



## Systematic Review

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# Aerobic Exercise in the Fasted State: the Effects on Energy Metabolism in Healthy Adults

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## Abstract

There are a number of factors that can affect energy metabolism in the context of aerobic exercise and potentially play a role in the increase of aerobic capacity. Reliance on fat oxidation is one such factor and strategies are sought to maximise adaptations in enhancing this metabolic switch. A strategy that has been explored in recent years is the nutritional pattern of the fasted state. With aerobic exercise and the fasted state harnessing congruent energy metabolism pathways, this literature review aimed to investigate an important interplay between aerobic exercise in the fasted state and potential benefits for energy metabolism. The hypothesis, 'aerobic exercise in the fasted state will enhance energy metabolism in healthy adults', was tested through an evaluation of energy metabolism patterns with aerobic exercise in the fasted state. A review of the relevant literature since 2005 relating to the healthy adult population was undertaken, resulting in the critical appraisal of 21 articles. The findings from this review support metabolic switching in fasted state aerobic exercise, demonstrating preferential reliance on fat oxidation, enhanced glucose metabolism and mitochondrial activity, all of which is coordinated through pathways regulated by nuclear hormone receptors. Fasted state aerobic exercise can be considered beneficial for enhanced energy metabolism in both the general and athlete population.

**Keywords:** Endurance Exercise, Fasted State, Energy Metabolism.

## INTRODUCTION

The practice of fasting has been observed religiously and culturally for a long time. In recent years, the fasted state has become a topic of scientific research interest. A variety of fasted state patterns, such as 'intermittent fasting' (IF) and the '5:2' diet, both of which hinge on caloric restriction for specified time periods and at defined intervals, have been studied to evaluate benefits in the field of nutrition and metabolism [1].

While the majority of people may find calorie restriction challenging to sustain over extended periods of time, IF provides a potential alternative in affording the similar benefits of weight loss and improved cardiometabolic health. The basis of improved cardiometabolic risk factors with IF seem to hinge on harnessing the same biological pathways that can attenuate insulin resistance, dyslipidaemia and inflammatory cytokines. The pattern of changes in metabolism is directed towards conserving carbohydrate availability and improves the use of fat as the foremost energy substrate [2]. More specifically, a metabolic switching occurs from glycogenolysis for glucose utilisation to the preferential use of ketones derived from fatty acids. This affords IF dietary patterns a greater potential in the context of a typical Western diet that broadly depends on the typical and minimum three daily meals. However, the switch in metabolism in these cases may take longer to be executed due to the increased insulin resistance in the context of increased weight and associated metabolic disorders [3]. Persynaki *et al.* (2017) discussed various effects of the fasted state on contributors to health and the ageing process [4]. The effects on body weight, glycaemia, cardiometabolic risk markers and oxidative stress parameters indicated an association with improved health and longer lifespan.

Cabo and Mattson (2019) reviewed IF regimens and the metabolic and cellular adaptive responses, noting that they are highly-integrated with the overarching theme of glucose regulation [5]. Blood levels of ketone bodies are low in the fed state, rising at 8-12 hours of a fasted state and reach levels of 2-5mmol/l at 24 hours. This timeframe is suggestive of and consistent with an appropriate duration for IF regimens.

After all the nutrients from the preceding meal have been absorbed from the small intestine, the post-absorptive period begins, which can range from three hours up to eight hours after the preceding meal.

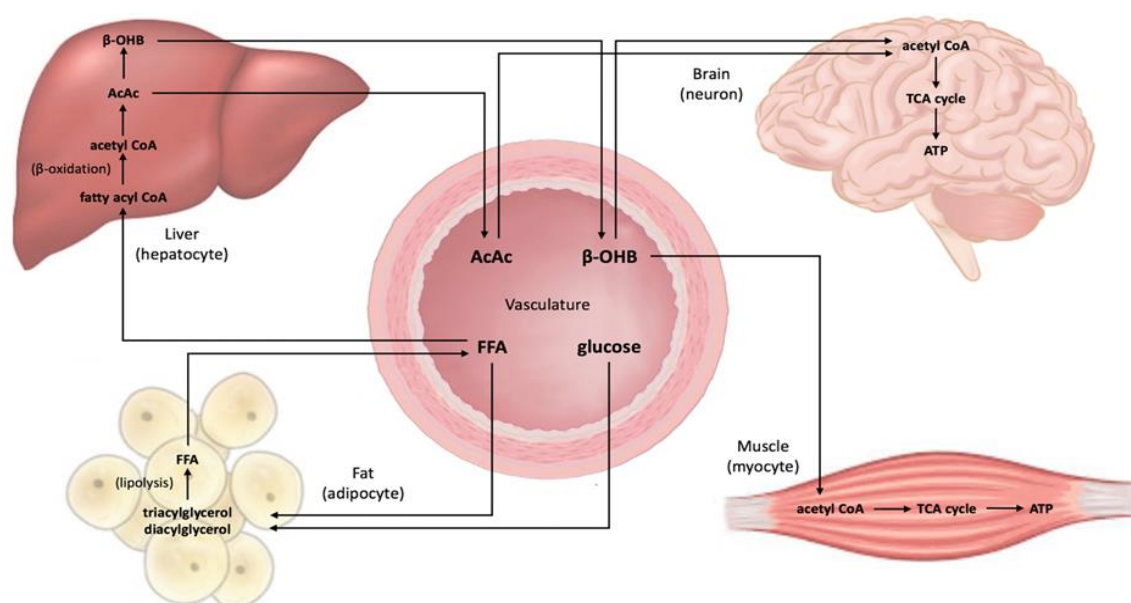
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Post-prandial glucose levels are initially elevated after a meal ingestion and then gradually start declining around six hours post-ingestion. This metabolic stage of fasting can last up to 24 hours as the body adapts to the lack of nutrition availability<sup>[6]</sup>. The reduction of serum glucose levels is concurrently associated with an increase in circulating free fatty acid (FFA) and ketone levels. This metabolic switching represents an interplay between metabolic pathways that are influenced by hormonal variations, including a reduction in circulating insulin and insulin-like growth factor 1 (IGF-1) levels whilst glucagon (in parallel with hepatic gluconeogenesis), catecholamines, growth hormone and thyroid stimulating hormones increase<sup>[2-6]</sup>.

Adaptations following this switchover are ensured systemically with oxidative metabolism predominating through a reliance on fat oxidation. This results in sufficient energy supply and carbohydrate reserves being shunted in the post-absorptive period to essential systems and organs, such as the central nervous system and the brain<sup>[2-6]</sup>.

The switch occurs between 12 and 36 hours after food consumption when the hepatocytes are depleted of glycogen stores and increasing FFAs ensue following accelerated adipose tissue lipolysis that acts on triacylglycerol and diacylglycerol, which ultimately also bolsters hepatic gluconeogenesis to promote carbohydrate availability<sup>[6]</sup>. The exact timing depends on the baseline glycogen liver content at the outset of the fast as well as the energy expenditure during the fasted state<sup>[2]</sup>.

The metabolism of FFAs occurs in the hepatocytes through  $\beta$ -oxidation to produce ketones ( $\beta$ -hydroxybutyrate and acetoacetate), which consequently stimulate mitochondrial biogenesis<sup>[2-5]</sup>. The ketones are metabolised to acetyl coenzyme A in cells with high metabolic requirements, such as muscle cells, to generate adenosine triphosphate (ATP) through the tricarboxylic acid cycle (Figure 1). The switch in metabolism is suggested to preferentially preserve muscle, with IF regimens retaining muscle mass when compared to continuous caloric restriction regimens<sup>[2]</sup>.



**Figure 1:** Overview of the major metabolic pathways involved in the metabolic switch and cellular involvement.  $\beta$ -OHB,  $\beta$ -hydroxybutyrate; AcAc, acetoacetate; ATP, adenosine triphosphate; FFA, free fatty acids; TCA, tricarboxylic acid (adapted from Anton *et al.*, 2017; Cabo and Mattson, 2019).

The metabolic switch is also reflected in a reduction of the respiratory exchange ratio (RER), which is the ratio of carbon dioxide production to oxygen consumption. This indicates an efficiency and flexibility of energy production through this adaptation<sup>[5]</sup>.

There are also implications in the alteration of gene and protein expression that can affect the activity of various molecules that influence energy pathways, such as peroxisome proliferator-activated receptor  $\gamma$  coactivator 1 $\alpha$  (PGC-1 $\alpha$ ), as well as activating signalling pathways that enhance mitochondrial biogenesis and function<sup>[5]</sup>. Specific downstream influential targets also include:

- pyruvate dehydrogenase kinase isoenzyme 4 (PDK4), which is intrinsically linked to the inactivation of pyruvate dehydrogenase;
- adenosine monophosphate-activated protein kinase (AMPK), which stimulates glucose uptake and fat oxidation;
- glucose transporter type 4 (GLUT4), which is upregulated to facilitate glucose transport during increased metabolic demand;
- mitochondrial enzymes, such as citrate synthase (CS) and  $\beta$ -hydroxyacyl coenzyme A dehydrogenase ( $\beta$ -HAD).

Intramuscular lipid utilisation and post-prandial glucose metabolism was studied by Edinburgh *et al.* (2019) to compare the effects of exercise performed before and after nutrient ingestion<sup>[7]</sup>. They observed that utilisation of intramuscular lipids was increased in type I muscle fibres compared to type II fibres with moderate-intensity training before breakfast. In six weeks of exercise training comparing carbohydrate ingestion before and after exercise, they observed a reduction in post-prandial insulinaemia with exercise performed before, but not after, carbohydrate ingestion. There was consequent increased insulin sensitivity and lipid utilisation during exercise. Regular exercise before nutrition was also indicative of phospholipid remodelling in skeletal muscle alongside the protein content of glucose-transporter 4 (GLUT4). Hong *et al.* (2014) observed that skeletal muscle adaptations take place by sparing glucose and switching to fatty acid oxidation, achieved through the activation of pyruvate dehydrogenase kinase 4 (PDK4)<sup>[8]</sup>.

The coherency of all these metabolic adjustments is suggestive of the rationale that training in a glucose-deprived, fasted state promotes fuel substrate efficiency and availability. Exploring the pattern of energy metabolism when combining the fasted state with aerobic exercise and understanding these interactions, their effects and potential underlying mechanisms holds wide-ranging importance.

The aim of this literature review was to investigate an important interplay between aerobic exercise in the fasted state and potential

benefits for energy metabolism. This could have implications for healthy adults undertaking recreational exercise in the general population and the training regimes of elite athletes.

## METHODOLOGY

This literature review drew upon sources including textbooks and an online literature search. Electronic databases included in this literature search included FINDit (University of South Wales' literature search facility), PubMed and OpenAthens. The keywords to inform the literature search included "fasted state", "aerobic exercise" and "energy metabolism". Equivalent terms, such as "fasting state" and "endurance exercise" were also used. Using the inclusion and exclusion criteria specified below, the online literature search resulted in 646 records. After screening for duplicates and relevance to the research objectives, cross-referencing of articles that met the inclusion criteria was undertaken and the resulting cross-referenced articles were also evaluated against the inclusion criteria. 21 items in the form of academic journal articles and books were ultimately used in the literature review.

### Inclusion Criteria

- Publications from year 2005 onwards in the English language.
- Human studies.
- Male and female adults of the healthy general and athlete population aged 18 years and older.

### Exclusion Criteria

- Publications prior to 2005 and not in the English language.
- Animal studies.
- The child and adolescent population aged less than 18 years.

## RESULTS AND DISCUSSION

### Fat Metabolism

One of the most common and easily-adopted forms of aerobic exercise in the general population is brisk walking. McIver *et al.* (2018) studied the metabolic responses in 12 recreationally active young men while undertaking brisk walking at low-moderate intensity (equated to approximately 50%  $\text{VO}_{2\text{max}}$ ) in the fed and fasted state [9]. The randomised crossover trial incorporated an overnight fast of 12 hours for all the participants, followed directly by 45 minutes of brisk walking (FASTED) or breakfast prior to the exercise (FED). The groups were switched over after seven days and the exercise session was repeated. Substrate utilisation analysis through expired air samples with  $\text{VO}_2$  and  $\text{VCO}_2$  indicated no significant difference in oxidation of fat or carbohydrate. FFA levels were noted to be greater in the FASTED component alone, as well as post-exercise at 120 minutes in both states. The findings from this trial, based on only one fasted exercise session per participant, suggested that low-moderate intensity exercise in the fasted state appeared to have limited effects on metabolic response with only tendency towards increased fat oxidation in the form of increased FFA levels.

In contrast, a study by Bouhlef *et al.* (2006) investigated fat oxidative metabolism in moderate-high intensity aerobic exercise undertaken by trained male rugby players observing RF [10]. The small sample size of nine participants adhered to five hours of weekly training through 29 days of consecutive RF, although there were no specific dietary control measures. Progressive submaximal ergometer testing was undertaken at approximately 12 hours of fasting since the previous food and fluid intake on three occasions: one week before the start of RF (Control), the first week of RF (Beg-R) and the fourth week of RF (End-R). RER was used

as the basis for metabolic analysis and parameters of 0.7 were equated to 100% energy from fat oxidation and an RER of 1.0 was associated with 100% energy from carbohydrate oxidation. A value of 0.91 represented the 'cross-over' point with 70% carbohydrate and 30% fat contribution. The RER was observed to be consistently lower during RF than Control and the cross-over point was seen at a greater power output at End-R. This suggested a pattern of increased reliance on fat oxidation during fasted submaximal exercise and that adaptations through RF training may enhance glucose metabolism pathways such that higher power outputs are then required to hit the cross-over point in switching from carbohydrate to fat oxidation. The authors did discuss potential limitations in sample size and inter-individual differences possibly due to variations in individual physical activity, dietary intake (with higher fat intake noted during RF compared to Control), and fitness levels.

The effect on intramuscular triacylglycerol (IMTG) by exercise in the fasted state compared with an optimal carbohydrate state was studied by De Bock *et al.* (2005) in a small group of physically active, young males [11]. The 9 participants were randomised to exercise in the fasted state (F, amounting to 13 hours) or exercise following carbohydrate feeding (CHO) and then crossed over to the opposite arm. The participants' diet was standardised for three days before the two sessions, which involved cycling at high intensity of 75%  $\text{VO}_{2\text{max}}$  with a three-week interval between the two sessions.

IMTG was noted to have depleted by approximately 60% in type I but not type IIa fibres during F, a pattern consistent with motor unit type activation and substrate preference during submaximal exercise (Figure 2).

This was the case despite a high level of circulating plasma FFAs at levels even higher than the CHO group (Figure 3A), suggesting that levels of FFAs do not play an influential role in IMTG metabolism. IMTG degradation appeared to have been blunted by carbohydrate intake in CHO as there was no notable depletion. The mean rate of glycogen resynthesis was approximately three-fold higher in F than CHO and consistent with enhanced insulin action. Although the role of insulin sensitivity could not be ascertained, insulin levels were almost double in F compared to CHO at four hours post-exercise in the recovery period (Figure 3B) despite equivalent recovery carbohydrate intake and identical blood glucose levels (Figure 3C).

There was also a marked increase in uncoupling protein 3 (UCP3) mRNA with F, with a significant difference pre-exercise and this was exaggerated post-exercise, but levels were completely unaffected in the CHO group (Figure 4).

A relationship between circulating FFA levels and UCP3 expression was discussed but there was no concordant increase in UCP3 expression with CHO despite a significant increase in FFA levels in this state, suggesting that UCP3 expression seems not to be linked with FFA levels or exercise but in fact the fasted state and possibly in combination with exercise. The specific underlying metabolic pathway would need further investigation.

Stannard (2011) reviewed studies employing the technique of RER to estimate substrate type contribution during fasted endurance exercise [12]. They concluded that there was a tendency towards lipid oxidation but this was not noted in either prolonged exercise or with submaximal exercise, suggesting that the training period may need to be extended to facilitate the metabolic switch, or that the duration of fasting may otherwise need to be prolonged.

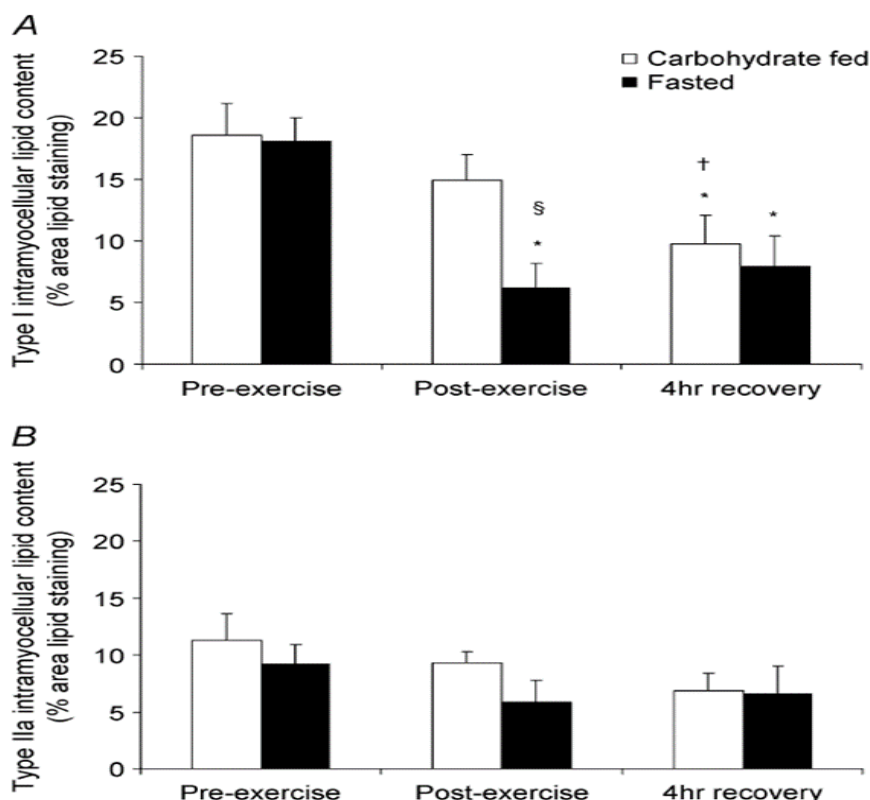
The uncertainty over the contribution of the training period seems to have been addressed in a recent study by Edinburgh *et al.* (2019) [17], which investigated the acute and chronic (training) effects of exercise-nutrient timing on lipid metabolism, skeletal muscle adaptations and oral glucose insulin sensitivity (OGIS). The acute component of the study

included 12 overweight or obese men with sedentary profiles, while the training component involved 30 men with similar sedentary characteristics. They undertook moderate intensity exercise in a single bout and six weeks of training, respectively. Both acute and training components involved a randomised, controlled comparison of a carbohydrate breakfast before fasted exercise (CHO-EX) and cross-over with carbohydrate breakfast after exercise (EX-CHO).

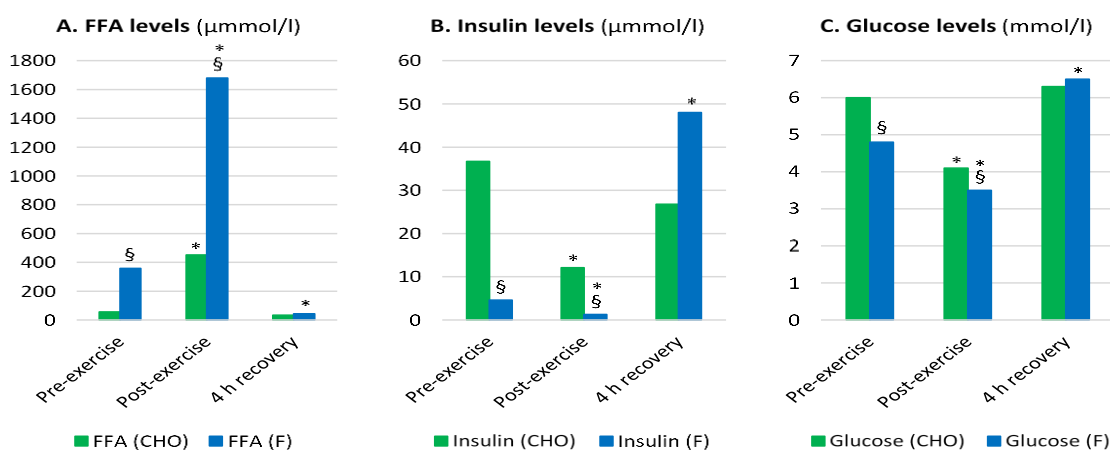
The acute component demonstrated that a single bout of moderate intensity exercise decreased skeletal muscle lipid content within type I fibres. Type II fibres tended towards the same but not at the threshold of significance. In contrast, within the chronic component, there was a

two-fold increase in skeletal muscle lipid utilisation with EX-CHO compared to CHO-EX, measured through lipid and carbohydrate oxidation by using RER.

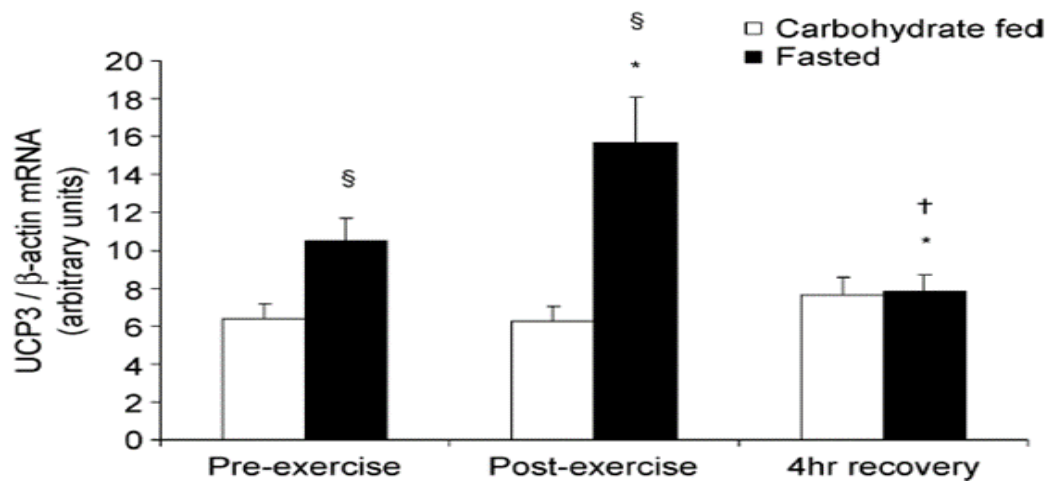
Although there was no differential in postprandial glycaemia, there was reduced postprandial insulinaemia and an increase in OGIS with EX-CHO compared to CHO-EX. In conjunction with this pattern, levels of the energy-sensing AMPK and GLUT4 glucose transport protein were increased with fasted exercise prior to nutrient provision, suggesting an association with increased fatty acid availability independent of muscle glycogen content and concentration of AMP. The net result was an improved OGIS index through enhanced GLUT4 translocation. The authors acknowledged that an additional component of a fasted group without exercise would have provided useful insight in to any effect of the fasted state alone.



**Figure 2:** Effect of exercise in the fasted versus carbohydrate-fed state on intramyocellular lipid content. Intramyocellular lipid content for type I (A) and type IIa fibres (B) before, immediately after and 4 h after exercise as determined by fluorescence microscopy on Oil red O stained muscle cross-sections. Data provided are expressed as means  $\pm$  S.E.M. ( $n = 9$ );  $\S P < 0.05$  versus carbohydrate fed;  $*P < 0.05$  versus pre-exercise;  $\dagger P < 0.05$  versus post-exercise (reproduced from De Bock *et al.*, 2005).



**Figure 3:** Effect of exercise in the fasted versus carbohydrate-fed state on A. FFA, B. Insulin, C. Glucose levels. Data provided are means  $\pm$  S.E.M. ( $n = 9$ );  $*P < 0.05$  versus pre-exercise;  $\S P < 0.05$  versus carbohydrate fed (produced based on data from Table 1, De Bock *et al.*, 2005).

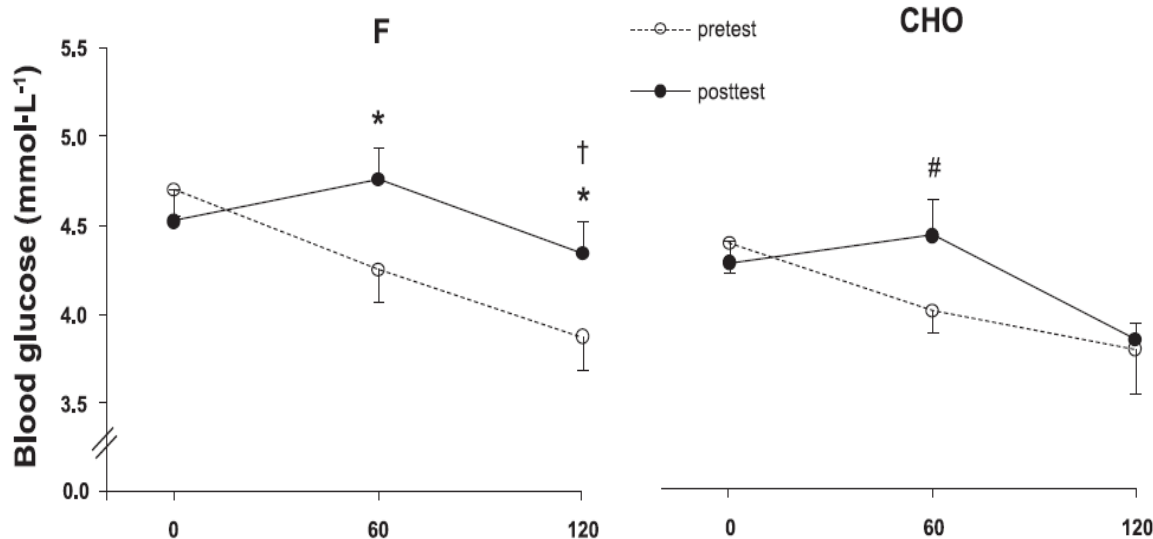


**Figure 4:** Effect of exercise in the fasted versus carbohydrate-fed state on muscle UCP3 mRNA content. Total UCP3 mRNA content in muscle before, immediately after and 4 h after exercise as measured by RT-PCR. Data provided are normalized for  $\beta$ -actin and expressed as means  $\pm$  S.E.M. ( $n = 9$ ); \* $P < 0.05$  versus pre-exercise; † $P < 0.05$  versus post exercise; § $P < 0.05$  versus carbohydrate fed (reproduced from De Bock *et al.*, 2005).

#### Glucose Metabolism

The theme of glucose metabolism and fat oxidation, along with ATP activity, in the context of fasted state endurance training was explored expansively by Van Proeyen *et al.* (2011) [13]. A six-week period of fed or fasted endurance training was undertaken in 20 young, physically active males. The participants were paired as duplets based on  $VO_{2max}$  and power outputs before being randomised to training in a 12-hour overnight fasted state (F) or with ample carbohydrates (CHO). Both groups had an equivalent isocaloric diet and maintained their weight

through the study. The duplets trained together with matched durations and high intensity for the four, weekly training sessions throughout the six weeks, undergoing maximal incremental exercise tests both pre and poststudy. The contribution of intramyocellular lipids (IMCL) to energy provision was significantly enhanced only in F, which also demonstrated stimulated activity of CS and  $\beta$ -HAD compared to CHO. In monitoring glycaemic parameters, F also appeared to prevent a drop in blood glucose levels and this was not the case in CHO (Figure 5).



**Figure 5:** Effects of training in the fasted state vs. training in the carbohydrate-fed state on blood glucose concentration during a 2-h constant load exercise bout. Data provided are means  $\pm$  SE (F:  $n = 10$ ; CHO:  $n = 10$ ) and represent values pre-test and post-test in either the fasted state (F) or with ample carbohydrate intake before and during the training sessions (CHO). Concentrations of blood glucose were measured before and at the end of a 2-h constant-load cycling bout. The workload was  $175 \pm 6$  W and corresponded to 65% of  $VO_{2max}$  in the pre-test vs. 60% of  $VO_{2max}$  in the post-test. \* $P < 0.05$  vs. pre-test. † $P < 0.05$  vs. CHO. # $P < 0.07$  vs. pre-test (reproduced from Van Proeyen *et al.*, 2010).

Both groups demonstrated increases in AMPK phosphorylation and a two-fold increase in muscle GLUT4 protein content, but no differential between F and CHO. The fasted state endurance exercise promoted the contribution of IMCL to energy provision and increased muscle oxidative capacity when compared with ample carbohydrate provision. The amelioration of a blood glucose drop during fasted exercise may have been due to homeostatic mechanisms that enhanced hepatic gluconeogenesis. This pattern was also a feature of the study cited earlier by Bouhlef *et al.* (2006) [10], who noted that there were also no changes in plasma glucose concentrations during the course of RF.

Zouhal *et al.* (2020) also emphasised the importance of homeostatic mechanisms in maintaining glucose levels, underpinned by fasted exercise inducing hormonal regulatory steps and physiological adaptations despite the lack of glycogen availability [2].

While carbohydrate limitation in a fasted state during exercise appeared to promote fat mobilisation, glycaemic regulation and muscle oxidative capacity, Van Proeyen *et al.* (2010) also contrastingly studied the role of a background high-fat, hypercaloric diet (HFD) with fasted state exercise and its effect on glucose metabolism [14]. In this study, 28 physically

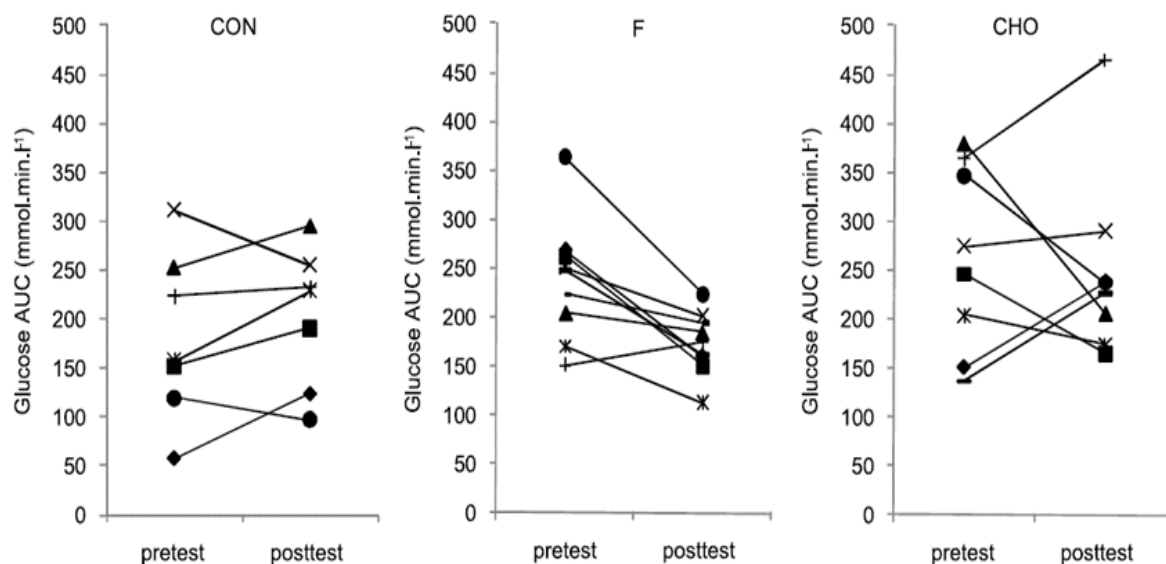


active, but not endurance-trained, healthy, young men were randomised after being matched as triplets (based on baseline  $\text{VO}_{2\text{max}}$  and energy intake patterns) to one of three arms, each of which was provided with the same HFD: Control (CON) with no training, endurance training in the fasted state (F) and endurance training with carbohydrate both before and after endurance training (CHO). Similar to the associated study, the high intensity training sessions spanned six weeks and consisted of a combination of cycling at 70-75%  $\text{VO}_{2\text{max}}$  and running at 85% maximal heart rate (MHR).

Compared to CON, F ameliorated the effect of a HFD on glucose tolerance (Figure 6) and whole-body insulin sensitivity. This was also

associated with an increase of GLUT4 muscle protein content in F but remained unchanged in CHO, suggestive of insulin mediation in muscular glucose uptake.

There were also patterns of molecular muscle energy metabolism adaptations noted with increased mRNA content of FAT/CD36 as well as AMPK phosphorylation in F but not in CHO. Although this was a short-term study in a specific population, in spite of a background HFD, there was indication of a role for fasted state exercise in specifically mediating glucose metabolism, insulin sensitivity and nuclear hormone receptors.



**Figure 6:** Effect of high-fat diet, alone or in conjunction with training in either the fasted or the carbohydrate-fed state, on individual responses on glucose tolerance. Data provided are individual values (CON:  $n = 7$ ; F:  $n = 9$ ; CHO:  $n = 8$ ) and represent area under the glucose curve (AUC<sub>gluc</sub>) during a 120 min OGTT. Values before (pre-test) and after (post-test) a 6-week hyper-caloric fat-rich diet, in either the absence (CON) or the presence of training in either the fasted state (F) or the carbohydrate-fed state (CHO) are shown. One outlier (CHO subject) is omitted from the glucose data analysis (reproduced from Van Proeyen *et al.*, 2010).

### Nuclear Hormone Receptors

A cohort of 10 healthy but overweight men were studied by Chen *et al.* (2017) while undertaking moderate intensity exercise at 60%  $\text{VO}_{2\text{max}}$  in fed and fasted state exercise, with the former yielding lower mRNA expressions of PDK4, CD36 and GLUT4 and indicating the effect of nutrient intake pre-exercise as well as the sensitivity of nuclear hormone receptors (NHRs) [15]. Hong *et al.* (2014) underlined the role of NHRs in coordinating adaptations to nutritional fluctuations and coordinating the genetic switches that govern nutritional and physiological homeostasis [8]. Adipose tissue highly expresses peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ), which plays a pivotal role in glucose homeostasis by influencing the expression of GLUT4. PPAR $\alpha$  is integral to the hepatic gluconeogenesis adaptive responses to fasting. Through the activation of PDK4 by PPAR $\alpha$ , muscle glucose uptake and utilisation are suppressed with a preferential reliance on lipid utilisation for fatty acid oxidation. PDK4 also inactivates the pyruvate dehydrogenase complex by phosphorylation, thereby preventing its oxidation and conserving both lactate and alanine for gluconeogenesis. Anton *et al.* (2018) also discuss the significance of molecular adaptations through gene activation that underpins metabolic switching in substrate selection with key components of PDK4, CD36 and UCP3 [3].

The precise role of NHRs in regulating energy metabolism appears dependent on specific organs' substrate availability and preference [8]. Stannard (2011) reviewed historic studies involving exercise during RF and concluded that skeletal muscle appears to adapt well to improved lipid utilisation and protect the use of carbohydrate during exercise with these adaptations appearing enhanced during RF [12]. However, a potential confounder in the RF model is the abstinence from any fluid

intake, meaning that fluid, electrolyte and hormonal regulatory mechanisms may obscure the effect of any metabolic adaptations. Nevertheless, the author indicates that exercise with RF can facilitate the versatility of skeletal muscle to optimise lipid utilisation.

Type I oxidative slow-twitch fibres rely on fatty acid oxidation, type II fibres rely on glucose metabolism, with type IIa categorised as mixed oxidative-glycolytic fast-twitch and IIb as glycolytic fast-twitch. PPAR $\delta$  is implicated in improving muscular fatty acid utilisation but also triggers a genetic cascade that results in a fibre type switch in type I muscle, consequently increasing its endurance capacity by oxidising both lipids and carbohydrates more efficiently [8]. Mitochondrial biogenesis has also been highlighted as an important intramuscular adaptation, with markers of mitochondrial biogenesis demonstrating beneficial effects under the influence of aerobic exercise with nutritional adjustments in the form of carbohydrate intake manipulation [16].

### Nutrient & Exercise Patterns

Trenell *et al.* (2008) investigated the influence of glycaemic index (GI) on carbohydrate intake prior to fasted moderate-high intensity exercise [17]. Seven endurance-trained cyclists consumed either high GI (HGI) or low GI (LGI) meals in the 12 hours prior to an overnight 12 hour fast. This was followed by a 90-minute cycling session at 70%  $\text{VO}_{2\text{max}}$ . The HGI group demonstrated a significant reduction in IMCL as well as reduced FFA availability. This indicates that HGI carbohydrate intake negatively affects lipolysis compared to LGI carbohydrate intake preceding overnight fasted aerobic exercise, resulting in reduced circulating FFA and greater dependence on IMCL as substrate selection. In contrast, Bennard and Doucet (2006) did not yield a differential in fat oxidation

between low and high GI meals preceding exercise, although there were significant differences in study design; the participants were untrained healthy young men, the meals were ingested at breakfast time prior to the exercise, compared to the 12-hour time lag with the cohort studied by Trenell *et al.* (2008), as well as an apparent lower intensity exercise regime [17,18]. The effect of contrasting variables in this area is exemplified further by Erdmann *et al.* (2010), who studied 20 obese participants and the effect on lipolysis of carbohydrate meal timing in relation to 30 minutes of low intensity cycling exercise [19]. They concluded that a carbohydrate meal prior to exercise suppressed lipolysis activity when compared with fasted state exercise.

Another common consideration is variance in exercise form, with high intensity interval training (HIIT) increasingly recognised as a time-efficient format of exercise to attain beneficial physiological adaptations that are usually associated with moderate intensity continuous exercise (MICE).

HIIT combined with a carbohydrate-restricted diet has been noted in the literature to result in a preferential reliance on fat oxidation when compared with MICE. However, this was based on observations in a clinical population. On the other hand, Gillen *et al.* (2013) compared HIIT undertaken in the fed and fasted state to evaluate the effect on muscle mitochondrial capacity as well as insulin sensitivity [20]. The 16 participants were overweight or obese women who were sedentary at baseline. The six-week HIIT programme entailed 18 sessions of HIIT, each composed of ten cycling bouts lasting 60 seconds and targeting 90% HR<sub>max</sub>. The FED group had breakfast prior to training whilst the overnight FASTED group were given breakfast 60 minutes following exercise, but there were no other dietary controls. There was no significant difference noted in muscle oxidative capacity (with reference to CS and  $\beta$ -HAD activity) nor glucose activity (GLUT4 protein content used as a marker) between HIIT in FED and FASTED. Given there was no apparent difference between the groups in terms of glucose utilisation and insulin sensitivity, it is possible that the short nature of the HIIT sessions would have favoured intramuscular substrate availability, likely to be glycogen. In addition, the high intensity exercise format could have superseded any potential for metabolic switching through the fasted state. There could also be considerations related to the population characteristics, specifically arising from gender differences and variations in body composition, as well as the time lag of 72-96 hours between completion of the last training session and the post-testing. This could potentially overlook any acute phase benefit for glucose tolerance and insulin sensitivity and indeed De Lorenzo *et al.* (2018) commented that HIIT, in comparison to continuous training, combined with fasted state may confer an advantage of reduced post-prandial glycaemic increment compared to exercise undertaken on a fed state after breakfast. They have published a study protocol for a randomised clinical trial to investigate these variables [21].

It is apparent that versatility in metabolic switching between glucose and fat oxidation appears integral to varying physiological conditions, specifically fasted state exercise inducing a mobilisation of adipose tissue lipids to increase circulating FFAs as well as imparting benefits to glucose regulation and insulin sensitivity. This metabolic shift is governed by complex but integrated signalling pathways particularly in skeletal muscle, which also demonstrates inherent fibre-type adaptivity. Considering the versatility and propensity of energy metabolism to adjust under the conditions of fasted state exercise, it would be useful to evaluate whether there are implications for aerobic capacity when undertaking aerobic exercise in the fasted state.

## CONCLUSION

The overall aim of this literature review was to investigate an important interplay between aerobic exercise in the fasted state and potential benefits for energy metabolism. Implications were considered for

healthy adults undertaking recreational exercise in the general population and the training regimes of elite athletes.

While low-moderate intensity exercise for short durations over a short study period indicated a tendency towards reliance on fat oxidation during fasted aerobic exercise, moderate-high intensity exercise during RF confirmed a reliance on fat oxidation as well as an increased efficiency of glucose metabolism pathways. High-intensity fasted exercise studies indicated fibre-type specific depletion of IMTG in type I fibres and not type IIa fibres, which is consistent with the established pattern of motor unit type activation and preference of substrate at this intensity of exercise. Glycogen resynthesis was also higher after fasted state aerobic exercise and consistent with increased insulin activity when compared with fed state aerobic exercise. Insulin sensitivity was increased at moderate intensity exercise with associated increases in AMPK and GLUT4 activity, but even at higher intensities in physically active populations. The homeostatic regulation of glucose metabolism appeared to be enhanced with fasted aerobic exercise in the context of a high fat diet, which yielded decreased glucose tolerance in conjunction with increased insulin sensitivity. When considering the glycaemic index of meals in relation to fasted aerobic exercise, there were variable responses on lipolysis. Both meal constitution and the effect of differing patterns of exercise, such as HIIT and MICE, warrant further investigation to elucidate clearer relationships.

Among the studies reviewed, the role of nuclear hormone receptors was apparent as mediators between glucose and fat metabolism pathways. Upregulation of AMPK and GLUT4 protein levels, increased levels of FAT/CD36 mRNA content in skeletal muscle, as well as reflections in mitochondrial activity with increased CS and  $\beta$ -HAD levels, suggest a highly coordinated metabolic response to fasted state aerobic exercise.

## Limitations

There were limitations encountered that need to be borne in mind when considering the conclusions and formulation of the recommendations. The heterogeneity in populations studied, the range of sample size and variations in study protocols are caveats to drawing firm conclusions with wide application. Although many of the studies aimed to objectively match the profile of participating cohorts, there were inter-individual physiological and lifestyle differences that may have confounded results. Controlling for dietary and training schedules within a study still meant that comparison with other studies was difficult due to differences in these factors between studies, as well as study durations. Studies used different measures of effect and there would also be inter-observer and technical variations. There were also no studies that incorporated the metabolic or aerobic capacity effect of fasted state aerobic exercise at differing intensities, nor evaluating long-term intervention durations beyond a few weeks.

## Recommendations

In adopting a tapered and gradual approach to adopting the fasted state, followed by the incorporation of aerobic exercise, low-moderate intensity aerobic exercise in the fasted state may be considered for the general population as this seems to result in beneficial metabolic switching. The reliance on lipid utilisation and fat oxidation, along with alterations in glucose metabolism, may improve insulin sensitivity and glucose tolerance. This may be of particular health promotion benefit in the sedentary overweight population as well as those with a high fat diet. Appropriate multi-disciplinary counselling, with particular consideration for medical and nutritional factors, would be helpful to avert any adverse effects and derive maximal health benefits.

## Conflicts of interest

None declared.

## Financial Support

None declared.

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