HELLENIC REPUBLIC
National and Kapodistrian University of Athens
EST. 1837

MEDICINE SCHOOL

Postgraduate Program
‘Molecular and Applied Physiology’

The role of exercise timing ("chrono exercise") on metabolic diseases

Master's dissertation

By

VASILIKI KOZANITI
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Athens,2023

ABSTRACT

Purpose: To determine whether acute or chronic exercise is more effective, when performed in the morning or in the evening as well as whether the metabolic changes induced by exercise differ after postprandial or preprandial exercise in individuals suffering from metabolic disorders.

Methods: A systematic review of 30 scientific studies that included 1,740 obese adults was conducted regarding the effects of various types of physical exercise, i.e., Aerobic Exercise (AE), Anaerobic Exercise (AnE), HIIT (High-Intensity Interval Training), Resistance Exercise (RE), and a combination of these types of exercise, on health indicators in patients suffering from metabolic disorders. Specifically, the health indicators that were evaluated included four categories:

a) Body Composition [Body Weight (BW), Body Mass Index (BMI), Waist Circumference (WC), Fat Mass (FM), Free Fat Mass (FFM)]

b) Postprandial/Fasting Metabolism [Glucose, HOMA Index (HOMA-IR), HbA1c]

c) Lipid Metabolism [Triglycerides (TAG), Total Cholesterol (TC), Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL)]

d) Appetite Indices [Energy Intake (EI)]

Results: When contrasting morning and evening exercise, evening workouts seem to excel in reducing Body Weight and Fat Mass, and they may also slightly improve Total Cholesterol. Conversely, morning exercise is more effective for trimming Waist Circumference. Regarding the timing of exercise in relation to meals, postprandial exercise stands out for its stronger impact on glucose and insulin levels, leading to more substantial benefits. As for the appetite indices, the morning exercise appeared to be more efficient.

Conclusion: It can be deduced that the decision regarding whether to engage in exercise in the morning or afternoon, and whether to do so before or after a meal, hinges on the particular outcome aimed to be enhanced. It appears that engaging in physical activity during the afternoon and exercising after meals might yield more favorable results. Similarly, similar outcomes in terms of glucose and insulin levels appear to be manifested following exercise in the afternoon.

Keywords: Metabolic diseases, Type 2 diabetes, Obesity, Aerobic exercise, Anaerobic exercise, Resistance exercise

Περίληψη

Σκοπός: Να συγκρίνει εάν μια μεμονωμένη συνεδρία άσκησης, ή η χρόνια (συστηματική) άσκηση είναι πιο αποτελεσματική όταν πραγματοποιείται το πρωί ή το απόγευμα, καθώς και εάν οι μεταβολικές αλλαγές που προκαλούνται είναι διαφορετικές μετά από μεταγευματική ή προγευματική άσκηση σε άτομα που πάσχουν από μεταβολικές διαταραχές.

Μέθοδοι: Πραγματοποιήθηκε συστηματική ανασκόπηση 30 επιστημονικών μελετών που συμπεριελάμβαναν συνολικά 1.740 υπέρβαρους ενηλίκους που έπασχαν από μεταβολικές διαταραχές. Οι μορφές άσκησης που εξετάστηκαν ήταν Αερόβια Άσκηση, Αναερόβια Άσκηση, Άσκηση με Αντιστάσεις, και συνδυασμός αυτών των τριών ειδών άσκησης. Αξιολογήθηκαν δείκτες υγείας σε τέσσερις επιμέρους κατηγορίες: α) Σύσταση σώματος [Σωματικό Βάρος(BW), Δείκτης Μάζας Σώματος(BMI), Περίμετρος Οσφύος(WC), Ποσοστό Λίπους(FM), Άλιπη Μάζα(FFM)] β) Προγευματικός/ Μεταγευματικός Μεταβολισμός (Γλυκόζη, Δείκτης HOMA-IR, HbA1c) γ) Λιπιδικός Μεταβολισμός [Τριγλυκερίδια(TAG), Συνολική Χοληστερόλη(TC), Χαμηλής Πυκνότητας Λιποπρωτεΐνη (LDL), Υψηλής Πυκνότητας Λιποπρωτεΐνη (HDL)],
δ) Δείκτης Πείνας [Πρόσληψη Ενέργειας(EI)]

Αποτελέσματα: Όταν συγκρίνεται η πρωινή με την απογευματινή άσκηση, οι απογευματινές συνεδρίες άσκησης φαίνεται ότι είναι αποτελεσματικότερες στη μείωση του σωματικού βάρους και λίπους, και ενδέχεται να βελτιώνουν ελαφρώς την ολική χοληστερόλη. Ωστόσο, η πρωινή άσκηση είναι πιο αποτελεσματική στη μείωση της περιμέτρου της οσφύος. Όσον αφορά τον χρονισμό της άσκησης σε σχέση με τα γεύματα, η μεταγευματική άσκηση υπερέχει ως προς την αποτελεσματικότερη επίδρασή της στη ρύθμιση των επιπέδων γλυκόζης και ινσουλίνης του αίματος.. Επίσης, τα ίδια αποτελέσματα, όσο αφορά τα επίπεδα γλυκόζης και ινσουλίνης, φαίνεται να επέρχονται μετά από απογευματινή άσκηση. Όσον αφορά τους δείκτες της όρεξης, η πρωινή άσκηση βρέθηκε να είναι πιο αποτελεσματική.

Συμπέρασμα: Η απόφαση σχετικά με το αν τα άτομα με μεταβολικές διαταραχές θα πρέπει να ασκούνται το πρωί ή το απόγευμα, και εάν αυτό θα πρέπει να γίνεται πριν ή μετά από ένα γεύμα, εξαρτάται από το ειδικό αποτέλεσμα που επιδιώκεται. Φαίνεται ότι η άσκηση το απόγευμα και μετά τα γεύματα μπορεί να αποφέρει συνολικά πιο ευεργετικά αποτελέσματα.

Λέξεις κλειδιά: Μεταβολικά νοσήματα, Διαβήτης τύπου 2, Παχυσαρκία, Αερόβια άσκηση, Αναερόβια άσκηση, Άσκηση με αντιστάσεις

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I also want to convey my deep gratitude to my family and friends who provided exceptional support during my academic journey. Their patience and encouragement were instrumental in helping me stay focused and determined to achieve my goals.

ABBREVIATIONS-ACRONYMS

BMI: Body Mass Index

HOMA – IR: Homeostatic Model Assessment for Insulin Resistance

T2D: Type 2 Diabetes

IR: Insulin Resistance

iAUC: Incremental area under the curve

WHO: World Health Organization

WC: Waist circumference

MS: Metabolic Syndrome

LDL: Low Density Lipoprotein

HDL: High Density Lipoprotein

CVDs: Cardiovascular Diseases

BF: Body Fat

BW: Body Weight

FFM: Free Fat Mass

EI: Energy Intake

ACE inhibitors: Angiotensin-converting enzyme inhibitors

HIIT: High Intensity Interval Training

VO2peak: Peak oxygen intake

VO2max: Maximal oxygen consumption

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1.INTRODUCTION

1.1. Statement of the problem

In recent years, metabolic syndrome has become a major concern for the medical and scientific communities. "Metabolic syndrome, also known as syndrome X, insulin resistance, etc., is defined by the WHO (World Health Organization) as a pathologic condition characterized by abdominal obesity, insulin resistance, hypertension, and hyperlipidemia,".[1] The consumption of fatty foods and a lack of exercise are the two main factors contributing to this disorder's continual global spread. Although it originated in the West and spread throughout the world because of the adoption of the Western way of life, it is currently one of the most significant global health issues. [1]

1.2 Definition of terms

1.2.3 Metabolic Syndrome

Metabolic syndrome is a clustering of hyperglycemia/insulin resistance, obesity, and dyslipidemia. [2] It has been a lot of effort to discover the most proper definition of it. In the last decades many organizations have differentiated the definition, but the most common ones are by WHO 1999, NCEP (National Cholesterol Education Program) ATP3 2005 and IDF (International Diabetes Federation) 2006 [1].

The patients that have been diagnosed with metabolic syndrome show waist > 94 cm (men) or > 80 cm (women) along with the presence of two or more of the following [1]:

- blood glucose, greater than 5.6 mmol/L (100 mg/dl) or diagnosed diabetes.
- HDL cholesterol < 1.0 mmol/L (40 mg/dl) in men, < 1.3 mmol/L (50 mg/dl) in women or drug treatment for low HDL-C
- blood triglycerides > 1.7 mmol/L (150 mg/dl) or drug treatment for elevated triglycerides

- blood pressure > 130/85 mmHg or drug treatment for hypertension

Metabolic syndrome often coincides with rising rates of obesity and the development of Type 2 Diabetes (T2D), which is one of the outcomes associated with Metabolic Syndrome (MS). According to data from the National Health and Nutrition Examination Survey (NHANES) spanning from 1988 to 2010, the average Body Mass Index (BMI) in the United States increased by approximately 0.37% annually for both men and women. Waist circumference (WC) also saw an increase, with women experiencing a rise of 0.37% per year, and men, 0.27% per year.[3]

In 2017, the Centers for Disease Control and Prevention reported that approximately 30.2 million adults in the United States, aged 18 and older, or roughly 12.2% of the adult population, had been diagnosed with T2D [4]. Alarmingly, nearly a quarter of these individuals (23.8%) were unaware of their condition. The incidence of T2D rose with age, peaking at 25.2% among seniors aged 65 and older.

Many large cardiometabolic imaging studies have shown that an excess accumulation of visceral adipose tissue (and not of subcutaneous fat) was a key correlate of the features of insulin resistance [5,6,7,8,9,10]

However, there are many opportunities for enhancing the patient's clinical image if these conditions can be changed in a healthier way. How can this disorder be prevented or reversed?

1. **Addressing Obesity and Body Fat Distribution:** The primary focus in treating MS should be on tackling obesity. The initial approach should emphasize weight reduction coupled with increased physical activity. Shedding excess weight has several positive effects, such as reducing cholesterol and triglyceride levels, elevating HDL cholesterol, lowering blood pressure and glucose levels, and decreasing insulin resistance. Therefore, the foremost aspect of clinical management should involve lifestyle modifications, primarily centered on losing weight and enhancing physical fitness. [11]
2. **Targeting Insulin Resistance:** It is well-established that weight loss and an uptick in physical activity can mitigate insulin resistance. However, pharmaceutical advancements have also led to the development of drugs

aimed at addressing insulin resistance. Currently, two classes of such drugs exist: metformin and insulin sensitizers like thiazolidinediones (TZDs). [11]

3. **Focusing on Specific Metabolic Risk Factors:** Atherogenic dyslipidemia, a condition characterized by unfavorable lipid profiles, is a critical concern. While statins are commonly known for their ability to lower LDL cholesterol levels, recent analyses of statin trials have unveiled their potential in reducing cardiovascular disease (CVDs) risk among individuals with MS. Additionally, post hoc evaluations of fibrate trials strongly suggest that these drugs can also reduce CVDs events in individuals with atherogenic dyslipidemia and MS.[12] Furthermore, clinical research demonstrates that combining statins and fibrates leads to a more significant improvement in abnormal lipoprotein patterns. [11]
   Blood pressure management involves the use of medications like ACE inhibitors, angiotensin receptor blockers, diuretics, and beta blockers. However, it is important to note that certain diuretics and beta blockers may increase the likelihood of developing T2D, particularly in individuals with MS. [11] For regulating blood sugar levels, insulin sensitizers like thiazolidinediones can be effective. Nevertheless, these drugs come with potential side effects such as liver damage, anemia, heart failure, and fluctuations in blood sugar levels, which can become either too low or too high. Blood triglyceride and "good" HDL cholesterol levels, medications like statins and niacin are commonly prescribed. They not only lower triglycerides and reduce "bad" LDL cholesterol but also elevate levels of "good" HDL cholesterol. In some cases, a combination of these medications may be necessary. However, it's important to be aware that these drugs can lead to digestive issues and some statins might increase the risk of T2D in individuals with MS. [13]

According to the American Heart Association the prevention of metabolic syndrome consists of [14]:

- controlling the body weight or losing weight
- exercising in a regular basis
- eating a healthy and balanced diet

- stopping smoking and drinking alcohol

Exercise is a key strategy for changing this situation. Exercise truly is medicine, as we frequently hear, and this situation is the perfect example. The importance of exercise in metabolic diseases, and specifically the timing of exercise, will be emphasized in this essay. Exercise timing in this context refers to morning or evening exercise as well as exercise after fasting or feeding situations. We will mainly concentrate on the timing of exercise and how it affects those with T2D and obesity. Will the individual experience more profound metabolic changes during exercise while feeding or fasted exercise, for instance? By the term ‘feeding or fed exercise’ we refer to the exercise after consumption of a meal, on the other hand by ‘fasting or fast exercise’ we refer to the exercise after a chronic period of fasting.

1.2.2 Obesity

Obesity is characterized by an excessive buildup of body fat or an abnormal distribution of Body Fat (BF) that has a detrimental impact on one's health.[15] It is primarily categorized based on BMI, which is a somewhat limited criterion for classification. [16]

Adult men and women can use the BMI, a scale based on height and weight, to determine their BF percentage. It is calculated by dividing a person's weight in kilograms (or pounds) by their height in square meters (or feet). According to the WHO, a BMI over 25 is considered overweight, and a BMI over 30 is obese. [17]

The surplus presence of BF is associated with numerous health disorders, including but not limited to T2D, hepatic steatosis, CVDs, stroke, dyslipidemia, hypertension, gallbladder issues, osteoarthritis, sleep apnea, and various respiratory problems. Additionally, it is linked to specific types of cancer such as endometrial, breast, ovarian, prostate, liver, gallbladder, kidney, and colon cancers, all of which elevate the risk of mortality.[18] Conditions associated with disorders of the pituitary, thyroid, and adrenal glands are typically viewed as distinct pathologies but can also serve as potential indicators of obesity. [19]

The cause is caused by environmental factors such as diet, lack of physical exercise, ultra-processed foods, fast food, microbiome, and the chemical contaminants, which can alter gene expression.[20]

1.2.3 Type 2 Diabetes

T2D is a multifaceted and intricate multisystem disorder with various associated comorbidities. Its management necessitates a customized and multifaceted approach. In contrast, during the 1920s, the scientific community held the belief that diabetes was a straightforward pancreatic disorder. [21,22]

In the past three decades, a better comprehension of previous discoveries, combined with fresh insights, has revealed an increasing number of significant contributors to diabetes. These contributors encompass various organs and systems, including the liver, muscles, kidneys, fat cells, the brain, alpha cells, and the gastrointestinal tract. Additionally, multiple hormones and factors such as systemic inflammation, genetics, and the environment play crucial roles in this context. [23,24,25]

As per the WHO, diabetes mellitus is a chronic metabolic disorder characterized by persistently high levels of blood glucose. This prolonged elevation in blood glucose can result in damage to vital organs such as the heart, blood vessels, eyes, kidneys, and nerves over time. More than 90% of diabetes mellitus cases fall under the category of T2D, a condition characterized by insufficient insulin production by pancreatic islet beta-cells, tissue resistance to insulin (IR), and an insufficient compensatory increase in insulin secretion. [26,27] In recent years, the percentage of people who suffer from T2D has increased remarkably, along with obesity. More than 37 million Americans have diabetes (about 1 in 10), and approximately 90-95% of them have T2D [28].

Primarily, treatment involves more exercise and caloric restriction. Weight loss improves the patient's metabolic state, with proportional decreases in blood pressure, blood glucose and lipid concentrations, and hepatic fat content. [29]

If the change in blood glucose values isn't big enough, then it may need to be medicated. The long-term consequences caused by high blood glucose can lead to heart disease, strokes, diabetic retinopathy that affects the vision, kidney failure, for which treatment requires hemodialysis, and bad blood circulation in the limbs. Patients who have MS are more likely to develop T2D. [30]

1.2.4 Hyperlipidemia

Hyperlipidemia is characterized by higher-than-normal levels of lipids or lipoproteins in the bloodstream, resulting from irregular fat metabolism or functioning. Its causes can range from dietary imbalances and obesity to genetic conditions like familial hypercholesterolemia (FH) or other medical conditions such as diabetes. [31]

The blood lipids can be:

a) cholesterol
b) triglycerides
c) phospholipids

Many studies show that hyperlipidemia is a strong risk factor for CVDs. [32]

A more straightforward explanation is that the person's blood contains an excessive amount of lipids (fats). Cholesterol is a substance that the human body needs because it aids in the formation of membranes for cells and steroid hormones. Additionally, it contributes to the production of the so-called bile acids, which aid in digestion. It is a substance that is crucial for healthy body functioning [33], but when it is present in large quantities, it can be extremely dangerous because it deposits in the artery cell walls and forms atheromatous plaque, which causes blockages in the arteries that can result in heart attacks (angina, myocardial infarction). [32] LDL-cholesterol (the 'bad cholesterol') is responsible for this mechanism, as it transfers the cholesterin from the liver to the periphery, resulting in accumulation in the vessels. On the other hand, HDL-cholesterol moves cholesterin from the peripheral to the liver, "cleaning" the cholesterin that exists in the vessels. [34]

The treatment of hyperlipidemia typically involves a combination of lifestyle modifications and medications. Here is a summary of the treatment options, along with a reference to the National Cholesterol Education Program (NCEP) guidelines, which provide comprehensive recommendations for managing hyperlipidemia [35]:

1. Dietary Changes: Adopting a heart-healthy diet, which includes reducing saturated and trans fats, increasing fiber intake, and limiting cholesterol-rich foods, is recommended for managing hyperlipidemia. [36]
2. Exercise: Regular physical activity, as recommended by guidelines, can help improve lipid profiles. [37]
3. Weight Management: Achieving and maintaining a healthy weight can positively impact lipid levels. [38]
4. Medications: Medications may be prescribed to manage hyperlipidemia when lifestyle changes are insufficient. The choice of medication depends on an individual's lipid profile and cardiovascular risk factors. [39]

Numerous research studies have demonstrated that hyperlipidemia, aside from its widely recognized contribution to the development of atherosclerosis in blood vessels, can also directly impact the heart. This influence leads to heightened damage during episodes of ischemia followed by reperfusion and diminishes the heart's ability to benefit from protective measures like ischemic preconditioning and post-conditioning. [40]

1.2.5 Insulin Resistance

Insulin Resistance (IR) is a physiological condition in which the body's cells become less responsive to the effects of insulin, a hormone produced by the pancreas. This diminished response to insulin leads to elevated blood sugar levels, known as hyperglycemia. IR is a central feature of several metabolic disorders, including T2D, obesity, and MS. We will explore the mechanisms, risk factors, clinical implications, and management of insulin resistance.[41]

Insulin plays a crucial role in regulating blood sugar levels by facilitating the uptake of glucose into cells. IR develops when cells, particularly muscle, liver, and fat cells, become less sensitive to insulin's signals.[42] This reduced sensitivity can be attributed to various factors, including:

1. **Obesity:** Excess fat, especially visceral adipose tissue, is strongly associated with insulin resistance. Adipose tissue secretes inflammatory molecules that can interfere with insulin signaling.
2. **Inflammation:** Chronic inflammation, often observed in obesity and metabolic syndrome, can disrupt insulin signaling pathways.

3. **Genetics:** Family history can influence an individual's susceptibility to insulin resistance, suggesting a genetic component.
4. **Physical Inactivity:** A sedentary lifestyle can contribute to insulin resistance by reducing the muscle's ability to use glucose.
5. **Hormonal Factors:** Conditions like polycystic ovary syndrome (PCOS) and hormonal imbalances can promote insulin resistance.

Clinical Implications:

IR is a key factor in the development of several health complications, including:

1. **Type 2 Diabetes:** Prolonged IR can lead to impaired glucose tolerance and eventually the onset of type 2 diabetes. [41]
2. **Cardiovascular Disease:** IR is associated with an increased risk of heart disease, as it can lead to dyslipidemia (abnormal lipid levels), hypertension, and atherosclerosis [43,44]
3. **Metabolic Syndrome:** A cluster of conditions, including obesity, high blood pressure, high blood sugar, and abnormal lipid profiles, often co-occur with insulin resistance. [45]
4. **Non-Alcoholic Fatty Liver Disease (NAFLD):** IR in the liver can result in the accumulation of fat in the liver cells, leading to NAFLD.[46]

1.2.6 Comorbidities

The clustering of abdominal obesity, IR, dyslipidemia, and hypertension is known as MS, which is also linked to other comorbidities such as prothrombotic, proinflammatory, nonalcoholic fatty liver disease, and reproductive disorders. [47]

Comorbidities are other medical conditions that exist alongside a primary condition or disease. In the context of MS, there are several comorbidities that are commonly associated with it:

1. **Obesity:** Metabolic syndrome is often closely linked to obesity, especially abdominal obesity. Excess body fat, particularly around the abdominal area, is a major risk factor for both metabolic syndrome and its associated comorbidities.

2. **Type 2 Diabetes:** Individuals with metabolic syndrome are at an increased risk of developing type 2 diabetes. High blood sugar levels and insulin resistance are common features of both conditions.
3. **Cardiovascular Disease:** Metabolic syndrome significantly increases the risk of heart disease and stroke. High blood pressure, abnormal lipid profiles, and obesity all contribute to the development of atherosclerosis (hardening and narrowing of the arteries), which can lead to heart attacks and strokes.
4. **Non-Alcoholic Fatty Liver Disease (NAFLD):** NAFLD is a condition characterized by the accumulation of fat in the liver. It is closely associated with metabolic syndrome and can progress to more severe liver conditions, including cirrhosis.
5. **Polycystic Ovary Syndrome (PCOS):** PCOS is a hormonal disorder that affects women and is often associated with metabolic abnormalities such as insulin resistance, obesity, and dyslipidemia.
6. **Sleep Apnea:** Obesity and metabolic syndrome are risk factors for obstructive sleep apnea, a condition in which a person's breathing is repeatedly interrupted during sleep.
7. **Kidney Disease:** Metabolic syndrome can contribute to the development of kidney problems, including chronic kidney disease.

It's important to note that not everyone with MS will develop all these comorbidities, and the severity of each condition can vary. Lifestyle changes, including a healthy diet, regular physical activity, and weight management, are often recommended to reduce the risk of both MS and its associated comorbidities. In some cases, medication may also be prescribed to manage individual components of metabolic syndrome, such as high blood pressure or high cholesterol.

1.2.7 The role of Exercise

Exercise plays a pivotal role in both the management and prevention of a range of metabolic diseases, such as type 2 diabetes, cardiovascular conditions, and obesity. In the following sections, I'll present a summary of exercise's significance in addressing these metabolic health issues and provide supporting citations.

Type 2 Diabetes:

- **Improvement in Insulin Sensitivity**: Exercise enhances insulin sensitivity, allowing the body to use glucose more effectively. This is particularly important in managing and preventing type 2 diabetes. [48]
- **Blood Glucose Control**: Regular physical activity helps regulate blood sugar levels, reducing the need for medication in individuals with type 2 diabetes [49]

Cardiovascular Diseases:

- **Improvement in Heart Health**: Exercise has a positive impact on cardiovascular health by reducing risk factors such as high blood pressure, high cholesterol, and inflammation. [50]
- **Reduction in Risk Factors**: Exercise helps reduce risk factors for heart disease, such as high triglycerides, low HDL cholesterol, and excess body weight. [51]

Obesity:

- **Weight Management**: Exercise, in combination with a balanced diet, is effective for weight loss and weight maintenance. It helps create a calorie deficit and contributes to fat loss. [52]
- **Metabolic Rate**: Exercise can increase resting metabolic rate, making it easier for individuals to maintain a healthy weight. [53]

1.2.8 Circadian Rhythm

The definition of circadian rhythm means "around the day" and is derived from the Latin phrase "circa diem". It alludes to the 24-hour cycle that regulates all bodily processes, from sleep to waking up, just as Wang stated. [54] Circadian rhythms help coordinate various physiological and behavioral processes with the Earth's Day-night cycle, as depicted in Figure 1: The 24-Hour Circadian Rhythm Cycle.

Figure 1: The 24-Hour Circadian Rhythm Cycle (https://www.news-medical.net/health/Circadian-Rhythm.aspx)

The circadian system is the most crucial regulator of nearly every aspect of human health and metabolism. Our daily rhythms are controlled by a main "Body Clock" in the human brain, a phenomenon that is also widely observed in nature in almost all living beings [55,56]. By regulating bodily processes and synchronizing peripheral clocks in almost every cell, including the body's central tissues like the heart, liver, muscle, and adipose tissue, this clock modifies the metabolism of the body [57].

It is a network of circadian pacemakers that affect the metabolic processes in the human cycle of sleep/wakefulness and feeding/fasting [58]. The suprachiasmatic nucleus (SCN), which is found at the base of the hypothalamus, synchronizes these pacemakers [59]. At the physiologic level, circadian clocks control the entire body's metabolism. At the molecular level, cell-autonomous circadian rhythms are produced by the activity of the transcriptional activators CLOCK and BMAL1 and their target genes. CLOCK and BMAL1 interact with the repressor complex to inhibit transcriptional activity. [60,61]

1.2.9 The role of exercise in the circadian clock

Physical activity is the regulator of the molecular clock in skeletal muscle, and of course it affects circadian rhythms. [62,63] Another regulator that seems to connect the metabolism with the muscles is the mitochondria. Mitochondria are the main energy suppliers that coordinate ATP production, reactive oxygen species (ROS) production, and calcium signaling. It has been found that a lower oxidative capacity of skeletal muscle is associated with lower exercise production, increasing the likelihood of developing T2D. [64,65]

On the best timing of exercise, there are a variety of different opinions. For some people, it is very helpful to get an exercise session during the evening, while at the same time, some other people cannot really sleep if they exercise late in the day. This is a very interesting field to explore. Because of the already existing research, it is known that the most efficient time to exercise if someone wants to improve strength and endurance is later in the day, during the afternoon-evening [66,67,68], and that can be explained because of the daily rhythm of the core body temperature. The temperature of the distal limbs reaches its maximum in the evening and its minimum in the morning. [69] In the late afternoon or early evening, the temperature of the skeletal muscle rises by 0.35 °C while the core body temperature rises by 0.8%. [70,71] Therefore, thermoregulatory processes are more effective in the afternoon, and as a result, maximum performance is typically maintained currently for activities that typically last only a short time or require only moderate intensity.

1.2.10 The role of sleep in the circadian clock

Sleep and recovery should also be included, even though managing exercise timing, intensity, duration, and frequency, as well as calorie intake and food composition, is complicated enough. Since the hormonal cycle depends on a regular sleep and wake cycle, sleep deprivation is the root of both severe psychosocial diseases and metabolic diseases. When the cycle of sleep is upset, many factors that affect our physiological performance can have negative consequences. [73]

Several studies have shown us that the risk of T2D is getting bigger and bigger with insufficient sleep. It increases by 2% every year if people don't sleep efficiently. [74] The findings related to obesity are similar. It has been shown that there is a danger of obesity in adults who sleep less than 5 hours per night and in children who sleep less than 10 hours per night. [75]

1.3 Purpose of the study

Considering the research that has already been done, the goal of this paper is to determine whether exercising in the morning vs. evening is more effective for people who disease from T2D and obesity, as well as whether the metabolic changes brought on by exercise are better after postprandial or pre-prandial exercise.

A current Systematic Review (SR) of the research is still lacking, even though the field of MS is very fragmented. Only a small percentage of the populations with diabetes and obesity were typically included in earlier studies. More studies tended to focus on middle-aged men. This review of the field is an important first step in contributing to practice. By indicating which topics and to what extent they have been covered thus far, as well as by pointing out potentially unexplored subfields. Furthermore, the growing body of recent scientific evidence has a direct practical impact as well, encouraging metabolic syndrome's specialists to incorporate exercise into their rehabilitation regimens and patients to incorporate exercise into their daily lives in addition to providing conclusive findings regarding the impact of exercise training on metabolic disorders.

This review provides a comprehensive overview of all randomized controlled trials (RCTs) and, as a result, the most significant scientific literature that has been written about the use of exercise training to treat some of the metabolic disorders. The review looks at all the RCTs that have been published as of late rather than narrowing in on a particular time frame.

The following three research questions were developed to direct the SR:

Research Question A: ‘’Does exercise timing and prandial status affect.

body composition, and metabolism in overweight / obese individuals?’’

Research Question B: "Is morning exercise better for people with T2D or obesity than evening exercise?"

Research Question C: "Is pre- or post-prandial exercise more effective for those with T2D or obesity?"

The following describes the study’s structure. In section two, we outline what sets an SR apart from a straightforward Literature Review and how to conduct one in accordance with the research. The methodology used and the results of this process are reported in sections 2 and 3, respectively. The discussion is presented in the fifth section, and the references are presented in the sixth section.

Kable *et al* (2012) Search Strategy
1. Provide a purpose statement
2. Document the databases or search engines used
3. Specify the limits applied e.g. dates, language
4. Inclusion and exclusion criteria
5. List the search terms used
6. Document the search process
7. Assess the retrieved articles for relevance
8. Document a summary table of included articles
9. Provide a statement specifying the number of retrieved articles at the end of the process
10. Conduct a quality appraisal
11. Critical review of the literature
12. Check reference list for accuracy

Figure 2. Kable et al (2012) Search Strategy

2.METHODOLOGY

The development of this study is analyzed in detail in this section.

2.1 Search strategy

As stated earlier, we formulated three sub-questions to serve as a roadmap for conducting this review. We adopted the strategy framework developed by Kable et al. in 2012 [76] to answer these questions effectively. This 12-step framework proved to be a valuable tool, providing comprehensive guidance to researchers in identifying pertinent literature. In this section, we will present and analyze each of the twelve steps employed in this review, highlighting how they aided us in the process of literature selection.

2.2 Purpose statement

After discussion with the project supervisors, Mr. Chryssanthopoulos and Mr. Philippou, the study's goal was decided. Finding out how exercise timing affects those with type 2 diabetes or obesity was the main goal of the study. Exercise timing has two directions. Firstly, morning vs. evening exercise, and secondly, pre-prandial vs. postprandial exercise.

2.3 Databases

Starting a literature search using electronic databases is highly effective, if not the most efficient method. With numerous databases at everyone's disposal, it is crucial to select the most relevant ones for research. To ensure comprehensive coverage of the topic, it is advisable to explore at least three databases pertinent to the area of interest. This approach allows for a more extensive and in-depth exploration of the subject matter. For this search, the databases that were used were PubMed, the Cochrane Library, and Web of Science. These three databases are versatile platforms that encompass a wide range of medical research fields and are regularly updated. This approach was chosen to guarantee that it will capture all relevant papers, considering the possibility that one database might overlook some important research. By using multiple databases, the aim is to ensure the comprehensive inclusion of relevant literature in a certain study.

2.4 Search limits

A specific search limit to our search strategy for the databases PubMed, Cochrane Library, and Web of Science. This limit restricted the search to only considering the title and abstract of the articles containing the search terms. In doing so, we aimed to focus our search on the most relevant and pertinent information related to our research topic.

2.5 Relevance assessment

In collaboration with Prof. Philippou and Dr. Chryssanthopoulos, our project supervisors, we established clear criteria for including or excluding the literature we retrieved. The primary objective was to focus solely on papers directly related to T2D and obesity and those that demonstrated the effects of exercise timing on the three parameters mentioned earlier.

Inclusion criteria:

1) Studies that were examining the exercise timing of people who suffer from metabolic disorders.
2) Research specifically focused on studies conducted on humans rather than animals.
3) >18-year-old (men and women)
4) BMI > 25kg/m2
5) Intervention: a) Acute Effect (single session)
   b) Short Term (2 sessions-3 weeks)
   c) Training-Long Term (>=4 weeks, frequency>=2/week)
   d) Type of Exercise: Any (Supervised, Unsupervised)
6) Randomized Control Trials
7) Cross Over Studies
8) Cross Sectional Studies
9) Epidemiological surveys

Exclusion Criteria:

1) Studies conducted on animals
2) No reviews, systematic reviews, or conferences
3) Grey Literature (no peer-reviewed studies, Editorials, Letters etc.)

4) Research on people whose BMI isn't >25kg/m2.

2.6 Search terms

The key words used to identify the relevant to the research questions articles were the following:

Metabolic Syndrome, Type 2 Diabetes, Obesity, BMI, Exercise Timing, Feeding Exercise, Postprandial Exercise, Fasting Exercise, Pre-prandial Exercise, Morning Exercise, Afternoon-Evening Exercise, Body Weight, Waist Circumference, Body Fat, Triglycerides, Total Cholesterol, LDL, HDL, Blood Glucose, Insulin Resistance, HbA1c.

2.7 Documentation of search process

Figure 3 displays the algorithm and the results of the explicit searches that were done from Pubmed, one of the three databases.

Search number	Query	Sort By	Filters	Search Details	Results	Time
42	#38 NOT #41			(("exercise timing"[Title/Abst	911	17:00:10
41	#39 NOT #40			"animals"[MeSH Terms] NO	5,076,889	16:59:51
40	humans[MeSH Terms]			"humans"[MeSH Terms]	20,954,158	16:58:22
39	animals[MeSH Terms]			"animals"[MeSH Terms]	26,031,047	16:57:53
38	#17 AND #33 AND #37			("exercise timing"[Title/Abstr	968	16:57:24
37	#34 OR #35 OR #36			"overweight"[Title/Abstract] (	388,706	16:54:33
36	obese[Title/Abstract]			"obese"[Title/Abstract]	146,339	16:54:14
35	obesity[Title/Abstract]			"obesity"[Title/Abstract]	309,126	16:54:02
34	overweight[Title/Abstract]			"overweight"[Title/Abstract]	85,331	16:53:48
33	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR			"body composition"[Title/Abs	352,534	16:53:20
32	glucose metabolism[Title/Abstract]			"glucose metabolism"[Title/A	43,183	16:53:00
31	Glycated hemoglobin[Title/Abstract]			"glycated hemoglobin"[Title/	11,234	16:52:48
30	Hemoglobin A1C[Title/Abstract]			"hemoglobin a1c"[Title/Abstr	12,871	16:52:37
29	HbA1c[Title/Abstract]			"HbA1c"[Title/Abstract]	48,301	16:52:25
28	serum glucose[Title/Abstract]			"serum glucose"[Title/Abstra	10,234	16:52:12
27	plasma glucose[Title/Abstract]			"plasma glucose"[Title/Abstr	37,883	16:51:59
26	very low density lipoprotein[Title/Abstract]			"very low density lipoprotein'	8,911	16:51:47
25	high density lipoprotein[Title/Abstract]			"high density lipoprotein"[Titl	57,137	16:51:31
24	low density lipoprotein[Title/Abstract]			"low density lipoprotein"[Title	77,32	16:51:16
23	triglycerides[Title/Abstract]			"triglycerides"[Title/Abstract]	71,963	16:51:00
22	fat free mass[Title/Abstract]			"fat free mass"[Title/Abstract	9,102	16:50:45
21	visceral fat[Title/Abstract]			"visceral fat"[Title/Abstract]	9,063	16:50:24
20	Abdominal Fat[Title/Abstract]			"abdominal fat"[Title/Abstrac	7,128	16:50:13
19	Body fat[Title/Abstract]			"body fat"[Title/Abstract]	36,994	16:50:01
18	Body Composition[Title/Abstract]			"body composition"[Title/Abs	44,842	16:49:47
17	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR			"exercise timing"[Title/Abstra	21,488	16:48:57
16	physical activity timing[Title/Abstract]			"physical activity timing"[Title	12	16:48:36
15	aerobic exercise[Title/Abstract]			"aerobic exercise"[Title/Abst	12,043	16:48:00
14	resistance exercise[Title/Abstract]			"resistance exercise"[Title/A	6,98	16:47:49
13	Fed. Exercise[Title/Abstract]			"fed exercise"[Title/Abstract]	26	16:47:36
12	Fast. Exercise[Title/Abstract]			"fast exercise"[Title/Abstract	32	16:47:24
11	Feeding Exercise[Title/Abstract]			"feeding exercise"[Title/Abst	1	16:47:06
10	Night Exercise[Title/Abstract]			"night exercise"[Title/Abstrac	10	16:46:53
9	Evening Exercise[Title/Abstract]			"evening exercise"[Title/Abs	79	16:46:40
8	Morning Exercise[Title/Abstract]			"morning exercise"[Title/Abs	129	16:46:25
7	acute exercise[Title/Abstract]			"acute exercise"[Title/Abstra	3,661	16:46:00
6	Fasting Exercise[Title/Abstract]			"fasting exercise"[Title/Abstr	42	16:44:09
5	Post meal Exercise[Title/Abstract]			"post meal exercise"[Title/Ab	11	16:43:25
4	Pre meal Exercise[Title/Abstract]			"pre meal exercise"[Title/Abs	6	16:38:36
3	Postprandial Exercise[Title/Abstract]			"postprandial exercise"[Title/	66	16:37:57
2	Preprandial Exercise[Title/Abstract]			"preprandial exercise"[Title/	8	16:37:21
1	Exercise Timing[Title/Abstract]			"exercise timing"[Title/Abstra	90	16:36:34

Figure 3. The results of the algorithm created for the PubMed database for each term or/and combination of terms.

2.8 Test relevance of retrieved articles

A three-step process based on the Bettany-Saltikov (2010) model was used to determine the relevance of the retrieved articles [77]. According to Bettany-Saltikov's suggestion, every piece of literature that was uncovered was assessed against the set of the inclusion and exclusion criteria.

Initially, we conducted an evaluation based on the article titles. This strategy had the benefit of swiftly excluding literature that did not support the study's goals. However, we decided to include a title for further examination if there was not enough information to determine its relevance. A partnership with Dr. Chrysanthopoulos was established during this title evaluation phase. When we came across opposing viewpoints, we had constructive group discussions and carefully considered each argument to come to an agreement.

Should any disagreements persist between the two assessors, we sought the guidance of our project supervisor, Dr. Philippou, who kindly reassessed the title and helped us resolve any remaining uncertainties. This process allowed us to maintain rigor and ensure that only the most relevant articles were included in this thesis.

The initial body of 10684 papers was screened for duplicates during this first evaluation process, which resulted in a reduction to 8631 papers. Then, all the remaining papers were screened, eliminating all the unnecessary literature because of reviews, systematic reviews, editorials, abstracts, and conferences, resulting in 986 articles being excluded.

In the next step, all 7645 remaining papers were identified via title. Unrelated articles based on title were excluded. If the title seemed relevant to the topic, then the next step was to read the abstract and check if the criteria were observed. If it still wasn't obvious if the article was eligible or not, then the whole article needed to be read. Because the relationship between exercise timing and the results of the studies was not included, 7627 articles were disregarded. So, 18 articles were found by following this method.

After checking the references and doing manual searches of other sources, eight additional papers were found. The alerts in the three databases retrieved another four articles. The final review body consists of 30 studies.

The flowchart of this assessment is presented in Figure 4.

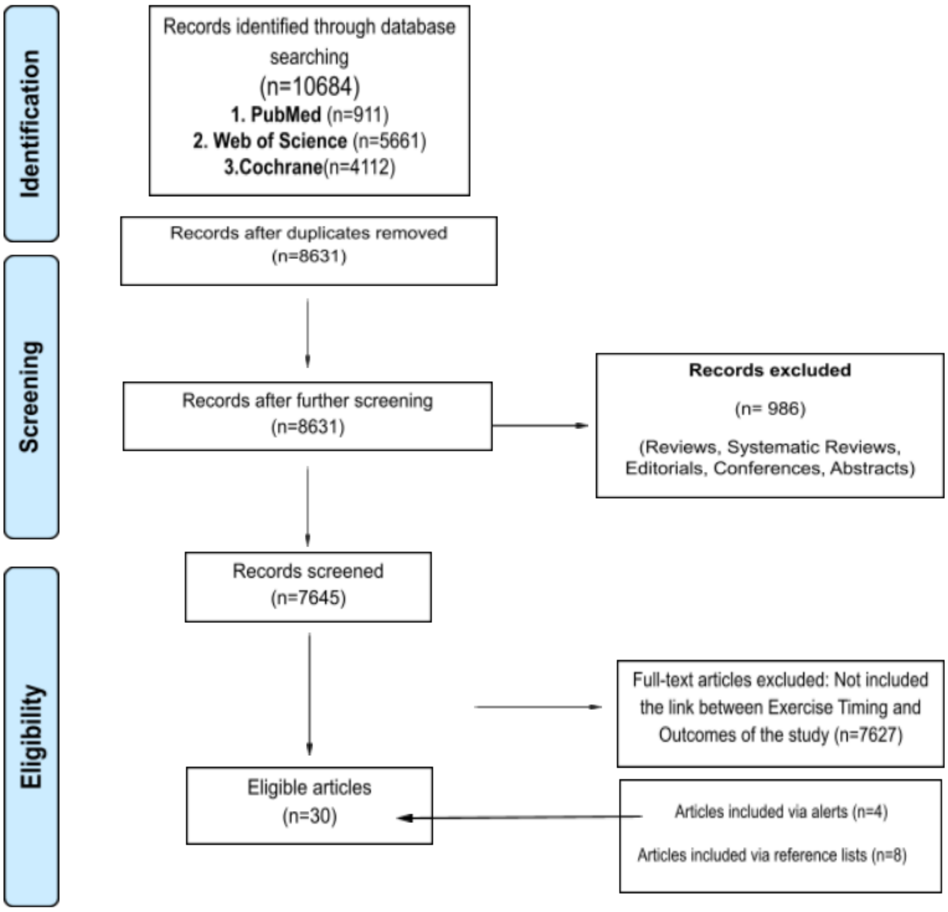

Figure 4.The flow chart of the Systematic Review Study

2.9 Summary table of included articles

A complete list of all the articles can be compiled and sent upon request.

2.10 Retrieved articles at end of the search process.

The search process initially produced 10684 results. A batch of 2053 articles was left for evaluation after the duplicate extraction step. Since three databases were used and searched, there were a lot of duplicates.

2.11 Check the reference list for further identification of relevant studies.

The 30 articles that were part of this review were then subjected to one more round of scrutiny. Each article's reference list was searched for pertinent materials that were not present in the 30 articles on the list. The main author alone undertook this process, so it may be subjectively biased.

3.RESULTS

3.1 Identification and selection of studies

Our research covered 10684 titles. After removing the duplicates and the records excluded (reviews, systematic reviews, editorials, abstracts, and conferences), 7645 possibly eligible articles remained. Following the review of both titles and abstracts, only 18 full papers were included. Additional eligible records were identified by searching the references of the already eligible articles one by one and by receiving alert articles from the databases. Through this processing, 18 articles were discovered. In the end, there were 30 articles that were eligible overall.

3.2 Description of included studies

A total of 1740 patients participated in the 30 trials-studies. The authors of the paper can be contacted for more information on the specifics of the study. Patients' average ages in the RCTs ranged from 18 to 68 years. Most patients (we do not know the precise number because some studies do not provide detailed information) were women. While some studies only looked at a single bout, the majority reported a 12-week exercise regimen. Most studies assessed moderate-to-vigorous aerobic intervention, and seven studies consisted of resistance exercise. Most of the studies that consisted of resistance exercise were in combination with aerobic exercise. Most exercise training sessions were conducted at centers, or at centers in addition to some at homes-or outside when it was just walking. The duration of exercise sessions varied greatly across studies, ranging from 20 to 60 minutes. Regarding the timing of the workouts, most studies comparing morning and evening workouts had the morning workout take place between 7 and 9 a.m. and the evening workout take place between 16 and 19 p.m., with some studies having the evening workout take place between 18 and 21 p.m. Three times per week was the typical frequency for many of the studies. Finally, the intensity was very variable, with the majority falling between 60 and 90%.

3.3 Outcomes

Most of the studies published the results as numbers on a typical table, but some of them depicted them in graphs. We used a web plot digitizer to analyze these graphs and get the exact values (https://automeris.io/WebPlotDigitizer/). Almost all the articles gave the data that we needed, so the main author didn't have to communicate via email. That happened only in one case, in which no response was given back to us, so we decided not to include the certain study. All the articles that were eligible met the criteria and studied one of the parameters, with most of them studied even more than one.

Based on the available data, 1740 adults participated in the studies. There were 3 studies conducted exclusively on females (106 females) and 9 studies exclusively on males (186 males). There were 15 studies that included both genders, but 5 of them didn't specify the number of males and females. Finally, 3 studies did not provide any results regarding gender. So, concerning the results that we have about the sex, they were 726 females and 660 males. The total of 30 studies covers the time between 2000 and 2023.The types of exercises included Aerobic Exercise (AET), Anaerobic Exercise (AnET), Resistance Exercise (RE), High-Intensity Interval Exercise (HIIE), a combination of Aerobic & Resistance Exercise and Aerobic-Anaerobic-HIIT & RE. The types of exercise concerned 61% AET, 10% of HIIT, 3% of RE, AET & RE of 16%, HIIT & AET of 7%, and AET & RE & AnET of 3%, as you can see in Figure 5. The duration of the training programs of most studies was 12 weeks, for 50-60 minutes with 3-4 sessions per week.

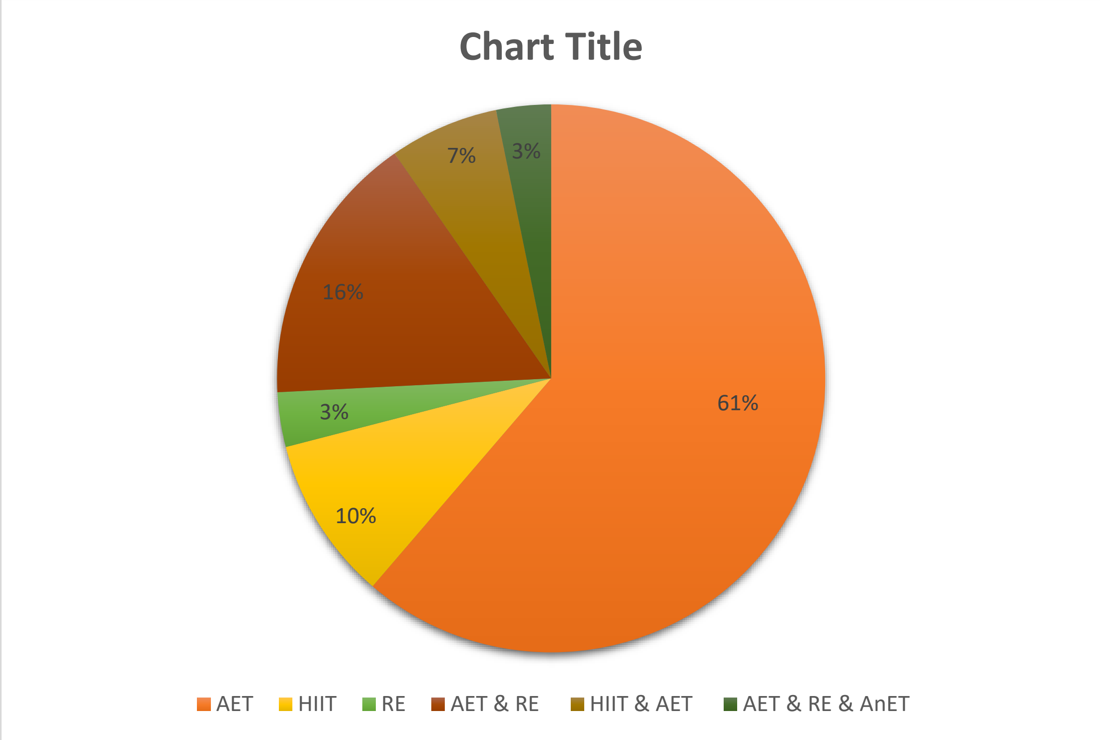

Figure 5. Types of exercise that were used in the studies that we examined. (AET=Aerobic Exercise, HIIT= High Intensity Interval Training, RE= Resistance Exercise, AET & RE = combination of Aerobic and Resistance Exercise, HIIT & AET=combination of High Intensity Interval Training and Aerobic Exercise, AET & RE & AnET = combination of Aerobic, Anaerobic and Resistance Exercise)

3.3.1 Body Composition (Body weight, BMI, Body Fat, Waist Circumference, Free Fat Mass)

The first part of the systematic review compares the variations in a patient's health that can happen after an exercise program. For this purpose, body composition was chosen as the key factor. More specifically, by body composition, we mean body weight, BMI, waist circumference, body fat, and free fat mass. That's because body composition is a widely repeated measure of the results of fitness, which most studies chose to use. The body weight was measured in kilograms (kg), the BMI in kg/m2, the body fat in percent (%) or in kilograms (kg), the waist circumference in centimeters (cm), and the free fat mass in kilograms (kg). Many studies used body weight as the main factor in determining outcomes.

3.3.2 Postprandial/Fasting Metabolism (Glucose, Insulin, HbA1c)

The second section of the analysis compares the differences that can occur following an exercise regimen in the Postprandial/Fasting Metabolism. The

Blood Glucose and the Insulin were measured in mg/dL or mmol/L and the HbA1c in percentage (%).

3.3.3 Lipid Metabolism (Triglycerides, Total Cholesterol, LDL, HDL)

The third section of the analysis compares the differences that can occur following an exercise regimen in the Lipid Metabolism.

The Triglycerides were measured in mg/dL or mmol/L, the Total Cholesterol, the LDL-lipoprotein and the HDL-lipoprotein in mmol/L or mg/dl.

3.3.4. Appetite Indices (Energy Intake)

The fourth section of the analysis compares the differences that can occur following an exercise regimen in the appetite indices, and more specifically in energy intake. The energy intake was measured in kcal/day or in kilojoules (KJ)/day .

The tables presented below, labeled as Tables 1, 2, 3, and 4, have been obtained through a comprehensive search for research studies that investigate the impact of exercise mostly on T2D and obesity. Prior to delving into these studies, we will provide a more detailed overview of their respective designs.

3.4. Presentation of Studies that examined the effect of acute morning vs. evening exercise.

The studies that have examined the effect of acute morning vs. evening exercise are presented in Table 1.

1)Ceylan et al., involved 10 overweight or obese males that participated in a moderate-intensity exercise regimen, which corresponded to a heart rate reserve of 55–59%, lasting for 30 minutes. The key factor under investigation in this study was the timing of the exercise sessions, categorized based on whether they occurred in the morning (between 08:00 and 10:00 a.m.) or in the evening (between 8:00 and 10:00 p.m.).It's important to note that the same group of participants took part in both exercise sessions, with a gap of at least 3 days between each session to ensure accurate observations and comparisons.[99]

2)In the study conducted by Velde et al., a substantial cohort of 775 obese participants was included, of which 42% were male. This research aimed to categorize individuals into three distinct groups based on the time of day when they engaged in physical activity. These three groups were defined as follows: morning exercisers (from 06:00 to 12:00 hours) and evening exercisers (from 18:00 to 00:00 hours). The type of physical activity involved moderate-to-vigorous intensity. [98]

Table 1. Table of studies that examined the effect of acute morning vs. evening exercise.

A/A	Author's name & Publication year	Number & Average Age of Participants	Comparison	Duration of the program	Design of the program	Results	ME vs. EE
1a.	Ceylan et al., 2020	N=10, AA:37.10 ± 4.33	ME	1 session	AET	↓:Serum Insulin	Serum Insulin: ME < EE
1b.	Ceylan et al., 2020	N=10, AA:37.10 ± 4.33	EE	1 session	AET	↓:Serum Insulin	
2a.	Velde et al., 2022	N=775, (M:42%) AA: mean (SD):56 (4)	ME	4 sessions	AET	↔: Insulin resistance	Insulin resistance: ME < EE
2b.	Velde et al., 2022	N=775, (M:42%) AA: mean (SD):56 (4)	EE	4 sessions	AET	↓: Insulin resistance	

↓: Decrease, ↔: No change, N=number of participants, AA=Average Age of participants, M=men, W=women, ME=Morning Exercise, EE =Evening Exercise, AET= Aerobic Exercise Training, INS=Insulin

3.5. Presentation of Studies that examined the effect of acute pre-prandial vs. postprandial exercise.

The studies that have examined the effect of acute pre-prandial vs. postprandial exercise are presented in Table 2.

1)Derave et al., enlisted the participation of seven sedentary men who had metabolic syndrome. The primary objective was to explore how a single session of exercise, either before or after eating, affected their blood sugar and insulin levels. To carry out the study, each of the seven participants went through three different scenarios, with each scenario occurring on separate days and spaced 1 to 3 weeks apart. The order in which these scenarios were assigned to the participants was randomized. Here are the three scenarios:

1. Control Day: We will not be concentrating on this group.
2. Pre-Breakfast Exercise Day: Participants engaged in a 45-minute exercise session on a stationary bike, at 60% of each participant's VO2max (99 - 25 watts).
3. Post-Breakfast Exercise Day: Participants exercised for 45 minutes on a stationary bike, but in this case, they did so after having breakfast.[91]

2)Colberg et al., investigated the effects of exercise timing on individuals with T2D who were managing their condition through diet and/or oral medications. They recruited twelve men and women with T2D and conducted three different trials on separate days:

1. Rest Day: We will not be concentrating on this group.
2. Pre-Dinner Exercise Day: Participants engaged in a single session of moderate aerobic exercise, specifically walking on a treadmill for 20 minutes, immediately before having dinner.
3. Post-Dinner Exercise Day: Like the PRE day, participants performed a 20-minute treadmill walk, but this time it took place 15 to 20 minutes after they had dinner.

Each participant went through these three trial scenarios on three different occasions. The study aimed to determine how the timing of exercise in relation to meal consumption (before or after dinner) affected blood glucose responses in individuals with type 2 diabetes.[92]

3)In Fauzi et al. study a total of 15 overweight males (BMI>25kg/m2) were assessed. After some dropouts, 10 of these overweight males completed three experimental trials, with each trial lasting 8.5 hours. These trials were conducted in random order, with a gap of 1 to 2 weeks between each trial. The three trial conditions were as follows:

Exercise Before Breakfast: Participants arrived at the metabolic suite at 08:00 hours after fasting overnight for 12 hours. The exercise session commenced at 09:00 hours (as indicated by the 290-minute). All participants engaged in a 60-minute treadmill walk set at an intensity of 50% of their individual VO2 max.
Exercise After Breakfast: After arriving at 08:00 hours and undergoing the 12-hour overnight fast, participants rested for 1 hour from 09:00 to 10:00 hours. The 1-hour exercise session was then conducted at 11:00 hours (as indicated by the 30-minute), which was 30 minutes after they had consumed the test breakfast.
Control trial: We will not be concentrating on this group.[93]

4)Heden et al. examined the effects of exercise before or after meal ingestion on fat balance and postprandial metabolism in overweight men. The participants were obese (BMI>30 kg/m2), and physician diagnosed with T2D. The exercise regimen involved resistance training. After some initial visits for familiarization (participants learned how to perform various exercises, such as leg press, calf raises, chest flies, and they underwent strength testing to determine their maximum weight capacity for their 10 repetitions maximum for each exercise) they went on to complete the three study days.
According to the above thirteen obese patients with T2D completed three trials in a random order in which they consumed a dinner meal with:
1) no exercise, we will not be concentrating on this group.
2) predinner RE (RE->Meal), and
3) post dinner RE beginning 45 min after dinner (Meal->RE).[95]

5) Kim et al., examined the effects of acute exercise on energy substrate and hormone levels in obese men under two conditions: exercising after an overnight fast and exercising two hours after breakfast. The study involved 10 obese male students, with a BMI exceeding 25 kg/m² and body fat levels over 20%. The participants underwent the first experiment, exercising after an overnight fast, after a week of initial testing. Subsequently, they performed the second experiment, exercising after a 2-hour interval post-breakfast, following a two-week gap from the first experiment. In both experiments, the subjects engaged in treadmill exercise at an intensity of 75% of their VO2max and expended up to 400 kilocalories. [94]

6)Terada et al., examined the immediate effects on blood sugar levels following two types of exercise: high-intensity interval exercise (HIIE) and moderate-intensity continuous exercise (MICE). These exercises were performed either after an overnight fast or after a meal. Ten individuals diagnosed with T2D participated in the study. They underwent testing in five different experimental conditions:

1. HIIE in a Fasted State performed on an empty stomach.
2. HIIE After Breakfast performed after a morning meal.
3. MICE in a Fasted State: Moderate-intensity continuous exercise conducted on an empty stomach.
4. MICE After Breakfast: Moderate-intensity continuous exercise performed after having breakfast.
5. No Exercise (Control). We will not be concentrating on this group.

The exercise sessions in all experimental conditions had a duration of 60 minutes and took place on a treadmill. During MICE, participants maintained a constant exercise intensity at 55% of their VO2peak, which was determined during a baseline test. In the case of HIIE, participants engaged in a series of exercise repetitions, each lasting three minutes at a workload equivalent to 40% of their VO2peak, followed by one minute at a workload corresponding to 100% of their VO2peak. This resulted in a total of 15 high-intensity intervals, with an average relative intensity of 55% of VO2peak. [100]

7) Chen et al., investigated how the feeding status of individuals affects how their adipose tissue responds to exercise. They enlisted the participation of ten healthy overweight men for these trials. This exercise was performed under two conditions: either in a fasted state or after having a meal. The order of these conditions was determined randomly and balanced, with a gap of 3 to 4 weeks between each trial. On the primary trial days, participants arrived at the laboratory between 8 and 9 AM after fasting for 12 hours. They were then divided into two groups: one group consumed a meal (fed), while the other group continued to fast (fasted). In both the fasted and fed conditions, participants walked on a treadmill at an intensity corresponding to 60% of their VO2max for the entire 60-minute duration.[101]

Table 2. Table of studies that examined the effect of acute pre-prandial vs. postprandial exercise.

A/A	Author's name & Publication year	Number & Average Age of Participants	Comparison	Duration of program	Design of program	Results	FAST Vs. FED
1a.	Derave et al., 2007	N=7, AA:45 +/- 11 years	FAST	one session	AET	↔: during exercise PGL ↓: during exercise INS	1. During exercise PGL: FAST < FED 2. During exercise INS: FED > FAST 3. Reduction of meal-induced glycemic and insulinemic response: FED > FAST 4. Breakfast-induced iAUC for glucose: FAST > FED 5. Breakfast-induced iAUC for insulin: FAST= FED 6. For lunch and supper, iAUC for glucose and insulin: FAST = FED
1b	Derave et al., 2007	N=7, AA:45 +/- 11 years	FED	one session	AET	↓: during exercise PGL, during exercise INS	
2a.	Colberg et al., 2009	N=12(M=6, W=6), AA:61,4 +/- 2.7 years	FAST	one session	AET	↓: BGL	BGL: FED > FAST
2b.	Colberg et al., 2009	N=12(M=6, W=6), AA:61,4 +/- 2.7 years	FED	one session	AET	↓: BGL	

3a.	Fauzi et al., 2012	N=15(M), AA:28·1(SD 10·7) years	FAST	one session	AET	↓: Postprandial INS response over the total 8·5 h observation period and the postprandial TAG response in the ‘breakfast to lunch’ period , FM ,postprandial TAG response	FM: FAST > FED the postprandial TAG response in the ‘breakfast to lunch’ period: Fast > Fed Postprandial INS response over the total 8·5 h observation period: Fed>Fast
3b.	Fauzi et al., 2012	N=15(M), AA:28·1(SD 10·7) years	FED	one session	AET	↓: FM, ↓: Postprandial INS response over the total 8·5 h observation period and the postprandial TAG response in the ‘breakfast to lunch’ period.	
4a.	Heden et al., 2014	N=13(M, W) AA:48.5 +/- 11.9 years	FAST	3 trials in total	RE	↓: postprandial total TAG iAUC,predinner glucose iAUC, postprandial glucose iAUC,INS	1. postprandial total TAG iAUC: FED > FAST 2. predinner glucose iAUC: FAST > FED 3.Postprandial glucose iAUC: FED > FAST 4.INS: FED = FAST

4b.	Heden et al., 2014	N=13(M, W) AA:48.5 +/- 11.9 years	FED	3 trials in total	RE	↓: postprandial total TAG iAUC, predinner glucose iAUC, postprandial glucose iAUC, INS	
5a.	Kim et al., 2015	N=10(M) AA:20.2±1.9 years	FAST	acute	AET	↑: 60 min after exercise BGL ↓: 60 min after exercise INS	60 min after exercise INS: FAST > FED
5b.	Kim et al., 2015	N=10(M) AA:20.2±1.9 years	FED	acute	AET	↓: 60 min after exercise BGL, 60 min after exercise INS	
6a.	Terada et al., 2016	N=10(M=8, F=2), AA:47-69 years	FAST	acute	HIIT	↓:24-h mean glucose, MAGE, pre-breakfast glucose, post-breakfast iAUC, post-lunch iAUC, post-dinner iAUC, fBGL	total post-meal iAUC, pre-breakfast glucose, post-breakfast iAUC: FAST > FED 24-h mean glucose, fBGL: FAST = FED
6b.	Terada et al.. 2016	N=10(M=8, F=2), AA:47-69 years	FED	acute	HIIT	↓:24-h mean glucose, pre-breakfast glucose, post-breakfast iAUC, post-lunch iAUC, fBGL. ↑: post-dinner iAUC ↔: MAGE	
6c.	Terada et al., 2016	N=10(M=8, F=2), AA:47-69 years	FAST	acute	AET	↓:24-h mean glucose, MAGE, pre-breakfast glucose, post-breakfast iAUC, post-lunch iAUC, post-dinner iAUC. ↔: Nocturnal glucose, fBGL	24-h mean glucose, MAGE, post-breakfast iAUC, post-lunch iAUC FAST > FED pre-breakfast glucose, post-dinner iAUC: FED > FAST
6d.	Terada et al., 2016	N=10(M=8, F=2), AA:47-69 years	FED	acute	AET	↓:24-h mean glucose, MAGE, pre-breakfast glucose, post-breakfast iAUC, post-lunch iAUC, post-dinner iAUC. ↔: Nocturnal glucose, fBGL	
7a.	Chen et al.,	N=10(M),	FAST	acute	AET	↓:PGL	PGL:

	2017	AA:26 +/- 5 years				↔:INS	FAST = FED Serum Insulin: FAST =FED
7b.	Chen et al., 2017	N=10(M), AA:26 +/- 5 years	FED	acute	AET	↓:PGL ,INS	

↑ = Increase; ↓= Decrease; ↔ =No change, N= Number of participants, W=Women, M=Men, AA=Average Age of participants , FAST= working out before eating a meal, FED=working out after eating a meal, PGL=plasma glucose, BGL=Blood glucose , iAUC=the incremental area under the curve, INS=insulin, FFA=free fatty acids, NEFA=non esterified fatty acids, TAG= Triglycerides, MAGE=mean amplitude of glycemic excursion , VO2max = Maximal Oxygen Consumption, AET= Aerobic Exercise Training ,AnET= Anaerobic Exercise Training, HIIE=high interval intensity exercise, RE= Resistance Exercise

3.6. Presentation of Studies that examined the training's effect on morning vs. evening exercise.

The studies that examined the training's effect on morning vs. evening exercise are presented in Table 3.

1)Di Blasio et al. conducted a study involving 42 sedentary postmenopausal women to compare the effects of morning versus evening exercise. However, only 33 women were able to complete the study, with 14 of them exercising in the morning and 15 in the afternoon. The exercise program consisted of 50 minutes of walking at an intensity level corresponding to 55% of each woman's heart rate reserve, which was monitored using a heart rate monitor. They exercised four days a week for a duration of three months. To ensure proper heart rate control, heart rate measurements were readjusted after six weeks of training. During the initial assessment, all participants were trained to calculate their own heart rates. Each woman could choose to exercise either in the morning between 7:00 AM and 9:00 AM after breakfast or in the evening between 6:00 PM and 8:00 PM before dinner. The final assessment of their aerobic fitness was conducted on a treadmill. [86]

3)Alizadeh et al. aimed to explore the impact of six weeks of aerobic exercise, conducted either in the morning or evening, on appetite and physical measurements in a group of 48 overweight females (BMI 25 to 29.9 kg/m²). They were divided into two groups: one group participated in morning aerobic exercise, consisting of 25 individuals, while the other group engaged in evening aerobic exercise, and included 23 participants. During the exercise sessions, participants aimed to maintain a target heart rate corresponding to their ventilatory threshold. The exercise sessions involved 30 minutes of treadmill running at the heart rate associated with the ventilatory threshold. The researchers also recorded the participants' Rating of Perceived Exertion (RPE), which measures the perceived intensity of exercise. These measurements were taken at the beginning of the trial, as well as in the third and sixth weeks. Over the course of six weeks, the participants visited the sports medicine department three times a week. Morning exercise sessions occurred between 8:00 AM and 10:00 AM, while evening sessions took place between 2:00 PM and 4:00 PM. [79]

4)Savikj et al. conducted a study to determine whether exercise at two different times of day would affect 24-hour blood glucose levels in men with T2D whose BMI ranged from 23 to 33 kg/m². The study involved eleven men with T2D, and they completed a randomized crossover trial. The participants were divided into two groups, either for morning training at 8:00 AM or afternoon training at 4:00 PM, with seven participants in the morning group and four in the afternoon group. Each group followed their assigned exercise regimen for two weeks, which included supervised exercise sessions on Mondays, Wednesdays, and Fridays, with the following day as a rest day, making a total of six exercise sessions. After a two-week "wash-out" period, the participants switched to the opposite exercise regimen. The exercise intervention took place at a gym, where participants cycled at 75 revolutions per minute (rpm) with a specific load that prompted a one-minute rest. This cycle was repeated six times with a one-minute rest in between. The load achieved during each one-minute interval was recorded, and the average of these six intervals was used for all HIIT sessions. HIIT sessions were carried out on a cycle ergometer, beginning with a seven-minute warm-up, followed by six one-minute intervals at a predetermined load, usually above 220 watts but within a range of 180 to 350 watts, with a pedaling rate of 75 rpm. After each one-minute interval, there was a one-minute recovery period at 75 rpm with minimal load.[97]

5)Willis et al. conducted a study to see how the timing of exercise affects weight loss and energy balance components in overweight or obese young adults who were physically inactive .51% of the adults were female and they had a BMI between 25.0 and 39.9 kg/m². The study lasted for 10 months and involved a supervised exercise program. During these 40 weeks of exercise, participants were asked to complete a total of 200 exercise sessions involving treadmill walking or jogging, and participants exercised 5 days a week. They were allowed to do different activities like stationary biking or outdoor walking/jogging on one day per week to add variety and reduce the risk of overuse injuries. The intensity of exercise sessions gradually increased, starting at 150 calories burned per session and reaching a target of either 400 or 600 calories burned per session by the end of the fourth month. The study categorized participants into four groups based on the timing of their exercise sessions:

1. Early exercisers: Those who did most of their sessions between 7:00 AM and 11:59 AM.
2. Late exercisers: Those who did most of their sessions between 3:00 PM and 7:00 PM.

6)Teo et al., 2020 investigated the impact of diurnal exercise scheduling on glycemic management in a 12-week supervised multimodal exercise training program. Forty sedentary, overweight adults (BMI 30.9 +/- 4.2 kg/m2) were enrolled. They were assigned at random to either a morning (finished their training session between 08.00-10.00 h) or an evening workout (finished their training sessions between 17.00-19.00h) program. Each training session lasted roughly 60 minutes and included both RE and aerobic exercise training (AET). Every workout began with the AET, which was 30 minutes of treadmill walking at 60%-70% of VO2peak. In the following set of exercises, individuals engaged in four separates RE that targeted the main muscular groups: leg press, bench press, military press, and lateral pulldown. During weeks 1-4, 5-8, and 9–12, respectively, three sets of each exercise were done at 45%, 50%, and 55% of individually assessed one-repetition maximums (1RM) for 18, 15, and 12 repetitions, with 60 s of rest in between sets. It was necessary to establish each participant's 1RM before the start of the training intervention. [102]

7)In a study conducted by Brooker et al., in 2019, the feasibility and acceptability of mandatory morning and evening exercise were assessed. The study involved twenty individuals, both males and females, who had a BMI exceeding 25kg/m2. These participants were randomly assigned to one of three groups: a waiting control group (consisting of 4 individuals), a morning exercise group (comprising 9 individuals), or an evening exercise group (comprising 7 individuals).During the 12-week program, participants in the morning exercise group were required to engage in a minimum of 250 minutes of exercise per week, specifically between 06:00 and 09:30. Conversely, participants in the evening exercise group had to complete their exercise sessions between 16:00 and 19:00. Initially, all participants underwent five 50-minute exercise sessions per week during the first four weeks of supervised training. Over the subsequent eight weeks, the frequency of exercise sessions was gradually reduced, with one session being eliminated every two weeks, until participants in both groups reached a maintenance level of two sessions per week. These supervised exercise sessions primarily consisted of self-paced treadmill running or brisk walking.[89]

8) De Brito et al., investigated the hypotensive (blood pressure-lowering) effects of aerobic exercise when performed in the morning versus the evening in individuals with treated hypertension. The participants in the study had an average BMI of 29.6 ± 3.1 in the morning exercise group and 30.7 ± 3.3 in the evening exercise group. Fifty men with treated hypertension were randomly assigned to one of three groups: the morning training group, the evening training group, and a control group. The participants in the training groups

engaged in cycling exercises for 45 minutes at a moderate intensity level. The intensity of the exercise progressed from the heart rate corresponding to the anaerobic threshold to 10% below the heart rate at the respiratory compensation point. We won't focus on the results of the control group in this discussion. The exercise interventions took place three times a week for a duration of 10 weeks. Clinic assessments were carried out in the morning (between 7:00 am and 9:00 am) and in the evening (between 6:00 pm and 8:00 pm). During the initial four weeks of the training program, the duration of exercise sessions gradually increased from 30 to 45 minutes. Starting from the fifth week, the intensity of the exercise was progressively raised every two weeks, moving from the heart rate associated with the anaerobic threshold to a level 10% below the heart rate corresponding to the respiratory compensation point. The intensity of the training was determined based on the results of a maximal cardiopulmonary exercise test, which was conducted at the same time of day as the training sessions. Throughout the training sessions, participants' heart rates were continuously monitored, and the workload was adjusted to achieve the target heart rate.[103]

9)Munan et al., investigated how the timing of exercise and its relationship with meal timing affect the 24-hour glucose profiles of individuals with T2D. Fourteen individuals with T2D were enrolled in the study, and they wore continuous glucose monitors for a period of 12 days. During this 12-day period, participants underwent four different conditions, following a randomized, crossover design:

1. Morning (fasting) exercise
2. Evening exercise
3. Seated control-We will not be focusing on this group.

The exercise sessions consisted of 50 minutes of walking at a speed of 5.0 km/h. Each exercise condition began with a 5-minute warm-up and ended with a 5-minute cool-down, both at a speed of 4.0 km/h and with no incline (0% grade). The main exercise portion of each session lasted for 40 minutes, during which participants walked at 5.0 km/h with a slight incline of 0.5% grade. [104]

10)Mancilla et al., examined how the timing of exercise, either in the morning or afternoon, affected the metabolic health of individuals with pre-existing metabolic concerns who were participating in a 12-week exercise training program. The study involved thirty-five male participants with a BMI exceeding 26 kg/m2 but thirty-two of them were included in the study.

They were divided into two groups based on their preferred exercise timing: a morning group (consisting of 12 individuals) and an evening group (comprising 20 individuals). The participants followed a closely monitored progressive exercise program that combined aerobic and resistance exercises, with three sessions per week. The aerobic exercise component involved 30 minutes of cycling on an ergometer at 70% of their previously determined maximum workload (Wmax), performed twice a week. The resistance exercise component included three sets of 10 repetitions at 60% of their previously determined maximal voluntary contraction and targeted major muscle groups in both the lower and upper limbs. These exercises included leg extension, leg press, chest press, lat pull-down, triceps and biceps curls, abdominal crunches, and horizontal row exercises. Each exercise session began with a 5-minute warm-up and concluded with a 5-minute cool-down on the ergometer, cycling at 45% Wmax at the start and end of the session, respectively. [81]

11)Moholdt et al., wanted to see if the time-of-day people exercise (morning or evening) would affect how a high-fat diet influences things like blood sugar control, overall health, and blood chemistry. They included overweight men with BMIs ranging from 27.0 to 35.0 kg/m2. They divided the participants into three groups: two groups that did exercise, with one group working out in the morning and the other in the evening and a third group that didn't exercise at all; they acted as the control group. The study lasted for 11 days. For the first 5 days, everyone ate the same high-fat diet and didn't do any exercise. Each day, participants had three pre-packaged meals (breakfast, lunch, and dinner), with each meal providing 33.3% of their daily energy intake. Starting from day 6 to day 10, the exercise groups did exercise once a day. The morning group worked out at 6:30 AM, and the evening group worked out at 6:30 PM. The exercise was done on special cycling machines. On certain days (6, 8, and 10), they did HIIT, which involved short bursts of intense exercise followed by easy cycling. On other days (7 and 9), they did moderate-intensity continuous cycling. The control group didn't exercise but continued their usual daily activities while sticking to the high-fat diet.

12)Saidi et al., wanted to find out if a 12-week exercise program would work better in the morning or evening for overweight and obese people. They also looked at how this exercise affected fatigue, and the quality of life. They selected adults of any gender, who were overweight or obese, didn't engage in much physical activity (less than 2 hours of moderate to vigorous activity per week), and were generally inactive. The participants were split into two groups: the morning group, where exercise sessions started at 9:00 AM and the evening group, where exercise sessions started at 6:30 PM. Both groups exercised three times a week, with each session lasting 90 minutes. These exercise sessions included a mix of aerobic activities (like using elliptical bikes, rowers, or treadmills) at a moderate intensity level (about 60% of their maximum heart rate). They also did strength training, working on different muscle groups with initial weights set at 60% of the maximum they could lift in one repetition. Every session started with a 10-minute warm-up that included stretching and light aerobic exercises. Participants wore heart rate monitors to make sure they were exercising at the right intensity [83].

13)The concept of the study that conducted by Teo et al., 2021 was the same as the one from the same team that conducted their 2020 study [102]. The only difference between was that in the earlier one, they were examining the effect of diurnal exercise on glycemic control in individuals enrolled in a 12-wk supervised multimodal exercise training program and in the other one the effect of diurnal exercise timing on appetite, energy intake and body composition in individuals with overweight or obesity. So, while both studies involved exercise timing, the 2020 study was more concerned with blood sugar control and supervised exercise, whereas the 2021 study focused on appetite, calorie consumption, and body composition in people with weight issues. The concept of the 2020 study has already been analyzed above. [87]

14)Creasy et al., wanted to find out if it was practical and acceptable to have adults with overweight or obesity exercise either in the morning (between 6:00 AM and 10:00 AM) or in the evening (between 3:00 PM and 7:00 PM). They grouped participants based on their sex and starting weight, and then randomly assigned them to either the morning or evening exercise group. For 15 weeks, participants had to do supervised aerobic exercise three times a week in-person, and one session on their own. They had access to various exercise machines like treadmills, stationary bikes, ellipticals, and more. The intensity of the exercise started moderate and gradually became more intense, and the number of calories burned per session increased too. Each person had a specific calorie-burning target for each session, which was determined based on their heart rate during a fitness test. The study staff made sure everyone exercised at the right intensity and for the right amount of time. They kept track of how often participants attended the exercise sessions and followed their prescribed workout plans, and participants received updates on their progress every two weeks via email. [84]

15)Menek et al., conducted a study to investigate the impact of exercise tailored to individuals' circadian rhythms on people with T2D. They enrolled thirty participants with a BMI between 25-30 kg/m2 and divided them into morning and evening preference groups. The study consisted of three phases: an initial 6-week control period with no specific exercise, followed by a 6-week exercise period, where the morning group exercised in the morning (1 hour after breakfast), and the evening group exercised in the evening (1 hour after dinner) and another 6-week exercise period, where the groups switched their exercise times. The exercise program included supervised aerobic and resistance training of moderate to vigorous intensity. Aerobic exercises involved repetitive movements and walking without equipment, and exercise intensity was determined using the Rating of Perceived Exertion (RPE) BORG scale. Strengthening exercises targeted various muscle groups and were adjusted over three segments of the 36-session program, progressing in resistance levels. Strengthening exercises consisted of exercises for shoulder girdle muscles, flexor and extensor muscles of knee and hip, abdominal muscles, and trunk extensor muscles. They used resistance bands, to make the strengthening exercises gradually harder. [96]

16)In 2022 Brooker et al., conducted a study to explore the impact of morning versus evening exercise on weight loss, cardiometabolic health, and energy balance components. They involved 100 inactive adults who were overweight or obese in their research. These participants were divided into three groups: one group exercised in the morning (between 6:00 AM and 9:00 AM), another group exercised in the evening (between 4:00 PM and 7:00 PM), and the third group served as a control (CON) with no prescribed exercise. For the two exercise groups, participants were instructed to engage in 250 minutes of self-paced aerobic exercise per week for 12 weeks. This exercise program included both supervised sessions, where they were guided during their workouts, and unsupervised sessions, where they exercised on their own. Participants were asked to keep a diary of their unsupervised exercise sessions, detailing the type, mode, time of day, and duration of the activity, which was collected weekly. During supervised training sessions, participants wore heart rate monitors to measure exercise intensity, expressed as a percentage of their peak heart rate determined during a previous test. In this test, participants walked or ran on a treadmill following a specific protocol until they decided to stop due to fatigue. Their V̇O2peak, which reflects their fitness level, was recorded as the highest average value reached during two 30-second intervals before they voluntarily stopped the test.[85]

17)Hetherington-Rauth et al., studied how physical activity in the morning and afternoon relates to blood sugar control, body composition, and fitness in people with T2D. They had 74 participants with a BMI less than 48 kg/m². This research was part of a year-long study where they tested the impact of different exercise programs on blood sugar control and health in adults with T2D. To track activity levels, participants wore a device on their right hip for a week, from when they woke up until 8:00 PM. They looked at how much moderate-to-vigorous physical activity (MVPA) people did during the morning (from waking up until noon) and the afternoon (noon to 8:00 PM) and adjusted it based on the number of hours recorded during each period. They also measured participants' VO2peak by performing a cardiopulmonary exercise test (CPET) using a motorized treadmill to exhaustion with a Bruce standard protocol. This helped them understand how exercise timing and intensity might affect diabetes and overall health.[105]

18)A study by Arciero et al., involved thirty women who were regular exercisers with an average and twenty-six men with a slightly higher BMI of 25.5 ± 3 kg/m². We will focus only on this group of men. The study lasted for 12 weeks, and it looked at how the timing of exercise (morning or evening) affected various aspects of health and fitness. The participants were randomly assigned to one of two exercise groups:

1. The morning exercise group (men AM, n = 14), which followed a training program called RISE (Resistance, Interval, Stretching, Endurance) that involved various types of exercises.
2. The evening exercise group (men PM, n = 12), which also followed the same RISE program but exercised in the evening.

The RISE training program included four types of exercises:

1. Resistance exercise: Participants did 10-15 repetitions for two to three sets.
2. Interval sprints: These involved 7-10 sets of 30-60 second near-maximal sprints with 2-4 minutes of rest in between.
3. Stretching/yoga/pilates: This included a combination of stretching, yoga poses, and pilates movements to engage all major muscles and joints.
4. Endurance exercise: Participants engaged in rhythmic aerobic activities such as running, cycling, rowing, or swimming for over 60 minutes at 60% of their maximum effort, based on their heart rate.

Each participant completed all four types of exercises once a week for a total of four training sessions per week. These sessions were relatively short, lasting less than an hour, except for the endurance training, which lasted 60 minutes or more. [106]

19)Moholdt et al., in 2023 investigated the effect of a high-fat diet on serum lipid subfractions in men with overweight/obesity and determined whether morning or evening exercise affected these lipid profiles. This study's overarching concept paralleled a previous study conducted by Trine Moholdt et al. in 2021. [82]

Table 3. Table of studies that examined the training effect on morning vs. evening exercise.

A/A	Author's name & Publication year	Number & Average Age of Participants	Comparison	Duration of program	Design of program	Results	ME vs. EE
1a.	Blasio et al., 2010	N=42(W), AA:53.46+/-3.32 years	ME	3 months 4 days/week	AET	↓:FM, WC	FM: EE > ME
1b.	Blasio et al., 2010	N=42(W), AA:53.46+/-3.32 years	EE	3 months 4 days/week	AET	↓: FM ↑: morning EI ↔: WC	
2a.	Alizadeh et al., 2017	N=48(W), AA:20-45 years	ME (n=25)	6 weeks 3 times/week	AET	↓: BW, BMI, WC, EI, FM ↑: FFM	WC, FM: ME > EE FFM: ME>EE
2b.	Alizadeh et al., 2017	N=48(W), AA:20-45years	EE (n=23)	6 weeks 3 times/week	AET	↓: WC, FM ↑: FFM ↔: EI, BW, BMI	
3a.	Savikj et al., 2018	N=11(M), AA:45-68 years	ME	2 weeks 3 times/week	HIIT	↓: HbA1c ↑: CGM, post morning INS, TAG ↔: HDL, LDL, TC	INS: ME = EE TC, HDL, LDL: ME=EE
3b.	Savikj et al., 2018	N=11(M), AA:45-68 years	EE	2 weeks 3 sessions/week	HIIT	↓: CGM, BGL ↑: post afternoon INS	

						↔: HbA1c, HDL, LDL, TC, TAG	
4a.	Willis et al., 2019	N=88(W=51%, AA:18–39 years	ME (n = 21)	40 weeks	AET	↓:BW,FM,EI	BW , FM: ME > EE
4b.	Willis et al., 2019	N=88(W=51%,AA:18–39 years	EE . (n = 25)	40 weeks	AET	↓:BW ,FM ↑:EI	
5a.	Teo et al., 2019	N=40(W=23), AA:51 ± 13 years	ME (n=20)	12 weeks 3 days/week	AET + RE	↓: HbA1c, HOMA2IR, fINS, 4-h PPI-AUC, fBGL	HbA1c, HOMA2IR, fINS, 4-h PPI-AUC, fBGL: ME = EE
5b.	Teo et al., 2019	N=40,(W=23), AA:51 ± 13 years	EE (N=20)	12 weeks 3 days/week	AET + RE	↓:HbA1c ,HOMA2IR,FINS,4-h PPI-AUC,fBGL	
6a.	Brooker et al., 2019	N=49, (M, W), AA:18-60 years	ME	12 weeks 2 times/week	AET	↓: DBP, SBP, BMI, WC, FM, FFM, TAG, TC ↔: BGL, HDL, LDL	BMI: ME > EE FM: EE > ME TC, TAG: ME = EE
6b.	Brooker et al., 2019	N=49, (M, W), AA:18-60 years	EE	12 weeks 2 times/week	AET	↓: BMI, FM, BGL, TAG, TC, DBP, SBP, VO2peak ↔: WC, FFM, HDL, LDL, VO2peak,	
7a.	Brito et al., 2019	N=88	ME (n = 15)	10 weeks 3 days/week	AET	↓: SBP, DBP ↑: VO2peak ↔: BW	SBP, DBP: EE > ME VO2peak: ME = EE

7b.	Brito et al., 2019	N=88	EE (n = 15)	10 weeks 3 days/week	AET	↓: SBP, DBP ↑: VO2peak ↔: BW	
8a.	Munan et al.. 2020	N=17(M=8/W=6), AA:65+/-9.0 years	ME	12 days	AET	↓: during exercise BGL ↔: 24-hour BGL,24-hour BG	During exercise BGL: EE > ME
8b.	Munan et al., 2020	N=17(M=8, W=6), AA:65+/-9.0 years	EE	12 days	AET	↓: during exercise BGL ↔: 24-hour BGL, 24-hour BGL	
9a.	Mancilla et al., 2020	N=35(M) , AA:58 ± 7 years	ME (n= 12)	12 weeks	AET + RE	↔:BW, BMI, FM, FFM ↑: VO2max, fBGL, Insulin Sensitivity	FM, Insulin Sensitivity: EE > ME
9b.	Mancilla et al., 2020	N=35(M) , AA:58 ± 7 years	EE (n= 20)	12 weeks	AET + RE	↓:BW, FM, fBGL, ↔: BMI, FFM ↑: VO2max, Insulin Sensitivity	
10a.	Moholdt et al., 2021	N=25(M), AA:30–45 years	ME (n=9)	11 consecutive days	HIIT + AET	↔:24 h BGL , INS	
10b.	Moholdt et al., 2021	N=25(M), AA: 30–45 years	EE (n=8)	11 consecutive days	HIIT + AET	↓: nocturnal BGL, fBGL, INS, TC, LDL, ↔:24 h BGL	
11a.	Saidi et al., 2021	N=36(M, W), AA:30-65 years	ME	12 weeks 3 days/week	AET + RE	↔:BW, BMI ↓: WC, FM	BW, BMI, FFM, 6MWT estimated VO2max:

						↑: FFM, 6MWT estimated VO2max	ME = EE FM: EE > ME
11b.	Saidi et al., 2021	N=36(M, W), AA:30-65 years	EE	12 weeks 3 days/week	AET + RE	↔:BW, BMI, WC, ↓:FM ↑: FFM,6MWT estimated VO2max	
12a.	Teo et al., 2021	N=40,(W=23), AA:51 ± 13 years	ME	12 weeks 3 days/week,	AET + RE	↓:BW, BMI, WC, FM, EI ↑: VO2peak ↔: FFM	BW, BMI, FM, FFM, EI, VO2peak: ME = EE WC: EE > ME
12b.	Teo et al., 2021	N=40,(W=23), AA:51 ± 13 years	EE	12 weeks 3 days/week	AET + RE	↓:BW, BMI, WC, FM, EI ↑: VO2peak ↔: FFM	
13a.	Creasy et al., 2022	N=36(M, W), AA:18-56 years	ME (n=18)	15 weeks	AET	↓:BW,FM ↑: EI, FFM	BW , FM: EE > ME
13b.	Creasy et al., 2022	N=36(M, W), AA:18-56 years	EE (n =15)	15 weeks	AET	↓:BW, FM, FFM, EI total daily energy expenditure, FM	
14a.	Menek et al., 2022	N=37, (W=19 M=11)	ME	>6 weeks	AET	↓: HbA1c, fBGL, LDL, TC, TAG ↑: HDL	HbA1c, fBGL: ME > EE HDL, LDL: ME = EE TC, TAG:
14b.	Menek et al., 2022	N=37, (W=19 M=11)	EE	>6 weeks	AET	↓: HbA1c, fBGL, LDL, TC, TAG	

						↑: HDL	EE > ME
15a.	Brooker et al., 2022	N=100 (M,W)	ME	12 weeks	AET	↓:BW, FM, SBP, DBP, EI ,TC ↑: V02peak, FFM ↔: BGL, TAG, HDL, LDL	BW, FM, EI, VO2peak: EE > ME BGL, HDL, LDL: ME = EE
15b.	Brooker et al., 2022	N=100 (M,W)	EE	12 weeks	AET	↓:BW, FM, FFM ,SBP, DBP, EI ↑: V02peak ↔: BGL, TAG, TC, HDL, LDL	
16a.	Hetherington-Rauth et al., 2022	N=80 (M=39, W=35), AA:58.5 ± 7.8 years	ME	7 days	AET	↓: FM ↔: FFM, fBGL, iAUC glucose, HbA1c, VO2peak	FM: EE > ME
16b.	Hetherington-Rauth et al., 2022	N=80 (M=39, W=35), AA:58.5 ± 7.8 years	EE	7 days	AET	↓: FM, FFM, fBGL, iAUC glucose, HbA1c ↑: V02peak	
17a.	Arciero et al., 2022	N=26(M) AA:45 ± 8 years	ME	12 weeks	AET RE AnET	↓: FM, EI ↑: FFM ↔: BGL, INS, TC, HDL, LDL, TAG, SBP, DBP	FM , FFM : ME = EE
17b.	Arciero et al., 2022	N=26(M) AA:45 ± 8 years	EE	12 weeks	AE RE AnET	↓: FM, TAG, TC, LDL, TC : HDL ,SBP ↑: FFM, HDL ↔: BGL, INS, EI, DBP	

18a.	Moholdt et al., 2023	N=25(M) AA:36 ± 4 years	ME	11 days	HIIT + AET	↓: LDL ↔: TC, HDL, TAG	LDL : EE > ME
18b.	Moholdt et al., 2023	N=25(M) AA:36 ± 4 years	EE	11 days	HIIT + AET	↓: LDL ↔:TC, HDL, TAG	

↑ = Increase, ↓= Decrease , ↔ =No change , N=number of participants, W=Women, M=Men, AA=Average Age, ME=Morning Exercise, EE=Evening Exercise, FM=Fat mass, BW=Body Weight, TAG=Triglycerides , FFM=Free Fat Mass, HbA1c=Hemoglobin A1c,BGL=Blood Glucose, fBGL=Fasting Blood Glucose, INS=Insulin, fINS=Fasting Insulin, BMI=Body Mass Index, CGM=Continuous Glucose Monitoring, TC=Total Cholesterol, HDL=High Density Lipoprotein, LDL=Low Density Lipoprotein, VLDL=Very low-density lipoprotein, DBP=Diastolic Blood Pressure, SBP=Systolic Blood Pressure, PPI-AUC= postprandial insulin-area under the curve, HOMA2-IR=Homeostatic Model Assessment-Insulin Resistance, TSC=Total Serum Cholesterol , WC=Waist Circumference, EI=Energy Intake,VO2peak=peak oxygen consumption, 6MWT=six-min-walk test ,HIIT = High Intensity Interval Training , AET= Aerobic Exercise Training ,AnET=Anaerobic Exercise Training, RE = Resistance Exercise

3.7. Presentation of Studies that examined the training effect on pre-prandial vs. post-prandial exercise.

The studies that examined the training effect on pre-prandial vs. post-prandial exercise are presented in Table 4.

1)Poirier et al., investigated how the timing of a meal before exercise affects the blood glucose response in men with T2D. Nineteen men with T2D participated in the study. The exercise regimen involved three sessions per week, all closely monitored by an exercise physiologist. During each session, participants used a vertical ergometer at an intensity level corresponding to 60% of their VO2peak. Heart rate was used to prescribe and monitor exercise intensity, and the appropriate heart rate was determined based on the results of the VO2peak test. The duration of exercise sessions was set at 30 minutes during the first week and increased to 45 minutes in the second week. Starting from the third week, all subjects exercised for 60 minutes per session. After three months of training, the measurement of VO2peak was repeated, and the target heart rate for exercise sessions was adjusted accordingly for the next three months. Exercise sessions were scheduled either in the morning between 6:00 AM and 9:00 AM or later in the day between 4:00 PM and 8:00 PM. [90]

2)Gillen et al., examined the effects of low-volume HIIT performed either in a fasted or fed state. Sixteen women with overweight or obesity, with an average BMI of 29 +/- 3, participated in the study.

The study consisted of three main phases:

1. Baseline Testing: During this phase, participants underwent an incremental VO2peak test using a cycle ergometer with electronic resistance control.
2. 6-Week HIIT Protocol: Participants completed a 6-week HIIT program while following one of two dietary interventions. The HIIT protocol involved 18 supervised sessions over the 6 weeks, with sessions held on Monday, Wednesday, and Friday each week. Each session comprised 10 sets of 60-second cycling intervals, separated by 60-second recovery periods. The cycling was done on an ergometer with a constant watt setting and a pedal cadence of 80-100 rpm. Individual

workloads were chosen to achieve a heart rate of 90% of their maximum heart rate during the intervals. During the 60-second recovery periods, participants either rested or cycled at a low resistance of 50 W. All training sessions were conducted in the morning between 7:00 AM and 10:00 AM.

3. Post-Training Measurements: After completing the 6-week HIIT program, participants underwent post-training measurements to assess the outcomes of the exercise intervention.[78]

3)Brinkmann et al., conducted a study to investigate whether training before having breakfast, while in an overnight-fasted state, is more effective in improving the health of patients with T2DM compared to training after having breakfast in a fed state. They enrolled thirty T2D patients, with an average age of 60 years and an average BMI of 33.7 kg/m2, and randomly divided them into two groups: the F group, which trained in the overnight-fasted state (consisting of 15 patients), and the C group, which trained after having breakfast (the control group, also consisting of 15 patients). All the patients completed an 8-week training program that combined endurance and strength training. [88]

Table 4. Table of studies that examined the effect of training on pre-prandial vs. postprandial exercise.

A/A	Author's name & Publication year	Number & Average Age of Participants	Comparison	Duration of program	Design of program	Results	FAST Vs. FED
1a.	Poirier et al., 2000	N=19(M) AA:49 +/- 8 years	FAST (n=10)	80 sessions 3 days/week	AET	↔:BGL	
1b.	Poirier et al., 2000	N=19(M) AA:49 +/- 8 years	FED (n=18)	351 sessions 3 days/week	AET	↓:BGL	
2a.	Gillen et al., 2013	N=16(W) AA:27 +/- 6-8 years	FED	>6 weeks <=2 sessions/week (18 sessions),	HIIT	↑: BW, FM, FFM, fINS, VO2peak, ↓: HOMA ↔: fBGL	BW, FM, FFM, VO2peak: FED = FAST fINS: FED = FAST HOMA: FED > FAST
2b.	Gillen et al., 2013	N=16(W), AA:27 +/- 6-8 years	FAST	>6 weeks <=2 sessions/week (18 sessions)	HIIT	↑:BW, FM, FFM, fINS, VO2peak ↓: HOMA ↔:BW, fBGL	
3a.	Brinkmann et al., 2019	N=30, (M=19, W= 11 women) AA:60 ± 8 years	FAST (n = 15)	8 weeks 3 times/week	AET + RE	↔:BMI , Serum LDL/HDL ratio ↓:FM, HbA1c, SGL,SINS,HOMA-IR ,STAG,STC,	FM, FFM, HOMA-IR, STAG: FAST > FED HbA1c , SGL , STC: FAST = FED

						↑:FFM	
3b.	Brinkmann et al., 2019	N=30, (M=19 men, W=11) AA:60 ± 8 years	FED (n = 15)	8 weeks 3 times/week	AET + RE	↔:BMI,SINS, Serum LDL/HDL ratio ↓:FM ,HbA1c ,SGL,HOMA-IR ,STAG,STC ↑:FFM	

↑ = Increase , ↓:Decrease , ↔ =No change; N=Number of Participants, W=Women ,M=men, AA=Average Age, FAST= working out before eating a meal, FED=working out after eating a meal, BW=Body Weight, FM=Fat Mass, FFM=Free Fat Mass, AF=Abdominal Fat, BMI=Body Mass Index, fINS=Fasting Insulin, HbA1C= glycated hemoglobin, BGL= Blood Glucose ,SGL=Serum Glucose, SINS=Serum Insulin, STAG=Serum triacylglycerol, STC=Serum Total Cholesterol , High Density Lipoprotein , LDL: Low Density Lipoprotein, VO2peak=peak oxygen consumption ,AET=Aerobic Exercise Training, HIIT= High Intensity Interval Training, RE = Resistance Exercise

Regarding the further analysis of the results for the examined indicators, significant findings emerged, such as the following Table of the results concerning the impact of regular exercise on the examined indicators in patients with Metabolic Disorders.

The following table (Table 5) shows the results of the effect of systematic exercise and acute exercise on investigated indicators in adult patients with metabolic disorders.

Table 5. Changes in Body Composition, Postprandial/Fasting Metabolism, Lipid Metabolism and Appetite after the stimulus of exercise

1)BODY COMPOSITION

	change	FED	FAST	FED Vs. FAST	ME	EE	ME Vs. EE
BW	-				3/8	3/8	N.S
	↓				5/8	5/8	N.S
	↑	1/1	1/1	N.S			
BMI	-	1/1	1/1	N.S	2/5	3/5	EE>ME
	↓				3/5	2/5	ME>EE
FM	-				1/11		ME>EE
	↓	2/3	2/3	FED<FAST	10/11	11/11	ME<EE
	↑	1/3	1/3	N.S			
WC	-					3/5	ME<EE
	↓				5/5	2/5	ME>EE
FFM	-				3/9	3/9	N.S
	↓				1/9	3/9	ME<EE
	↑	2/2	2/2	FED<FAST	5/9	3/9	ME>EE

2) POSTPRANDIAL/FASTING METABOLISM

	change	FED	FAST	FED vs. FAST	ME	EE	ME vs. EE
GL	-	1/9	3/9	FAST>FED	6/10	4/10	ME>EE
	↓	8/9	4/9	FED>FAST	2/10	6/10	EE>ME
	↑		2/9	FAST>FED	2/10		ME>EE
INS	-		1/7	FAST>FED	2/5	1/5	ME>EE
	↓	7/7	6/7	FED>FAST	2/5	3/5	EE>ME
	↑				1/5	1/5	N.S
Insulin Sensitivity	-				1/2		ME>EE
	↑				1/2	2/2	EE>ME
HbA1c	-				1/4	1/4	N.S
	↓	1/1	1/1		3/4	3/4	N.S

3) LIPID METABOLISM

	change	FED	FAST	FED vs. FAST	ME	EE	ME vs. EE
TAG	-				3/6	3/6	N.S
	↓	3/3	3/3	N.S	2/6	3/6	EE>ME
	↑				1/6		ME>EE
TC	-				3/7	3/7	N.S
	↓	1/1	1/1	N.S	3/7	3/7	N.S
	↑						
HDL	-				5/6	4/6	ME>EE
	↓						
	↑				1/6	2/6	EE>ME
LDL	-				4/7	3/7	ME>EE
	↓				3/7	4/7	EE>ME

4)APPETITE CHANGES

	change	FED	FAST	FED vs. FAST	ME	EE	ME vs. EE
EI	**-**					2/7	EE>ME
	↓				5/7	3/7	ME>EE
	↑				1/7	2/7	ME>EE

↑ = Increase , ↓:Decrease , - =No change ,FED= Post-prandial exercise, Fast= Pre-prandial exercise, ME=Morning Exercise, EE=Evening Exercise, N.S.= Not significant between conditions, BW=Body Weight, BMI=Body Mass Index, FM= Fat Mass, WC= Waist Circumference, FFM=Fat Free Mass, GL= Glucose, INS=Insulin, HbA1c =Hemoglobin A1C, TAG= Triglycerides, TC=Total Cholesterol, HDL=High Density Lipoprotein, LDL=Low Density Lipoprotein, EI=Energy Intake

4.DISCUSSION

The purpose of this study was to investigate the effects of exercising timing on people who have diseases from Metabolic Disorders such as T2D and Obesity. The comparison came from 4 different 'timing' groups: a) acute effect of morning vs. evening exercise b) acute effect of pre- vs. post-prandial exercise c) training effect of morning vs. evening exercise d) training effect of pre- vs. post-exercise. The parameters that were assessed were the Body Composition, the Postprandial/Fasting Metabolism, the Lipid Metabolism, and the Appetite Indices.

The results we found, after comparing the 30 articles, were not as representative as they should have been to form a comprehensive final opinion. The variety of results was quite large, making it challenging to have clear data on which time would be the most effective for a patient with a metabolic disorder to exercise. Clearly, our results showed that among the comparisons between pre- and post-prandial exercise, the latter condition prevailed, as well as between ME vs. EE. However, one could argue that it is a bit more complex, as it depends on the parameter, we are evaluating each time. For example, for some parameters, it may be more effective to exercise in the morning, while for others, the opposite may be true. Therefore, it is important to know the specific goal we want to achieve through exercise and act accordingly. The positive effects on most examined indicators regarding exercise, in general, are notable.

- **Regarding the first category of our results:**

BODY WEIGHT When examining the impact of exercise timing, nine studies conducted before-and-after interventions on BW. Among these studies, only one focused on the differences between exercising in a fed vs. fasting state (training effect) and didn't show significant difference, while the remaining eight investigated the effects of ME vs. EE. Out of these eight studies, three of them didn't find any difference on the BW, as it stayed unchanged in both interventions, and the other five showed a decrease on both groups. Alizadeh et al. and Willis et al. discovered a significant change in BW in the morning group as weight loss was significantly greater in the morning than the evening group. Teo et al., found a reduction in both groups with no differences between. On the other hand, Creasy et al., Brooker et al., and Mancilla et al., discovered that the evening group had significantly greater training-induced reductions in BW compared to the morning group.
Our conclusion is that both groups reduced the BW. In five studies both groups reduced the BW, 3 showed better reduction after EE and 2 showed better reduction after ME.

BMI In relation to BMI, only one study provided findings comparing fed to fast exercise, and the difference was not significant, as the parameter of BMI remained unchanged. The BMI had no impact from the training. Five studies, however, contrasted the BMI following ME vs. EE. Three studies showed a decrease in BMI after ME, while only two studies showed the same result after EE. Alizadeh et al. and Brooker et al. showed that the differences were more pronounced after the ME, while Teo et al., showed reduction in both groups without differences. On the other hand, Mancilla et al. and Saidi et al. found that the BMI didn't change in either group.
Despite the small number of studies, it's more likely that the group participating in morning exercise reaped more significant benefits.

FAT MASS As for the FM, we have results of 14 studies. Three of them compared the effect of Fed vs. Fast exercise. So, Fauizi et al. and Brinkmann et al., both found reduction with a favor to the fasting group. Gillen et al. showed an increase in both Fast and Fed intervention with no differences in between. According to Di Blasio et al., Mancilla et al., Saidi et al., Creasy et al., Brooker et al. (2019), Brooker et al., (2022) and Hetherington et al. showed that EE reduced FM more than the ME while two other studies by Alizadeh et al. and Willis et al., showed that the training effect during the morning was more efficient. Teo et al. and Arciero et al. found a reduction, but no difference between morning and evening group.

We conclude that the EE is by far more efficient at reducing FM. As for the intervention between Fast vs. Fed, is more likely fasting exercising to be more effective.

WAIST CIRCUMFERENCE Five studies comparing the training effect between ME vs. EE focused on finding results in terms of WC, and four of them discovered that ME was more effective at doing so. Di Blasio et al., Alizadeh et al., Brooker et al., and Saidi et al. not only discovered that ME was more effective in reducing WC on overweight adults, but also that EE kept unchanged the parameter of WC. Only one study conducted by Teo et al. found that the EE lowered the WC more than the ME.

FREE FAT MASS As for the FFM, we have results from eleven studies in total, nine of them coming from the training effect between ME vs. EE, and only two of them from training effect between fed vs. fast exercise. Gillen et al. found an increase after both interventions (fed and fast) with no significant differences between the groups, but in the study by Brinkmann et al. showed a bigger increase after the fast intervention. Alizadeh et al., Creasy et al. and Brooker et al., (2022) observed a notable rise in FFM in the morning group. However, Creasy et al. and Brooker et al., both showed the FFM decreased after EE. Almost the same results showed the study by Hetherington et al., with non-change after ME and a decrease after EE. However, another study by Brooker at al., showed decrease after the morning intervention and non-change after the evening one. Saidi et al., and Arciero et al., didn’t find a difference between the groups, only that the FFM was increased. Mancilla et al. and Teo et al. showed non-change after both interventions.

It is a variety of results for this parameter because the results were very different. We conclude on the fact that three out of nine studies show a better increase after ME and only one out of two studies show a better increase after

Fast exercise. The results are negative for the evening group concerning the parameter of FFM.

- **Regarding the second category of our results:**

BLOOD GLUCOSE In the context of immediate/acute effects, feeding exercise led to glucose reduction in six out of six studies, as Derave et al., Colberg et al., Heden et al., Kim et al., Terada et al., and Chen at el., said. Terada et al., noticed that after HIIT, the reduction of the 24h-mean glucose wasn't significantly different between the groups, while after Aerobic Exercise the fasting group showed a bigger reduction.

Regarding training effects of the intervention between Fast vs. Fed we had results from three studies, Poirer et al. and Brinkmann et al., showed that feeding exercise resulted in glucose reduction, with the last one showing non-significant differences between the two groups. Gillen et al., showed no change.

Poirier et al. highlighted that postprandial exercise was particularly effective in improving glucose concentration in men with T2D, a finding supported by Derave et al., Colberg et al., and Kim et al. in various studies involving overweight individuals, T2D patients, and obese males. Heden's et al. study revealed that performing RE in the evening had a positive impact on glucose response in relation to meal timing. Conversely, fast exercise had mixed results, maintaining, or lowering blood and serum glucose levels in different studies.

When comparing the training effect of ME vs. EE, we had results from 10 studies. Six studies conducted by Savikj et al., Teo et al., Brooker et al., Mancilla et al., Menek et al., and Hetherington et al., showed that the reduction after EE was significantly more important. On the other side, Teo et al. and Menek et al., beside the reduction after the EE, showed a reduction after the morning intervention and only Menek et al. found that ME was more effective for improving blood glucose in T2D-affected men. Four studies conducted by Munan et al., Moholdt et al., Brooker et al. and Arciero et al., showed no change after both interventions. However, Moholdt et al., even though he found no change in the 24h blood glucose in both groups, he discovered a reduction on nocturnal Blood Glucose after the EE.

As we understand there are various perspectives on the glucose parameter. In summary, postprandial exercise is more effective at lowering glucose levels, according to five out of nine studies, while only one study showed better results after fasting exercise and we believe that is because of the type of the exercise (Terada et al.). When comparing morning vs. evening training, six out of ten studies found better outcomes for the evening training and just one for the morning training as concerned the glucose levels.

INSULIN In comparing the effects of Fed vs. Fast exercise, we also had results of seven studies. The studies conducted by Gillen et al. and Brinkmann et al., examined the HOMA-IR index. Their results showed a reduction of HOMA-IR index in both interventions, but Gillen et al. showed a greater reduction after Fed exercise and Brinkmann et al. after Fast exercise. Derave et al., showed a reduction in insulin during exercise and a reduction of meal induced insulinemic response in both groups, with a greater change after the Fed exercise. Same as the last author, was the results from Fauzi et al., who showed a greater postprandial insulin response after Fed exercise. Heden et al., showed a reduction in both groups, without differences between them. On the other side, Kim et al., even though the reduction was for both groups, showed a greater result after Fast exercise. One last study conducted by Chen et al., was positive only for the Fed group, that showed reduction in insulin, compared with the non-change that the Fast group showed.

In comparing the effects of different exercise timings (ME vs. EE), we had results of seven studies. Two studies conducted by Velde et al. and Mancilla et al., examined the insulin sensitivity and they both found that it was increased after the EE. Ceylan et al., Teo et al. and Moholdt et al., in three different studies found reduction in values of insulin after the evening intervention. Only Savikj et al., found an increase in post afternoon insulin after the EE. Arciero et al., found no change in both groups.

To conclude, five of the seven studies that examined the effect between morning vs. evening exercise came up with more positive results for the evening exercise. Four out of seven studies showed that exercising after having a meal is more efficient regarding the parameter of ‘insulin’, in contrast with two out of seven studies that showed the opposite.

HbA1c The results that we have about the last parameter of this category are less than the previous two parameters. Four studies compared the difference in HbA1c after ME vs. EE. Menek et al. found that the evening group had experienced the greatest decline. Only in those with T2D did ME result in greater HbA1c improvement than EE. Teo et al., also found reduction in HbA1c after both interventions, with no significant difference between the groups. Savikj et al. and Hetherington et al., came into confrontation, as the first author showed that the ME led to reduction in HbA1c and the EE to no-change, while on the other hand, the second author showed exactly the reverse effects (that the EE led to no-change and the ME to reduction).

Unfortunately, there were fewer studies examining pre- vs. post-prandial exercise, with only one study available, which one showed that both types of exercise led to a decrease in HbA1c.Specifficaly Brinkmann et al. did not find any significant differences between fast and fed exercise.

To conclude, because of the lack of results, we cannot say which intervention is the best to follow, in purpose to lower the level of HbA1c. Exercise helps to reduce the level of HbA1c, but we aren’t able to decide which timing is the most efficient.

- **Regarding the third category of our results:**

TAG(Triglycerides) When it comes to the effect of exercise on TAG levels, whether in the acute or training context, the results appear consistent.

Comparing the training effects between ME and EE, six studies gave us results. Two of them, by Brooker et al. and Moholdt et al., didn’t show any differences for both groups. Another study by Brooker et al. and one by Menek et al., showed that the level of TAG was lower in both groups, with the second author saying that the difference was greater for the Evening group. Savikj et al., showed an increase of TAG level after ME and no change after EE, while on the other hand, Arciero et al., showed a non-change after ME and a decrease after EE.

Three studies examined the impact of exercise on TAG, finding that both fed and fast exercise led to decreases in TAG values. In one study by Fauzi et al., they assessed the postprandial TAG response in the breakfast to lunch period, and they found that the reduction after the Fast exercise was greater. In another study, by Brinkmann et al., both fed and fast exercise resulted in reduced serum TAG levels, with the notable difference being that the reduction was significantly greater after fast exercise. Only the study conducted by Heden et al., showed greater reduction in the postprandial total TAG iAUC after the Fed intervention.

To conclude, three out of six studies comparing morning vs. evening exercise showed greater results after evening exercise, while only two studies showed positive results after morning exercise, even if the results were not as important as the ones after the evening intervention. Three out of three studies showed a reduction in both Fed and Fast groups, two of which showed greater reduction after the Fast intervention.

TC In the analysis of training effects seven studies compared ME vs. EE and only one study Fed vs. Fast intervention. Only Brinkmann et al. talked about the parameter of Total Cholesterol. He mentioned that both groups (Fed and Fast) showed an important reduction in TC levels but no differences between them.

On the other side, similar are the results for the intervention between morning vs. evening exercise. Brooker et al. and Menek at el., found reduction for both groups with no differences. Two out of seven studies, by Savikj et al. and Moholdt et al., showed no change in no group. Lastly, Arciero et al., and another study by Brooker et al., encountered a conflict as the first author noticed no change in the morning group and decrease in the evening group, while the second author noticed exactly the reverse outcomes (no change in the evening and decrease in the morning).

To conclude, four out of seven studies showed a reduction after the EE, and three out of seven studies showed a reduction after the ME.

HDL There were limited studies assessing this parameter, primarily focusing on the comparison between ME and EE. Six studies investigated this parameter. Four studies by Savikj et al., Brooker et al. (2019), Brooker et al. (2022), and Moholdt et al., didn't show any differences. The parameter of HDL remained unchanged. Menek at al., showed an equal increase in both groups. Arciero et al., showed an increase in the HDL after the EE. Regarding the Fed vs. Fast intervention Brinkmann et al., showed no difference in the LDL/HDL ratio.

To conclude, two out of seven studies showed an increase in the evening group, one out of seven in the morning group and four out of seven studies showed no change in HDL.

LDL Similar to HDL, the results obtained from the studies we reviewed focused on the comparison between ME and EE groups. However, we have a better picture of how LDL changed before and after exercise. More specifically, three out of seven studies, by Savikj et al., Brooker et al. (2019) and Brooker et al. (2022), showed that the LDL remained unchanged in both intervention groups. On the other hand, Moholdt et al., Arciero at al. and Moholdt et al. showed a greater reduction in LDL after the EE. Also, Menek at al., showed reduction in both groups.

To conclude, comparing ME vs. EE, three out of seven studies showed a greater decrease in LDL in the evening group, while only one out of seven studies found no difference between the reduction in morning and evening group after exercise. So, EE is more likely to reduce the level of LDL.

- **Regarding the fourth category of our results:**

Energy Intake Seven studies, in total, examined the change on the Energy Intake before and after training. The results come from the comparison between the ME vs. EE. We have a variety of results, but we can conclude that five out of seven studies conducted by Willis et al., Alizadeh et al., Teo et al., Brooker et al. and Arciero et al. showed a greater reduction in the morning group, while two studies by Alizadeh et al. and Arciero et al. shows no change in the evening group, and only three studies by Teo et al., Creasy et al. and Brooker et al., show a reduction in the evening group. Also, Di Blasio et al. and Willis et al., show an increase in the energy intake after the EE. To conclude, it seems that ME is more efficient in reducing energy intake.

In summary, regarding the studies, the EE was more efficient for reducing the BW. As for the BMI, 3 studies showed better reduction after EE. The EE was more efficient at lowering the FM. As for the WC, five studies showed that the ME was superior. Lastly for this category, we didn't have enough results to determine whether is the best exercise timing to increase the FFM, but reg three out of nine studies is more likely the ME to be more efficient. So, positive results were reported after EE for lowering the BW and the FM while ME is more likely to be more efficient for lowering the BMI, WC and increasing the FFM.

Engaging in physical activity following a meal has consistently shown the most significant reduction in blood glucose levels, as supported by findings from five to nine studies. This pattern is mirrored in the context of insulin levels, where exercise after eating has yielded positive outcomes. Additionally, EE has proven to be highly effective in lowering blood glucose and insulin levels. However, when it comes to the impact of exercise timing on HbA1c levels, there is insufficient data available to draw definitive conclusions.

In terms of lipid metabolism, it appears that both ME and EE contribute to improvements in TAG levels. EE is more effective in achieving this outcome. Additionally, fast exercise has demonstrated better results in this regard. Regarding total cholesterol (TC), EE appears to be more effective in lowering TC levels. However, there is a lack of sufficient data to draw conclusions regarding high-density lipoprotein (HDL) levels. When it comes to low-density lipoprotein (LDL), EE is more likely to lead to a reduction in LDL levels.

Last, the EI was significantly improved after the ME.

Therefore, we conclude that the choice between morning or evening exercise, as well as pre- or post-meal exercise, depends on the specific parameter we want to improve. In all four cases, exercise has beneficial effects for individuals with metabolic diseases, but our goal is to maximize the benefits. It seems that exercise during the evening hours, as well as post-meal exercise, may be more effective. However, more studies would certainly be useful in the future. There is a gap in the bibliography concerning parameters such as HbA1c for example, a medical test that measures the average blood sugar level over the past two to three months. HbA1c is a very important index for the medical course of the patient. Also, few are the data that we have concerning the pre- vs. postprandial intervention. Many studies have investigated BGL and INS indexes but not furthermore than that. Additionally, all the studies we examined focused on adults, which is reasonable regarding T2D, but there is certainly a gap in the literature regarding other metabolic conditions in minors such as childhood obesity. Furthermore, when comparing acute effects with training effects, the results were more positive in the latter case.

As for fitness trainers, it would be useful for them to fully leverage the numerous benefits of exercise and, depending on the patient's goals, choose the appropriate time for exercise during the specific period. It's crucial to prioritize safety, individualization, and a holistic approach to fitness and health. It’s important to conduct a thorough assessment to understand the client's medical history, current health status, medications, and specific metabolic condition.

I believe there is a need for more studies, perhaps more specific ones, regarding the evaluation of parameters in this context.

5.MECHANISMS

In our study, we acknowledge the importance of investigations comparing morning vs. evening exercise and pre-versus vs. postprandial exercise. However, it's essential to note that the focus of our research may not extensively delve into the underlying mechanisms of these temporal differences because we didn't have much information from the studies that we decided to examine. Instead, our study primarily aims to assess the practical outcomes of exercise timing on changes in body composition and metabolic responses. While we may not provide an exhaustive exploration of mechanistic pathways, our findings can still offer valuable insights into the real-world implications of exercise timing for individuals seeking to optimize their health. Although some of the mechanisms will be explained below.

Colberg et al.,2009 The fact that post-meal exercise can mitigate increases in blood glucose levels is well-established. When individuals with T2D engage in moderate-intensity exercise for about 2 hours after breakfast, it leads to a more significant reduction in glucose levels compared to fasting conditions. However, this effect doesn't persist beyond lunchtime without additional exercise. In this study, where none of the diabetic participants were receiving external insulin treatment, it's likely that a meal with moderate glycemic impact prompted the release of more endogenously produced insulin, which, when combined with exercise, further reduced their post-meal blood sugar responses. Insulin binds cellular receptors in muscles and adipose tissues, recruiting GLUT4 transport proteins to the cell surface, facilitating glucose transport. Muscle contractions themselves can stimulate glucose transport into muscle cells independently of insulin but in an additive manner, thereby enhancing the impact of exercise performed after a meal. [92]

Heden et al.,2014 Insulin levels decrease either with pre-prandial Resistance Exercise (RE) or with postprandial RE, but the mechanisms differ: pre-dinner RE enhances estimated insulin clearance, while post-dinner RE reduces estimated insulin secretion and enhances clearance. In both cases, post-meal insulin levels drop, aligning with other research. Pre-dinner RE reduces post-meal insulin levels primarily through enhanced clearance, while glucose levels decrease without a significant reduction in insulin secretion, possibly because insulin-potentiating hormones like GLP-1 or GIP remain largely unaffected. Post-dinner RE reduces insulin levels by increasing clearance and reducing secretion, although the increase in clearance is less pronounced than with pre-dinner RE. Lower post-meal insulin secretion in post-dinner RE may be related to reduced GLP-1 and glucose levels rather than changes in GIP or beta-cell function, as these factors remained stable. It's speculated that the mechanism through which RE boosts insulin clearance could be linked to increased blood flow in skeletal muscles, potentially allowing more insulin to interact with its receptor, be internalized, and degraded. This theory finds support in related research showing enhanced blood flow in response to prior RE. [95]

Saidi et al., 2021 Although there is agreement that people who exercise in the morning tend to experience more significant weight loss, it's been revealed only marginal distinctions in the components of energy balance. The exact reasons for the differences in weight loss remain uncertain. One hypothesis is that variations in circadian rhythm or how individuals respond to sleep between morning and evening exercise could be a contributing factor. This is significant because circadian rhythms and sleep have been associated with the regulation of energy balance and metabolism, such as glucose tolerance and insulin sensitivity. [83]

Menek et al.,2022 This study indicated that afternoon exercise training had a greater impact on improving blood glucose levels in men with type 2 diabetes compared to morning exercise training and that can maybe happen because human skeletal muscle strength and mitochondrial activity reach their peak during the late afternoon, suggesting that oxidative metabolism follows a daily circadian pattern.[96]

Hetherington-Rauth et al., 2022 In individuals with type 2 diabetes, structured exercise conducted in the afternoon has demonstrated more significant improvements in glycemic outcomes. This phenomenon may be linked to disruptions in circadian rhythms often observed in individuals with type 2 diabetes, which lead to the "dawn phenomenon," where insulin sensitivity is lower in the morning. Therefore, aligning physical activity or exercise with these circadian metabolic fluctuations could be a promising approach to maximize the benefits of glycemic control. Notably, various exercise-related pathways downstream of the molecular clock genes have been identified. One of these pathways, the AMPK signaling pathway, has been found to influence the stability of key clock genes, namely period and cryptochrome. [105]

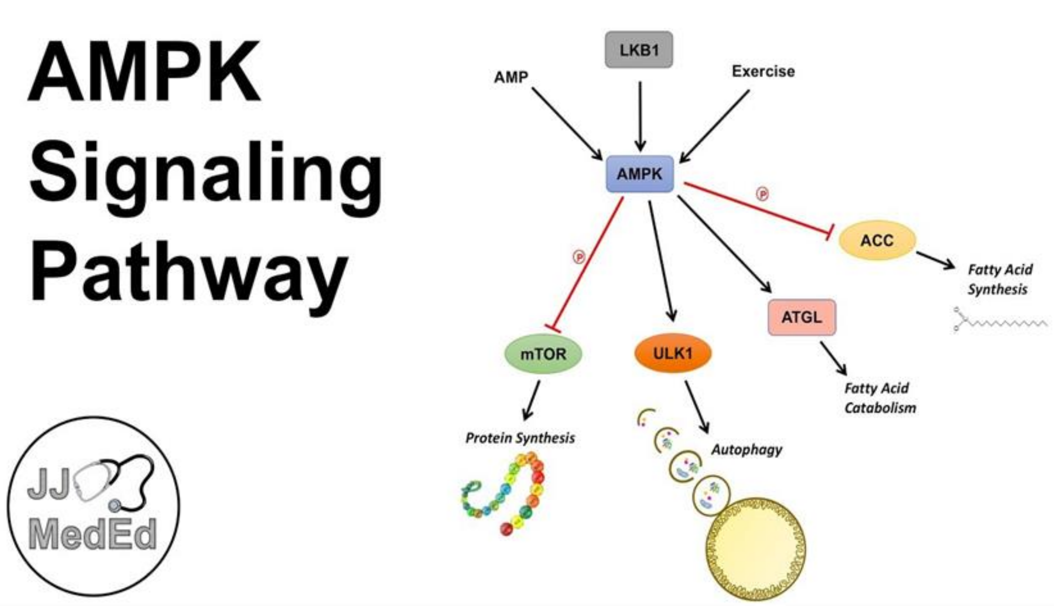

Figure 6. AMPK Signaling Pathway(https://www.youtube.com/watch?v=4G56m9fyNWY)

6.CONCLUSION

This systematic review aimed to present significant findings regarding the impact of regular exercise on individuals with metabolic diseases, particularly focusing on adults with Type 2 Diabetes or Obesity. After conducting a thorough analysis of the available literature, it becomes evident that the consensus tends to favor specific exercise approaches. These include aerobic exercise, high-intensity interval training, resistance exercise and a combination of them, all of which have demonstrated notable benefits. Resistance training, on the other hand, appears to play a relatively smaller role in these cases. The review involved 1740 adult participants, and while it revealed positive effects on various measured parameters, it does not offer definitive answers to our specific questions.

In summary, determining the optimal timing and conditions for exercise in individuals with metabolic diseases remains a challenging task. Deciding whether morning or evening exercise is preferable, as well as whether it should be done before or after meals, remains a complex issue with no clear-cut solutions.

So, we can provide an answer to our research question and state that the results from the systematic review have revealed multiple outcomes. Regarding the comparison between morning and evening exercise, evening exercise was more effective in reducing BW and FM. According to some studies, TC slightly improved more with evening exercise. Morning exercise was more effective in reducing WC and BMI. As for the comparison between pre- vs. postprandial exercise, the effects on glucose and insulin were more significant after postprandial exercise. Additionally, engaging in exercise during the evening has demonstrated a high degree of effectiveness in reducing both blood glucose and insulin levels.

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