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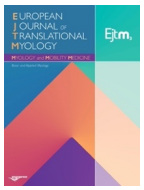

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Cannabidiol and skeletal muscle insulin resistance: translational implications for exercise and rehabilitation medicine

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Abstract
Insulin Resistance (IR) is a central pathophysiological mechanism underlying obesity, type 2 diabetes mellitus, metabolic syndrome, and metabolic dysfunction-associated steatotic liver disease, with significant implications for skeletal muscle function, exercise capacity, and rehabilitation outcomes. Because skeletal muscle represents the primary site of insulin-stimulated glucose disposal, muscle insulin resistance is a key determinant of both metabolic health and physical performance. Cannabidiol (CBD), a non-intoxicating phytocannabinoid derived from *Cannabis sativa*, has attracted increasing scientific interest due to its anti-inflammatory, antioxidant, and pleiotropic signaling properties. This narrative review aims to examine the relationship between CBD and insulin resistance, with a particular focus on skeletal muscle biology and its relevance for exercise and rehabilitation medicine. A structured literature search was conducted using major biomedical databases, including PubMed, Scopus, and Web of Science, to identify relevant preclinical and clinical studies. Evidence was synthesized narratively, with emphasis on skeletal muscle insulin resistance, endocannabinoid system signaling, potential mechanisms of CBD action, and clinical outcomes. Preclinical data suggest that CBD may influence several pathways involved in skeletal muscle insulin resistance, including chronic low-grade inflammation, oxidative stress, lipotoxicity, and ceramide accumulation. However, current human studies remain limited and do not demonstrate consistent improvements in glycemic control or insulin sensitivity with CBD alone. Furthermore, evidence regarding its effects on muscle function, exercise performance, or rehabilitation outcomes is lacking. In conclusion, CBD represents a biologically plausible but clinically unproven modulator of skeletal muscle insulin resistance. At present, it should be considered an experimental adjunct rather than an established therapeutic strategy. Future research should focus on well-designed clinical trials integrating metabolic and functional endpoints to determine its potential role alongside exercise-based interventions in rehabilitation medicine.

Key words: cannabidiol; insulin resistance; skeletal muscle; rehabilitation; metabolic syndrome.

Insulin Resistance (IR) is a central pathophysiological feature of obesity, type 2 diabetes mellitus, metabolic syndrome, and metabolic dysfunction-associated steatotic liver disease.

Beyond its metabolic definition, however, IR has important implications for skeletal muscle biology, exercise capacity, and functional health. Because skeletal muscle accounts for the majority of insulin-stimulated glucose disposal, impairment of muscle insulin sensitivity represents a key determinant of whole-body metabolic control as well as physical performance.[1,2] In addition to its role in glucose homeostasis, skeletal muscle is increasingly recognized as a key determinant of metabolic flexibility, defined as the capacity to adapt substrate utilization according to energy demands. Impaired metabolic flexibility is a hallmark of insulin-resistant states and has been associated with reduced exercise responsiveness, diminished functional capacity, and poorer rehabilitation outcomes.[3,4]

In insulin-resistant states, skeletal muscle exhibits a complex pattern of metabolic and structural alterations, including impaired insulin signaling, reduced glucose transport, mitochondrial dysfunction, increased intramyocellular lipid accumulation, and chronic low-grade inflammation.[1,3] These changes are not only relevant to glycemic regulation but are also associated with decreased exercise tolerance, early fatigue, and reduced responsiveness to training interventions. Consequently, skeletal muscle insulin resistance occupies a central position at the interface between metabolic disease and rehabilitation medicine.[4]

Over the past two decades, the Endocannabinoid System (ECS) has emerged as an important regulator of energy balance, lipid metabolism, and glucose homeostasis. Recent evidence suggests that ECS signaling may also influence skeletal muscle metabolism through effects on lipid utilization, mitochondrial function, and inflammatory pathways. Consequently, dysregulation of ECS activity has been implicated not only in systemic metabolic disease but also in mechanisms directly relevant to muscle insulin resistance and physical performance.[5,6]

Dysregulation of ECS signaling, particularly through cannabinoid receptor 1 (CB1), has been linked to adipose tissue inflammation, hepatic steatosis, and impaired insulin action in peripheral tissues, including skeletal muscle.[5,6] This has stimulated interest in cannabinoid-related pathways as potential modulators of metabolic dysfunction.

Cannabidiol (CBD), a non-intoxicating phytocannabinoid derived from *Cannabis sativa*, has gained increasing scientific attention because of its anti-inflammatory, antioxidant, and pleiotropic signaling properties. Unlike Δ9-tetrahydrocannabinol, CBD has low affinity for classical cannabinoid receptors but can modulate ECS activity indirectly and interact with multiple molecular targets, including transient receptor potential channels, peroxisome proliferator-activated receptors, and G protein-coupled receptors.[7] This broad pharmacological profile is particularly relevant in IR, which arises from the interaction of inflammatory, oxidative, and lipid-mediated mechanisms rather than from a single molecular defect.

From a translational perspective, the potential relevance of CBD extends beyond metabolic biomarkers to include skeletal muscle function and adaptation. Exercise remains the most effective non-pharmacological intervention for improving insulin sensitivity, largely through its direct effects on skeletal muscle glucose uptake and metabolic flexibility.[4,8] Therefore, any proposed adjunctive strategy, such as CBD, should be evaluated in the context of its potential to influence muscle physiology, exercise responsiveness, and rehabilitation outcomes.

Despite compelling mechanistic hypotheses and encouraging findings in experimental models, clinical evidence regarding CBD and insulin resistance remains limited and

inconsistent. Moreover, the growing interest in CBD within sports medicine and rehabilitation has further highlighted the need to clarify whether its biological effects translate into measurable improvements in muscle function, exercise adaptation, or recovery-related outcomes.[13] The most cited randomized clinical trial in patients with type 2 diabetes did not demonstrate significant improvements in glycemic control with CBD alone.[9] More recent studies in individuals with overweight or obesity have also reported no meaningful effects on glucose tolerance.[10] Moreover, very few studies have specifically addressed skeletal muscle–related endpoints or functional outcomes relevant to rehabilitation[9,10,13]. This gap highlights the need for a more integrated, muscle-centered, and translational approach to the topic.

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Aim of the study

The aim of the present narrative review is to examine the relationship between CBD and insulin resistance with a particular focus on skeletal muscle biology and its relevance for exercise and rehabilitation medicine. Specifically, this review aims to: summarize current knowledge on the role of skeletal muscle in insulin resistance and its interaction with the endocannabinoid system; analyze potential mechanisms through which CBD may influence muscle-related metabolic pathways, including inflammation, oxidative stress, and lipid metabolism; and critically evaluate the available preclinical and clinical evidence, with emphasis on translational implications for exercise responsiveness and rehabilitation outcomes.

Materials and Methods

This narrative review was conducted to synthesize current evidence on the relationship between CBD, skeletal muscle insulin resistance, and their potential relevance for exercise and rehabilitation medicine.

A structured literature search was performed using major biomedical databases, including PubMed/MEDLINE, Scopus, and Web of Science, to identify relevant studies published up to January 2026. The search strategy combined keywords and Medical Subject Headings (MeSH) terms related to the topic, including “cannabidiol”, “CBD”, “insulin resistance”, “skeletal muscle”, “endocannabinoid system”, “exercise”, and “rehabilitation”. Boolean operators (AND/OR) were applied to refine the search and ensure adequate sensitivity and specificity. The literature selection process was guided by predefined inclusion and exclusion criteria to ensure the relevance and quality of the evidence included in this narrative review. The criteria applied during the screening process are summarized in Table 1.

Original research articles, randomized controlled trials, experimental animal studies, and relevant review articles were considered eligible for inclusion. Particular emphasis was placed on studies addressing i) mechanisms of insulin resistance in skeletal muscle, ii) the role of the endocannabinoid system in metabolic regulation, and iii) the metabolic and cellular effects of CBD. Studies focusing exclusively on Δ9-Tetrahydrocannabinol (THC) without relevance to CBD were excluded.

Additional relevant publications were identified through manual screening of reference lists of selected articles. Priority was given to peer-reviewed studies, recent publications, and articles with clearly described methodologies. Clinical studies were critically evaluated with regard to

sample size, study duration, outcomes assessed, and translational relevance to exercise and rehabilitation.

Given the heterogeneity of the available evidence and the limited number of high-quality clinical trials, a narrative synthesis approach was adopted. The findings were organized into thematic sections focusing on skeletal muscle insulin resistance, endocannabinoid signaling, potential mechanisms of CBD action, clinical evidence, and implications for exercise and rehabilitation medicine.

Results

Skeletal muscle insulin resistance as a central metabolic and functional impairment

Skeletal muscle represents the primary site of insulin-stimulated glucose disposal and plays a critical role in maintaining whole-body metabolic homeostasis.[1,2] In insulin-resistant states, skeletal muscle demonstrates impaired insulin signaling, reduced Glucose Transporter (GLUT4) translocation, mitochondrial dysfunction, and accumulation of intramyocellular lipids.[3] These alterations are strongly associated with decreased metabolic flexibility, reduced exercise capacity, and impaired functional performance.

Lipotoxic intermediates, particularly ceramides and diacylglycerols, have been identified as key mediators of disrupted insulin signaling in skeletal muscle.[3] In addition, chronic low-grade inflammation contributes to the activation of stress kinases that further inhibit insulin receptor signaling pathways.[5] These molecular disturbances not only promote metabolic disease progression but also negatively affect muscle quality and rehabilitation outcomes.

Endocannabinoid system dysregulation in metabolic disease

The Endocannabinoid System (ECS) has emerged as a significant regulator of energy balance, lipid metabolism, and glucose homeostasis.[5] Dysregulation of ECS signaling, particularly through overactivation of cannabinoid receptor 1 (CB1), has been linked to obesity, adipose tissue inflammation, hepatic steatosis, and impaired insulin sensitivity in peripheral tissues, including skeletal muscle.[5,6]

Experimental evidence suggests that CB1 activation promotes lipogenesis, reduces fatty acid oxidation, and enhances inflammatory signaling, thereby contributing to insulin resistance.[6] Conversely, modulation of ECS activity has been proposed as a potential therapeutic strategy to improve metabolic function, although central CB1 antagonism has been limited by adverse neuropsychiatric effects.

Mechanistic effects of cannabidiol relevant to skeletal muscle insulin resistance

Mechanism 1. Modulation of chronic low-grade inflammation

Chronic low-grade inflammation is a key contributor to insulin resistance and impaired skeletal muscle metabolism. Pro-inflammatory cytokines, including TNF-α and IL-6, interfere with insulin signaling pathways and promote metabolic dysfunction. Preclinical studies have demonstrated that CBD may exert anti-inflammatory effects through modulation of cytokine production and endocannabinoid-related signaling pathways. These actions may contribute to a more favorable metabolic environment within skeletal muscle tissue[5,7].

Mechanism 2. Reduction of oxidative stress
Oxidative stress plays an important role in the development of skeletal muscle insulin resistance by disrupting insulin receptor signaling and mitochondrial function. Experimental evidence indicates that CBD possesses antioxidant properties and may reduce oxidative damage in metabolically stressed tissues. Such effects could theoretically support muscle metabolic homeostasis and recovery[7,11].

Mechanism 3. Attenuation of lipotoxicity and ceramide accumulation
Lipotoxicity represents one of the major mechanisms underlying skeletal muscle insulin resistance. In animal models of high-fat diet-induced obesity, chronic CBD administration has been associated with reduced ceramide synthesis in skeletal muscle and improved insulin-related signaling pathways. Since ceramides are recognized mediators of insulin resistance, these findings provide a mechanistic basis for further investigation[7,11].

Mechanism 4. Endocannabinoid system modulation
CBD exhibits a complex pharmacological profile and interacts with multiple molecular targets beyond classical cannabinoid receptors. CBD may influence CB1- and CB2-mediated signaling indirectly through modulation of endocannabinoid system activity. Given that excessive CB1 activation has been linked to metabolic dysfunction, inflammation, and impaired insulin sensitivity, ECS modulation represents a potential pathway through which CBD could affect skeletal muscle metabolism[5,6,7].

Mechanism 5. Regulation of PPAR-related metabolic pathways
Experimental and molecular studies suggest that CBD may interact with peroxisome proliferator-activated receptors (PPARs), particularly PPARγ, which plays an important role in lipid metabolism and insulin sensitivity. Activation of these pathways could contribute to improved metabolic regulation, although current evidence remains largely preclinical[7].

Mechanism 6. Interaction with TRPV1 signaling
CBD has also been shown to interact with transient receptor potential vanilloid 1 (TRPV1) channels. These channels participate in calcium signaling and metabolic regulation and may influence cellular responses related to energy metabolism. However, their specific contribution to skeletal muscle insulin sensitivity remains incompletely understood, and the clinical significance of this interaction is currently unclear[7].
The proposed mechanisms through which CBD may influence skeletal muscle insulin resistance are summarized in Table 2.

Interaction between exercise, skeletal muscle, and metabolic regulation
Exercise is a cornerstone intervention in the management of insulin resistance and type 2 diabetes.[4,8] Muscle contraction stimulates glucose uptake through insulin-independent pathways and enhances insulin sensitivity over time. Regular physical activity improves mitochondrial function, reduces intramuscular lipid accumulation, and attenuates inflammatory signaling.

These adaptations are directly relevant to rehabilitation medicine, as improved muscle function translates into enhanced physical capacity, reduced fatigue, and better clinical outcomes. Therefore, skeletal muscle represents a critical therapeutic target at the intersection of metabolic disease and functional recovery.

Clinical evidence on cannabidiol and insulin resistance

Human studies evaluating the metabolic effects of CBD remain limited and heterogeneous. In a randomized, double-blind, placebo-controlled trial involving patients with type 2 diabetes, CBD alone did not significantly improve glycemic control or insulin sensitivity compared with placebo.[9] Although some changes in metabolic biomarkers were observed, these findings were not sufficient to support a clear clinical benefit.

More recent evidence in adults with overweight or obesity indicates that short-term administration of low-dose CBD does not significantly influence glucose tolerance or metabolic outcomes.[10] These results highlight the discrepancy between promising preclinical findings and the lack of consistent clinical efficacy.

Importantly, current clinical studies have not specifically evaluated outcomes related to skeletal muscle function, exercise performance, or rehabilitation, representing a significant gap in the literature. A summary of the current evidence is presented in Table 3.

Overall, current evidence supports several biologically plausible mechanisms through which CBD may influence skeletal muscle metabolism; however, robust clinical evidence demonstrating meaningful effects on insulin sensitivity, exercise performance, or rehabilitation outcomes remains insufficient[9,10,13].

Safety considerations

Recent clinical data indicate that CBD is not without risk. In controlled studies, CBD administration has been associated with elevations in liver enzymes and potential drug–drug interactions.[7] These safety concerns are particularly relevant in populations with metabolic disorders, where comorbidities and polypharmacy are common.

Discussion

The present narrative review highlights the complex and still unresolved relationship between CBD and insulin resistance, with particular emphasis on skeletal muscle as a central metabolic and functional organ. While the mechanistic rationale supporting a potential role of CBD is biologically plausible, current evidence remains insufficient to support its clinical application in metabolic or rehabilitation settings.

A key strength of the CBD–insulin resistance hypothesis lies in its alignment with the multifactorial nature of skeletal muscle insulin resistance. IR in muscle is driven by interconnected processes, including chronic low-grade inflammation, oxidative stress, mitochondrial dysfunction, and lipotoxicity.[1-3] These same pathways have been identified as potential targets of CBD in preclinical models, suggesting a theoretical capacity of CBD to modulate the muscle metabolic environment.

Among these mechanisms, lipid-induced insulin resistance, particularly through ceramide accumulation, appears especially relevant. Experimental evidence indicates that ceramides

impair insulin signaling and mitochondrial function in skeletal muscle, thereby contributing to metabolic inflexibility and reduced exercise capacity.[3,11] In this context, preclinical findings showing that CBD may attenuate ceramide synthesis provide a mechanistically coherent, though still preliminary, basis for further investigation.

An additional challenge in interpreting the available evidence relates to the substantial heterogeneity of CBD preparations and administration protocols. Differences in formulation, route of administration, dosage, treatment duration, and bioavailability may significantly influence biological responses and partly explain the inconsistency observed across clinical studies.[15,16] Moreover, the pharmacokinetic profile of CBD remains highly variable among individuals, making direct comparisons between studies difficult and limiting the generalizability of current findings.

From a translational perspective, the most important question is not whether CBD affects isolated molecular pathways, but whether it can influence clinically meaningful outcomes related to skeletal muscle function. Exercise remains the most effective intervention for improving insulin sensitivity, primarily through its direct effects on skeletal muscle glucose uptake, mitochondrial biogenesis, and metabolic flexibility.[4,8,12] Therefore, any proposed adjunctive strategy, including CBD, should be evaluated in relation to its potential to enhance or complement exercise-induced adaptations.

The interaction between CBD and exercise-induced adaptations remains insufficiently explored. Exercise exerts profound effects on skeletal muscle metabolism through mechanisms involving enhanced glucose uptake, mitochondrial biogenesis, improved metabolic flexibility, and reduced inflammation. While CBD has been proposed as a potential adjunctive strategy capable of influencing some of these pathways, current evidence does not demonstrate that CBD enhances exercise responsiveness, training adaptations, or functional recovery[13]. Consequently, its role should be regarded as complementary and investigational rather than synergistic or performance-enhancing.

At present, there is no convincing evidence that CBD improves exercise performance, muscle strength, or functional recovery in populations with metabolic disease. Reviews examining CBD in the context of sport and muscle recovery report heterogeneous findings, with no consistent benefit for performance or recovery outcomes.[13] Moreover, existing human studies have largely focused on metabolic biomarkers rather than muscle-specific or rehabilitation-relevant endpoints.

From a rehabilitation perspective, particular interest exists regarding populations characterized by both metabolic dysfunction and impaired physical performance, including individuals with obesity, type 2 diabetes, metabolic syndrome, and sarcopenic obesity.[17] In these populations, skeletal muscle dysfunction contributes not only to metabolic impairment but also to reduced mobility, exercise intolerance, and diminished quality of life.[18] Future studies should therefore evaluate whether CBD may influence clinically meaningful outcomes beyond traditional metabolic biomarkers, including muscle strength, physical function, fatigue, and rehabilitation-related endpoints.

Another important consideration is the gap between preclinical and clinical evidence. While animal and in vitro studies frequently demonstrate anti-inflammatory, antioxidant, and lipid-modulating effects of CBD, these findings have not translated into clear improvements in

glycemic control or insulin sensitivity in human trials.[9,10] This discrepancy may be explained by differences in dosing, bioavailability, study duration, and population characteristics, as well as by the complexity of human metabolic disease.

Safety also represents a critical translational barrier. Recent randomized clinical data indicate that CBD can lead to elevations in liver enzymes and may interact with commonly used medications.[14] Given that patients with insulin resistance often present with comorbidities such as obesity, type 2 diabetes, and metabolic liver disease, these safety concerns are particularly relevant in both clinical and rehabilitation contexts.

Importantly, the current literature lacks studies specifically designed to evaluate the role of CBD in rehabilitation settings. No trials have examined whether CBD influences exercise adherence, fatigue perception, muscle recovery, or functional outcomes in patients undergoing structured rehabilitation programs. This represents a significant gap, especially considering that skeletal muscle dysfunction is a key determinant of disability and quality of life in metabolic disease.

Future research should adopt a more integrative and translational approach. Well-designed randomized controlled trials are needed to evaluate CBD as a potential adjunct to exercise-based interventions in clearly defined populations, such as individuals with obesity-related insulin resistance, prediabetes, or sarcopenic obesity. Such studies should incorporate both metabolic endpoints and functional outcomes, including muscle strength, endurance, exercise capacity, and patient-reported measures.

In addition, future investigations should address key methodological challenges, including standardization of CBD formulations, dosing strategies, treatment duration, and safety monitoring. Mechanistic studies in human skeletal muscle, including biopsy-based analyses, may further clarify whether CBD exerts direct effects on muscle metabolism or primarily acts through systemic pathways.

In summary, CBD represents a biologically plausible but clinically unproven candidate in the context of skeletal muscle insulin resistance. Its potential relevance to rehabilitation medicine lies not in replacing established interventions such as exercise, but in the possibility of modulating the metabolic environment in which these interventions operate. At present, however, the available evidence remains insufficient to support definitive conclusions regarding its clinical utility, and further robust clinical validation is warranted.

Limitations

This review has several limitations that should be considered when interpreting the findings. First, the available evidence on CBD and insulin resistance is limited and highly heterogeneous, particularly with respect to study design, dosing regimens, and outcome measures. The majority of mechanistic data are derived from preclinical models, which may not fully translate to human physiology.

Second, clinical studies evaluating the metabolic effects of CBD are relatively few, often involve small sample sizes, and do not consistently assess skeletal muscle–specific outcomes. As a result, the relevance of CBD to muscle insulin sensitivity, exercise performance, and rehabilitation remains largely speculative.

Third, variability in CBD formulations, bioavailability, and treatment duration across studies complicates direct comparisons and limits the ability to draw firm conclusions. In addition, potential confounding factors, including differences in baseline metabolic status, physical activity levels, and concomitant therapies, are not uniformly controlled.
Finally, long-term safety data, particularly in populations with metabolic disease and comorbidities, remain insufficient. These limitations highlight the need for cautious interpretation of current evidence and emphasize the importance of well-designed clinical trials.

Future directions
Future research should adopt a more integrative and translational approach to better define the role of cannabidiol in skeletal muscle insulin resistance. Well-designed randomized controlled trials are needed to evaluate CBD as a potential adjunct to exercise-based interventions in clearly characterized populations, including individuals with obesity-related insulin resistance, prediabetes, and sarcopenic obesity.
Such studies should incorporate both metabolic and functional endpoints, including muscle insulin sensitivity, mitochondrial function, muscle strength, exercise capacity, and patient-reported outcomes. The use of advanced methodologies, such as muscle biopsies and imaging techniques, may further elucidate the direct effects of CBD on skeletal muscle tissue.
In addition, future investigations should focus on standardizing CBD formulations, dosing strategies, and treatment duration, as well as systematically assessing safety and drug–drug interactions. Particular attention should be given to the interaction between CBD and exercise, as this represents a key area of translational relevance for rehabilitation medicine.

Conclusions
CBD represents a biologically plausible but clinically unproven modulator of pathways involved in skeletal muscle insulin resistance. Preclinical evidence suggests that CBD may influence key mechanisms underlying insulin resistance, including inflammation, oxidative stress, lipid metabolism, and ceramide accumulation. These processes are closely linked to skeletal muscle function and metabolic flexibility, which are central to both metabolic health and rehabilitation outcomes.
However, current human evidence does not support CBD as an effective intervention for improving insulin sensitivity or glycemic control. Moreover, there is a lack of studies specifically addressing skeletal muscle–related endpoints, exercise performance, or rehabilitation outcomes. The discrepancy between promising mechanistic findings and limited clinical efficacy highlights the need for cautious interpretation.
From a translational perspective, skeletal muscle remains the primary therapeutic target in insulin resistance, with exercise-based interventions representing the most effective and evidence-based approach. At present, CBD should be regarded as a potential experimental adjunct rather than a validated therapeutic strategy in metabolic or rehabilitation settings.
Future research should focus on well-designed clinical trials that integrate metabolic, functional, and rehabilitation-relevant outcomes to determine whether CBD has any

meaningful role alongside established interventions. Until such evidence is available, its use in the context of insulin resistance and rehabilitation should remain investigational.

List of Abbreviations
CBD, Cannabidiol
ECS, Endocannabinoid System
IR, Insulin Resistance
CB1, Cannabinoid Receptor Type 1
CB2, Cannabinoid Receptor Type 2
GLUT4, Glucose Transporter Type 4
PPAR, Peroxisome Proliferator-Activated Receptor
TRPV1, Transient Receptor Potential Vanilloid 1
ROS, Reactive Oxygen Species
ATP, Adenosine Triphosphate

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Contributions:

Gergana Todorova conceptualized the study, performed the analysis, and drafted the manuscript; Gergana Todorova and Anna Mihaylova contributed to the curation and analysis of the data. Tanya Gesheva contributed to the methodology and revision of the manuscript; Anna Mihaylova supervised the study. All authors contributed to the interpretation of the results and approved the final manuscript.

Conflict of interest: the authors declare no potential conflict of interest, and all authors confirm accuracy.

Ethics approval: the Scientific Ethics Committee at the Medical University – Plovdiv approved this study (P-KHE-16/02-02-2026). The study is conformed with the Helsinki Declaration of 1964, as revised in 2013, concerning human and animal rights.

Informed consent: all patients participating in this study signed a written informed consent form for participating in this study.

Patient consent for publication: written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

Availability of data and materials: all data generated or analyzed during this study are included in this published article.

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Table 1. Inclusion and exclusion criteria applied during literature selection.

Inclusion criteria	Exclusion criteria
Original research articles, randomized controlled trials, experimental studies, and relevant review articles	Conference abstracts without sufficient methodological information
Studies investigating cannabidiol (CBD) and its metabolic, inflammatory, or physiological effects	Studies focused exclusively on Δ9-tetrahydrocannabinol (THC) without relevance to CBD
Studies addressing insulin resistance, glucose metabolism, skeletal muscle physiology, or the endocannabinoid system	Studies unrelated to metabolic regulation, skeletal muscle, or rehabilitation

Human, animal, and mechanistic studies providing relevant translational evidence	Duplicate publications
Peer-reviewed articles published in English	Non-English publications lacking an accessible scientific translation
Publications with relevance to exercise, physical activity, or rehabilitation medicine	Publications with insufficient methodological description or unclear outcomes

Table 2. Summary of the proposed mechanisms through which cannabidiol may influence skeletal muscle insulin resistance.

Mechanism	Pathophysiological role in skeletal muscle IR	Proposed effects of CBD	Supporting evidence	Translational relevance
Chronic low-grade inflammation	Cytokines (TNF-α, IL-6) impair insulin signaling pathways	Anti-inflammatory effects; modulation of cytokine production	Preclinical studies; ECS-related pathways[5–7]	May improve muscle metabolic environment
Oxidative stress	ROS disrupt insulin receptor signaling and mitochondrial function	Antioxidant properties; reduction of oxidative damage	Experimental models[7]	Potential support for muscle recovery and function
Lipotoxicity (ceramides)	Ceramides inhibit insulin signaling and mitochondrial activity	Reduction of ceramide synthesis in skeletal muscle	Animal studies[11]	Relevant for metabolic flexibility and exercise response
Mitochondrial dysfunction	Reduced oxidative capacity and ATP production	Possible indirect effects via reduced oxidative stress and lipid burden	Limited evidence	May influence fatigue and exercise tolerance
Endocannabinoid system modulation	CB1 overactivation promotes metabolic dysfunction	Indirect ECS modulation; interaction with CB1/CB2 signaling	Review and experimental data[5–7]	Potential systemic and muscle-related effects
PPAR activation	Regulation of lipid metabolism and insulin sensitivity	Activation of PPARγ-related pathways	Molecular and preclinical data[7]	Possible metabolic improvement
TRPV1 signaling	Calcium signaling and metabolic regulation	Interaction with TRPV1 channels	Experimental data[7]	Unclear clinical relevance

Table 3. Current evidence regarding cannabidiol, skeletal muscle insulin resistance, and implications for rehabilitation medicine.

Evidence domain	Key findings	Relevance to skeletal muscle	Translational implications	Limitations
Skeletal muscle insulin resistance	Impaired insulin signaling, GLUT4 translocation, mitochondrial dysfunction, lipid accumulation	Central site of glucose disposal and determinant of metabolic flexibility	Target for exercise-based interventions and rehabilitation	Multifactorial pathophysiology
Endocannabinoid system (ECS)	CB1 overactivation linked to inflammation, lipogenesis, insulin resistance	ECS influences muscle metabolism indirectly via systemic and local pathways	Potential target for metabolic modulation	Limited direct human muscle data
Preclinical CBD studies	Anti-inflammatory, antioxidant effects; reduced ceramide synthesis in muscle models	Suggests potential improvement in muscle metabolic environment	Supports hypothesis of metabolic modulation	Mostly animal/in vitro data
Clinical studies (CBD)	No consistent improvement in glycemic control or insulin sensitivity	No direct evidence for muscle-specific effects	Limited support for clinical use	Small sample sizes, heterogeneous study populations, short intervention periods
Exercise and muscle metabolism	Improves insulin sensitivity, mitochondrial function, lipid metabolism	Directly enhances muscle function and metabolic health	Gold standard intervention in IR and rehabilitation	Requires adherence and long-term implementation
CBD and exercise interaction	Limited and inconsistent evidence; no clear performance or recovery benefit	No proven effect on muscle function or exercise adaptation	Potential adjunctive role remains hypothetical	Lack of randomized controlled trials evaluating exercise-related outcomes

	demonstrated to date			
Safety of CBD	Elevated liver enzymes; drug–drug interactions	Relevant for metabolic patients with comorbidities	Important consideration in clinical and rehab settings	Long-term safety unclear