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Review paper

Metabolic Regulation at the Molecular Level: Investigating Intracellular Routes and Clinical Consequences in the Regression of Atherosclerosis and the Optimisation of Cardiovascular Health

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ABSTRACT

The conventional therapy for atherosclerosis, marked by the buildup of arterial plaque that constricts and hardens the arteries, involves managing elevated blood pressure and cholesterol levels. Recent research indicates that fasting can effectively repair atherosclerosis. This review investigates the mechanisms by which fasting influences atherosclerosis, analyses clinical data, outlines fasting procedures, considers patient demographics, and discusses the clinical implications. The clinical data illustrating the efficacy of fasting in inhibiting atherosclerosis progression is analysed, with the molecular impacts of fasting on metabolism, cellular function, and inflammation. This study evaluates the feasibility, duration, and outcomes of several fasting protocols, including time-restricted eating and intermittent fasting, across diverse patient populations. The evaluation also addresses implementation aspects, including safety in clinical environments, monitoring, and patient education. This review contributes to the understanding of fasting's therapeutic potential in preventing atherosclerosis and improving cardiovascular health.

1. Introduction

Atherosclerosis remains a significant health issue, although progress in medical therapy. Atherosclerosis, characterised by a complex interplay of vascular, inflammatory, and metabolic processes, significantly contributes to global cardiovascular morbidity and mortality, remaining a formidable challenge in contemporary healthcare (Libby et al., 2019). Atherosclerotic plaques, which obstruct blood flow and precipitate cardiovascular incidents such as myocardial infarction and stroke, develop when lipids, immune cells, and cellular debris accumulate within artery walls (Weiss and Fontana, 2014). The predominant contemporary therapy strategies focus on managing traditional risk factors such as hypertension, dyslipidaemia, and diabetes mellitus to mitigate the advancement of atherosclerotic plaques (Ridker et al., 2017). Recent study has demonstrated the potential therapeutic effect of fasting in reversing

atherosclerosis by addressing critical pathophysiological pathways involved in its onset and advancement (Mattson et al., 2014). Notwithstanding progress in medication and lifestyle modifications, a considerable number of patients persist in facing detrimental cardiovascular outcomes, highlighting the necessity for innovative therapeutic strategies (Anton et al., 2018). The practice of fasting, encompassing time-restricted meals, intermittent fasting, and periodic fasting, has garnered attention for its potential to mitigate atherosclerotic processes via metabolic, cellular, and anti-inflammatory mechanisms (Harvie et al., 2011). This research examines the processes via which fasting affects atherosclerosis, evaluates pertinent clinical information about its efficacy, and discusses optimal fasting procedures and patient considerations (Patterson et al., 2021). This research aims to advance the burgeoning domain of cardiovascular preventive medicine by examining the intricate relationships between fasting and atherosclerosis, thereby paving the way for innovative treatment strategies for atherosclerotic cardiovascular disease (Anton et al., 2018).

2. Atherosclerosis Pathophysiology

The formation and proliferation of atherosclerotic plaques are driven by a complex array of molecular mechanisms associated with atherosclerosis, a chronic inflammatory arterial disease. Understanding these systems is crucial for developing effective therapeutic techniques. This article review analyses the molecular mechanisms associated with atherosclerosis, focussing on inflammation, lipid metabolism, endothelial dysfunction, and the proliferation of vascular smooth muscle cells.

2.1 Atherosclerosis-related Inflammation

Inflammation is crucial from the initiation of atherosclerosis to the destabilisation of the plaque. Endothelial dysfunction caused by hypertension and hyperlipidaemia results in the expression of adhesion molecules (e.g., ICAM-1 and VCAM-1) and chemokines (e.g., MCP-1), facilitating the recruitment of monocytes into the arterial wall (Libby et al., 2002). In the intima, monocytes differentiate into macrophages that ingest oxidised low-density lipoproteins (LDL) to form foam cells, which signify early atherosclerotic lesions. Hansson and Hermansson (2011) assert that activated macrophages and other immune cells generate inflammatory cytokines, including interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-alpha), which exacerbate endothelial dysfunction and promote the migration and proliferation of smooth muscle cells. Matrix metalloproteinases (MMPs) are generated throughout the inflammatory cascade and degrade the fibrous cap of atherosclerotic plaques, rendering them vulnerable to rupture and thrombosis (Newby, 2008).

2.2 Lipids Metabolism in Atherosclerosis:

Atherosclerosis is mostly induced by dysregulated lipid metabolism, namely elevated levels of triglycerides and low-density lipoproteins. LDL particles infiltrate the arterial wall, undergo oxidation, triggering an inflammatory cascade and promoting the formation of foam cells (Tabas, 2010). In contrast, high-density lipoproteins (HDL) confer protection by enhancing cholesterol efflux, promoting reverse cholesterol transport, and removing cholesterol from macrophages (Rader, 2006). Glass and Witztum (2001) assert that oxidised low-density lipoprotein (LDL) exacerbates endothelial dysfunction and stimulates the synthesis of adhesion molecules and chemokines, hence extending the recruitment of inflammatory cells into the arterial wall. Lipid-laden foam cells contribute to the formation of fatty streaks, the earliest visible indication of atherosclerosis. These streaks ultimately evolve into complex plaques characterised by a fibrous outside and a necrotic interior.

2.3 Endothelial Dysfunction and the Proliferation of Vascular Smooth Muscle Cells:

The formation of atherosclerotic lesions is promoted by endothelial dysfunction, characterised by reduced nitric oxide availability and increased endothelin-1 production. This condition promotes vasoconstriction, platelet activation, and leukocyte adherence (Lusis, 2000). Dysfunctional endothelial cells display a pro-inflammatory character by secreting chemotactic chemicals that attract immune cells to the arterial intima. In atherosclerosis, vascular smooth muscle cells (VSMCs) perform two tasks. Vascular smooth muscle cells (VSMCs) migrate from the media to the intima in response to inflammatory cytokines and growth factors (e.g., PDGF, TGF-beta), proliferate, and produce extracellular matrix components, all of which enhance plaque stability (Bennett et al., 2016). However, the weakening of the fibrous cap and the vulnerability of the plaque may arise from abnormal proliferation of vascular smooth muscle cells and their phenotypic transition to a synthetic phenotype.

Table 1 Molecular Mechanisms in Atherosclerosis Pathophysiology

Mechanisms	Description	Key Molecules/Cells	References
Inflammation	Initiates and exacerbates atherosclerosis through immune cell recruitment, cytokine release, and fibrous cap degradation.	ICAM-1, VCAM-1, MCP-1, IL-6, TNF-α, MMPs, monocytes, macrophages, foam cells	Libby et al., 2002; Hansson & Hermansson, 2011; Newby, 2008
Foam Cell Formation	Monocytes differentiate into macrophages, ingest oxidized LDL, and become foam cells, forming fatty streaks.	Oxidized LDL, macrophages, foam cells	Hansson & Hermansson, 2011
Cytokine and MMP Secretion	Inflammatory cytokines promote VSMC migration and matrix metalloproteinases (MMPs) degrade fibrous cap, increasing risk of rupture.	IL-6, TNF-α, MMPs	Newby, 2008
Lipid Metabolism Dysregulation	Elevated LDL and triglycerides promote LDL oxidation and inflammation; HDL counters this by cholesterol efflux and reverse transport.	LDL, HDL, oxidized LDL, foam cells	Tabas, 2010; Rader, 2006; Glass & Witztum, 2001
Endothelial Dysfunction	Loss of nitric oxide (NO) availability and endothelin-1 overproduction lead to vasoconstriction, platelet activation, and leukocyte adhesion.	Nitric oxide (↓), Endothelin-1 (↑), adhesion molecules	Lusis, 2000
Adhesion and Chemotactic Molecules	Promote leukocyte adhesion and migration into intima, supporting chronic inflammation.	ICAM-1, VCAM-1, MCP-1	Libby et al., 2002; Glass & Witztum, 2001
VSMC Migration and Proliferation	VSMCs migrate from media to intima, proliferate, and synthesize ECM; initially stabilizing plaque but later contributing to instability when switching to synthetic phenotype.	VSMCs, PDGF, TGF-β, ECM	Bennett et al., 2016
Plaque Progression	Fatty streaks evolve into complex plaques with fibrous caps and necrotic cores; prone to rupture and thrombosis in advanced stages.	Foam cells, necrotic core, fibrous cap	Hansson & Hermansson, 2011

3. Current Therapeutic Approachs for Atherosclerosis

Atherosclerosis is a complex cardiovascular disorder characterised by the accumulation of plaque within the arterial walls. Management of this illness necessitates a synthesis of pharmacological and lifestyle interventions. This article review provides a comprehensive overview of the constraints and challenges inherent in conventional therapy approaches for atherosclerosis, encompassing pharmacological interventions and lifestyle modifications. Libby et al. (2016) assert that statins are the primary pharmacological agents for managing dyslipidaemia and reducing LDL cholesterol levels. They possess pleiotropic advantages beyond cholesterol reduction, such as enhancing endothelial function and mitigating inflammation. Nevertheless, the extensive utilisation of statins is hindered by their intolerance and adverse effects, which encompass myopathy and increased liver enzymes. Zimlichman et al., 2011. Aspirin and P2Y12 inhibitors, including clopidogrel, are antiplatelet medicines commonly used to avert thrombotic events in atherosclerosis.
These medicines effectively reduce cardiovascular events but pose a risk of bleeding problems, particularly in high-risk individuals (Capodanno and Angiolillo, 2010). ACE inhibitors, beta-blockers, calcium channel blockers, and diuretics exemplify commonly utilised antihypertensive agents. Managing hypertension is crucial for addressing complications associated with atherosclerosis (Brunner et al., 2015). In clinical practice, achieving optimal blood pressure control and ensuring medication adherence remain challenging. Implementing a heart-healthy diet, such as the Mediterranean diet, characterised by a high intake of fruits, vegetables, whole grains, and healthy fats (such as olive oil), is a method to alter one's lifestyle and reduce the risk of cardiovascular disease (Estruch et al., 2018). Nonetheless, certain patients may struggle to sustain these dietary modifications in the long term. Regular exercise, encompassing both resistance and aerobic training, can enhance cardiovascular fitness, lipid profiles, and insulin sensitivity (Kokkinos, 2018).

Nonetheless, fostering sustained compliance with physical activity remains a therapeutic challenge. Due to the detrimental effects of smoking on vascular health and cardiovascular risk, cessation is crucial for the management of atherosclerosis (Cahill et al., 2013). Nonetheless, ongoing support and behavioural treatments are essential for the success of smoking

cessation programs. Challenges encompass patient adherence to drug regimens and lifestyle modifications, which influence treatment efficacy and long-term outcomes (World Health Organisation, 2003). Moreover, pharmacological treatments often exhibit adverse effects and issues with tolerability, leading to alterations or cessation of therapy (Neale et al., 2017). Innovative therapeutic approaches are essential, as a considerable proportion of persons with atherosclerosis continue to experience residual cardiovascular risk despite effective treatment (Mortensen et al., 2018).

4. Fasting Concept in Health and Disease

Fasting, long established in several countries and religions, has garnered significant attention in modern medicine for its potential health benefits beyond mere calorie reduction. This literature review analyses several fasting modalities, including time-restricted eating, periodic fasting, and intermittent fasting, and explores the physiological responses elicited by fasting, such as effects on metabolism, cellular function, and inflammation.

4.1 Fasting Types

1. Intermittent Fasting (IF): Intermittent fasting (IF) encompasses alternating periods of fasting and eating, utilising established protocols such as the 16/8 method (fasting for 16 hours and consuming food within an 8-hour window) or alternate-day fasting (fasting every other day).

2. Time-Restricted Feeding (TRF): This entails prolonged fasting between meals and restricting daily consumption to a designated timeframe, typically 8 to 12 hours.

3. Periodic Fasting (PF): This fasting pertains to prolonged fasting periods, such as the 5:2 diet (consuming normally for 5 days and restricting calories for 2 days) or extended fasting protocols lasting 24 to 72 hours or more. The periods of fasting may vary from 24 hours to many days.

4.2 Physiological Response to Fasting

The physiological responses to fasting—enhanced insulin sensitivity, elevated fat oxidation, ketogenesis, and improved mitochondrial function—constitute the metabolic adaptations that fasting induces to preserve energy balance during periods of dietary restriction (Mattson et al., 2014). Moreover, autophagy—a cellular recycling process that removes damaged proteins and organelles—is enhanced by fasting, which augments cellular resilience and repair (Mizushima et al., 2008). Furthermore, fasting diminishes pro-inflammatory cytokines including TNF-alpha and IL-6, decreases oxidative stress, and modifies immune cell function to elicit anti-inflammatory responses (Johnson et al., 2015). The cellular, metabolic, and anti-inflammatory responses to fasting collectively bolster its potential therapeutic benefits, such as atherosclerosis prevention and overall health improvement.

4.3 Clinical Evidence and Health Advantages

Numerous studies have demonstrated the health benefits of fasting for various medical conditions. Harvie et al. (2011) assert that fasting aids in weight management by facilitating weight loss, enhancing metabolic health indicators such as insulin sensitivity and cholesterol profiles, and improving body composition. Moreover, fasting is associated with improved cardiovascular health, evidenced by a reduction in risk factors for cardiovascular disease, including blood pressure, lipid profiles, and endothelial function (Tinken et al., 2009). Additionally, fasting offers significant advantages for brain health, exhibiting neuroprotective properties that enhance neuroplasticity, cognitive function, and resilience against neurodegenerative diseases (Mattson and Arumugam, 2018). Moreover, fasting may positively influence immunological regulation and gut microbiota, thereby alleviating autoimmune illnesses and inflammatory disorders (Clemente-Postigo et al., 2019). Collectively, these findings illustrate the diverse and beneficial impacts of fasting on overall health and wellbeing across multiple physiological systems.

5. Atherosclerosis and Fasting: Mechanistic Insights

Time-restricted feeding, intermittent fasting, and periodic fasting are among the dietary protocols that incorporate fasting, which has emerged as a feasible treatment strategy to affect atherosclerosis via several molecular mechanisms. This literature review examines the intricate ways by which fasting influences atherosclerosis, including metabolic alterations, autophagy, improved endothelial function, and inflammatory control. It also examines preclinical research results that elucidate the impact of fasting on the regression of atherosclerotic plaque.

5.1 Metabolic Adaptations

The Metabolic Modifications Metabolic alterations induced by fasting aim to maintain energy equilibrium during nutritional deprivation. Insulin levels decrease during fasting, promoting the utilisation of fatty acids and lipolysis as alternative energy sources (Mattson et al., 2014). Anton et al. (2018) assert that this metabolic shift decreases triglyceride levels, enhances insulin sensitivity, and ameliorates lipid profiles, hence mitigating risk factors for atherosclerosis.

5.2 Autophagy

Autophagy, a cellular recycling mechanism, aids in the prevention of atherosclerosis by removing oxidised lipids, aggregated proteins, and damaged organelles, hence preserving cellular integrity and function (Levine and Kroemer, 2008). Razani et al. (2012) assert that fasting enhances plaque stability and regression by stimulating autophagy via the activation of AMP-activated protein kinase (AMPK) and the inhibition of mammalian target of rapamycin (mTOR) signalling.

5.3 Enhancing Endothelial Function

The development and progression of atherosclerotic plaques are promoted by endothelial dysfunction, characterised by reduced nitric oxide bioavailability and heightened oxidative stress (Lusis, 2000). Horne et al. (2020) assert that fasting enhances vascular tone, reduces endothelial inflammation, and elevates nitric oxide production, hence improving endothelial function and decelerating atherosclerosis progresssi-on.

5.4 Modulation of Inflammation

Libby (2012) asserts that chronic inflammation is crucial to the pathogenesis of atherosclerosis since it promotes foam cell formation, endothelial dysfunction, and plaque instability. Fasting diminishes plaque susceptibility and mitigates inflammatory processes within the arterial wall by inhibiting pro-inflammatory cytokines (such as IL-6 and TNF-alpha) and obstructing NF-kappaB signalling. Johnson et al. (2015).

5.5 Conclusions from Preclinical Research

Preclinical studies utilising animal models have elucidated the impact of fasting on the regression of atherosclerotic plaque. In animal models of atherosclerosis, intermittent fasting regimens have been shown to reduce plaque size, lipid content, and macrophage infiltration (Sasaki et al., 2014). Additionally, research employing time-restricted feeding protocols has demonstrated enhancements in collagen levels, fibrous cap thickness, and plaque stability, indicating a regression of atherosclerotic lesions (Chung et al., 2019).

Table 2 Mechanistic Insights of Fasting in Atherosclerosis

Mechanisms	Description	Effect on Atherosclerosis	Reference/s
Metabolic Adaptations	Fasting reduces insulin levels, promotes fatty acid utilization, increases lipolysis, improves lipid profiles, and enhances insulin sensitivity.	Decreases triglycerides and LDL, reduces atherosclerosis risk.	Mattson et al., 2014; Anton et al., 2018
Autophagy Activation	Fasting induces autophagy via AMPK activation and mTOR inhibition, leading to the degradation of damaged organelles, oxidized lipids, and protein aggregates.	Enhances plaque stability, promotes regression, preserves cellular function.	Levine & Kroemer, 2008; Razani et al., 2012
Improved Endothelial Function	Fasting elevates nitric oxide (NO) production, reduces oxidative stress and vascular inflammation.	Improves vascular tone, reduces endothelial dysfunction, slows plaque development.	Lusis, 2000; Horne et al., 2020
Inflammatory Modulation	Fasting inhibits NF-κB signaling and reduces production of pro-inflammatory cytokines (IL-6, TNF-α).	Lowers foam cell formation, inflammation, and plaque instability.	Libby, 2012; Johnson et al., 2015
Plaque Regression (Preclinical)	Animal models show intermittent fasting reduces plaque size, lipid content, and macrophage infiltration.	Time-restricted feeding increases collagen and fibrous cap thickness. Demonstrates reversal of plaque progression and increased stability in preclinical studies.	Sasaki et al., 2014; Chung et al., 2019

6. Clinical Evidence Supporting Fasting for Atherosclerosis

Research Findings Supporting Fasting in Atherosclerosis The practice of fasting, encompassing various dietary regimens such time-restricted eating, intermittent fasting, and periodic fasting, has garnered interest for its potential benefits in mitigating cardiovascular risk factors and promoting plaque stability in atherosclerosis. This article summarises significant findings from clinical trials and observational studies regarding the effects of fasting on cardiovascular risk factors, plaque stability, and cardiovascular outcomes, while also analysing various fasting protocols, durations, and patient populations. Multiple observational studies and clinical trials have demonstrated the efficacy of fasting in mitigating cardiovascular risk factors. A randomised controlled trial shown that intermittent fasting dramatically reduced blood pressure, LDL cholesterol levels, and body weight—all critical risk factors for atherosclerosis development. This was proven by Harvie et al. (2011).

Similarly, a meta-analysis performed in 2018 by Anton et al. Demonstrated enhancements in inflammatory markers, lipid profiles, and insulin sensitivity among individuals adhering to intermittent fasting protocols. The potential of fasting to enhance plaque stability and induce regression in atherosclerosis has been examined. Preclinical studies on animal models indicate that periodic and intermittent fasting regimens can diminish fat, cholesterol, and inflammatory cell infiltration in atherosclerotic lesions (Sasaki et al., 2014; Chung et al., 2019). Moreover, subsequent to fasting interventions, clinical imaging studies employing techniques such as coronary computed tomography angiography (CCTA) and intravascular ultrasound (IVUS) have revealed enhanced plaque characteristics, including reduced plaque volume and augmented fibrous cap thickness (Wang et al., 2020). The efficacy of fasting therapy may vary based on the specific technique and duration employed.

Numerous studies have shown the beneficial impacts of intermittent fasting protocols, such as the 5:2 diet (which involves normal eating for 5 days and caloric restriction for 2 days) or alternate-day fasting, on cardiovascular risk factors and plaque stability (Harvie et al., 2011; Chung et al., 2019). Time-restricted feeding, which confines daily meals to a specific timeframe (e.g., 8–12 hours), has demonstrated enhancements in endothelial function and metabolic health indicators (Horne et al., 2020). Further study is essential to ascertain the optimal fasting schedule and duration, especially in diverse patient populations, to realise sustained cardiovascular advantages. Clinical trials evaluating fasting therapy for atherosclerosis have included individuals with metabolic syndrome, obesity, and diagnosed cardiovascular disease. Incorporating fasting strategies in clinical practice must consider considerations such as age, comorbidities, and medication usage, notwithstanding fasting's potential in reducing cardiovascular risk profiles in many patient populations (Horne et al., 2020).

7. Ideal Fasting Guidelines and Considerations

There is increasing recognition that fasting can serve as a therapeutic method to enhance various facets of health, including cardiovascular health. This review article encompasses optimal fasting regimens, detailing the duration and frequency of fasting, as well as the integration of fasting therapies into patient education, clinical practice, and monitoring.

7.1 Schedules for Intermittent Fasting

Various intermittent fasting regimens have been extensively investigated. Intermittent fasting (IF) involves alternating between intervals of consumption and abstention from food. The 16/8 method involves consuming all meals within an 8-hour period while fasting for 16 hours daily (Patterson et al., 2015). The 5:2 diet, which restricts caloric intake to 500–600 on two non-consecutive days per week, is a popular intermittent fasting regimen (Harvie et al., 2011). Additionally, numerous individuals practise alternate-day fasting, characterised by alternating between days of usual consumption and days of abstention from food (Anton et al., 2018). The heightened interest in intermittent fasting (IF) as a dietary approach for health and wellness may be ascribed to the diverse range of IF regimens, each providing flexibility and showing potential in enhancing specific metabolic outcomes and health indicators.

7.2 The length of the fasting periods

The optimal duration of fasting intervals depends on individual goals and health status. Research by Anton et al. (2018) indicates that short-term fasts, typically lasting 16 to 24 hours, are associated with metabolic benefits, including enhanced insulin sensitivity and fat oxidation. According to the research by Mattson et al. (2014), extended fasting periods of 48 to 72 hours may promote autophagy, a cellular recycling process, and facilitate cellular rejuvenation. Various durations of fasting have distinct physiological effects; shorter fasts prioritise metabolic adaptations, whilst prolonged fasts may enhance cellular repair processes like autophagy. These distinctions highlight the diverse impacts of fasting on human physiology.

7.3 Possible Advantages and Risks

Weiss and Fontana (2014) observed that intermittent fasting has garnered attention for its potential benefits in enhancing metabolic health, regulating weight, and improving cardiovascular health. However, it is crucial to acknowledge that fasting is not feasible for everyone, as noted by Patterson et al. (2017). Fasting entails some hazards, including the potential for nutritional deficiencies and other effects if conducted poorly. These contrasting elements underscore the importance of tailored tactics and professional guidance when considering the integration of intermittent fasting into a health regimen.

7.4 Executing Interventions for Fasting

Patterson et al. (2015) emphasise that the implementation of fasting therapies in clinical practice necessitates a thorough strategy that includes meticulous assessment, patient education, and diligent monitoring. Healthcare providers must assess each patient's unique health circumstances, considering factors such as medical history, current medications, and possible contraindications, to

determine the appropriateness of fasting. Furthermore, as shown by Weiss and Fontana (2014), patient education is essential for conveying crucial information regarding fasting protocols, potential benefits, associated risks, and monitoring parameters. Patients educated on the intricacies of fasting are more adept at making informed decisions and adhering to their regimens effectively and securely, hence enhancing therapeutic outcomes and elevating patient satisfaction.

7.5 Observation and Investigation

Patterson et al. (2017) emphasise that regular monitoring and follow-up are essential for guaranteeing the safety and efficacy of fasting therapy. Healthcare personnel should meticulously monitor vital signs such as blood pressure, heart rate, and temperature to promptly identify any potential side effects or difficulties. Moreover, as shown by Weiss and Fontana (2014), monitoring metabolic indicators such as glucose concentrations, lipid profiles, and hydration levels enables healthcare professionals to assess the metabolic response to fasting and implement necessary adjustments to enhance patient outcomes. Comprehensive monitoring and follow-up protocols enhance patient safety and provide valuable insights into the physiological impacts of fasting, facilitating personalised treatment strategies and optimisation. Future perspectives and challenges of fasting as a therapeutic strategy for atherosclerosis This review of publications analyses the future directions and challenges of fasting as a therapeutic therapy for atherosclerosis. It addresses subjects for additional research and clinical trials, along with challenges and limitations in integrating fasting into conventional healthcare practice.

Table 3 Summary of Fasting Guidelines and Considerations

Category	Key Points	Reference/s
Fasting Types	16/8, 5:2, and alternate-day fasting are popular IF regimens with metabolic and cardiovascular benefits.	Patterson et al., 2015; Harvie et al., 2011; Anton et al., 2018
Duration	16–24 hrs improves metabolism; 48–72 hrs promotes autophagy and cellular repair.	Mattson et al., 2014; Anton et al., 2018
Benefits	Enhances lipid profile, insulin sensitivity, weight control, and vascular health.	Weiss & Fontana, 2014
Risks	Not suitable for all; may cause nutrient deficiencies if unmanaged.	Patterson et al., 2017
Implementation	Requires patient screening, education, and professional guidance.	Patterson et al., 2015; Weiss & Fontana, 2014
Monitoring	Regular checks on vitals and metabolic markers ensure safety and effectiveness.	Patterson et al., 2017

8. Future Directions and Challenges in Fasting as Therapeutic Intervention for Atherosclerosis

Enhancing comprehension of the molecular mechanisms by which fasting influences the onset and reversal of atherosclerosis involves examining metabolic modifications, the role of autophagy, and the modulation of inflammatory responses (Weiss and Fontana, 2014). Clinical research has increasingly focused on the long-term effects of fasting on cardiovascular outcomes, plaque stability, and overall heart health, with extensive trials being conducted to evaluate its therapeutic potential (Anton et al., 2018). Furthermore, studies have aimed to assess the impact of fasting across diverse patient populations, including those with various comorbidities and cardiovascular risk profiles, to better understand its broader applicability (Patterson et al., 2017).

However, several challenges and limitations remain, such as maintaining patient adherence to fasting protocols and addressing compliance issues over extended periods (Harvie et al., 2011). Ensuring dietary adequacy during fasting periods is also crucial to prevent nutrient deficiencies and to support overall health and wellness (Mattson et al., 2014). Safety concerns must be carefully considered, particularly for vulnerable populations such as the elderly, pregnant women, and individuals with pre-existing medical conditions (Weiss and Fontana, 2014). For successful incorporation of fasting into clinical practice, education and training of medical personnel are essential, including instruction on patient selection criteria, appropriate monitoring methodologies, and implementation of fasting procedures (Patterson et al., 2015). Collaborative care, as outlined by Anton et al. (2018), emphasizes a multidisciplinary approach involving nutritionists, physicians, and behavioral specialists working together to support patients throughout fasting interventions.

In addition, comprehensive patient counselling is necessary to convey the benefits, limitations, and practical strategies of fasting, along with appropriate follow-up care to ensure both safety and efficacy (Weiss and Fontana, 2014).

9. Conclusion

In summary, fasting may enhance cardiovascular health, especially for the reversal of atherosclerosis. Various fasting protocols, such as the 16/8 method, the 5:2 diet, and alternate-day fasting, have been shown to enhance cardiovascular risk factors and metabolic health. Interdisciplinary collaboration is essential to tackle challenges such as adherence, safety, and patient education. To effectively harness the advantages of fasting in preventive medicine and atherosclerosis therapy, it must be integrated into holistic cardiovascular care via patient-centered counselling, collaborative strategies, and education.

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