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RESEARCH ARTICLE

Reverse Remodeling of Methamphetamine-Associated Cardiomyopathy: An Update on Mechanisms for Recovery

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ABSTRACT

Methamphetamine (MA) use continues to rise worldwide. The adverse effects of MA on the cardiovascular system include cardiomyopathy, dysrhythmias, coronary arterial vasospasm, and atherosclerosis. Methamphetamine-associated cardiomyopathy (MACM) affects predominantly younger male patients and is responsible for an increasing proportion of heart failure emergency department visits, hospital admissions/readmissions, morbidity, and mortality. Reverse remodeling of MACM and full cardiac recovery is achievable in patients who cease using MA and remain abstinent with self-direction, cognitive behavioral therapy, brief interventions, contingency management, motivational interviewing, and residential rehabilitation. Recovery is further enhanced by the addition of an exercise program and guideline-based pharmacotherapy for heart failure, which includes β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers or angiotensin receptor-neprilysin inhibitors, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter 2 inhibitors. Alternative heart failure treatment with isosorbide dinitrate plus hydralazine, ivabradine, vericiguat, and omecamtiv mecarbil represent further adjuncts which may promote reverse remodeling. Antioxidant compounds such as coenzyme-Q10, omega-3 polyunsaturated fatty acids, resveratrol, and cannabidiol may aid in cardiac restoration. Diet changes, metformin and glucose control, stem cell therapy, melatonin, and sleep quality improvement are further steps on the road to recovery. In this article we review the cardiotoxicity of MA, pathogenesis of MACM, and evidence behind pharmacologic and lifestyle interventions to reverse its progression.

Introduction

Methamphetamine (MA) and other amphetamine-related derivatives are the second most used illicit drugs worldwide after cannabis[1]. Chronic methamphetamine use over an average period of 12 months leading to methamphetamine-associated cardiomyopathy (MACM) represents a global epidemic that continues to grow[2,3]. Compared with non-MA users with heart failure, patients with MACM tend to be younger and male[4]. These patients also have fewer concomitant medical diagnoses, but more psychiatric issues and social stressors[4]. The clinical and economic burden of MACM has been studied in the United States and Worldwide[5,6]. Over a 10-year period in California, hospitalizations for MACM increased by 585%, and annual inflation-adjusted cost of medical care increased from $42 million to $390 million[7]. Authors of a retrospective study of veterans with heart failure reported 5% were associated with MA use, with the incidence of MACM doubling over a 10-year period[8]. Veterans diagnosed with MACM were more likely to be younger, homeless, unemployed, and have post-traumatic stress disorder and/or depression.

The first reports detailing MACM were published in the 1970s[9,10]. On echocardiography, MACM is typically characterized by decreased left ventricular ejection fraction, higher left ventricular end diastolic volume, and greater right ventricular dilation[10–12]. Catecholaminergic surges may also result in Takotsubo or reverse Takotsubo patterns observed with echocardiography[11,12]. The overall prognosis is poor for patients with MACM and interminable MA use[13]. However, a particular feature of MACM is the potential for reversal of pathologic remodeling and recovery of cardiac function after MA cessation and abstinence[14]. Although this process may take as little as six weeks under optimal circumstances, advanced myocardial fibrosis and ventricular enlargement may limit the possibility of significant repair[15]. This recovery process may be enhanced by the addition of rehabilitation, counseling, and behavioral therapy, as well as an exercise program, guideline-based and alternative pharmacotherapy, phytotherapy, diet changes, stem cell therapy, and sleep quality improvement. In this article we review the cardiotoxicity of MA, pathogenesis of MACM, and evidence behind interventions to reverse its progression.

Methamphetamine Pharmacology and Toxicity

Methamphetamine use results in increased sympathetic nervous system activation through a variety of mechanisms[16]. Due to its high lipid solubility, MA traverses the blood-brain barrier and penetrates the central nervous system (CNS). Methamphetamine is an indirect agonist at norepinephrine, dopamine, and serotonin receptors, and thus stimulates releases of these monoamines in the CNS and peripheral nervous system[17]. Methamphetamine increases extracellular monoamines through non-exocytotic mechanisms and direct interaction with monoaminergic cells[18]. Due to its structural similarity to dopamine, MA is transported to the cytosol via the dopamine transporter (DAT) in exchange for intracellular dopamine. The norepinephrine transporter (NET) is similarly affected. The DAT exchange of extracellular MA for intracellular dopamine increases extracellular dopamine. Methamphetamine impairs vesicular monoamine transporter 2 (VMAT2) function, which is responsible for monoamine storage into synaptic vesicles. At a certain concentration threshold, lipophilic MA diffuses into the cytosol and may also enter synaptic vesicles by diffusion. This results in the release of stored vesicular dopamine into the cytosol, which is ultimately transferred to the extracellular space via DAT reverse transport[16].

Methamphetamine increases tyrosine hydroxylase activity while decreasing monoamine oxidase (MAO) activity, thus adversely affecting monoamine synthesis and metabolism[18]. Methamphetamine is directly toxic to mitochondria with adverse changes in mitochondrial morphology, homeostasis, and oxidative stress metabolism[19]. This increased oxidative stress results from production of reactive oxygen species (ROS), such as hydroxyl radicals, hydrogen peroxide, and superoxide anions[20]. Cell death occurs from resultant lipid peroxidation, protease activation, and peroxynitrite ion generation from ROS reacting with nitric oxide (NO) to damage phospholipids, proteins, and nucleic acids, respectively[21]. The half-life of MA is over 10 hours, and while the euphoric effect usually recedes by four hours, MA-induced tachycardia and hypertension may persist for over 24 hours[17]. Repetitive use of MA may lead to a stacking of cardiovascular effects and sensitization to chronic tachycardia and hypertension with resultant cardiac inflammation and necrosis[22].

Methamphetamine Cardiotoxicity

Methamphetamine-associated cardiomyopathy develops from chronic MA use and repeated sympathetic nervous system activation. A heightened and prolonged catecholaminergic state leads to tachycardia, hypertension, coronary arterial and microvascular vasospasm and/or vasoconstriction with increased myocardial wall

stress and ischemia[23]. Methamphetamine is directly toxic to cardiomyocytes through myriad mechanisms. In addition to increased oxidative stress, MA causes apoptosis via increased p53 activity, alters gene expression, and disrupts intracellular calcium hemostasis[23]. Methamphetamine also interacts with α2 adrenergic receptors, trace amino acid receptor 1 (TAAR1), and sigma-1 receptors (σ1R)[24]. These pathologic processes result in disordered electrical-mechanical coupling and contractile dysfunction[25]. In animal studies of MACM, histopathological examination reveals cardiomyocyte atrophy, lysis, and necrosis[26–28]. Inflammation, interstitial edema and fibrosis, mitochondrial degeneration, and perivascular fibrosis are also noted. In one animal study, these histopathological changes occur even when controlling for MA-related tachycardia and hypertension with a β-blocker[29]. Endomyocardial biopsies from MACM patients demonstrate significant inflammation from increased numbers of macrophages and T-lymphocytes compared to heart failure patients who do not use MA. In a case series of MA-related deaths, MACM was noted in 68 of 100 autopsies[30]

In animal studies, MACM was reversible after withdrawal of the drug[31–33]. In a case series of 19 MACM patients with severe left ventricular dysfunction as indicated by an average ejection fraction of 20%, six patients achieved recovery of left ventricular function at six weeks after MA cessation. Smaller left ventricular and left atrial size, shorter duration of MA use, a reverse Takotsubo pattern, and no evidence of myocardial fibrosis were characteristics associated with recovery[15]. In a study of MACM patients who underwent endomyocardial biopsy, the finding of little to no fibrosis was an independent predictor of cardiac recovery and was also confirmed in case reports using cardiac magnetic resonance imaging to identify fibrosis[34,35] The processes behind the direct and indirect cardiotoxicity of MA and established and experimental countermeasures is highlighted in Figure 1.

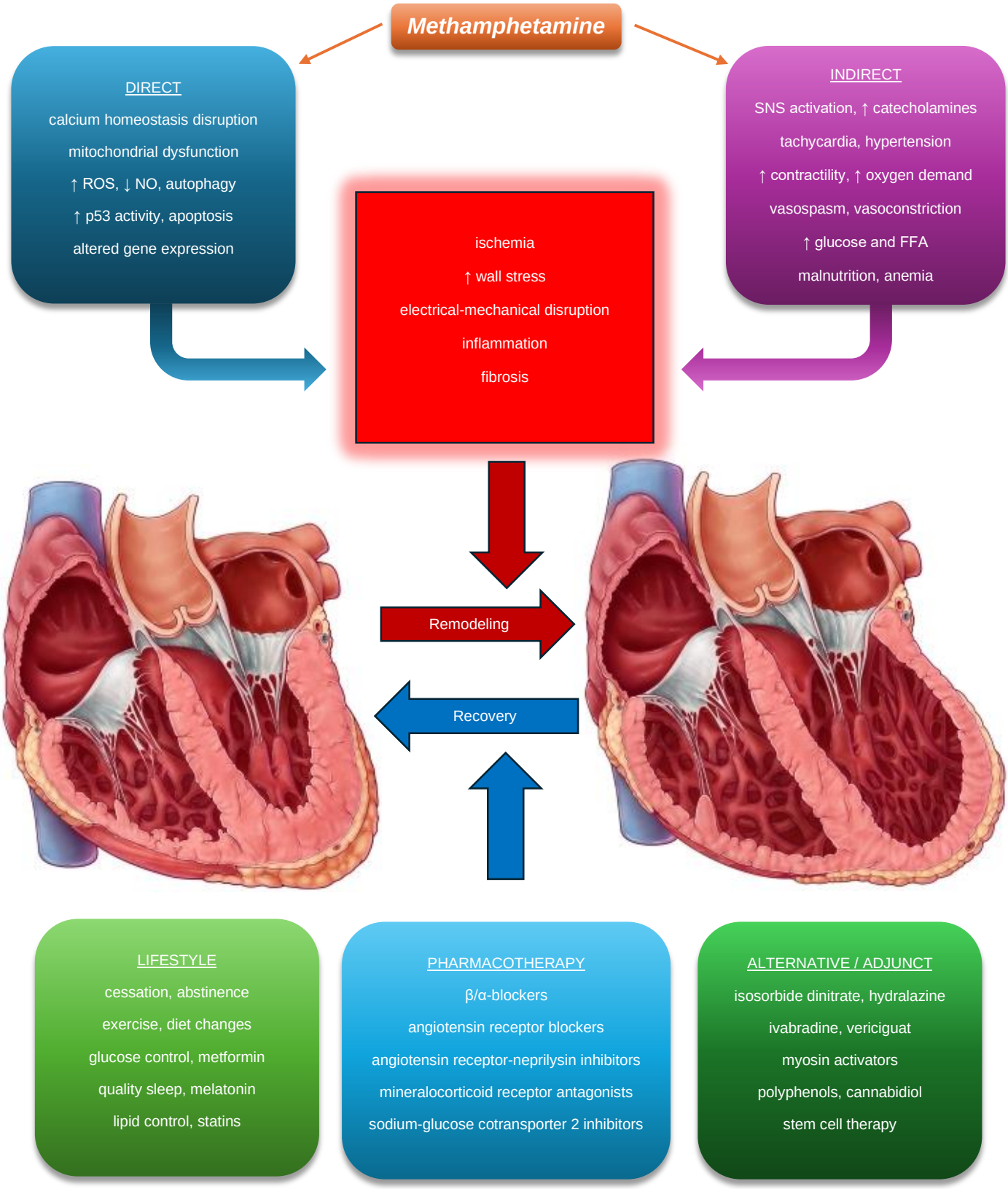

Figure 1. Mechanisms of methamphetamine-associated direct and indirect cardiotoxicity and recovery. Abbreviations: ROS: reactive oxygen species; NO: nitric oxide; SNS: sympathetic nervous system; FFA: free fatty acids.

Therapies for Reversal of MACM Remodeling

CESSATION AND ABSTINENCE

Reverse remodeling of MACM can only be achieved with complete cessation of MA use and abstinence going forward. This has been problematic, as there are no current pharmacotherapeutics with proven efficacy to treat MA dependence and protract abstinence[36–38]. A systemic review of 49 studies involving 20 potential pharmacotherapies for MA cessation and abstinence identified four agents (methylphenidate, bupropion, modafinil, and naltrexone) with limited and inconsistent evidence of benefit[37]. Other human trials of antipsychotics, anticonvulsants, opioid antagonists, selective norepinephrine reuptake inhibitors, nicotinic receptor agonists, and immunotherapy have not shown promising results[38,39]. As such, psychosocial interventions such as cognitive behavioral therapy with relapse prevention, brief interventions, contingency management, motivational interviewing, and residential rehabilitation have become essential tools in the successful transition to abstinence[40,41]. Referral to substance use and mental health services from the emergency department or clinic is especially helpful, as these chronic MA users are at risk of withdrawal, negative peer influence, and often have psychiatric disorders independent of MA use. Unfortunately, intervention programs for MA use experience significant rates of discontinuation[42]. On a more positive note, several studies demonstrated more encouraging results when aerobic exercise programs are added to interventions programs. Exercise is shown to reduce MA craving and depression[43–45].

EXERCISE

In the distant past, vigorous exercise for patients with heart failure was discouraged out of concern for increasing myocardial oxygen demand, rate-pressure product, tachydysrhythmia, afterload, and dyspnea. This dogma changed with growing evidence of bioenergetic and functional improvement of skeletal muscle in heart failure patients who exercised. In sedentary heart failure patients, atrophy of skeletal muscle ensues (including muscles of respiration), inefficient metabolism of adenosine triphosphate (ATP), and supranormal production of lactic acid[46]. Atrophy of respiratory muscles leads to dyspnea on exertion and respiratory failure during acute exacerbations of heart failure. In addition to skeletal muscle meliorism, exercise also improves cardiac muscle function, with improvement in left ventricular ejection fraction and end-diastolic diameter[47]. In a study of over 2,000 subjects from 2009, the safety of exercise for patients with reduced left ventricular ejection fraction was established and was also confirmed in several meta-analyses, as well as improvement in left ventricular function and quality of life[47–50].

Exercise enhances efficiency of oxygen utilization, with lower minute ventilation and rate-pressure product. Sympathetic nervous system tone decreases while parasympathetic nervous system tone increases, leading to lower baseline heart rate and blood pressure[51]. There is also decreased neurohumoral activation and release of angiotensin, B-type natriuretic peptide, aldosterone, and vasopressin. Exercise promotes NO formation in endothelial cells with improved vasodilation in both skeletal and cardiac muscle. Exercise also curtails release of proinflammatory cytokines, mediators of apoptosis, and oxidative stress[50,51]. These salubrious effects may aid in reverse remodeling in MACM[52]. Different forms of exercise have been shown to benefit heart failure patients in their road to recovery, such as aerobic, high-intensity interval training (HIIT), and resistance training[53].

GUIDELINE-BASED PHARMACOTHERAPY

Several major societies and organizations such as the American Heart Association, American College of Cardiology, Heart Failure Society of America, and the European Society of Cardiology have published evidence-based guidelines for the pharmacotherapy of heart failure with reduced left ventricular ejection fraction as in MACM[54–56]. These guidelines have established the four pillars of heart failure treatment with β-blockers, angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers or angiotensin receptor-neprilysin inhibitors (ARNi), mineralocorticoid receptor antagonists (MRA), and sodium-glucose cotransporter 2 (SGLT2) inhibitors. These drugs should be taken concurrently with a program of abstinence to optimize reverse remodeling and recovery of cardiac function in MACM patients[57]. A study of guideline-based treatment of patients with idiopathic dilated cardiomyopathy revealed 31% achieved left ventricular reverse remodeling[58]. In the case of MACM patients with advanced heart failure characterized by low left ventricular ejection fraction and extensive fibrosis, referral for cardiac transplant or mechanical circulatory support devices is indicated, as hope for recovery may be futile.

The heart becomes more dependent on afterload as MACM progresses; small decreases in afterload may result in large increases in stroke volume. Reducing afterload in MACM patients with guideline-based pharmacotherapy is beneficial from increasing cardiac output and slowing or reversing the rate of pathological remodeling.

Neurohormonal activation from progressive heart failure, such as stimulation of angiotensin II, represents an initial compensatory mechanism but is deleterious over the long term from its contribution to remodeling. Randomized human trials demonstrated ARNi and ACEi inhibitors improve survival and regress remodeling[59]. Sacubitril-valsartan is the preferred first-line agent, with alternates including lisinopril, ramipril, enalapril, captopril, losartan, candesartan, and valsartan[60]. Angiotensin II also enhances secretion of aldosterone, which is implicated in the development of cardiac hypertrophy and fibrosis. Blockade of mineralocorticoid receptors within the heart with MRA agents such as spironolactone or eplerenone results in reverse remodeling and recovery of cardiac function[61,62].

Beta-blockers have been used for decades in the treatment of heart failure[63,64]. This class of medication results in decreased heart rate and contractility and is beneficial for patients with MACM and compensatory sympathetic nervous system activation, as well as mitigation of acute MA toxicity[65]. The combined β1/β2/α1-selective blocker carvedilol is preferred as a first line agent, with metoprolol succinate and bisoprolol (both β1-selective) as alternates. An advantage of carvedilol is α1-blockade leading to decreased afterload, peripheral vascular resistance, and blood pressure[66]. Unopposed α-stimulation, the theoretical sudden increase in blood pressure after β-blocker initiation in MACM patients with acute MA toxicity, has never been reported and is not a valid concern in their treatment[67]. The use of β-blockers has been shown to reverse pathologic remodeling and promote cardiac recovery[68–70].

Sodium glucose cotransporters are found primarily in the kidneys but also in the heart and maintain plasma glucose balance. Sodium-glucose cotransporter 2 (SGLT2) inhibitors affect glucose reabsorption from glomerular filtration, lowering serum glucose levels and promoting glucosuria. These medications are recommended for heart failure patients with and without type 2 diabetes mellitus (DM2). Cardioprotective mechanisms include weight loss, reduction of plasma sodium, glucose, and insulin levels[71]. Improvement in blood pressure occurs from reduced renin-angiotensin-aldosterone system activation and diminished sodium reabsorption. Reversal of remodeling has been reported with SGLT2 use from anti-inflammatory effects, decreased fibrosis, ketone metabolism, and promotion of angiogenesis[71]. Meta-analyses have shown use of SGLT2 inhibitors in heart failure patients decreased hospitalization, mortality, and improved left ventricular ejection fraction, exercise capacity, and quality of life[72–74]. The first line SGLT2 inhibitors are dapagliflozin and empagliflozin, with canagliflozin as an alternate.

Other classes of medication mentioned in some heart failure guidelines may be added or substituted based on clinician discretion and/or patient intolerance[75]. For patients who cannot take ARNi/ACEi agents, isosorbide dinitrate plus hydralazine may be used instead for vasodilation and afterload reduction[76]. Ivabradine, a cardiac pacemaker current (I_f) inhibitor, may be added for heart rate control for patients on maximal β-blocker therapy or substituted for patients intolerant to β-blockers[77]. Meta-analyses of ivabradine use in heart failure patients with decreased left ventricular ejection fraction highlighted significant reverse remodeling as an added benefit[78,79]. Another alternative medication is vericiguat, a guanylate cyclase stimulator. Reduced synthesis and increased metabolism of NO and decreased guanylate cyclase activity is associated with heart failure[61]. Nitric oxide binds to guanylate cyclase to produce cyclic guanosine monophosphate (cGMP) with resultant smooth muscle relaxation and vasodilation. Vericiguat binds to and stimulates guanylate cyclase to increase NO[80]. Human trials have shown decreased hospitalization and mortality in heart failure patients taking vericiguat versus placebo[81].

METFORMIN

In addition to SGLT2 inhibitors for heart failure and glucose regulation, metformin may have an important role in reverse remodeling of MACM. Metformin is the most used DM2 agent in the world and is considered a first-line therapy. The nexus between heart failure and DM2 is significant: 44% of patients hospitalized with heart failure also have DM2, and the incidence of new-onset DM2 in heart failure patients is approximately 2% per year. Heart failure patients with DM2 have a 37% higher mortality rate than patients without DM2[82]. The supranormal levels of free fatty acids (FFA) in DM2 and metabolic syndrome have been implicated in the development of heart failure from abnormal deposition of lipid in the myocardium leading to fibrosis and remodeling. Insulin resistance and FFA oxidation to produce ATP increases cardiac workload[83]. In heart failure, metformin enhances mitochondrial biogenesis and metabolism in cardiomyocytes through increase in adenosine monophosphate-activated protein kinase (AMPK) activity, endothelial nitric oxide synthase (eNOS) expression, and peroxisome proliferator-activated receptor gamma (PPARγ)[84]. Metformin also inhibits

collagen synthesis in myocardium from inhibition of transforming growth factor beta 1 (TGF-β1), which is pro-fibrotic. Human trials of metformin use in heart failure have demonstrated improvement in left ventricular ejection fraction, exercise capacity, and reduction in myocardial oxygen consumption[85]. Another benefit of metformin is its unexpected anxiolytic and antidepressant effect in the setting of MA use through direct activation of the cAMP response element binding protein (CREB)/brain-derived neurotrophic factor (BDNF) and protein kinase B (Akt)/glycogen synthase kinase 3 (GSK3) signaling pathways in the CNS[86,87].

STATINS

Statins have pleiotropic effects that theoretically could benefit patients with MACM, such as anti-atherogenesis, endothelial plaque-stabilization, and improvement in endothelial function. Statins also inhibit proinflammatory cytokine activity, modulate the sympathetic nervous system, and have antidysrhythmic effects[88]. However, statins lower lipoprotein levels, which counter bacterial lipopolysaccharide endotoxins entering the circulation and may increase risk of infection. Statins reduce plasma levels of mitochondrial ubiquinone (coenzyme Q10), which may lead to increased oxidative stress and cell death[89]. This adverse effect may be enhanced by concomitant MA use. Meta-analyses reported that use of statins in heart failure patients was associated with reductions in mortality, rehospitalization, low-density lipoprotein cholesterol, and increase in left ventricular ejection fraction[90,91].

MYOSIN ACTIVATORS

Omecamtiv mecarbil and danicamtiv are myosin activators that bind to the catalytic S1 domain of cardiac myosin to increase contractility[92]. The main mechanism of action for these agents is acceleration of ATP hydrolysis to adenosine diphosphate (ADP) and phosphate, thus increasing the number of actin-myosin interactions, myocyte contraction, ventricular force, and systolic ejection time[93]. Other benefits include reduced heart rate, peripheral vascular resistance, afterload, and left ventricular end-diastolic pressure[94,95]. Gains in stroke volume and cardiac output have also been reported in human trials[95–97].

STEM CELL THERAPY

Stem cell therapy represents a promising treatment for reverse remodeling that is still under investigation. Inoculated stem cells do not directly engraft into the myocardium to differentiate in cardiomyocytes. The beneficial effects of stem cells are instead linked to paracrine and endocrine mediation of inflammation, fibrosis, angiogenesis, and apoptosis[93]. A meta-analysis of bone marrow-derived mesenchymal stem cells to treat patients with cardiomyopathy reported improvement in left ventricular ejection fraction and exercise tolerance[98]. Another meta-analysis focused on mesenchymal stem cells and found a reduction in hospitalization rate and mortality, as well as improvement of left ventricular ejection fraction and exercise tolerance[99]. Further research incorporating c-kit-positive cardiac stem cells, cardiac progenitor cells, and cardiosphere-derived cells isolated from biopsy-obtained cardiac tissue suggests the enhanced potential for regeneration from direct cardiomyocyte stimulation and/or paracrine signaling[93,100].

DIETARY INTERVENTIONS

Methamphetamine users may experience malnutrition due to poor dietary choices[101]. Deficiencies in certain nutrients, such as iron, are common in patients with heart failure. Anemia from iron deficiency may compromise oxygen delivery to the heart, and iron supplementation has been shown to be of particular benefit in heart failure patients[102]. Western diets are typically high in sodium, saturated fat, refined carbohydrates, preserved meat, and glucose, which are pro-inflammatory, increase oxidative stress, and damage cardiomyocytes[103]. Dietary interventions, such as sodium restriction and implementation of the Mediterranean, Dietary Approaches to Stop Hypertension (DASH), or High Exogenous Antioxidant, Restorative Treatment (HEART) diets can reduce the progression of heart failure[103–105]. In a meta-analysis, the addition of antioxidant coenzyme Q10 supplementation was associated with lower mortality and improvement of left ventricular ejection fraction[106]. Evidence also supports the addition of omega-3 polyunsaturated fatty acids supplements to the diet contributes to reverse remodeling from anti-inflammatory and antioxidant effects, and enhanced cardiomyocyte mitochondrial function[107,108]. Gut microbiota may produce deleterious metabolites and cause adverse immune signaling tied to the development and progression of heart failure[109]. The addition of probiotics may represent a therapeutic strategy to counter these negative effects[110]. Phytogenic polyphenols such as resveratrol, quercetin, curcumin, and silymarin decrease ROS generation and enhance NO production in the endothelium[111,112]. The omission of alcoholic beverages from the diet of MACM patients is important for reverse remodeling, as concurrent use of alcohol with MA increased the rate-pressure product compared with MA use alone[113,114].

CANNABIDIOL

The endocannabinoid system is involved in all functions of the body, including allostasis, homeostasis, inflammation, oxidation, metabolism, memory, learning, mood, and immune response[115]. Cannabidiol (CBD) is one of more than 80 different cannabinoids that are present in the *Cannabis* plant. Unlike tetrahydrocannabinol (THC), CBD does not have psychoactive side effects. Cannabidiol has myriad mechanisms of action, including stimulation of CB1 and CB2 receptors, transient receptor potential vanilloid (TRPV) receptors, serotonin 5HT1A receptor, and PPARγ[116]. Cannabidiol interaction with TRPV receptors modifies gamma-aminobutyric acid (GABA) and glutamate release, with anti-inflammatory, anxiolytic, analgesic, and anticonvulsant effects[117]. Stimulation of 5HT1A receptors de-escalates anxiety, fear, and the autonomic stress response to promote allostasis. Like metformin, CBD interaction with PPARγ influences glucose and lipid metabolism and storage, as well as mitigates inflammation. Cannabidiol possesses antioxidant effects from increased expression of superoxide dismutase, glutathione peroxidase, and nuclear complex erythroid 2-related factor (Nrf2)/Keep1. It also inhibits expression of nuclear factor kappa B (NF-κB) and genes encoding proinflammatory cytokines and metalloproteinases[117]. Additional therapeutic targets of CBD include certain G protein-coupled receptors, structures involved in calcium homeostasis, glycinergic receptors α1 and α1β, adenosine receptors A1 and A2, and lipoxygenase and cyclooxygenase type 2 receptors[117]. Animal studies have shown CBD to have cardioprotective effects against MA toxicity via the protein kinase A/CREB pathway[118,119]. Cannabidiol also attenuates myocardial damage from its interaction with adenosine receptors[120]. The anti-inflammatory and antioxidative properties of CBD, combined with its lack of psychoactive side effects, makes it a compelling adjunct in reverse remodeling of MACM, but no human trials exist currently[119].

SLEEP

Methamphetamine users typically have poor sleep quality from alternating periods of stimulation and withdrawal[121]. One theory of MA cardiotoxicity and development of MACM involves MA alteration of genes in the CNS involved in circadian rhythm[122]. The neuropeptide orexin is produced exclusively in the hypothalamus and is involved in sleep-wake regulation and appetite. Methamphetamine users have been shown to have higher orexin levels and disordered sleep than non-MA users[117]. The diagnosis of sleep apnea is also important in heart failure patients. Obstructive sleep apnea (OSA) and central sleep apnea (CSA) worsen heart failure through several mechanisms. Intermittent hypoxemia in OSA and sudden arousals result in catecholaminergic surges, with reactionary and rapid negative intrapleural pressures increasing ventricular wall stress, afterload, and atrial dilation[123]. Hypocapnia in CSA leads to periods of Cheyne-Stokes breathing with prolonged periods of apnea. Over time, a pro-inflammatory, pro-fibrotic state within the heart is established unless positive pressure treatment is initiated[123]. Patients with OSA and CSA plus heart failure have a significantly higher mortality rate than heart failure patients without sleep apnea[124,125]. Diagnosis and treatment of OSA and CSA in MACM patients is thus very important in the path to reverse remodeling and cardiac recovery[126].

Melatonin, which is endogenously produced in the pineal gland, is a commonly used sleep aid. It is also an antioxidant and anti-inflammatory agent through several different mechanisms, such as maintaining mitochondrial homeostasis[127]. Other mechanisms include direct detoxification of ROS and reactive nitrogen species. Melatonin chelates transition metals, preventing formation toxic hydroxyl radicals. Pineal melatonin secretion and circulating melatonin levels are reduced in patients with heart failure[128]. Animal studies of heart failure have shown melatonin to be cardioprotective[129]. Melatonin may be helpful in reverse remodeling by attenuating fibrosis, extracellular matrix deposition, and availability of cardiac collagen[130]. Melatonin has also been shown to protect against MA-associated neurotoxicity[131]. The addition of melatonin in MACM patients may be useful in reverse remodeling with the added benefit of sleep quality improvement.

Conclusion

Methamphetamine use and development of MACM in younger patients represents a growing societal economic burden and epidemiological problem worldwide. However, reversal of MACM pathologic remodeling and return of normal cardiac function is achievable with cessation of MA use and abstinence. Evidence-directed pharmacotherapy and anti-inflammatory/antioxidative agents may accelerate cardiac healing. Lifestyle changes, including exercise, diet, and sleep quality improvement are also essential to this process.

Conflict of Interest Statement:

The authors have no conflict of interest to declare.

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