

Review

Electroceuticals for Metabolic Syndrome: Historical Milestones, Neuronal Pathways, Challenges, and Technological Advances

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Abstract

Bioelectric signaling plays an essential role in regulating cellular, tissue, and organ functions. Electroceuticals (ECs) are device-mediated interventions that modulate biological activity through controlled electrical stimulation or related neuromodulatory approaches. They have attracted interest as potential therapeutic strategies for complex disorders, including metabolic syndrome (MetS), which involves interconnected metabolic abnormalities and neurophysiological dysregulation, involving pathways associated with autonomic control, inflammation, and brain-derived neurotrophic factor (BDNF). This narrative review examines the historical development, potential mechanisms, therapeutic applications, technological advances, limitations of ECs in the context of MetS, and identifies priorities for future research. The relevant literature was identified through searches of PubMed, Embase, Scopus, Web of Science, Google Scholar, and ClinicalTrials.gov using related keywords and phrases. The available evidence suggests that EC modalities may influence neuro-metabolic and autonomic pathways relevant to glucose regulation, energy balance, inflammation, and other components of MetS. However, the strength of the evidence varies across interventions and outcomes. Interpretation of clinical findings is complicated by heterogeneous stimulation protocols and the frequent co-administration of dietary interventions, exercise, weight-management strategies, or interventions associated with substantial weight loss. These factors limit the ability to isolate the independent effects of neuromodulation. Further challenges include the absence of standardized stimulation parameters, uncertainty regarding optimal treatment protocols, potential adverse effects, and limited long-term clinical evidence. Accordingly, ECs should currently be considered investigational approaches rather than established treatments for MetS. Well-designed long-term clinical trials are needed to determine their efficacy, safety, durability, and optimal therapeutic parameters.

Keywords: metabolic syndrome; electroceutical; bioelectricity; obesity; brain-derived neurotrophic factor



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1. Introduction

Bioelectronic medicine (BEM) and its subset, electroceuticals (ECs), are medical disciplines that employ electrical stimulation of organs to treat diseases and improve health [1,2]. Bioelectric signaling influences many metabolic processes, mainly ion and metabolite transport and electrochemical synapses, and its modulation can modify pathogenesis [3,4]. EC modalities can be classified according to the energy type, namely electrical, magnetic, electromagnetic, optogenetic/photostimulatory, and focused ultrasound, or based on delivery/target, including invasive and noninvasive tools for the nervous system [1–3]. External nerve stimulation alters cellular membrane potential and triggers sequential changes at the cellular and systemic levels [1]. In fact, neural stimulation can alter cellular bioelectric signaling, presenting changes in excitability, function, production, and survival of cells [1,2].

For this review, ECs are defined as therapeutic interventions that intentionally deliver externally or internally generated electrical, electromagnetic, or bioelectrically mediated stimulation to a defined biological target to produce a reproducible physiological or therapeutic effect. The target may be a central or peripheral neural structure, autonomic nerve, neuromuscular tissue, vascular sensor, or another metabolically relevant tissue. Under this definition, ECs refer to the therapeutic intervention, not simply the presence of endogenous bioelectricity within the target tissue. This operational definition has three essential elements: (1) intentional delivery of an externally controlled bioelectrical, electrical, electromagnetic, or electrostatic stimulus; (2) application to a defined anatomical or physiological target; and (3) an intended biological or therapeutic effect that can be assessed using physiological, metabolic, or clinical outcomes. Accordingly, studies describing endogenous bioelectric signaling without therapeutic stimulation were not considered studies of ECs, although such mechanisms are discussed when they provide a biological rationale for electroceutical interventions.

In sum, ECs can be classified according to the physical energy delivered, anatomical target, mode of action, and invasiveness. In the present review, the core EC framework comprises (i) direct electrical stimulation, in which electrodes deliver controlled electrical currents or pulses to neural, muscular, or other biological targets; (ii) electromagnetic stimulation, in which therapeutic effects are produced through externally applied or induced electric or magnetic fields, including transcranial magnetic stimulation (TMS), repetitive TMS (rTMS), and pulsed electromagnetic field therapy (PEMF); and (iii) electrical neuromodulatory blockade or inhibition, exemplified by vagal nerve blockade (vBloc). Within these categories, interventions may be invasive, minimally invasive, or noninvasive and may target the central nervous system, peripheral nerves, autonomic pathways, skeletal muscle, or other metabolically relevant tissues. This framework is intended to distinguish mechanistically heterogeneous modalities while retaining their common feature of deliberate, device-mediated modulation of biological function using controlled electrical or electromagnetically induced energy.

Within this framework, direct electrical stimulation includes implanted and noninvasive interventions such as deep brain stimulation (DBS), vagus nerve stimulation (VNS), transcutaneous or transcutaneous auricular vagus nerve stimulation (tVNS/taVNS), transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), cranial electrotherapy stimulation (CES), electroconvulsive therapy (ECT), transcutaneous electrical nerve stimulation (TENS), electrical muscle stimulation (EMS), neuromuscular electrical stimulation (NMES), whole-body electromyostimulation (WB-EMS), baroreflex activation therapy (BAT), gastric electrical stimulation, and electroacupuncture (EA) [1–3,5,6]. Electromagnetic stimulation includes TMS, rTMS, and PEMF, while low-frequency electrostatic field (LFEF) stimulation is considered within the broader field-

based category. vBloc represents a distinct inhibitory form of electrical neuromodulation in which electrical energy is used to reversibly reduce vagal neural transmission rather than to produce conventional neural excitation. In contrast, photobiomodulation, optogenetic stimulation, and focused ultrasound are not classified as core EC modalities in this review because their primary therapeutic energy is optical or acoustic rather than electrical or electromagnetically induced [1,2,7]. These approaches are considered adjacent technologies within the broader field of bioelectronic and device-based medicine. This distinction is important because the modalities reviewed here differ substantially in mechanism, anatomical target, invasiveness, waveform, stimulation intensity, frequency, treatment duration, and clinical purpose; consequently, their metabolic effects should not be interpreted as interchangeable.

To sum up, electroceutical modalities can be classified along several complementary dimensions rather than by energy type alone (Figure 1). The first dimension is the physical mode of stimulation, which includes direct electrical stimulation, magnetic induction, electromagnetic fields, and electrostatic fields. The second is the anatomical target, which may be central nervous system structures, peripheral or autonomic nerves, skeletal muscle, vascular sensors, or broader tissue-level targets. The third is invasiveness, ranging from implanted interfaces to noninvasive surface or field-based approaches. The fourth is the intended physiological effect, including neural excitation or inhibition, autonomic modulation, neuromuscular activation, conduction blockade, vascular modulation, or metabolic regulation. Finally, stimulation parameters, including amplitude or field strength, frequency, pulse width, waveform, duty cycle, treatment duration, and anatomical targeting, must be considered because two interventions belonging to the same broad class may produce substantially different biological effects. Therefore, EC modalities are heterogeneous and should not be regarded as a single mechanistic class. For conceptual clarity, we classify the modalities considered in this review according to the physical energy delivered, the biological target, and the mode of intervention.

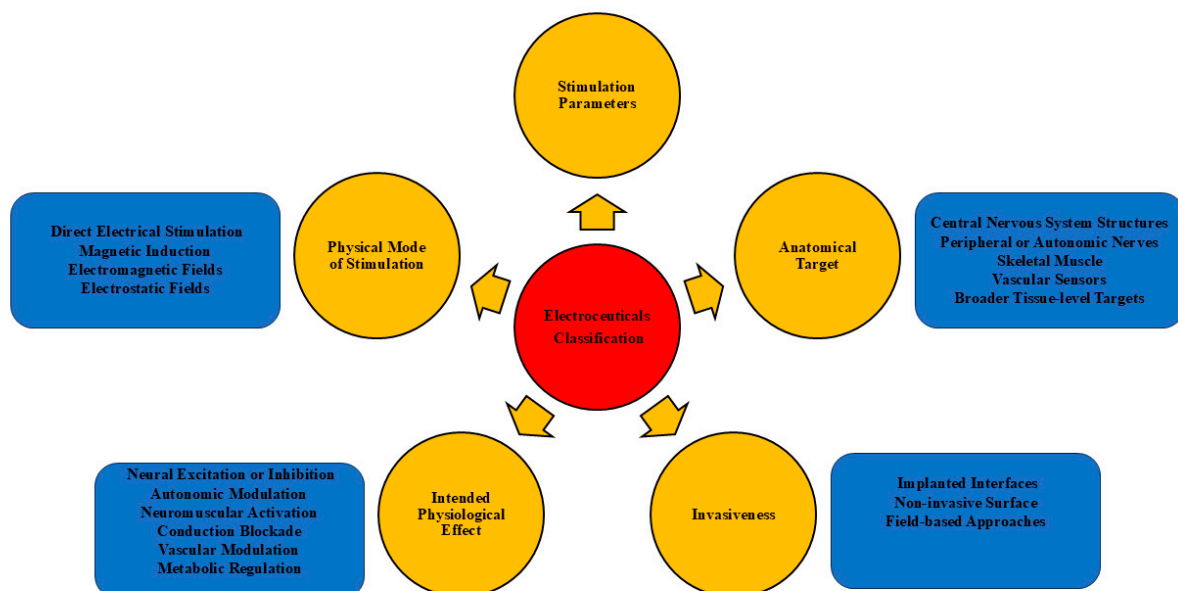


Figure 1. Basis of various electroceutical classifications. Electroceuticals can be categorized based on the physical mode of stimulation, anatomical target, physiological effects, invasiveness, and stimulation parameters. The subcategories of each category are listed in the blue box next to it.

Within this framework, electrical stimulation delivered through implanted electrodes includes DBS and implanted VNS, whereas surface electrical stimulation includes tVNS/taVNS, TENS, tDCS, tACS, CES, EMS, and NMES. TMS is classified separately as magnetic neuromodulation because its therapeutic effect is mediated by an externally generated magnetic field which induces electrical currents in neural tissue. PEMF and LFEF are classified as non-contact field-based EC approaches because they deliver electromagnetic or electrostatic energy without direct electrode-mediated current flow through the target tissue. EA is classified as a specialized peripheral electrical stimulation approach in which current is delivered through acupuncture needles. Vagal blockade is considered a distinct electroceutical strategy because its intended therapeutic effect is neural conduction blockade rather than excitation. This classification is employed throughout the present review to avoid treating these modalities as interchangeable interventions.

The present review does not treat all forms of bioelectrical or physical stimulation as mechanistically equivalent. Rather, it employs the term *electroceutical* as an umbrella therapeutic designation while explicitly distinguishing modalities according to energy modality, anatomical target, invasiveness, stimulation mechanism, and clinical purpose. This framework is particularly relevant to metabolic syndrome (MetS), in which candidate targets range from central metabolic circuits and autonomic nerves to skeletal muscle, vascular sensors, and metabolically active peripheral tissues.

BEM has a long history and dates back to ancient civilizations, particularly Greece and Egypt, when electric fish were used therapeutically for pain and arthritis [8] (Figure 2). In the 18th and 19th centuries, electrical devices replaced these living sources of electricity. During this period, experiments dubbed as *Galvani* demonstrated the effects of electricity on animals, and the foundations of electrical priming and neuromodulation were established [9]. The 19th century saw a major expansion of electrotherapy for psychiatric disorders and pain management [10–12]. The mid-nineteenth century saw the use of artificially generated electrical currents to control pain and paralysis [12]. In the 1930s, the development of external cardiac pacing concepts began [13], which in the 1950s led to the fabrication of the first implantable human pacemaker [14]. It was not until 1967 that the first clinical trials of DBS and spinal cord stimulation (SCS) for chronic pain and movement disorders were conducted, and the therapeutic effectiveness of DBS began to be discussed [15,16]. In the 1960s and 1970s, experiments were conducted on electrical brain stimulation to treat psychiatric, motor, and pain disorders, as well as early tDCS [17,18]. VNS was first used in 1974 for epilepsy, and later DBS became a therapeutic option for Parkinson's disease and tremors between 1987 and 1990 [15,19,20]. From the 1970s to 1990s, the impact of SCS on pain control was further developed, and the need for improved implant hardware became more apparent [21,22]. The 1980s–1990s saw an increasing emphasis on hardware engineering and optimizing implantation techniques. During this period, peripheral nerve stimulation and SCS made significant advances in pain management, besides advances in DBS programming, especially for Parkinson's disease and essential tremor [20,23–25]. Collectively, these basic and empirical studies contributed to the rapid expansion and advancement of ECs and BEM from 2000 onward (*vide infra*).

In 1997, VNS received premarket approval (PMA) from the Food and Drug Administration (FDA) for epilepsy; it was the first peripheral EC device approved for neuromodulation of a central nervous system disorder [3,26,27]. In the 2000s, increasing attention was directed toward functional neuromodulation for the treatment of depression, cognitive impairment, and post-stroke recovery, and closed-loop neuromodulation and responsive devices (e.g., responsive neurostimulation) were introduced during this period to improve therapeutic precision and efficacy [28,29]. The first FDA clearance for noninvasive EC therapies for treatment-resistant depression was rTMS in 2008 [30]. Another device that received

FDA 510(k) clearance in 2013 for drug-resistant major depressive disorder is BrainsWay Deep TMS [31]. In the 2020s, the field has increasingly focused on improving functionality and general usability, including customized miniaturized design, more precise targeting, repurposing, biomarker-guided treatment, and new therapeutic indications for cognitive, immune, and metabolic disorders.

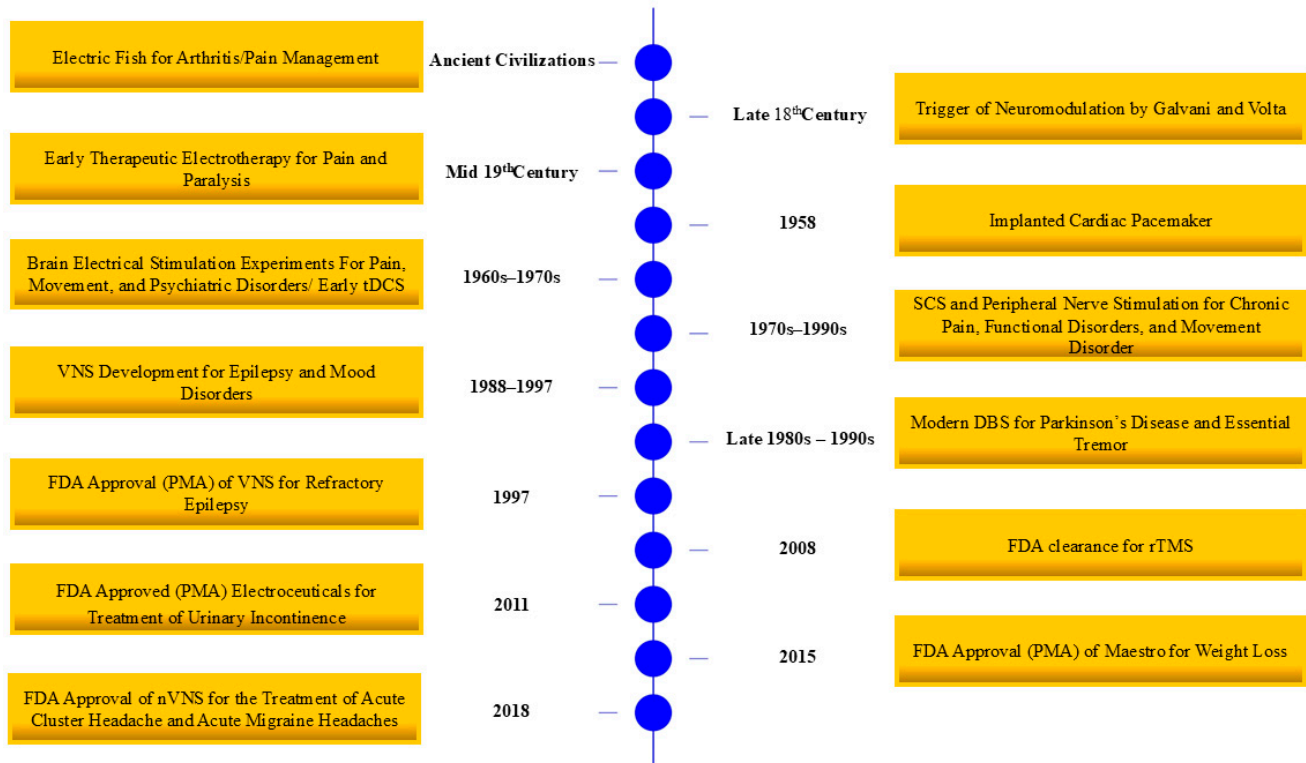


Figure 2. Timeline of key electroceuticals (EC) milestones. The timeline summarizes the most important periods of time in the advancement of ECs. DBS: deep brain stimulation; FDA: Food and Drug Administration; rTMS: repetitive transcranial magnetic stimulation; SCS: spinal cord stimulation; nVNS: noninvasive VNS; tDCS: transcranial direct current stimulation; VNS: vagus nerve stimulation.

Despite the FDA-PMA history for VNS in 1997, the applications of ECT are not limited to direct neurological diseases and include more recent applications (*vide infra*). The FDA approved VNS under PMA in 1997 and 2005 for treatment-resistant epilepsy and depression, respectively [3]. Intermittent theta-burst stimulation (iTBS) received FDA clearance for major depressive disorder in individuals with no significant improvement from their previous antidepressant medication [3], DBS received FDA approval under PMA for Parkinson's disease [3], the InterStim system was FDA-approved (PMA) for the treatment of urinary incontinence [26]. Deep transcranial magnetic stimulation (dTMS) received FDA clearance for depression and obsessive-compulsive disorder [32]. Pain management through neuromodulation via SCS is another FDA-approved application under PMA [32]. Noninvasive VNS (nVNS) received FDA clearance for the treatment of acute cluster headache and acute migraine headaches in 2018 [33]. The Maestro rechargeable system received FDA PMA approval in 2015 for weight reduction in adults meeting specified BMI and obesity-related comorbidity criteria; its mechanism is vagal block therapy; however, the PMA was withdrawn in 2021, and this historical regulatory authorization should not be interpreted as evidence of a current FDA-approved indication for MetS [26]. The Medtronic Enterra device received FDA authorization under a Humanitarian Device Exemption (HDE; H990014) for gastroparesis-associated refractory nausea/vomiting by

gastric electrical stimulation; therefore, it should not be interpreted as an FDA-approved indication for metabolic syndrome or diabetes [26]. Overall, it should be mentioned that FDA regulatory authorization of a device for a neurological, cardiovascular, gastrointestinal, pain, or obesity-related indication does not establish regulatory authorization for its use in MetS.

Recent advances have substantially transformed peripheral ECs. These developments include (1) high-density, multi-contact nerve interfaces that enable fascicle-level selectivity and reduce off-target activation [34]; (2) chronically stable, soft conductive coatings and hydrogels that lower impedance and attenuate foreign-body responses, thereby maintaining long-term signal quality [35]; (3) miniaturization and wireless, battery-free power-delivery strategies (magnetolectric or ultrasonic powering of millimetric implants) that allow less invasive placement near peripheral targets [36]; (4) closed-loop sensing and control algorithms that use neural or physiological biomarkers to adapt stimulation in real time, enhancing efficacy and reducing side effects [37]; and (5) new stimulation modalities and waveform strategies, notably Kilohertz-frequency conduction block and optimized multi-contact waveforms, along with emerging optical/optogenetic methods for fiber-type specificity, which together enable selective excitation or reversible blockade of peripheral fibers [38]. These innovations in neural interfaces, materials, power/packaging, algorithms, and waveforms form the current technical foundation for precise, durable peripheral EC therapies. The application of these technologies to MetS has attracted increasing attention in recent years. Against this background, this review aims to comprehensively examine the development of ECs in relation to MetS, with particular emphasis on relevant neuro-metabolic pathways, available clinical and preclinical evidence, technical challenges, and recent technological advances. Importantly, this review also considers the current limitations of the evidence base and the extent to which existing findings support future clinical translation of EC approaches in MetS.

2. Search Strategy and Scope of the Review

This article is a narrative review and was not designed or reported as a systematic review or meta-analysis. Nevertheless, we performed a structured, transparent literature search to identify relevant evidence on ECs, BEM, neuromodulation, electrical and electromagnetic stimulation, and their potential applications in MetS and related metabolic disorders. The search was conducted in PubMed, Embase, Scopus, Web of Science, Google Scholar, and ClinicalTrials.gov. The databases were searched from inception to September 2026.

Because the scope of ECs relevant to MetS extends beyond VNS and general neuromodulation, the search strategy incorporated modality-specific terms representing the interventions subsequently discussed in this review. These included, but were not limited to, VNS, transcutaneous vagus nerve stimulation (tVNS/taVNS), vBloc, BAT, TMS/rTMS/iTBS/dTMS, transcranial direct and alternating current stimulation (tDCS/tACS), EMS, NMES, WB-EMS, TENS, EA, PEMF, LFEF, mild electrical stimulation, gastric electrical stimulation, spinal cord stimulation, deep brain stimulation, and other relevant forms of peripheral or central neuromodulation. Search terms related to the metabolic context included MetS, obesity, central obesity, adiposity, insulin resistance, type 2 diabetes mellitus (T2DM), impaired glucose tolerance, hyperglycemia, dyslipidemia, hypertension, blood pressure, glucose metabolism, lipid metabolism, inflammation, energy expenditure, appetite, and brain-derived neurotrophic factor (BDNF).

The principal conceptual structure of the search combined three domains: (1) electroceutical, bioelectronic, neuromodulatory, electrical, magnetic, or electromagnetic interventions; (2) MetS and its major metabolic components; and (3) relevant neuro-metabolic

mechanisms, including BDNF and autonomic or neuroimmune pathways. A representative conceptual search structure was therefore:

([electroceutical* OR “bioelectronic medicine” OR bioelectric* OR neuromodulat* OR “electrical stimulation” OR “electrical muscle stimulation” OR EMS OR “neuromuscular electrical stimulation” OR NMES OR “whole-body electromyostimulation” OR WB-EMS OR “transcutaneous electrical nerve stimulation” OR TENS OR “vagus nerve stimulation” OR VNS OR “transcutaneous vagus nerve stimulation” OR tVNS OR taVNS OR “vagal nerve blockade” OR vBloc OR “baroreflex activation therapy” OR BAT OR “transcranial magnetic stimulation” OR TMS OR rTMS OR iTBS OR dTMS OR “transcranial direct current stimulation” OR tDCS OR “transcranial alternating current stimulation” OR tACS OR electroacupuncture OR “electro-acupuncture” OR “pulsed electromagnetic field*” OR PEMF OR “low-frequency electrostatic field*” OR LFEF OR “gastric electrical stimulation” OR “spinal cord stimulation” OR “deep brain stimulation” OR “peripheral nerve stimulation”) AND (“metabolic syndrome” OR “metabolic syndrome X” OR obesity OR “central obesity” OR adiposity OR “insulin resistance” OR “type 2 diabetes” OR “impaired glucose tolerance” OR hyperglycemia OR dyslipidemia OR hypertension OR “blood pressure” OR “glucose metabolism” OR “lipid metabolism” OR inflammation OR “energy expenditure” OR appetite OR BDNF OR “brain-derived neurotrophic factor”).

ClinicalTrials.gov was searched using combinations of intervention- and condition-related terms to identify relevant completed, ongoing, and registered clinical studies that could provide additional information on emerging EC applications in metabolic disorders.

In addition to database searching, reference lists of relevant primary studies and review articles were manually screened to identify potentially eligible publications not retrieved by the electronic searches.

The screening process consisted of an initial screening of retrieved records based on title and abstract, followed by full-text assessment of potentially relevant publications. Duplicate records were removed. Publications were retained when they addressed an EC, electrical, magnetic, electromagnetic, or neuromodulatory intervention with a relevant metabolic, neurophysiological, autonomic, inflammatory, or mechanistic outcome. For this narrative review, particular emphasis was placed on studies directly involving individuals with MetS. Evidence from populations with individual components or closely related metabolic disorders, including obesity, insulin resistance (IR), T2, hypertension, dyslipidemia, and metabolic dysfunction-associated steatotic liver disease (MASLD), was considered separately as indirect or component-specific clinical evidence. Preclinical animal and in vitro studies were included when they provided relevant mechanistic or translational evidence concerning neuro-metabolic regulation or the biological effects of EC interventions.

Eligible publication types included original research articles, clinical trials, randomized and non-randomized studies, observational studies, preclinical studies, systematic reviews, and high-quality narrative reviews when these provided relevant mechanistic, clinical, historical, or technological information. Human, animal, and in vitro studies were considered because the objectives of this review included both clinical evidence and mechanistic understanding of EC-mediated metabolic regulation. Duplicate reports and publications with insufficient relevance to the review objectives were excluded. Only full-text publications in English were considered.

The evidence was subsequently organized into three categories according to its relevance to MetS: (1) direct clinical evidence involving participants with MetS; (2) clinical evidence addressing individual components or closely related metabolic disorders; and (3) preclinical or experimental mechanistic evidence. This categorization was employed to

differentiate evidence directly applicable to MetS from evidence that is mechanistically or translationally relevant but does not directly establish efficacy in MetS.

Study selection was based on relevance to the objectives and clinical relevance. This narrative review aims to provide a broad and integrated overview of the development of ECs in relation to MetS, with particular emphasis on relevant neuronal and neuro-metabolic pathways, clinical and preclinical evidence, technical challenges, and emerging technological advances.

3. Overview of Metabolic Syndrome and Its Electroceuticals

An Overview of Metabolic Syndrome

The development of MetS, syndrome X, is influenced by genetics, modern hypokinetic and sedentary lifestyle, high-calorie diet, sleep disorders, noise pollution, aging, and sociocultural conflicts [39]. Epidemiological studies presented a prevalence rate of 14 to 39% for this disease [40,41]. Major agencies have defined coherent diagnostic criteria for MetS in different ways [41,42]. For instance, according to the National Cholesterol Education Program and Adult Treatment Panel III, the presence of 3 out of 5 factors in an individual is essential as a diagnostic criterion for this syndrome: 1. Waist circumference: men ≥ 102 cm (40 in) and women ≥ 88 cm (35 in), 2. Triglycerides: ≥ 150 mg/dL (1.7 mmol/L), 3. High-density lipoprotein cholesterol: men < 40 mg/dL (1.04 mmol/L) and women < 50 mg/dL (1.29 mmol/L), 4. Blood pressure: systolic ≥ 130 mmHg and/or diastolic ≥ 85 mmHg, 5. Fasting plasma glucose: ≥ 110 mg/dL (6.1 mmol/L); however, the corrected value has been updated to ≥ 100 mg/dL (5.6 mmol/L). MetS is a multisystem disorder involving multiple organs and physiological pathways, while its major complications include central obesity [43], ectopic fat accumulation [44], IR [45], and T2 [46], cardiovascular diseases [47], non-alcoholic fatty liver [43], neurohormonal regulatory disorders [48] (Figure 3). Inflammatory conditions occurring in MetS [49] and other molecular changes, including BDNF and cerebral/blood supply [50], polycystic ovary syndrome [51], and even Alzheimer's disease (AD) [52], are not far from being expected. Collectively, the multisystem nature of MetS and the involvement of interconnected neural, endocrine, metabolic, and inflammatory pathways provide a rationale for investigating novel bioelectronic approaches. However, whether BEM-based interventions can provide clinically meaningful benefits in MetS remains to be established through rigorous clinical research.

After Kyler identified the relationship between hypertension, hyperglycemia, and gout; Vague emphasized the component of obesity and metabolic disorders in 1947, and about 40 years later, Reaven proposed 'Syndrome X' for a set of metabolic disorders centered on IR, not obesity [41]. In 1989, Kaplan added the obesity factor to Kyler's proposal and named this syndrome the 'Deadly Quartet' [41]. The naming of MetS as 'IR syndrome' finally happened in 1992 [41,53]. Routine treatment for MetS is currently mainly symptomatic, involves lifestyle improvement, and pharmacological interventions are directed toward specific components of MetS, such as antihypertensive drugs [54], beta blockers [39], angiotensin-converting enzyme inhibitors [54], diuretics [39], statins [54], hypoglycemic agents like thiazolidinediones [54], fibrates [54], bile acid sequestrants [39], niacin [39], rapamycin [39], metabolic/bariatric surgical interventions [55], device-based therapies, molecular/gene therapy, and EC [39]. Therefore, it is necessary to explore the etiology and novel therapies that address the causes of this syndrome.

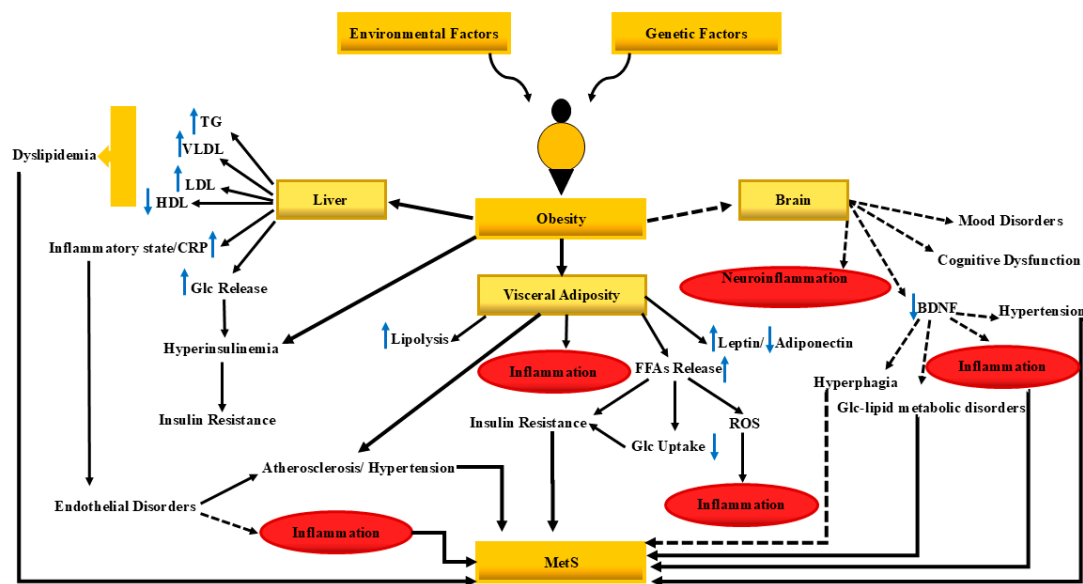


Figure 3. Proposed pathological mechanisms linking metabolic dysfunction, inflammation, and central nervous system alterations in metabolic syndrome (MetS). Schematic representation of established and proposed interactions contributing to MetS and its associated metabolic and neurobehavioral alterations. Visceral adiposity is associated with increased free fatty acid release, chronic low-grade inflammation, and insulin resistance, which may contribute to dyslipidemia, hyperglycemia, endothelial dysfunction, and hypertension. Metabolic and inflammatory signals may also influence the central nervous system and have been associated with neuroinflammation, altered BDNF signaling, cognitive dysfunction, and mood-related disturbances. The bidirectional communication between peripheral organs and the central nervous system highlights potential neuromodulatory targets for electroceutical therapies aimed at improving metabolic regulation and reducing inflammation. Importantly, not all pathways depicted represent established causal relationships. BDNF, brain-derived neurotrophic factor; CRP, C-reactive protein; FFAs, free fatty acids; Glc, glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ROS, reactive oxygen species; TG, triglyceride; VLDL, very low-density lipoprotein. Note: Solid arrows represent relationships supported by established human/clinical and/or strong pathophysiological evidence, whereas dashed arrows represent relationships supported predominantly by mechanistic, associative, or preclinical evidence and should not be interpreted as established causal relationships. ↑ indicates an increase or upregulation, whereas ↓ indicates a decrease or downregulation in the corresponding biological parameter.

4. Electroceuticals: From Neurobioelectronic Regulation of Intermediary Metabolism to Metabolic Syndrome

Glucose metabolism and blood sugar regulation are closely linked to bioelectric signaling, as glucose metabolism in beta cells increases the ratio of adenosine triphosphate (ATP) to adenosine diphosphate (ADP), which causes the closure of ATP-sensitive potassium channels (K_{ATP}) and membrane depolarization [56]; voltage-gated calcium channels (Cav) then open, which causes calcium cation (Ca²⁺) entry and insulin granule exocytosis [56]. Insulin sensitivity and glucose uptake by muscle cells, which are essential for maintaining glucose homeostasis, are regulated by membrane excitability and Ca²⁺ handling [57]. Normal lipid metabolism is dependent on the proper functioning of bioelectricity-dependent events, for example, lipolysis and adipokine (leptin and adiponectin) secretion; activities of metabolic enzymes in adipocytes and hepatocytes are controlled by intracellular Ca²⁺ signaling regulated by ion channels such as transient receptor potential (TRP) channels and Cav [58]. Therefore, appropriate regulation of bioelectric signaling is important for basic cell function.

The electrical and chemical synapses are dependent on bioelectricity, and this is crucial for transmission of central metabolic regulatory messages to organs via peripheral nerves.

Sensory vagus afferents induce satiety, prevent overeating, and regulate glucose homeostasis [59]. These signals arise from mechanical signals from gastric distension, chemical signals from gut hormones, and inflammatory signals from the gut, liver, and adipose tissue, which are conveyed to the brainstem [60]. Hepatic glucose production, insulin secretion, and gut motility are under the control of efferent vagal activity, and dysfunctions in this pathway may contribute to pro-inflammatory conditions, IR, or glucose intolerance [60]. Thus, these afferent and efferent nervous systems, by transmitting adipose and enteric messages including cholecystokinin and glucagon-like peptide-1 (GLP-1) to the hypothalamus and brainstem, can regulate glucose production, hepatic gluconeogenesis, adipose tissue lipolysis, brown adipose tissue thermogenesis, insulin secretion, gastric emptying rate, and even satiety duration [61–63]. Notably, neuroimmune cholinergic anti-inflammatory processes can reduce inflammation and its complications, such as atherosclerosis and IR [64,65].

The sympathetic nervous system, through its innervation of the vasculature, liver, pancreas, and adipose tissue, plays a regulatory role in blood pressure, hepatic glucose output, and lipolysis [66,67]. In stressful conditions and sympathetic hyperactivity, an increase in blood pressure, stimulation of lipolysis, and blood sugar disorders may occur [68,69]. In conclusion, maintaining an appropriate balance of autonomic peripheral nerve signaling is vital for metabolic processes, and any malfunction of this system can lead to secondary metabolic disorders. These above-mentioned physiological relationships provide a biologically plausible rationale for investigating neuromodulation as a means of influencing metabolic processes relevant to MetS. However, the existence of such regulatory connections does not, by itself, demonstrate that electrical modulation of these pathways produces clinically meaningful improvement in the overall MetS phenotype.

For normal and efficient metabolism, not only the health of the endocrine glands and nerves individually, but also their proper relationship and the neuroendocrine axes (e.g., hypothalamic–pituitary–adrenal and hypothalamic–pituitary–thyroid axes) are coordinated interactions [69]. Therefore, correcting dysfunctions within these neuroendocrine pathways may significantly improve the metabolic status. Bioelectricity may regulate metabolic processes and energy supply since it contains central neural circuits located in the hypothalamus, brainstem centers, mesolimbic dopamine system, and limbic structures [70–72]. These centers integrate afferent inputs with hormonal signals of GLP-1, leptin, ghrelin, and insulin [71,72]. The encoding of hormonal signals, nutrient sensing, appetite, ingestive motivation, glucose-gut-brain signaling, and signaling originating from peripheral nerves are governed centrally [71,72]; therefore, dysregulation of these centers can give rise to hyperphagia, weight gain, and metabolism-driven behavioral disorders. Neurotransmitters and neuromodulators, including serotonin, dopamine, acetylcholine, norepinephrine, and neuropeptides such as orexin, neuropeptide Y (NPY), alpha-melanocyte-stimulating hormone, and activation of agouti-related peptide (AgRP), can influence neuronal activity and downstream peripheral metabolic organs [55,71,72]. Neural firing rate, burst patterns, and oscillatory synchronization encode metabolic states [73]. All neurotransmitter reuptake [74,75], cellular ionic homeostasis [76], and cellular reactions to metabolic processes, inflammation, and toxic substances are regulated by astrocytes and other glial cells [55]. Therefore, EC interventions on the brain and spinal cord may regulate metabolism and influence MetS through modifying both neuronal and non-neural circuits. Accordingly, EC modulation of these neuroendocrine pathways should currently be considered a potential mechanism of action rather than an established therapeutic mechanism for the treatment of MetS.

Interestingly, EC interventions modulate BDNF, an imperative regulator of neuro-metabolic functions. This neurotrophin supports neuronal survival and neuronal func-

tion [77] and controls metabolic processes [78]. BDNF transcription and secretion are influenced by neuronal depolarization and calcium influx through voltage-gated Ca^{2+} channels and N-methyl-D-aspartate receptors [79]. In addition, BDNF and its specific receptor, tropomyosin receptor kinase B participate in the regulation of ion channels and metabolism [78]. Centrally, BDNF modulates the activity of anti-inflammatory pro-opiomelanocortin and appetitive AgRP/NPY neurons, and its consequences include reduced food intake [80] and increased energy expenditure, enhanced satiety signaling, and altered motivational aspects of ingesting behavior [81]. The peripheral effects of BDNF are related to energy expenditure [81], thermogenesis [80], anti-inflammatory effects [82], peripheral insulin sensitizing [81], and reduced hepatic glucose production [83]. BDNF improves mitochondrial ATP synthesis for cellular ion pumps, membrane potentials, and cellular excitability [84]. Evidently, reduced BDNF levels lead to hyperphagia, obesity, reduced energy expenditure, and impaired glucose homeostasis, which reflects its lower levels in patients with MetS, DM, and obesity [85]. Exercise or intake of some antidepressants increases BDNF levels, which highlights its lower levels in depressed individuals [86]. The changes in BDNF signaling have also been associated with many neurometabolic diseases, such as MetS and AD [50–87]. Some of the literature points to various ECs that enhance BDNF signaling following DBS [88], and rTMS [89]. These observations provide a biologically plausible rationale for considering BDNF-related signaling as one of several pathways potentially influenced by neuromodulation. However, the available evidence should be interpreted cautiously, because evidence that EC interventions modify BDNF has largely been obtained in neurological or psychiatric conditions rather than in patients with MetS. In sum, these findings support the possibility that BDNF signaling may be responsive to neuromodulation, but they do not establish that EC-induced modulation of BDNF improves MetS or its individual diagnostic components.

Accordingly, BDNF should currently be regarded as a candidate mechanistic biomarker or potential pathway of interest rather than an established therapeutic target for MetS. Future studies should determine whether EC-induced changes in BDNF are reproducible in individuals with MetS, whether they are temporally related to changes in clinically relevant metabolic outcomes, and whether modulation of BDNF contributes causally to therapeutic benefit.

The manipulation of bioelectricity for reprogramming of metabolism seems reasonable concerning experimental studies, and it possibly could trigger a cascade of therapeutic effects; for instance, electrical stimulation of carotid baroreceptors, hypothalamus, vagus nerve, gastric areas, and muscles can trigger a cascade of neurometabolic events, such as regulation of appetite, brain reward system and emotional behavior, hepatic glucose production, insulin secretion, lipolysis, thermogenesis, and inflammation [90]. This electrical manipulation has been investigated as a potential means of influencing physiological processes relevant to MetS, including controlling blood pressure, improving blood sugar and lipid profile, reducing inflammation, and decreasing appetite [27]. However, evidence that these effects translate into clinically meaningful and durable improvements in MetS remains limited and requires further validation. The ECs also have been investigated for their potential effects as anti-inflammatory, anti-apoptotic agents, and changes in metabolism, especially brain glucose access through DBS or tDCS techniques [91–93]. Taken together, these findings provide mechanistic rationale for further investigation about controlling inflammatory and metabolic pathways by ECs but do not, by themselves, establish ECs as clinically effective treatments for MetS.

To summarize, ECs are being investigated as a potential new therapeutic approach in MetS in several ways, including multi-axis modulation, balanced energy intake, glucose and lipid metabolism, autonomic system-related responses, systemic inflammation, induced

neurotrophic signaling, specifically BDNF [2,94], programmability, temporal precision, and access to deep neural targets (Figure 4). These observations suggest that bioelectric modulation could potentially influence several components of MetS. Notably, ECs could be considered as a possible approach for MetS, and their potential effects on modifying the individual's behavioral responses, such as greater interest and motivation for exercise or dietary choices, can be the subject of future studies. Nevertheless, the presence of an experimentally modifiable pathway should not be equated with demonstrated clinical efficacy. The magnitude, reproducibility, and clinical relevance of these effects vary according to the stimulation modality, anatomical target, stimulation parameters, and population studied. Therefore, current evidence supports the investigation of bioelectric modulation as a potential therapeutic strategy, but does not yet establish that ECs can reliably improve the overall MetS phenotype. In other words, at present, direct clinical evidence demonstrating that ECs improve the overall MetS phenotype remains limited. Accordingly, ECs may be considered an emerging and potentially complementary therapeutic approach, but their clinical efficacy for MetS remains to be established.

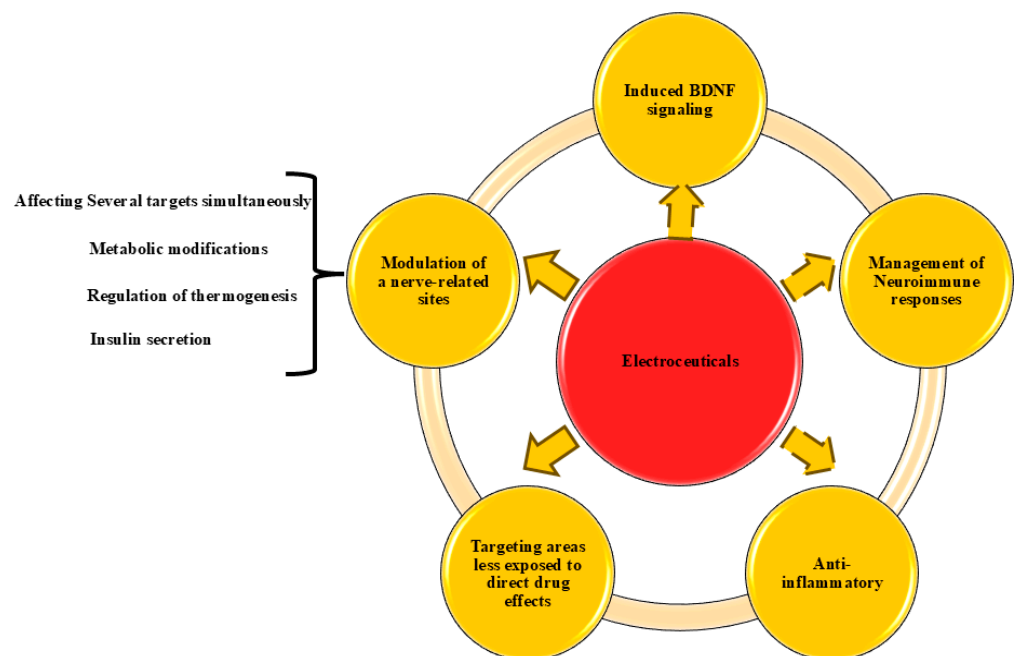


Figure 4. Proposed multimodal mechanisms and potential therapeutic effects of electroceuticals (ECs) in metabolic syndrome (MetS). Schematic overview of proposed mechanisms through which electroceutical therapies may influence metabolic and inflammatory pathways relevant to MetS. Depending on the modality and target, ECs may modulate neural circuits involved in metabolic regulation, influence BDNF-related signaling, and affect neuroimmune and inflammatory responses. Preclinical studies suggest that the modulation of these pathways may influence physiological processes including metabolism, thermogenesis, appetite regulation, and insulin secretion. The strength and level of evidence supporting individual pathways vary, and the mechanisms depicted should not be interpreted as uniformly established causal relationships. BDNF, brain-derived neurotrophic factor. Note: Solid arrows indicate mechanisms or targets supported by established neurostimulation evidence, whereas dashed arrows indicate mechanisms supported predominantly by preclinical or mechanistic evidence.

5. Technical Development and Challenges in Electroceutical Design: Overview

EC-based interventions are being investigated for their ability to modulate physiological processes; however, they carry specific risks and technical challenges that must be addressed to determine whether EC systems can achieve safe, reproducible, and clinically

significant effects. In this context, radiofrequency and some electromagnetic modalities can produce tissue heating and tissue property changes; *electrome* anatomy, electrode and device geometry, and electromagnetic exposure parameters must be carefully evaluated in any conceptual design and optimization of EC systems [2]. Adverse effects of ECs across modalities include infection, hematoma, pulmonary embolism, respiratory issues, transient cognitive decline, headaches, voice changes, and neuropsychiatric outcomes [2,3,33]. Technically, device design and reliability are also important. Implants and stimulators face hardware failure modes (lead breakage, battery depletion, encapsulation) and software issues (bugs, connectivity loss) [2,33]. High treatment and device costs are a general consideration in nearly all types of EC design [3]. More biocompatible, resilient, and recyclable materials are desirable to reduce foreign-body reactions, biofouling, and long-term failure.

Technical progress in ECs has moved from large, open-loop stimulators toward compact, target-specific systems that integrate sensing, stimulation, and communication [95]. Early devices focused on delivering safe, reproducible pulses to relatively accessible nerves; present-day efforts prioritize precision targeting, programmable waveforms, and compatibility with ambulatory use [96]. The engineering challenge is to deliver therapeutically effective electrical doses while minimizing off-target effects, power consumption, and device footprint. Therefore, progress in microfabrication, low-power electronics, and materials science strengthens advancement.

The electrode–tissue interface is a crucial hardware element that determines selectivity, efficacy, and longevity of stimulation, and designs range from cuff and penetrating micro-electrodes to conformable surface arrays [97]. Key technical goals are to maximize charge transfer efficiency, reduce impedance and inflammatory encapsulation, and maintain stable contact despite tissue motion [98]. Novel geometries (e.g., multi-contact cuffs, thin-film arrays) and surface coatings (e.g., conductive polymers, porosity-enhancing treatments) improve stimulation selectivity and long-term performance [99]. Device developers must balance invasiveness against precision, as more selective interfaces often require more complex implantation techniques and surgical approaches.

Beyond simple pulse amplitude and frequency, modern ECs exploit a broad parameter space including waveform shape, pulse width, burst patterns, and inter-pulse timing to tune neural recruitment and therapeutic outcomes [100]. Optimization requires understanding the electrophysiology of the target (fiber types, conduction velocities, and refractory dynamics), and may employ computational models to predict which parameters preferentially activate desired pathways while minimizing activation of neighboring structures [101]. Energy-efficient waveforms and staggered multi-site stimulation strategies can reduce battery drain and side effects [102]. Standardizing parameter reporting and dose metrics is essential for comparing studies and translating protocols between systems.

The precise targeting of neural structures is essential for reproducible metabolic effects, but autonomic nerves are often small anatomical entities intertwined with other fibers [103]. Advances in intraoperative mapping (electrophysiologic recording, evoked potentials), imaging co-registration (ultrasound, magnetic resonance imaging), and neuronavigation tools have improved localization and reduced implantation variability [104]. For noninvasive approaches, biomarker-guided positioning (e.g., heart-rate variability, reflex responses) helps identify effective stimulation sites [105]. Robust surgical workflows and training protocols are equally important to ensure consistent outcomes across centers.

Power autonomy and secure wireless telemetry govern device usability and patient comfort; rechargeable batteries, inductive charging, and energy harvesting are all active strategies to extend runtime without enlarging implants [106]. Low-power system-on-chip designs, duty-cycling of stimulation, and local processing to reduce wireless traffic improve energy efficiency [107]. Telemetry protocols must ensure reliable, low-latency data transfer

for programming and diagnostics while maintaining patient security and privacy [108]. Miniaturization of electronics and packaging enables less-invasive implants and broader adoption among ambulatory populations [97].

The next generation of ECs moves to closed-loop control by integrating sensors (biopotentials, biochemical sensors, motion/respiratory monitors) that provide real-time feedback to adapt stimulation [109]. Closed-loop systems promise better efficacy and fewer side effects by delivering stimulation when physiological biomarkers indicate a therapeutic need, and by dynamically adjusting stimulation parameters [110]. Implementing robust control algorithms requires reliable biomarkers, artifact-resilient sensing, and safety-constrained controllers that avoid runaway stimulation [111]. Demonstrating that sensor-driven adaptation improves clinical outcomes remains a central translational milestone [111].

Chronic implantation exposes devices to biofouling, fibrosis, corrosion, and mechanical fatigue; therefore, appropriate material selection and hermetic packaging are crucial for long-term reliability [112]. Biocompatible polymers, thin ceramic coatings, and silicone encapsulation are commonly used, and each impacts stiffness, conformability, and immune response [113]. Designing devices with predictable failure modes (e.g., predictable end-of-life behavior) also helps with regulatory approval and patient safety [114].

Software ecosystems, including firmware, clinician programming tools, and cloud analytics, are essential components that affect usability, reproducibility, and regulatory classification [115]. Data pipelines that convert raw sensor streams into actionable biomarkers need validated algorithms, secure storage, and transparent performance metrics; regulatory agencies are also increasingly evaluating software as a medical device [116]. From a manufacturing standpoint, reproducible microfabrication, quality control of electrode properties, and scalable assembly processes determine commercial viability. Regulatory pathways, clinical trial design, and reimbursement strategies must be planned in parallel to technical development to ensure timely translation.

In sum, the technical development of ECs for MetS should be considered in relation to the specific physiological and clinical requirements of metabolic therapy rather than as a generic extension of neurotechnology. In MetS, the principal engineering challenge is not simply to deliver electrical stimulation safely, but to selectively modulate autonomic and neuro-metabolic pathways while continuously accounting for dynamic metabolic states. This requires technologies that can improve target selectivity, detect clinically relevant metabolic signals, deliver stimulation at appropriate times and doses, and maintain reliable operation during long-term ambulatory use.

Selective targeting is a major technical requirement for metabolic applications because autonomic nerves contain multiple fiber populations with different and sometimes opposing physiological functions. Broad stimulation of mixed autonomic fibers may therefore produce unintended cardiovascular, gastrointestinal, respiratory, or other autonomic effects while simultaneously limiting the ability to isolate a desired metabolic response [26,90,103]. This issue is particularly important for potential targets such as the vagus nerve and carotid sinus nerve, where afferent and efferent fibers and different functional pathways are anatomically intermingled.

Recent developments in high-density, multi-contact nerve interfaces, selective cuff electrodes, and advanced electrode geometries provide an opportunity to address this limitation by recruiting specific fiber populations rather than activating the entire nerve [34]. For MetS, the relevance of these technologies lies in their potential to preferentially modulate pathways associated with glucose regulation, insulin secretion, appetite, hepatic metabolism, energy expenditure, or inflammatory signaling while minimizing off-target autonomic effects. Similarly, emerging stimulation approaches such as kilohertz-frequency conduction block and optimized multi-contact waveforms may provide additional con-

trol over which neural populations are activated or inhibited [38]. However, whether the anatomical and functional selectivity achievable with these interfaces is sufficient to produce reproducible metabolic benefits in humans remains to be established.

5.1. Electrode–Tissue Interfaces and Long-Term Metabolic Therapy

The electrode–tissue interface is another important determinant of the feasibility of chronic EC therapy for MetS. Metabolic disorders are generally chronic conditions requiring sustained management rather than short courses of treatment. Therefore, electrode impedance, foreign-body responses, fibrosis, corrosion, and mechanical instability can progressively alter stimulation thresholds and therapeutic effects during long-term use [98,112,113].

Advances in conductive polymers, porous interfaces, hydrogels, and conformable electrode designs can improve charge transfer and maintain more stable electrical coupling with neural tissue [35,98,99]. For metabolic applications, this stability is particularly relevant because changes in the electrode–tissue interface could alter the effective stimulation dose over time and thereby compromise the reproducibility of metabolic responses. Future autonomic interfaces should therefore be evaluated based on not only their initial stimulation efficiency but also their ability to maintain stable neural recruitment and safe stimulation thresholds during prolonged treatment. This is essential if ECs are ultimately intended as ambulatory or implantable therapies for chronic MetS.

5.2. Stimulation Parameters and Metabolic Dose Definition

Unlike conventional pharmacotherapy, for which dose can often be expressed in standardized mass-based units, an EC “dose” is multidimensional and may include stimulation site, amplitude, pulse width, frequency, waveform, duty cycle, treatment duration, and temporal relationship to physiological events [100]. This shows a particular challenge in MetS because metabolic responses are dynamic and may differ depending on nutritional state, physical activity, circadian rhythm, autonomic tone, and disease severity.

Advanced waveform design and computational modeling can help identify stimulation parameters that preferentially recruit metabolically relevant neural pathways while reducing activation of neighboring structures [100,101]. Energy-efficient waveforms and multi-site stimulation may additionally reduce power requirements and unwanted physiological effects [102]. For MetS, however, technical optimization should be linked to predefined metabolic outcomes rather than electrophysiological performance alone. Future studies should therefore report stimulation parameters together with metabolic endpoints such as fasting and postprandial glucose, insulin sensitivity, blood pressure, body weight, appetite, energy expenditure, and inflammatory biomarkers. Establishing reproducible relationships between stimulation parameters and metabolic responses will be necessary before a standardized therapeutic dose for MetS can be defined.

5.3. Target Localization and Patient-Specific Autonomic Mapping

Precise localization is particularly challenging for metabolic ECs because relevant autonomic targets may be small, anatomically variable, and composed of mixed functional fibers [103]. Conventional anatomical targeting alone may therefore be insufficient to predict which neural structures will produce a desired metabolic response.

Advances in imaging, electrophysiological mapping, neuronavigation, and multi-modal physiological monitoring can improve target localization and reduce interindividual variability [104]. For metabolic applications, these approaches could be combined with physiological markers such as heart-rate variability, reflex responses, glucose dynamics, or other autonomic measurements to identify stimulation sites associated with a favorable metabolic response. Such patient-specific mapping may be particularly important because

the autonomic phenotype of individuals with MetS is heterogeneous, and the optimal neural target or stimulation parameters may not be identical across patients.

5.4. Continuous Metabolic Sensing and Treatment Timing

One of the most important technological gaps in MetS is the limited integration of EC systems with continuous metabolic sensing. Most current neuromodulation systems operate according to predefined stimulation schedules, whereas metabolic physiology changes continuously with meals, fasting, exercise, sleep, stress, and medication use. Consequently, a fixed stimulation schedule may not provide the appropriate intervention at the time when a metabolic abnormality is developing.

Continuous glucose monitoring provides a clinically established example of a physiological signal that could potentially inform adaptive EC therapy. Recent evidence evaluating vagus nerve stimulation with continuous glucose monitoring illustrates the feasibility of assessing glucose dynamics during neuromodulation, although current clinical evidence does not yet establish a validated glucose-driven closed-loop EC strategy for MetS [117]. In future systems, glucose excursions could be combined with other signals, including heart-rate variability, blood pressure, physical activity, respiratory patterns, body temperature, appetite-related hormones, inflammatory biomarkers, or neural activity. The objective would be to determine when metabolic intervention is required and to adjust stimulation intensity or duration accordingly.

For example, stimulation could theoretically be synchronized with postprandial glucose excursions, abnormal autonomic responses, or periods of reduced energy expenditure rather than being delivered continuously. Such treatment timing may reduce unnecessary stimulation and could potentially improve both safety and energy efficiency. However, these applications require validated biomarkers that reliably predict when neuromodulation will produce a clinically meaningful metabolic response. At present, this remains an important research gap.

5.5. Wireless Telemetry, Power Management, and Ambulatory Metabolic Care

Long-term management of MetS also places specific requirements on device size, power consumption, wireless communication, and patient usability. Rechargeable batteries, inductive charging, energy harvesting, and low-power electronics can extend device operating time while reducing implant size [106,107]. Wireless telemetry can additionally enable programming, physiological monitoring, and transmission of device data without repeated clinical visits.

For metabolic applications, however, wireless telemetry has a function beyond convenience. A chronic EC device may need to receive information from wearable or implanted metabolic sensors and communicate treatment parameters to an external controller or clinical platform. Reliable low-latency communication would therefore be important for adaptive stimulation, while encryption and secure data handling are necessary because metabolic and physiological data are sensitive health information [108]. Miniaturized and energy-efficient systems may also facilitate ambulatory use, which is particularly relevant to MetS because therapeutic effects may need to be maintained during routine activities, meals, sleep, and exercise rather than only under supervised clinical conditions.

The engineering goal should therefore be to develop sufficiently small and energy-efficient systems that can support prolonged operation without frequent recharging, surgical replacement, or intensive clinical supervision. These characteristics would be particularly valuable if EC therapy is eventually used as a long-term adjunct to lifestyle and pharmacological management of MetS.

5.6. Closed-Loop Systems for Biomarker-Guided Metabolic Neuromodulation

Closed-loop EC systems represent a potentially important transition from fixed-dose neuromodulation toward precision metabolic therapy. Such systems combine physiological sensing with stimulation and use feedback algorithms to adjust treatment according to the patient's current physiological state [37,109,110]. For MetS, the central requirement is to identify biomarkers that are sufficiently sensitive, reliable, and temporally responsive to guide stimulation.

Candidate signals include continuous glucose trajectories, heart-rate variability, blood pressure, inflammatory markers, appetite-related hormones, BDNF, physical activity, and neural or autonomic activity. These biomarkers may provide complementary information about different dimensions of MetS, including glycemic regulation, autonomic imbalance, inflammation, energy balance, and treatment response. Nevertheless, the presence of an association between a biomarker and metabolic disease does not necessarily mean that the biomarker can serve as a control signal. Closed-loop systems therefore require prospective validation demonstrating that biomarker-guided stimulation improves clinically relevant metabolic outcomes compared with predefined open-loop stimulation.

Safety-constrained controllers are also essential because inappropriate stimulation could produce excessive autonomic activation or other adverse physiological responses. Future systems should consequently incorporate predefined stimulation limits, artifact-resistant sensing, failure detection, and safe fallback modes [110]. This approach could eventually allow stimulation to be individualized according to metabolic state while reducing unnecessary stimulation exposure.

6. Discussion: Evidence Synthesis

The evidence reviewed in this article spans several mechanistically distinct electroceutical classes. These include central and autonomic neuromodulation (e.g., TMS and VNS/taVNS), neural conduction blockade (vagal blockade), peripheral neuromuscular electrical stimulation (EMS, NMES, and WB-EMS), electrostimulation delivered through acupuncture needles (i.e., EA), and non-contact field-based approaches (PEMF and LFEF). These modalities differ in energy delivery, anatomical target, invasiveness, stimulation parameters, and intended therapeutic effect. Consequently, their findings are synthesized separately where appropriate rather than being interpreted as evidence for a single uniform electroceutical mechanism.

Accordingly, evidence was synthesized by metabolic outcome and clinical evidence level rather than by assuming that all EC modalities have equivalent mechanisms or therapeutic effects. To facilitate a structured interpretation of the evidence, the evidence was further examined across three levels: Category 1, direct clinical evidence of an electroceutical intervention in patients with MetS; Category 2, clinical evidence addressing one or more individual components of MetS; and Category 3, preclinical mechanistic evidence from animal or laboratory models. This hierarchical framework distinguishes direct evidence for MetS from indirect evidence derived from individual metabolic abnormalities or experimental models. A summary of the studies reviewed in Categories 1, 2, and 3 are presented in Tables 1–3.

EC interventions encompass neuromodulatory approaches including TMS [118], LFEF [118], EMS [119] and WB-EMS [120], mild electrical stimulation combined with heat shock (MES + HS) [121], NMES [122], and PEMF [123].

Table 1. Clinical evidence for electroceutical and neuromodulation interventions relevant to metabolic syndrome and its individual components. Category A: Direct clinical evidence from participants with diagnosed metabolic syndrome (MetS).

Study Design	Subjects (n)	Intervention	Stimulation site	Frequency	Intensity/amplitude	Pulse width	Session duration	Treatment Schedule	Comparator	Main Outcomes	Adverse events	Citation
Open-label, randomized (2:1), two-arm, parallel-group controlled trial	Patients with MetS (<i>n</i> = 30)	taVNS	Left cymba conchae	25 Hz	0.1–5.0 mA	500 μ s	30 min	Once weekly for 8 weeks	No treatment	Reduced HR and BP; improved sympathovagal balance; anti-inflammatory effects	NR	[123]
Randomized controlled pilot trial	Obese women diagnosed with MetS (<i>n</i> = 29; WB-EMS, <i>n</i> = 15, control, <i>n</i> = 14)	WB-EMS + caloric restriction	Whole body; trunk, arms, thighs, buttocks and major muscle groups	85 Hz	Individually adjusted to produce a tolerable muscle contraction	350 μ s	20 min	2 sessions/week for 12 weeks; 6 s stimulation/4 s rest	Inactive control + caloric restriction/nutritional counseling	Decreased body weight, body-fat percentage and total cholesterol; improved cardiometabolic risk score and body composition	NR	[124]
Randomized controlled trial	Patients with MetS (<i>n</i> = 90)	LFEF + TMS + diet, antihypertensive drugs and physiotherapy exercises	As specified in the original protocol	LFEF: 100 Hz; TMS: 1–10 Hz	LFEF: 50%; TMS: 10–30 mT	NR	LFEF: 10–12 min; TMS: 7–12 min	10 daily sessions	TMS alone or LFEF alone + background treatment	Reduced cholesterol and improvement in metabolic outcomes; combined LFEF + TMS showed greater effects than either modality alone	NR	[118]
Randomized, sham-controlled trial	Adults with mild-to-moderate MetS (PEMF, <i>n</i> = 23; sham, <i>n</i> = 21)	PEMF	NR	NR	NR	NR	16 min	3 sessions/day for 12 weeks	Sham	Reduced systolic and diastolic BP and mean arterial pressure; improved BP response during exercise; NO-related effects reported	NR	[122]

Abbreviations: BP, blood pressure; EMS, electrical muscle stimulation; HR, heart rate; LFEF, low-frequency electrostatic field; MetS, metabolic syndrome; NR, not reported; PEMF, pulsed electromagnetic field; taVNS, transcutaneous auricular vagus nerve stimulation; TMS, transcranial magnetic stimulation; WB-EMS, whole-body electromyostimulation. Note: NR indicates that the parameter was not reported or could not be reliably verified from the primary publication.

Table 2. Clinical evidence for electroceutical and neuromodulation interventions relevant to metabolic syndrome and its individual components. Category B: Component-specific clinical evidence from populations with individual metabolic abnormalities or related disorders.

Study Design	Subjects (n)	MetS-Related Component	Intervention	Stimulation Site	Frequency	Intensity/Amplitude	Pulse Width	Session Duration	Treatment Schedule	Comparator	Main Outcomes	Adverse Events	Citation
Open-label randomized crossover trial	Subjects with MetS or T2DM (<i>n</i> = 40)	MetS/T2DM; visceral adiposity and glucose metabolism	MES + HS	NR	NR	NR	NR	NR	12 weeks MES + HS followed by 12 weeks no treatment, or reverse sequence	No treatment	Reduced visceral adiposity; fasting plasma glucose and insulin; improved metabolic and inflammatory parameters; increased HSP72 expression	NR	[121]
Randomized, double-blind, sham-controlled trial	Adults with abdominal obesity (<i>n</i> = 60)	Abdominal obesity	EMS	Abdominal muscles	5, 55, 6, 65 and 4 Hz	NR	250, 300, 180, 300 and 160 μ s	66 min	5 days/week for 12 weeks	TENS/sham stimulation	Reduced waist circumference; greater reduction with EMS than TENS; changes in fasting free fatty acids	NR	[125]
Double-blind randomized controlled trial (ReCharge)	Obese participants with ≥ 1 obesity-related comorbidity (<i>n</i> = 84)	Obesity	vBloc + weight-management counseling	Bilateral abdominal vagal trunks	NR	NR	NR	Intermittent	Long-term daily stimulation; 12-month follow-up	Sham device + weight-management counseling	Greater weight loss with vBloc than sham control	Device/procedure-related adverse events reported	[126]
Randomized, double-blind, sham-controlled clinical trial	Obese participants with ≥ 1 obesity-related condition (<i>n</i> = 239)	Obesity	vBloc + weight-management program	Bilateral abdominal vagal trunks	NR	NR	NR	Intermittent	12 months	Sham device + weight-management program	Greater weight loss with vBloc than sham; coprimary prespecified efficacy objectives were not met	NR	[127]
Patient-assessor-blinded, randomized, sham-controlled clinical trial	Obese participants (<i>n</i> = 168)	Central obesity	Electroacupuncture	Abdominal acupuncture points	50 Hz	50 V	NR	30 min	2 sessions/week for 8 weeks (16 sessions)	Sham acupuncture	Improved waist circumference and body-fat percentage; reduced body weight, BMI, hip circumference and waist-to-hip ratio	NR	[128]
Double-blind, randomized controlled trial	Obese participants (<i>n</i> = 239)	Obesity/ cardiometabolic risk	vBloc	Bilateral abdominal vagal trunks	NR	NR	NR	Intermittent	24-month follow-up	Sham	Significant weight loss; improved lipid profile, HbA1c and systolic/ diastolic BP	NR	[129]
Randomized controlled open-label trial	Dyslipidemic patients (<i>n</i> = 60)	Dyslipidemia	Electroacupuncture	Body acupuncture points/ Fenglong	NR	NR	NR	NR	4 weeks	No acupuncture intervention	Improved serum lipid profile; lipid-lowering effects observed after treatment	NR	[130]

Table 2. Cont.

Study Design	Subjects (n)	MetS-Related Component	Intervention	Stimulation Site	Frequency	Intensity/Amplitude	Pulse Width	Session Duration	Treatment Schedule	Comparator	Main Outcomes	Adverse Events	Citation
Randomized controlled crossover trial	Patients with T2DM (<i>n</i> = 14)	T2DM/glucose metabolism	NMES	Lower-limb and gluteal muscle groups	4 Hz	Maximum tolerable intensity	200 µs	40 min	5 sessions/week for 8 weeks	Control	Improved fasting glucose concentration and body-fat percentage; significant BDNF changes; no significant changes in HbA1c or blood lipid profile	NR	[131]
Prospective, single-arm, before–after interventional study	Obese individuals with T2DM (<i>n</i> = 15)	T2DM/obesity	EMS	Trunk, leg and arm muscles	NR	NR	NR	20 min	2 sessions/week for 10 weeks	Baseline/pre-intervention values	Decreased fasting blood glucose and HbA1c; no significant change in body weight or body-fat percentage	NR	[132]
Open-label multicenter clinical trial	Obese individuals with T2DM (<i>n</i> = 28)	T2DM/obesity	vBloc	Bilateral abdominal vagal trunks	NR	NR	NR	Intermittent	12 months	Baseline/pre-intervention values	Reduced mean %EWL, HbA1c and mean arterial pressure	One serious implant-site pain event was reported and resolved	[133]
Pilot randomized clinical trial	Participants with impaired glucose tolerance (<i>n</i> = 102)	Impaired glucose tolerance/dysglycemia	taVNS	Auricular concha	20 Hz	1 mA	≤1 ms	20 min	2 sessions/day for 12 weeks	Sham taVNS	Reduced 2-h glucose level and systolic BP	NR	[134]
Randomized, sham-controlled trial	Individuals with T1DM/T2DM and diabetic autonomic neuropathy (<i>n</i> = 145)	Diabetes/diabetic autonomic neuropathy	Cervical tVNS	Bilateral cervical vagus nerves	5 kHz	0–60 mA; highest non-painful tolerable intensity	NR	120 s per side	4 sessions/day during week 1, followed by 2 sessions/day for 8 weeks	Sham tVNS	No significant improvement in glycemic variability or HbA1c	NR	[117]
Randomized controlled trial	Patients with T2DM receiving oral antidiabetic drugs (<i>n</i> = 160)	T2DM/glycemic control	TENS	Bilateral abdominal wall	1–20,000 Hz programmed waveform	Mean 7.2 Vpp	NR	60 min/day	≥5 days/week for 20 weeks	Placebo	No statistically significant reduction in HbA1c	NR	[135]
Double-blind, randomized, prospective, multicenter, placebo-controlled phase III trial	Patients with resistant hypertension (<i>n</i> = 265)	Resistant hypertension	Baroreflex activation therapy	Carotid sinus region	NR	NR	NR	NR	6 months	Delayed-treatment control	Reduction in systolic BP; long-term efficacy and device safety were reported	Procedure-related and device-related safety outcomes reported	[136]

Table 2. *Cont.*

Study Design	Subjects (n)	MetS-Related Component	Intervention	Stimulation Site	Frequency	Intensity/Amplitude	Pulse Width	Session Duration	Treatment Schedule	Comparator	Main Outcomes	Adverse Events	Citation
Pilot study; within-person experimental design	Hypertensive subjects (<i>n</i> = 20)	Hypertension	RAVANS	Left cymba concha	2, 10, 25 and 100 Hz	Individually adjusted to moderate, non-painful sensation	300 µs	30 min stimulation within a 50-min session	5 sessions, ≥24 h apart	Sham	Reduced HR, mean arterial BP and DBP; acute frequency-dependent effects were observed	NR	[137]

Abbreviations: BDNF, brain-derived neurotrophic factor; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; EMS, electrical muscle stimulation; HbA1c, hemoglobin A1c; HR, heart rate; MES + HS, mild electrical stimulation with heat shock; MetS, metabolic syndrome; NMES, neuromuscular electrical stimulation; NR, not reported; RAVANS, respiratory-gated auricular vagal afferent nerve stimulation; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; taVNS, transcutaneous auricular vagus nerve stimulation; TENS, transcutaneous electrical nerve stimulation; tVNS, transcutaneous vagus nerve stimulation; vBloc, vagal nerve blockade. Note: NR indicates that the parameter was not reported or could not be reliably verified from the primary publication.

Table 3. Clinical evidence for electroceutical and neuromodulation interventions relevant to metabolic syndrome and its individual components. Category C. Indirect clinical evidence to MetS.

Evidence Category	Study Design	Population	Intervention	Stimulation site	Frequency	Intensity/Amplitude	Pulse width	Session duration	Treatment Schedule	Comparator	Main Findings	Relevance to MetS	Citation
Indirect evidence	Clinical trial; within-person experimental design	Patients with stable VNS therapy for refractory epilepsy (<i>n</i> = 15)	VNS	Implanted cervical vagus nerve	NR	NR	NR	NR	2 weeks	VNS ON vs VNS OFF	Higher basal metabolic rate and increased energy expenditure	Indirect evidence from a non-MetS population	[138]
Indirect/component-specific evidence	Meta-analysis of 9 RCTs; 180 participants	Mixed populations including healthy-weight, obese, T2DM and SCI populations	NMES	Varied	Varied	Varied	Varied	Varied	Varied	Control/placebo	Reduced fasting blood glucose and improved glycemic control	Indirect/component-specific evidence; heterogeneous populations	[139]

Abbreviations: MetS, metabolic syndrome; NMES, neuromuscular electrical stimulation; NR, not reported; SCI, spinal cord injury; T2DM, type 2 diabetes mellitus; VNS, vagus nerve stimulation. Note: NR indicates that the parameter was not reported or could not be reliably verified from the primary publication.

An important consideration throughout the clinical evidence synthesis is the potential for confounding by concurrent interventions and changes in body weight. Several clinical studies evaluated EC interventions in the context of caloric restriction, weight-management strategies, exercise-related interventions, or substantial weight loss. Because reductions in body weight and energy intake can independently improve insulin sensitivity, glycemic control, lipid concentrations, blood pressure, and other cardiometabolic outcomes, improvements observed after EC treatment cannot necessarily be attributed to the electrical or neuromodulatory intervention itself. Accordingly, metabolic outcomes are interpreted cautiously when concomitant weight loss or lifestyle modification occurred, particularly when studies were not designed to isolate the independent contribution of EC treatment. Where body weight or other relevant co-interventions remained unchanged, the possibility of an independent metabolic effect may be more plausible, although it cannot be established solely from within-group changes.

6.1. Category 1: Direct Clinical Evidence

Studies investigating the effects of ECs across the full range of diagnostic parameters of MetS are limited, making it difficult to draw definitive conclusions about their overall therapeutic efficacy. The study by de Moraes et al. (2023) on 30 MetS patients was conducted as an open-label, randomized (2:1), two-arm, parallel-group controlled trial that investigated the effect of taVNS [123]. This study resulted in reductions in systolic and diastolic blood pressure and heart rate after this electrical intervention, but the study did not evaluate or report the effects of taVNS on other parameters, especially metabolic parameters of this syndrome [123]. Notably, another point of this study was a shift toward a less inflammatory immune profile in patients following taVNS, which can be interpreted beyond the usual expectations of the effect of modulation of vagal activity [123]. It appears that clinical studies specifically designed to simultaneously evaluate all diagnostic components of MetS while adequately controlling for relevant confounding factors and establishing the therapeutic efficacy of ECs are currently lacking. However, several studies have investigated the effects of different EC modalities on one or more components of MetS, as discussed in the following section.

6.2. Category 2: Clinical Evidence on Individual Components of MetS

6.2.1. Adiposity and Body Composition

Studies evaluating electrical stimulation for visceral adiposity and obesity have yielded mixed results. Kondo et al. (2014) reported that mild electrical stimulation combined with heat shock (MES + HS) reduced visceral adiposity in patients with MetS and T2DM [121]. In contrast, Choi et al. (2018) found that EMS did not significantly reduce visceral or total abdominal fat in adults with abdominal obesity, despite a significant reduction in waist circumference [125]. Similarly, WB-EMS has been associated with reductions in body weight and body fat in obese women with MetS [125].

vBloc produced significant weight loss in a double-blind, randomized controlled trial involving individuals with moderate obesity [126]. However, the intervention did not meet the prespecified co-primary efficacy endpoints reported by Ikramuddin et al., despite producing greater weight loss among participants with severe obesity than in the sham-control group [127]. Another neuromodulatory approach, VNS, was evaluated in a small study involving 15 participants and was associated with a significant increase in energy expenditure and changes in physical activity. These findings may provide a possible mechanistic context for the secondary weight-loss effects reported with this approach, although their clinical significance remains uncertain [138]. In addition, Lam et al. (2024)

reported that EA may reduce waist circumference, hip circumference, body weight, body mass index, and waist-to-hip ratio [128].

6.2.2. Dyslipidemia

Studies investigating the effect of ECs on lipid profile have been less extensive, and it seems that most of the possible changes in blood lipids may be secondary to factors such as body weight loss. An example of this can be seen in the study by Apovian et al. (2017) on the effect of vBloc on obesity, which reported a decrease in low-density lipoprotein (LDL), triglycerides, and an increase in high-density lipoprotein (HDL) following the use of this technology in individuals, but given the significant weight loss, these lipid profile changes may be more related to this weight change [129]. Another example of the effect of ECs on lipid profile is the reduction in cholesterol following the combination of LFEF + TMS in the study by Benkov et al. (2022) on patients with MetS [118], although given the limited 10-session treatment intervention, the certainty of the effectiveness of this technique may still require further investigation.

Based on a randomized controlled trial conducted by Rerksuppaphol & Rerksuppaphol (2014) on the effect of EA on regulating blood lipid levels in dyslipidemic patients, a significant reduction in serum lipid levels was reported after the completion of the aforementioned treatment period, and even a reduction in LDL cholesterol and total cholesterol was reported at the follow-up visit [130]. Of course, it should be remembered that perhaps, based on the scope and specificity of the studies conducted in this field, these changes should be considered more as secondary metabolic outcomes. Therefore, although different electrical and neuromodulatory approaches have demonstrated potential benefits for reducing body weight, adiposity, and anthropometric measures, the available evidence remains heterogeneous, and further well-designed clinical studies are required to establish their efficacy and clinical relevance in the management of MetS.

6.2.3. Glycemic Regulation and Insulin Resistance

Existing reports indicate that different EC modalities may influence another important component of MetS, namely hyperglycemia and IR, although the magnitude and statistical significance of these effects have varied across studies. NMES has been reported to significantly reduce fasting blood glucose [139]. However, in the study by Miyamoto et al., despite a significant change in fasting glucose concentration, no significant change was observed in hemoglobin A1c (HbA1c) levels [131]. Another notable finding of the same study was a change in plasma BDNF levels [131]. EMS has also been reported to reduce fasting blood glucose and HbA1c according to van Buuren et al. (2015); however, mean body weight and body-fat percentage did not change significantly following the intervention [132].

In a study by Shikora et al. (2013) involving 28 patients with obesity and type 2 diabetes, implantation of an intermittent vBLOC device was associated with reductions in HbA1c, body weight, and mean arterial pressure [133]. However, because weight loss and improved glycemic control occurred concurrently following vBLOC treatment, a definitive causal conclusion regarding the independent effect of the intervention on blood glucose cannot be drawn. In individuals with impaired glucose tolerance (IGT), taVNS has been reported to produce significant changes in glycosylated hemoglobin (HbA1c), 2 h plasma glucose (2hPG), and fasting plasma glucose (FPG), suggesting its potential utility in the management of IGT and prediabetes. However, further well-designed and specialized clinical studies are required to confirm these findings and establish the therapeutic efficacy of taVNS in this population [134]. However, these findings do not indicate that electrical stimulation is consistently effective in improving glycemic control. Kufaishi et al. (2025),

for example, reported no significant benefit of tVNS for glycemic control in the studied diabetic population [117]. Similarly, Lu et al. (2023) reported no significant reduction in HbA1c following TENS in patients with diabetes [135].

Overall, although several studies have reported beneficial effects of electrical interventions on blood glucose and related metabolic parameters, the available evidence remains inconsistent. Therefore, it is premature to draw general conclusions regarding the efficacy of ECs for glycemic control in MetS. Further well-designed clinical and mechanistic studies are needed to clarify the effects of different electrical stimulation modalities and to elucidate the underlying mechanisms responsible for their effects on glucose metabolism.

6.2.4. Blood Pressure and Vascular Function

Blood pressure can also be modulated by EC interventions. For example, BAT has been reported to reduce systolic blood pressure in patients with resistant hypertension [136]. Similarly, respiratory-gated auricular vagus afferent nerve stimulation has been shown to decrease heart rate, mean arterial pressure, and diastolic blood pressure. However, Garcia et al. (2022) reported that these rapid, frequency-dependent effects may vary according to sex and race, highlighting the potential influence of individual characteristics on responses to neuromodulation [137].

PEMF represents another emerging approach being investigated for blood pressure control. Kim et al. (2020) reported that PEMF increased nitric oxide levels and reduced systolic blood pressure, diastolic blood pressure, and mean arterial pressure in hypertensive patients with MetS at rest, while also improving blood pressure responses during exercise [122]. Therefore, although these findings suggest that different EC modalities may have beneficial effects on blood pressure through distinct neurovascular and physiological mechanisms, the available evidence remains limited and heterogeneous. Further controlled clinical studies are needed to determine the efficacy, durability, and patient-specific responses to EC interventions for blood pressure management in MetS.

6.3. Category 3: Preclinical Mechanistic Evidence

Preclinical studies provide important information regarding biological plausibility, potential mechanisms of action, and preliminary safety; however, they do not establish clinical efficacy in patients with MetS. This distinction is particularly important when interpreting studies in which electrical stimulation modifies individual metabolic pathways or biomarkers without demonstrating improvement in the overall clinical phenotype. Several preclinical studies have investigated ECs in relation to metabolic processes relevant to MetS. Evidence from preclinical models suggests that electrical stimulation can influence several metabolic parameters relevant to MetS, including glucagon-like peptide-1 (GLP-1) signaling, insulin sensitivity, insulin and glucagon secretion, and glucose tolerance following VNS in animal models [140–146]. Direct EMS may also enhance glucose uptake [147–149].

Electrical neuromodulation can also influence adipose tissue and metabolic processes, resulting in changes in appetite, body-weight gain, mitochondrial function, and thermogenesis [150–153]. Inflammation, another important component of MetS, has also been modulated by electrical interventions such as vagal stimulation and EA. These approaches have been associated with changes in inflammatory cytokines, macrophage activity, and nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) signaling [154,155]. In a preclinical macrophage model, electrical stimulation reduced pro-inflammatory cytokine expression and reactive oxygen species (ROS) generation while increasing NADPH production and metabolites of the pentose phosphate pathway, suggesting a potential metabolic mechanism underlying its anti-inflammatory effects [156]. Reduction in blood pressure through suppression of sympathetic activity using electrically mediated baroreceptor stim-

ulation represents another investigated effect of ECs on cardiovascular parameters relevant to MetS [157–159]. Importantly, a preclinical study in spontaneously hypertensive rats demonstrated that the effects of carotid sinus stimulation on blood pressure and resistance vessel function depended on the stimulation protocol and duration [158].

Collectively, these findings indicate that EC approaches can influence multiple components of MetS, however it should be considered that as mechanistic and translational evidence not evidence of clinical therapeutic efficacy. However, the optimal EC modality, stimulation parameters, and treatment protocols required to produce reliable and reproducible therapeutic effects remain unclear. In addition, some preclinical studies have reported contradictory findings. For example, Yin et al. (2019) and Payne et al. (2020) reported increases in glucose and glucagon following VNS [141,142]. Similarly, vagal afferent stimulation has been reported to inhibit brown adipose tissue thermogenesis in some experimental models [150,160]. These discrepancies highlight the complexity of neuro-metabolic responses to electrical stimulation and the importance of considering stimulation modality, anatomical target, stimulation parameters, and experimental model when interpreting preclinical findings. Accordingly, future studies should determine whether specific preclinical mechanisms can be reproduced in humans and whether modulation of these pathways is associated with clinically meaningful improvements in MetS outcomes.

Several considerations should be addressed in future preclinical studies of ECs. First, greater diversity in animal models should be encouraged, while selecting species that adequately reflect relevant human physiological mechanisms. Reliance on a single animal species may limit the generalizability of findings and may fail to account for interspecies differences that influence the efficacy and safety of EC interventions. Second, preclinical study designs should incorporate translational strategies that facilitate the subsequent application of experimental findings to human clinical research. Ideally, potential differences between animal and human responses should be anticipated during the initial study-design stage rather than recognized only after the completion of preclinical and clinical studies. Therefore, careful consideration of species-specific physiology, stimulation parameters, target anatomy, and clinically relevant outcome measures is essential for improving the translation of preclinical EC research into safe and clinically meaningful human applications.

7. Limitations and Future Perspectives

BEM is an interdisciplinary field that integrates medicine, physics, engineering, and related biomedical sciences. Further development of this field requires new perspectives on the opportunities, limitations, and challenges associated with EC technologies. The modulation of bioelectric signaling involved in intermediary metabolism may represent a novel and currently underexplored research avenue in MetS. However, increasing therapeutic efficacy while minimizing off-target autonomic effects remains a major challenge in the development of EC interventions.

An additional and important limitation of the current clinical evidence is the potential confounding of metabolic outcomes by concurrent weight-related and lifestyle interventions. Several studies evaluated ECs in combination with caloric restriction, weight-management strategies, exercise-related interventions, or interventions that produced substantial weight loss. Because changes in body weight and energy intake can independently improve glycemic control, lipid profiles, blood pressure, insulin sensitivity, inflammation, and other cardiometabolic outcomes, improvements observed following EC treatment cannot necessarily be attributed to neuromodulation itself. In some studies, body-weight changes occurred simultaneously with metabolic improvements, making it difficult to determine whether the observed benefits resulted from a direct effect of ECs, an indirect effect

mediated through weight loss or behavioral changes, or a combination of mechanisms. This issue is particularly relevant when interpreting studies of obesity and MetS, in which weight reduction is itself a major therapeutic determinant.

Future clinical trials should therefore incorporate appropriate strategies to address this potential confounding. At a minimum, studies should prospectively monitor body weight, waist circumference, caloric intake, physical activity, dietary interventions, medication changes, and other weight-management strategies throughout the intervention and follow-up periods. Where feasible, factorial designs, adequately matched control groups, mediation analyses, or statistical adjustment for longitudinal changes in body weight should be considered to distinguish direct EC effects from secondary metabolic effects associated with weight reduction.

Another critical consideration is the determination and standardization of appropriate stimulation parameters and therapeutic dosing. In addition, battery life and power-efficiency constraints may limit the long-term use of implantable and wearable EC devices; therefore, improved power-management strategies, rechargeable or wireless energy solutions, and energy-efficient device architectures should remain priorities for future development.

Sustained progress in EC technology will require close collaboration among researchers from multiple disciplines, including medicine, neuroscience, bioengineering, materials science, and computational sciences. Overall, larger, well-designed, adequately controlled, and sufficiently long-term preclinical and clinical studies are needed to establish the efficacy, safety, optimal dosing parameters, long-term durability, and patient-specific responses to EC interventions. Such studies should distinguish direct neuromodulatory effects from metabolic changes that may occur secondary to weight loss or lifestyle modification. This distinction will be essential for determining whether ECs provide independent therapeutic benefits beyond established approaches to weight management and metabolic risk reduction.

8. Conclusions

ECs represent an emerging investigational approach for modulating neural, autonomic, and peripheral bioelectric pathways that are biologically relevant to metabolic regulation. Experimental and early clinical evidence indicates that different EC modalities can influence processes associated with appetite regulation, glucose homeostasis, lipid metabolism, autonomic function, inflammation, and energy expenditure. However, the strength of evidence differs substantially across these domains. Mechanistic and preclinical studies provide biological plausibility, whereas clinical studies have primarily evaluated individual metabolic components or intermediate biomarkers. Direct clinical evidence demonstrating improvement of the overall MetS phenotype remains limited. Accordingly, the mechanistic relevance of these pathways should not be interpreted as evidence of established therapeutic efficacy.

The EC field encompasses a heterogeneous group of device-mediated interventions that intentionally modulate electrical or electromagnetic physiology through different physical mechanisms, anatomical targets, and modes of delivery. ECs represent a promising but still emerging therapeutic strategy for MetS because they can modulate neural circuits involved in appetite regulation, glucose homeostasis, lipid metabolism, autonomic balance, inflammation, and energy expenditure. Among the potential therapeutic targets, vagal, sympathetic, hypothalamic, gastric, and neuroimmune pathways appear particularly relevant to MetS because they connect central metabolic regulation with peripheral organs, including the liver, pancreas, gut, adipose tissue, and skeletal muscle. However, the field has not yet reached the level of mechanistic precision or clinical evidence required for

routine application in metabolic disorders. Current evidence is insufficient to establish the efficacy, reproducibility, and safety of ECs for the clinical management of MetS, representing an important gap in this field.

The key unresolved challenges extend beyond the general feasibility of electrical stimulation and include target specificity, biomarker selection, dose definition, treatment durability, device reliability, and clinical validation. First, the autonomic and metabolic circuits relevant to MetS are anatomically and functionally complex, and current stimulation approaches often lack sufficient selectivity to distinguish beneficial metabolic effects from off-target autonomic, cardiovascular, gastrointestinal, or neuropsychiatric responses. Second, there is no standardized EC “dose” for MetS. The absence of standardized parameters for stimulation site, frequency, amplitude, pulse width, timing, and treatment duration, together with the limited comprehensive assessment of patients’ metabolic status during EC therapy, makes it difficult to compare and reproduce findings across studies. Third, reliable biomarkers for closed-loop control remain underdeveloped. Measures such as glucose excursions, heart-rate variability, inflammatory markers, appetite-related hormones, BDNF, vagal activity, and neural activity are promising candidates; however, their causal relationships with clinical improvement require more rigorous investigation. Fourth, long-term safety and device durability remain unresolved, particularly for implanted systems exposed to fibrosis, biofouling, battery limitations, hardware failure, and changes in the tissue–device interface. Moreover, most available evidence is fragmented across individual conditions or components, including obesity, diabetes, hypertension, inflammation, and gastrointestinal dysfunction, rather than being evaluated directly in well-characterized populations with MetS. Most studies have also focused on one or a few diagnostic components of MetS, while comprehensive studies simultaneously evaluating the effects of ECs across all diagnostic components remain lacking. Therefore, the absence of adequately designed studies in well-characterized MetS populations represents another important challenge for the development of this therapeutic approach.

Therefore, an important direction for future research is to integrate translational neuro-metabolic phenotyping with closed-loop device development. Progress will depend on identifying which patient subgroups respond to specific neural targets, which biomarkers most reliably reflect therapeutic benefit, and how stimulation parameters should be adapted over time. Future studies should aim to identify neural targets and stimulation parameters capable of producing reproducible and clinically meaningful metabolic effects. Large, controlled, and long-term clinical studies are needed to evaluate clinically relevant outcomes, including waist circumference, insulin sensitivity, postprandial glucose control, blood pressure, lipid profiles, inflammatory status, body weight, quality of life, and medication requirements. Although such studies may be costly, they are essential for establishing the clinical value of ECs. In parallel, engineering efforts should focus on selective peripheral nerve interfaces, stable biocompatible materials, low-power systems, secure telemetry, and adaptive algorithms capable of personalizing stimulation while minimizing adverse effects.

In summary, ECs should currently be regarded as a complementary and investigational approach rather than a replacement for lifestyle modification, pharmacological therapy, or surgical management of MetS. Their greatest potential may lie in the precision modulation of neuro-metabolic circuits, particularly when stimulation can be guided by validated biomarkers and adapted to individual physiological responses. Future studies should progressively move from broad proof-of-concept stimulation experiments toward mechanistically grounded, biomarker-driven, and clinically rigorous trials capable of determining where ECs provide meaningful additional value in the management of MetS. Ultimately, the clinical value of ECs will depend on whether they can deliver sufficiently precise and

mechanistically informed stimulation to produce effective, durable, reproducible, and clinically meaningful metabolic benefits in appropriately selected populations with MetS.

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