. A., Fathi, M., Sardar, M. A., & Khazaei, M. (2020). The effect of aerobic, resistance, and combined training on PPAR-alpha, SIRT1 gene expression, and insulin resistance in high-fat diet-induced NAFLD male rats. Physiol Behav, 227, 113149. https://doi.org/10.1016/j.physbeh.2020.113149

Olgoye, A. M., Samadi, A., & Jamalian, S. A. (2021). Effects of a home based exercise intervention on cardiac biomarkers, liver enzymes, and cardiometabolic outcomes in CABG and PCI patients. J Res Med Sci, 26, 5. https://doi.org/10.4103/jrms.JRMS_25_20

Pedersen, B. K., & Febbraio, M. A. (2012). Muscles, exercise and obesity: skeletal muscle as a secretory organ. Nature Reviews Endocrinology, 8(8), 457-465.

Perry, R. J., Samuel, V. T., Petersen, K. F., & Shulman, G. I. (2014). The role of hepatic lipids in hepatic insulin resistance and type 2 diabetes. Nature, 510(7503), 84-91. https://doi.org/10.1038/nature13478

Ratziu, V., Bellentani, S., Cortez-Pinto, H., Day, C., & Marchesini, G. (2010). A position statement on NAFLD/NASH based on the EASL 2009 special conference. J Hepatol, 53(2), 372-384. https://doi.org/10.1016/j.jhep.2010.04.008

Rector, R. S., Uptergrove, G. M., Morris, E. M., Borengasser, S. J., Laughlin, M. H., Booth, F. W., . . . Ibdah, J. A. (2011). Daily exercise vs. caloric restriction for prevention of nonalcoholic fatty liver disease in the OLETF rat model. Am J Physiol Gastrointest Liver Physiol, 300(5), G874-883. https://doi.org/10.1152/ajpgi.00510.2010

Robbins, J. M., & Gerszten, R. E. (2023). Exercise, exerkines, and cardiometabolic health: from individual players to a team sport. J Clin Invest, 133(11). https://doi.org/10.1172/JCI168121

Rochlani, Y., Pothineni, N. V., Kovelamudi, S., & Mehta, J. L. (2017). Metabolic syndrome: pathophysiology, management, and modulation by natural compounds. Ther Adv Cardiovasc Dis, 11(8), 215-225. https://doi.org/10.1177/1753944717711379

Rohrbach, S., Niemann, B., Silber, R. E., & Holtz, J. (2005). Neuregulin receptors erbB2 and erbB4 in failing human myocardium -- depressed expression and attenuated activation. Basic Res Cardiol, 100(3), 240-249. https://doi.org/10.1007/s00395-005-0514-4

Sabaratnam, R., Wojtaszewski, J. F. P., & Hojlund, K. (2022). Factors mediating exercise-induced organ crosstalk. Acta Physiol (Oxf), 234(2), e13766. https://doi.org/10.1111/apha.13766

Sanousi, H. A., & Hashim, A. S. (2021). The Positive Impact of Weight Management on Liver Cirrhosis.

Schok, K., Jasek, J., Wiejak, K., Skoczylas, K., Mikulska, J., & Rokicki, S. (2023). The relationship between hypothyroidism and physical exercise: impact on exercise tolerance and health. Journal of Education, Health and Sport.

Seldin, M. M., Peterson, J. M., Byerly, M. S., Wei, Z., & Wong, G. W. (2012). Myonectin (CTRP15), a novel myokine that links skeletal muscle to systemic lipid homeostasis. Journal of Biological Chemistry, 287(15), 11968-11980.

Stefan, N., Haring, H. U., & Cusi, K. (2019). Non-alcoholic fatty liver disease: causes, diagnosis, cardiometabolic consequences, and treatment strategies. Lancet Diabetes Endocrinol, 7(4), 313-324. https://doi.org/10.1016/S2213-8587(18)30154-2

Swarup, S., Goyal, A., & Grigorova, Y. (2023). Metabolic Syndrome [Updated 2022 Oct 24]. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing.

Talabér, G., Jondal, M., & Okret, S. (2013). Extra-adrenal glucocorticoid synthesis: immune regulation and aspects on local organ homeostasis. Molecular and cellular endocrinology, 380(1-2), 89-98.

Tanaka, A., & Node, K. (2020). Crosstalk between the liver and heart: revisited for prevention and treatment. ESC Heart Fail, 7(6), 4489-4490. https://doi.org/10.1002/ehf2.13034

Thyfault, J. P., & Bergouignan, A. (2020). Exercise and metabolic health: beyond skeletal muscle. Diabetologia, 63(8), 1464-1474. https://doi.org/10.1007/s00125-020-05177-6

Trefts, E., Williams, A. S., & Wasserman, D. H. (2015). Exercise and the Regulation of Hepatic Metabolism. Prog Mol Biol Transl Sci, 135, 203-225. https://doi.org/10.1016/bs.pmbts.2015.07.010

van der Velden, J., Merkus, D., Klarenbeek, B. R., James, A. T., Boontje, N. M., Dekkers, D. H., . . . Duncker, D. J. (2004). Alterations in myofilament function contribute to left ventricular dysfunction in pigs early after myocardial infarction. Circ Res, 95(11), e85-95. https://doi.org/10.1161/01.RES.0000149531.02904.09

Verboven, K., & Vechetti, I. J. (2023). Editorial: Inter-organ crosstalk during exercise in health and disease: Extracellular vesicles as new kids on the block [Editorial]. Front Physiol, 14, 1180972. https://doi.org/10.3389/fphys.2023.1180972

Wasserman, D. H., & Ayala, J. E. (2005). Interaction of physiological mechanisms in control of muscle glucose uptake. Clin Exp Pharmacol Physiol, 32(4), 319-323. https://doi.org/10.1111/j.1440-1681.2005.04191.x

Zolfaghari, R., Haghighi, A. H., Askari, R., & Hejazi, K. (2020). The Effect of Eight Weeks Aerobic Interval Exercise with Different Types of Volumes on Cardiovascular Risk Factors and Liver Enzymes in Women with Dyslipidemia.