Scientific Challenges on Theory of Fat Burning by Exercise

M. Brennan Harris1 and Chia-Hua Kuo2*

1 Department of Health Sciences, College of William and Mary, Williamsburg, VA, United States, 2 Laboratory of Exercise Biochemistry, College of Kinesiology, University of Taipei, Taipei, Taiwan

Exercise training decreases abdominal fat in an intensity-dependent manner. The fat loss effect of exercise has been intuitively thought to result from increased fat burning during and after exercise, defined by conversion of fatty acid into carbon dioxide in consumption of oxygen. Nevertheless, increasing exercise intensity decreases oxidation of fatty acids derived from adipose tissue despite elevated lipolysis. The unchanged 24-h fatty acid oxidation during and after exercise does not provide support to the causality between fat burning and fat loss. In this review, alternative perspectives to explain the fat loss outcome are discussed. In brief, carbon and nitrogen redistribution to challenged tissues (muscle and lungs) for fuel replenishment and cell regeneration against abdominal adipose tissue seems to be the fundamental mechanism underlying the intensity-dependent fat loss effect of exercise. The magnitude of lipolysis (fatty acid release from adipocytes) and the amount of post-meal carbon and nitrogen returning to abdominal adipose tissue determines the final fat tissue mass. Therefore, meal arrangement at the time when muscle has the greatest reconstruction demand for carbon and nitrogen could decrease abdominal fat accumulation while increasing muscle mass and tissue repair.

Keywords: resistance training, fat loss, intensity, carbon and nitrogen redistribution theory, fatty acid oxidation, aerobic training, fat burner, obesity

THE SCIENTIFIC CHALLENGES

Exercise training decreases abdominal fat, in which high-intensity exercise produces more prominent fat loss than low and moderate intensity exercise (Vissers et al., 2013; Viana et al., 2019). Fat burning is a classic theory to describe the abdominal fat-reducing outcome of exercise training. This theory is built on the intuition that exercise as an energy consuming behavior will increase fatty acid oxidation from abdominal fat stores compared with sedentary condition, and thus accounts for the fat loss outcomes of exercise training (Abbasi, 2019). Increased lipolysis with elevated circulating fatty acids together with increased oxygen consumption during exercise seems to favor this explanation (Romijn et al., 1993; Mora-Rodriguez and Coyle, 2000). However, the absolute energy contribution from plasma fatty acids (assuming all from adipose tissue) decreases as exercise intensity increases (from 25 to 85% VO2max) and is consistent with decreased tissue fatty acid uptake during exercise (Romijn et al., 1993). Furthermore, increased energy expenditure, especially during high intensity exercise, comes from fuel stored in skeletal muscle (mostly glycogen), not adipose tissue (fatty acids) (Romijn et al., 1993). Neither aerobic exercise nor resistance exercise increases 24-h fatty acid oxidation (Melanson et al., 2002).
A number of clinical studies divulge a paradox between fat burning and fat loss outcome. A 15-weeks sprint training depending primarily on anaerobic metabolism effectively decreases abdominal fat, whereas moderate-intensity exercise training depending on aerobic metabolism with similar energy expenditure (60% VO$_{2max}$ consuming $\sim$200 kcal, three times per week) failed to decrease body fat in young women (Trapp et al., 2008). Similarly, no fat loss effect was observed following 12-weeks of aerobic training at both low-intensity (40% VO$_{2max}$) and moderate-intensity (70% VO$_{2max}$) among obese men ($\sim$350 kcal, three times per week) (Aggel-Leijssen et al., 2002). Therefore, an alternative theory to explain the fat loss outcome of exercise should be explored in order to provide robust scientific basis for designing effective fat loss training regimens.

Lipolysis appears to be more relevant with fat loss than fatty acid oxidation. Exercise increases plasma epinephrine levels at high intensities (Mora-Rodriguez and Coyle, 2000). Epinephrine stimulates lipolysis and inhibits the esterification of triglycerides via adrenergic receptors of adipocytes (Reilly et al., 2020), leading to release of free fatty acid from adipose tissue into circulation (Urhausen et al., 1994). Long-term adrenergic stimulation (i.e., clenbuterol and ractopamine) has been shown to decrease fat mass, and increase muscle mass without changes in food intake and body temperature (Page et al., 2004). Abdominal adipocytes show much higher lipolytic response to epinephrine than gluteal adipocytes, which may partly explain the commonly observed abdominal fat loss response to high-intensity exercise training (Wahrenberg et al., 1989; Thompson et al., 2012).

The physiological significance of the enhanced release of fatty acids from lipolysis without the corresponding increase in fatty acid oxidation during and after exercise remains unclear. However, a proposed role of adipocyte-derived fatty acids in tissue repair has been recently described elsewhere (Shook et al., 2020). Fatty acids (e.g., eicosapentaenoate, linoleate, α-linolenate, γ-linolenate, and arachidonate) have been found to accelerate wound healing (Ruthig and Meckling-Gill, 1999). In addition, vascular structure formation can be enhanced by fatty acids, which is mediated by increasing reactive oxygen species and activating endothelial NOS synthase (Taha et al., 2020). Both findings implicate a possible role of elevated fatty acid concentrations in the repairing mechanism of exercise-induced tissue damage.

**BASIC ASSUMPTION OF FAT BURNING THEORY**

The first basic assumption of fat burning theory is that fat cell death has no role in fat loss. However, this assumption is unlikely valid since fat cells are continuously dying and regenerating throughout our life. Approximately 8.4% of subcutaneous abdominal adipocytes are renewed annually with an average half-life of 8.3 years in human adults (Spalding et al., 2008). Abdominal fat mass is determined by the balance of fat cell death and regeneration of adipose tissue, which is influenced by exercise (Allerton et al., 2021). Acute adrenergic stimulation has been reported to induce fat cell death (Kim et al., 2010). The balance between fat cell death and regeneration is also strongly influenced by plasma insulin concentrations, which varies with exercise habit, meals, and sleeping fast. Lowering insulin for 2 weeks causes a massive fat loss > 70%, associated with the death of adipocytes and endothelial cells in adipose tissues (Géloën et al., 1989). Lowering physical activity increases plasma insulin concentration and waist circumference without an observable change in body weight (Chen et al., 2006). In a contrast, high-intensity exercise lowers fasting and post-meal insulin levels while increasing the insulin sensitivity of exercised muscle (Ivy et al., 1999; Rice et al., 1999; Trapp et al., 2008), which partly explains the decreases in fat mass and increases in muscle mass among training individuals.

The second basic assumption of the fat burning theory is that muscle and fat cells are not interconvertible in a human body. However, we could not preclude the possibility that the fat mass loss concurrent with muscle mass gain after exercise training is associated with conversion between muscle and fat progenitor cells, derived from circulating bone marrow stem cells. Conversion from muscle satellite cells to an adipogenic lineage contributes the development of obesity and muscle mass loss in animals (Durschlag and Layman, 1983; Scarda et al., 2010). Glucose and reactive oxygen species (ROS) also stimulate the adipogenic conversion from muscle-derived stem cells (Aguiari et al., 2008). Both plasma glucose and ROS elevate with age and weight growth (Ho et al., 2019; Wang et al., 2019). However, exercise training lowers plasma glucose (Colberg et al., 2010) and ROS (Vinetti et al., 2015) in animals and humans. Circulating myokines released from contracting muscle also suppress adipogenesis and stimulate myogenesis (Barra et al., 2012; Ma et al., 2019). As a result, exercise appears to, at the very
muscle demand at the time when post-meal nutrients are carbon and nitrogen returning to adipose tissue. Increasing nitrogen (Ivy et al., 1988) and therefore decreases post-meal skeletal muscle is a competitor for the post-meal carbon and nitrogen returning to fat cells determines the daily triglyceride partitioning into adipose tissue and muscle tissues thus determines the daily

CONCLUDING REMARKS AND FUTURE PERSPECTIVE

Fatty acids (from lipolysis) are continuously released from abdominal adipose tissue into the circulation and fat cells are continuously dying in normal human adults. The size of adipose
tissue is determined by the magnitude of nutrient competition from muscle and lungs for cell regeneration and energy replenishment after exercise. This is varied by types of exercise (aerobic or resistance exercise). Despite the fact that lower exercise intensity relies more on fatty acid oxidation, high-intensity exercise training (anaerobic in nature) provides a superior abdominal fat loss effect than low- and moderate-intensity exercise training. Given the fact that exercise does not increase 24-h fatty acid oxidation during and after exercise training, the carbon and nitrogen redistribution theory is more suitable to explain the abdominal fat loss outcome of exercise training than fat burning theory. This reasonably explains why low- and moderate-intensity exercise often fail as strategies for fat loss despite the greater percentage of fatty acid oxidation compared with high intensity exercise. Studies on inter-tissue communication during exercise (such as muscle-derived extracellular vesicles) for post-meal carbon and nitrogen redistribution are promising and may provide useful application to normalize body composition and prevent obesity. Furthermore, the role of fatty acids on repairing post-exercise damage deserves further investigation. More data are needed to support the carbon and nitrogen redistribution theory on fat loss effect of exercise.

AUTHOR CONTRIBUTIONS

Both authors contributed significantly to this work.
Mora-Rodriguez, R., and Coyle, E. F. (2000). Effects of plasma epinephrine on fat metabolism during exercise: interactions with exercise intensity. *Am. J. Physiol. Endocrinol. Metab.* 278, E669–E676. doi: 10.1152/ajpendo.2000.278.4.E669

Murphy, J., Summer, R., Wilson, A. A., Kotton, D. N., and Fine, A. (2008). The prolonged life-span of alveolar macrophages. *Am. J. Respir. Cell Mol. Biol.* 38, 380–385. doi: 10.1165/rcmb.2007-0224rc

Page, K. A., Hartzell, D. L., Li, C., Westby, A. L., Della-Fera, M. A., Azain, M. I., et al. (2004). beta-Adrenergic receptor agonists increase apoptosis of adipose tissue in mice. *Domest. Anim. Endocrinol.* 26, 23–31. doi: 10.1016/j.domaniend.2003.08.004

Rawlins, E. L., and Hogan, B. L. (2008). Ciliated epithelial cell lifespan in the mouse trachea and lung. *Am. J. Physiol. Lung Cell. Mol. Physiol.* 295, L231–L234. doi: 10.1152/ajplung.90209.2008

Reilly, S. M., Hung, C. W., Ahmadjian, M., Zhao, P., Keinan, O., Gomez, A. V., et al. (2020). Catecholamines suppress fatty acid re-esterification and increase oxidation in white adipocytes via STAT3. *Nat. Metab.* 2, 620–634. doi: 10.1038/s42255-020-0217-6

Rice, B., Janssen, I., Hudson, R., and Ross, R. (1999). Effects of aerobic or resistance exercise and/or diet on glucose tolerance and plasma insulin levels in obese men. *Diabetes Care* 22, 684–691. doi: 10.2337/diacare.22.5.684

Rochefort, G. Y., Vaudin, P., Bonnet, N., Pages, J. C., Domenech, J., Charbord, P., et al. (2005). Influence of hypoxia on the domiciliation of mesenchymal stem cells after infusion into rats: possibilities of targeting pulmonary artery remodeling via cells therapies? *Respir. Res.* 6:125. doi: 10.1186/1465-9921-6-125

Romijn, J. A., Coyle, E. F., Sidossis, L. S., Gastaldelli, A., Horowitz, J. F., Endert, E., et al. (1993). Regulation of endogenous fat and carbohydrate metabolism in relation to exercise intensity and duration. *Am. J. Physiol. 265*, E380–E391. doi: 10.1152/ajpendo.1993.265.3.E380

Ruthig, D. J., and Meckling-Gill, K. A. (1999). Both (n-3) and (n-6) fatty acids stimulate wound healing in the rat intestinal epithelial cell line, IEC-6. *J. Nutr.* 129, 1791–1798. doi: 10.1093/jn/129.10.1791

Saat, T. C., Vanden Engle, S., Bijman-Lachger, W., Buchholz, B. A., Roux, G., and Van Den Engel, S. (2007). Dynamics of fat cell turnover in humans. *Aging (Albany NY)* 9, 2124–2130. doi: 10.1038/nature21365

Suzuki, M., Doi, T., Lee, S., Okamura, K., Shimizu, S., Okano, G., et al. (1999). Circulating ginsenoside Rg1 supplementation clears senescence-associated β-galactosidase in exercising human skeletal muscle. *Cell Stem Cell* 171, 372–384. doi: 10.1172/jci116813

Thomou, T., Mori, M. A., Dreyfuss, J. M., Konishi, M., Sakaguchi, M., Wolfrum, C., et al. (2017). Adipose-derived circulating miRNAs regulate gene expression in other tissues. *Nature* 542, 430–455. doi: 10.1038/nature21365

Thompson, D., Karpe, F., Lafontan, M., and Frayn, K. (2012). Physical activity and exercise in the regulation of human adipose tissue physiology. *Physiol. Rev.* 92, 157–191. doi: 10.1152/physrev.00012.2011

Tidball, J. G. (2017). Regulation of muscle growth and regeneration by the immune system. *Nat. Rev. Immunol.* 17, 165–178. doi: 10.1038/nri.2016.150

Trapp, E. G., Chisholm, D. J., Freund, J., and Bouthier, S. H. (2008). The effects of high-intensity intermittent exercise training on fat loss and fasting insulin levels of young women. *Int. J. Obes.* 32, 684–691. doi: 10.1038/sj.ijo.0803781

Urhausen, A., Weiler, B., Coen, B., and Kindermann, W. (1994). Plasma catecholamines during endurance exercise of different intensities as related to the individual anasorothetical threshold. *Eur. J. Appl. Physiol. Occup. Physiol.* 69, 16–20. doi: 10.1007/bf00867921

Viana, R. B., Naves, J. P. A., Coswig, V. S., De Lira, C. A. B., Steele, J., Fisher, J. P., et al. (2019). Is interval training the magic bullet for fat loss? A systematic review and meta-analysis comparing moderate-intensity continuous training with high-intensity interval training (HIIT). *Br. J. Sports Med.* 53, 655–664. doi: 10.1136/bjsports-2018-099928

Vinetti, G., Mozzini, C., Desenzani, P., Boni, E., Bolla, L., Lorenzetti, I., et al. (2015). Supervised exercise training reduces oxidative stress and cardiometabolic risk in adults with type 2 diabetes: a randomized controlled trial. *Sci. Rep.* 5:8239.

Vissers, D., Hens, W., Taeymans, J., Baeyens, J. P., Poortmans, J. M., and Van Gaal, L. (2013). The effect of exercise on visceral adipose tissue in overweight adults: a systematic review and meta-analysis. *PLoS One* 8:e86415. doi: 10.1371/journal. pone.0086415

Wahrenberg, H., Lönnqvist, F., and Arner, P. (1989). Mechanisms underlying regional differences in lipolysis in human adipose tissue. *J. Clin. Invest.* 84, 458–467. doi: 10.1172/jci114187

Wang, C., Zhang, Y., Li, F., and Wei, Y. (2019). Conserved roles of glucose in suppressing reactive oxygen species-induced cell death and animal survival. *Aging (Albany NY)* 11, 5726–5743. doi: 10.18632/aging.102155

Wills, I. L., Slentz, C. A., Bateman, L. A., Shields, A. T., Piner, L. W., Bales, C. W., et al. (2012). Effects of aerobic and/or resistance training on body mass and fat mass in overweight or obese adults. *J. Appl. Physiol.* 113, 1831–1837. doi: 10.1152/japplphysiol.00370.2011

Wu, J., Saovien, S., Cheng, I. S., Liu, T., Hong, S., Lin, C. Y., et al. (2019). Ginsenoside Rg1 supplementation clears senescence-associated β-galactosidase in exercising human skeletal muscle. *J. Ginseng Res.* 43, 580–588. doi: 10.1016/j.jgr.2018.06.002

Xu, T., Zhou, Q., Che, L., Das, S., Wang, L., Jiang, J., et al. (2016). Circulating miR-21, miR-378, and miR-940 increase in response to an acute exhaustive exercise in chronic heart failure patients. *Oncotarget* 7, 12414–12425. doi: 10.18632/oncotarget.6966

Yang, C., Jiao, Y., Wei, B., Yang, Z., Wu, J. F., Jensen, J., et al. (2018). Aged cells in human skeletal muscle after resistance exercise. *Aging (Albany NY)* 10, 1356–1365. doi: 10.18632/aging.101472

Ying, W., Rispel, M., Bandopadhyay, G., Dong, Y., Birmingham, A., Seo, J. B., et al. (2017). Adipose tissue macrophage-derived exosomal miRNAs can modulate in vivo and in vitro insulin sensitivity. *Cell* 171, 372–384. doi: 10.1016/j.cell.2017.08.035

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.