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Metabolic Syndrome and Migraine: Current Evidence, Pathophysiological Mechanisms and Clinical Implications

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ABSTRACT: Migraine and metabolic syndrome are highly prevalent disorders that increasingly appear to intersect through shared metabolic, inflammatory, neurovascular, and neuroendocrine pathways. Migraine is now recognized as a complex neurological disorder involving trigeminovascular activation, calcitonin gene-related peptide (CGRP) signaling, cortical hyperexcitability, neuroinflammation, and central sensitization, whereas metabolic syndrome comprises central obesity, insulin resistance, dyslipidemia, hypertension, and associated cardiometabolic abnormalities. Epidemiological evidence indicates that these conditions frequently coexist and that obesity, insulin resistance, adverse lipid profiles, blood-pressure abnormalities, and sex-related factors may influence migraine frequency, severity, and chronification. Mechanistically, visceral adiposity and adipokine dysregulation promote chronic low-grade inflammation, while cytokines such as TNF- α , IL-1 β , and IL-6 activate NF- κ B, Toll-like receptor, and NLRP3 inflammasome pathways. These processes interact with oxidative and nitrosative stress, mitochondrial dysfunction, impaired endothelial signaling, autonomic imbalance, hypothalamic dysfunction, blood–brain barrier alterations, and gut–brain axis disturbances. CGRP provides a particularly important neuro-metabolic interface because it contributes to trigeminovascular transmission while also participating in vascular and metabolic regulation. Mitochondrial energy failure, reactive oxygen species generation, impaired calcium handling, and ATP depletion may further lower the threshold for cortical spreading depolarization and trigeminal activation. Collectively, current evidence supports a bidirectional metabolic–inflammatory–mitochondrial–neurovascular model linking metabolic syndrome with migraine. Recognition of this overlap may facilitate improved cardiometabolic screening, individualized migraine management, and development of integrated therapeutic

strategies targeting both neurological and metabolic dysfunction.

INTRODUCTION

Migraine is a common, recurrent, and disabling primary neurological disorder characterized by episodic attacks of moderate-to-severe headache accompanied by a constellation of neurological, autonomic, gastrointestinal, and sensory manifestations [1]. Rather than being considered merely a vascular headache, migraine is now understood as a complex neurobiological disorder involving altered excitability of central neuronal networks, activation of the trigeminovascular system, neuropeptide release, cortical and subcortical dysfunction, and abnormal processing of sensory information. According to the International Classification of Headache Disorders, migraine is principally categorized into migraine without aura and migraine with aura, although several additional subtypes and complications are recognized [2]. Migraine without aura is typically characterized by recurrent headache attacks lasting several hours, often presenting with unilateral location, pulsating quality, moderate-to-severe intensity, aggravation by routine physical activity, and associated symptoms such as nausea, vomiting, photophobia, and phonophobia. In contrast, migraine with aura involves transient and usually fully reversible neurological manifestations that generally precede or accompany headache. Aura most frequently presents with visual disturbances but may also include sensory, speech, language, motor, brainstem, or retinal symptoms. The distinction between these phenotypes is clinically important because migraine with aura has been associated with particular vascular and cerebrovascular risk profiles [3]. Nevertheless, individual patients may experience attacks both with and without aura during their lifetime. Migraine is also classified according to attack frequency into episodic and chronic forms. Chronic migraine is defined by headache occurring on at least 15 days per month for more than three months, with migraine features present on at least eight days per month. This distinction has major clinical significance because chronification is associated with greater disability, medication overuse, reduced quality of life, psychiatric comorbidity, increased healthcare utilization, and greater socioeconomic burden. Current concepts of migraine pathophysiology emphasize an integrated neural and vascular mechanism rather than the historical concept of simple intracranial vasodilatation [4]. Activation of the trigeminovascular system results in release of vasoactive neuropeptides, particularly calcitonin gene-related peptide (CGRP), which contributes to nociceptive transmission, neurogenic signaling, and sensitization of trigeminal pathways. Peripheral sensitization of trigeminal nociceptors and subsequent central sensitization within the trigeminal nucleus caudalis, thalamus, and cortical regions may contribute to prolonged headache and cutaneous allodynia. Cortical spreading depolarization is considered an important electrophysiological substrate of migraine aura and can influence meningeal nociceptive pathways [5]. Dysfunction of hypothalamic, brainstem, thalamic, and limbic networks may additionally explain premonitory symptoms, autonomic disturbances, altered appetite, sleep abnormalities, emotional changes, and heightened sensory sensitivity. Increasing attention has also been directed toward mitochondrial dysfunction, oxidative stress, neuroinflammation, altered glucose metabolism, endothelial dysfunction, and disturbances in neuroendocrine regulation [6]. These mechanisms are particularly relevant to the proposed relationship between migraine and cardiometabolic disorders. Migraine susceptibility is influenced by genetic predisposition, sex hormones, age, sleep disturbances, psychological stress, dietary factors, physical inactivity, obesity, medication overuse, and environmental triggers. Important comorbidities include depression, anxiety, epilepsy, sleep disorders, obesity, hypertension, dyslipidemia, insulin resistance, cardiovascular disease, and certain cerebrovascular disorders. The clustering of several metabolic abnormalities among migraine patients has therefore stimulated considerable interest in whether migraine and metabolic syndrome share common pathophysiological pathways [7,8].

Overview of Metabolic Syndrome

Metabolic syndrome is a cluster of interconnected metabolic and cardiovascular abnormalities that substantially increase an individual's risk of developing type 2 diabetes mellitus, atherosclerotic cardiovascular disease, and other cardiometabolic complications. Its principal components include central or abdominal obesity, impaired glucose regulation or insulin resistance, elevated triglycerides, reduced high-density lipoprotein cholesterol, and elevated blood pressure. Although several organizations have proposed diagnostic criteria, contemporary clinical definitions generally identify metabolic syndrome when multiple metabolic abnormalities coexist within the same individual [9]. For example, commonly applied criteria recognize metabolic syndrome when at least three of five abnormalities involving waist circumference, triglycerides, HDL cholesterol, blood pressure, and fasting glucose are present, while International Diabetes Federation criteria historically place particular

emphasis on central adiposity. Importantly, ethnicity-specific differences in waist circumference and metabolic risk should be considered when assessing central obesity. Central obesity is a major pathophysiological driver of metabolic syndrome because visceral adipose tissue functions as an active endocrine and immunological organ rather than merely an energy-storage compartment [10]. Expansion and dysfunction of visceral adipose tissue promote release of free fatty acids, inflammatory mediators, adipokines, and other signaling molecules that interfere with insulin action and vascular homeostasis. Insulin resistance subsequently reduces the ability of insulin-responsive tissues, particularly skeletal muscle, liver, and adipose tissue, to respond appropriately to circulating insulin. Compensatory hyperinsulinemia may initially maintain glycemic control; however, progressive pancreatic β -cell dysfunction can ultimately result in impaired fasting glucose and type 2 diabetes. Insulin resistance also promotes hepatic triglyceride synthesis, increased very-low-density lipoprotein production, accumulation of atherogenic lipoproteins, and reduction in protective HDL cholesterol [11]. Consequently, the characteristic dyslipidemic profile of metabolic syndrome consists predominantly of hypertriglyceridemia, low HDL cholesterol, and increased concentrations of small dense LDL particles. Hypertension frequently accompanies these abnormalities because of sympathetic nervous system activation, renal sodium retention, renin–angiotensin–aldosterone system dysregulation, insulin-mediated vascular alterations, oxidative stress, and impaired endothelial nitric oxide availability [12]. Metabolic syndrome is therefore characterized by much more than the simultaneous presence of conventional cardiovascular risk factors. It represents a systemic pathophysiological state involving chronic low-grade inflammation, oxidative stress, endothelial dysfunction, altered adipokine signaling, mitochondrial abnormalities, autonomic imbalance, vascular remodeling, and disturbances in cellular energy metabolism [13]. These processes contribute to accelerated atherosclerosis and cardiovascular disease but may also influence cerebral vascular function, neuronal metabolism, nociceptive signaling, and neuroinflammation. This provides a biologically plausible framework for understanding why metabolic syndrome and migraine may coexist and potentially interact. The emerging cardiovascular-kidney-metabolic framework further emphasizes that obesity, abnormal glucose metabolism, renal dysfunction, and cardiovascular disease form interconnected rather than isolated pathological processes [14,15].

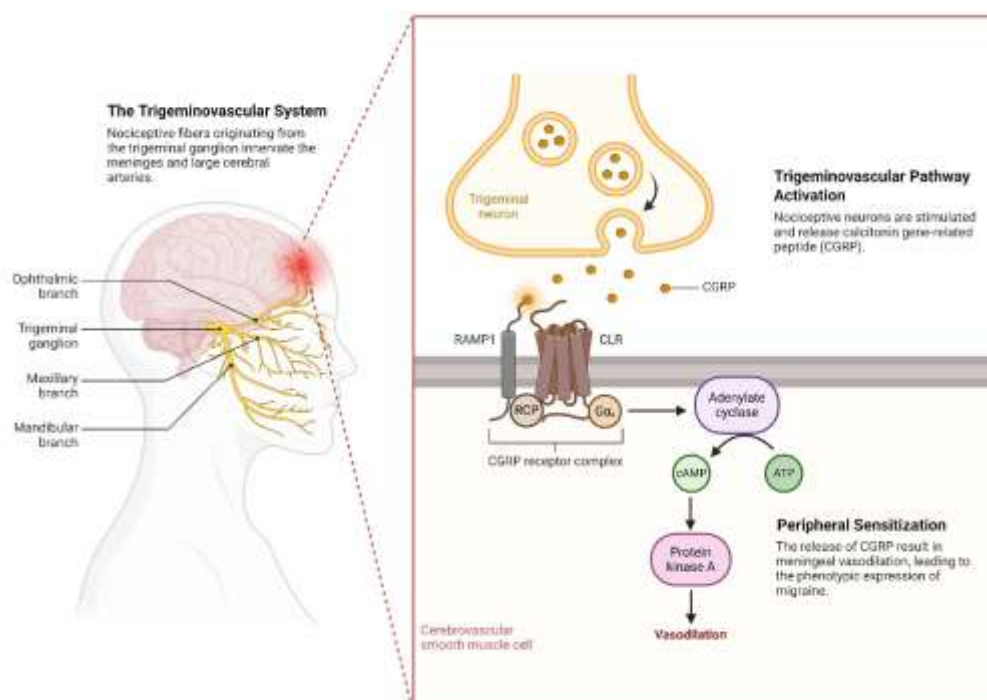


Fig: 1 Pathophysiology of Migraine

Epidemiological Association Between Metabolic Syndrome and Migraine

Epidemiological investigations increasingly suggest that migraine and metabolic abnormalities frequently coexist, although the magnitude and direction of individual associations remain heterogeneous across populations. Several studies have reported a

higher burden of obesity, insulin resistance, dyslipidemia, and blood-pressure abnormalities among individuals with migraine, thereby raising the possibility that metabolic syndrome may represent an important comorbid condition in a clinically relevant subset of migraine patients [16]. An early study specifically evaluating migraine in individuals with metabolic syndrome reported migraine prevalence of approximately 11.9% in men and 22.5% in women, illustrating both the coexistence of these disorders and the pronounced sex difference in migraine occurrence. However, prevalence estimates vary according to geographic region, study population, age distribution, diagnostic definitions, metabolic criteria, and whether migraine is identified through physician diagnosis, structured interviews, questionnaires, or self-report. Among the individual components of metabolic syndrome, obesity has demonstrated one of the more consistent relationships with migraine burden. Excess adiposity does not necessarily appear to determine whether an individual will develop migraine in a simple dose-dependent manner, but it has been associated in several studies with increased headache frequency, greater disability, and progression toward chronic migraine. Visceral adiposity may be especially important because of its inflammatory and endocrine activity [17]. Adipose-derived mediators such as leptin, adiponectin, inflammatory cytokines, and free fatty acids can interact with pathways involved in trigeminal activation and nociceptive sensitization. Insulin resistance has also attracted considerable attention because both peripheral metabolic dysfunction and impaired cerebral energy metabolism could theoretically alter migraine susceptibility. Earlier clinical observations suggested that insulin resistance may occur more frequently among migraine patients, although associations between overt diabetes and migraine have been inconsistent. Dyslipidemia has similarly been linked with migraine in some cohorts, particularly through elevated triglycerides, unfavorable cholesterol profiles, and altered HDL concentrations, but findings remain variable. Sex and age substantially modify the observed association. Migraine is more prevalent among women, particularly during reproductive years, whereas metabolic syndrome becomes increasingly common with advancing age. Hormonal fluctuations, especially estrogen-related effects on CGRP signaling, vascular reactivity, glucose metabolism, adipose distribution, and inflammatory pathways, may contribute to sex-specific relationships [18]. Menopause may further strengthen the convergence between migraine history and cardiometabolic risk because declining estrogen levels are accompanied by changes in body-fat distribution, insulin sensitivity, lipid metabolism, and vascular function. Age-related metabolic deterioration may therefore influence migraine phenotype differently across the lifespan. The relationship between metabolic abnormalities and migraine frequency or chronification is particularly important clinically. Obesity, sleep disorders, psychological stress, physical inactivity, medication overuse, and other metabolic or behavioral factors may facilitate transformation from episodic to chronic migraine. Chronic migraine itself may also promote sedentary behavior, sleep disruption, reduced physical activity, stress, and weight gain, suggesting that the association could be bidirectional [19]. Consequently, migraine may worsen metabolic health while metabolic dysfunction may increase susceptibility to frequent or persistent headache. Despite accumulating population-based and clinical evidence, causality has not been firmly established. Much of the available literature is cross-sectional, making it difficult to determine whether metabolic syndrome precedes migraine progression or develops as a consequence of shared lifestyle, genetic, endocrine, or inflammatory determinants. Differences in migraine classification, metabolic syndrome definitions, ethnicity, body composition, medication exposure, hormonal status, diet, smoking, physical activity, and socioeconomic characteristics further complicate comparisons among studies. Confounding by migraine-preventive treatments is another concern because some drugs can promote weight gain or metabolic abnormalities whereas others facilitate weight reduction. Thus, the current evidence supports meaningful biological and epidemiological overlap between migraine and metabolic syndrome, but the association should be interpreted as heterogeneous and potentially bidirectional rather than as a simple causal relationship. Large prospective cohorts, standardized metabolic phenotyping, longitudinal assessment of migraine activity, and mechanistically informed studies are required to determine which metabolic abnormalities most strongly influence migraine development, severity, and chronification [20].

Table 1. Diagnostic Criteria and Major Components of Metabolic Syndrome

Component	Diagnostic criterion	Major pathophysiological significance
Central/abdominal obesity	Waist circumference ≥ 102 cm in men and ≥ 88 cm in women; for individuals of Asian ancestry, ≥ 90 cm in men and ≥ 80 cm in women	Reflects visceral adiposity and is associated with adipokine imbalance, insulin resistance, chronic low-grade inflammation, endothelial dysfunction, and increased cardiometabolic risk.
Elevated	≥ 150 mg/dL (≥ 1.7 mmol/L) or receiving	Indicates atherogenic dyslipidemia, increased VLDL

triglycerides	treatment for hypertriglyceridemia	production, altered fatty-acid metabolism, and greater cardiovascular risk.
Reduced HDL-C	<40 mg/dL (<1.03 mmol/L) in men and <50 mg/dL (<1.29 mmol/L) in women, or receiving treatment for low HDL-C	Represents impaired reverse cholesterol transport and is commonly associated with insulin resistance and an atherogenic lipid profile.
Elevated blood pressure	SBP $\geq$ 130 mmHg and/or DBP $\geq$ 80 mmHg, or use of antihypertensive medication	Associated with sympathetic overactivity, vascular remodeling, endothelial dysfunction, oxidative stress, and increased cardiovascular and cerebrovascular risk.
Elevated fasting glucose	$\geq$ 100 mg/dL ($\geq$ 5.6 mmol/L) or treatment for hyperglycemia/diabetes	Reflects impaired glucose regulation and insulin resistance and may progress to type 2 diabetes mellitus.
Diagnostic requirement	Presence of any 3 or more of the 5 components	Identifies individuals with clustering of cardiometabolic abnormalities and elevated risk of diabetes and cardiovascular disease.

Obesity as a Link Between Metabolic Syndrome and Migraine

Obesity represents one of the most important biological interfaces between metabolic syndrome and migraine because excessive adiposity simultaneously alters inflammatory, endocrine, vascular, and energetic homeostasis [21]. The relationship appears to be particularly relevant for visceral adiposity, which is metabolically more active than subcutaneous fat and is strongly associated with insulin resistance, dyslipidemia, hypertension, and systemic inflammation. Epidemiological and clinical observations indicate that increasing adiposity may be associated with greater migraine frequency, disability, and risk of progression toward chronic migraine, although obesity should not be interpreted as a universal or isolated cause of migraine. Instead, excess adiposity appears to modify disease expression in susceptible individuals through several converging mechanisms. Visceral fat accumulation increases the release of free fatty acids, inflammatory cytokines, chemokines, and adipokines and promotes oxidative stress, endothelial dysfunction, and impaired insulin signaling. These abnormalities overlap substantially with pathways implicated in trigeminovascular activation and central nociceptive sensitization. Recent reviews therefore characterize obesity and migraine as interacting disorders connected by metabolic inflammation rather than by body weight alone [22].

Adipose tissue is now recognized as a highly active endocrine and immunological organ capable of producing numerous biologically active mediators that influence appetite, energy expenditure, insulin sensitivity, vascular function, immunity, and inflammatory signaling. Among these mediators, leptin, adiponectin, and resistin have received particular attention in migraine research. Leptin is primarily secreted by adipocytes and normally signals energy sufficiency to the hypothalamus, but circulating concentrations generally rise with increasing adiposity because of leptin resistance [23]. Beyond metabolic regulation, leptin has immunomodulatory and predominantly pro-inflammatory properties and can facilitate secretion of cytokines such as TNF- α and IL-6. Because hypothalamic dysfunction, inflammatory signaling, and altered energy balance are all implicated in migraine, dysregulated leptin signaling provides a plausible mechanistic bridge. Clinical studies and meta-analytic evidence have reported altered leptin concentrations in individuals with migraine, although values vary according to body mass index, sex, fasting state, migraine phase, and other metabolic variables. Adiponectin differs from leptin in that its circulating concentration often declines with visceral obesity and insulin resistance. It exerts insulin-sensitizing, anti-inflammatory, anti-atherogenic, and endothelial-protective effects through receptors expressed in several tissues, including the nervous system. However, adiponectin exists in different molecular forms with potentially distinct biological effects, which may partly account for inconsistent findings in migraine studies. Resistin, originally associated with insulin resistance, is produced predominantly by inflammatory cells in humans and has pro-inflammatory effects capable of enhancing cytokine signaling and endothelial activation. Meta-analytic data support associations between migraine and altered circulating

adipokines, particularly leptin and adiponectin, but considerable heterogeneity prevents these molecules from being regarded as validated diagnostic biomarkers at present [24].

Obesity-associated neuroinflammation may be especially important for migraine chronification. Adipose tissue expansion is accompanied by macrophage infiltration, activation of innate immune pathways, and persistent elevations of inflammatory mediators such as IL-1 β , IL-6, TNF- α , C-reactive protein, and resistin. These peripheral signals can influence the nervous system through humoral, endothelial, and neural routes and may enhance microglial reactivity, trigeminal nociceptive transmission, and CGRP-associated neurogenic inflammation. Oxidative stress and mitochondrial impairment further amplify these processes by lowering the threshold for neuronal activation [25]. Obesity may additionally alter sleep, mood, physical activity, autonomic function, and medication response, all of which can modify migraine burden. Consequently, the association between obesity and chronic migraine is probably multifactorial and bidirectional. Frequent migraine attacks may promote inactivity, sleep disruption, stress-related eating, and weight gain, whereas excess adiposity may facilitate increased attack frequency and sensitization. The observation that weight-reduction interventions can decrease headache frequency and disability in some patients supports the clinical relevance of this relationship, although additional controlled studies are required to identify which metabolic phenotypes derive the greatest benefit [26].

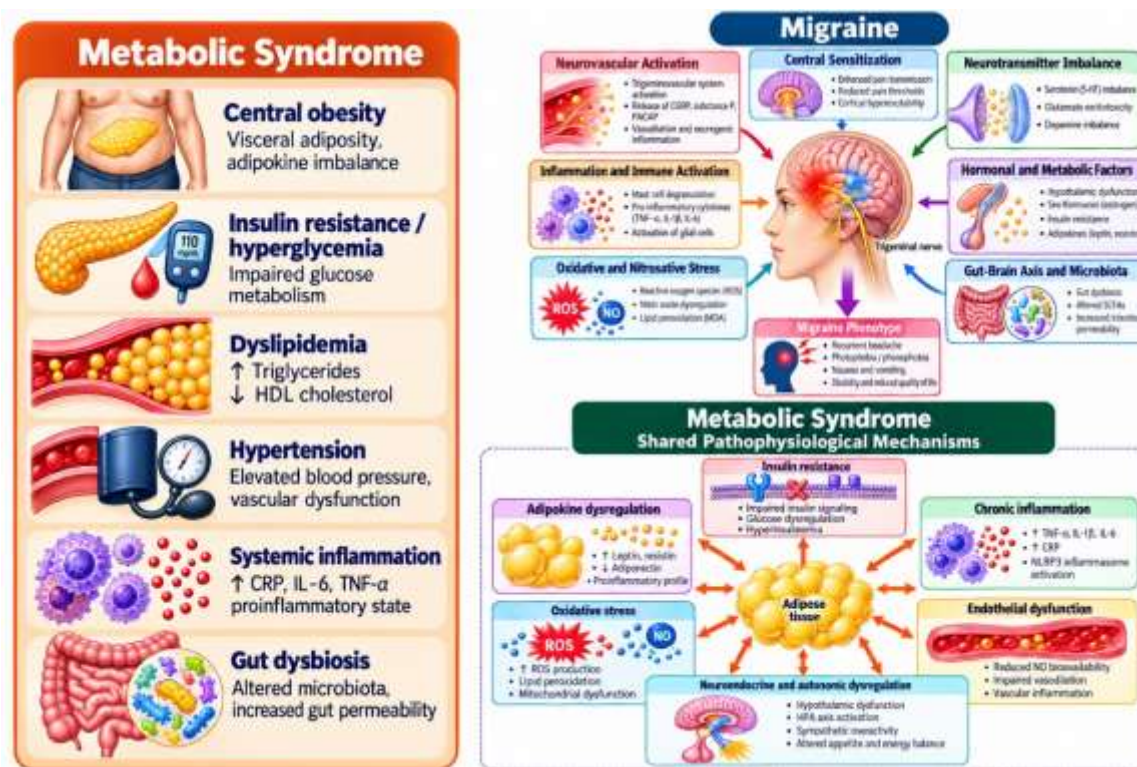


Fig: 2 Bidirectional Pathophysiological Interplay Between Metabolic Syndrome and Migraine

Insulin Resistance and Glucose Dysregulation in Migraine

Insulin resistance provides another major mechanistic connection between metabolic syndrome and migraine. Under normal physiological conditions, insulin regulates peripheral glucose uptake, hepatic glucose output, lipid metabolism, and cellular energy utilization while also exerting important actions within the central nervous system [27]. Insulin receptors are expressed in the hypothalamus, hippocampus, cortex, and other brain regions involved in energy homeostasis, cognition, autonomic regulation, and nociception. In insulin-resistant states, canonical insulin receptor signaling becomes impaired, particularly through insulin receptor substrate and phosphoinositide 3-kinase/protein kinase B pathways. The resulting metabolic disturbance can produce compensatory hyperinsulinemia, fluctuating glucose availability, mitochondrial stress, oxidative injury, and inflammatory activation. Recent mechanistic literature supports significant overlap between insulin resistance, hyperinsulinemia, neurogenic inflammation, and migraine susceptibility [28].

Hyperinsulinemia may influence migraine through several pathways. Persistent high insulin concentrations can enhance sympathetic activity, alter vascular tone, contribute to sodium retention, promote inflammatory signaling, and modify neuronal excitability. Metabolic dysfunction may also sensitize transient receptor potential channels and facilitate CGRP release, thereby lowering the threshold for activation of trigeminal nociceptive pathways. Furthermore, selective insulin resistance can preserve some lipogenic insulin actions while weakening glucose-lowering pathways, promoting dyslipidemia and further metabolic stress. This phenomenon is highly relevant to the broader metabolic syndrome phenotype because abnormalities in glucose and lipid metabolism rarely occur independently. Insulin resistance also interacts with mitochondrial dysfunction, which is increasingly considered important in migraine. Neurons have high energetic demands, and disturbances in glucose utilization or oxidative phosphorylation may impair maintenance of ionic gradients and increase susceptibility to depolarization. An energetically vulnerable cortex may therefore exhibit a reduced threshold for cortical spreading depolarization and sensory hyperexcitability [29].

Acute reductions in circulating glucose have long been recognized by many patients as potential migraine triggers. Prolonged fasting, skipped meals, excessive exercise without adequate energy intake, and rapid glucose fluctuations can initiate attacks in susceptible individuals. Several explanations have been proposed, including activation of counter-regulatory hormones, sympathetic stimulation, increased cerebral excitability, altered hypothalamic activity, and reduced availability of metabolic substrates for neuronal ATP production. Importantly, the association between hypoglycemia and migraine does not imply that all migraine patients have impaired glucose regulation; rather, energetic instability may act as a trigger when superimposed on genetically or metabolically susceptible neural networks. Brain glucose metabolism is also affected by mitochondrial efficiency. When ATP production becomes insufficient, neuronal membrane stabilization, glutamate handling, calcium homeostasis, and antioxidant defense are compromised. This may facilitate oxidative stress, cortical excitability, and trigeminovascular activation [30].

The relationship between migraine and overt diabetes is complex. Some studies have reported positive associations between insulin resistance or prediabetic metabolic abnormalities and migraine, whereas the epidemiology of established diabetes and migraine has been less consistent. Differences in disease duration, glycemic control, medication use, neuropathy, age, sex, and vascular status may contribute to the variability. Consequently, insulin resistance may be biologically more relevant to migraine than diabetes as a categorical diagnosis [31]. Intracellular metabolic pathways provide additional mechanistic support. PI3K/Akt signaling is essential for insulin-mediated glucose transport and cell survival, and disruption of this pathway promotes insulin resistance, oxidative stress, and inflammatory responses. AMP-activated protein kinase acts as a cellular energy sensor that is activated when the AMP-to-ATP ratio rises. AMPK stimulates energy-producing pathways while suppressing energy-consuming processes and interacts with mitochondrial biogenesis, lipid oxidation, autophagy, and inflammatory regulation. Alterations in AMPK signaling may therefore connect impaired systemic metabolism with neuronal energy deficiency. Together, PI3K/Akt and AMPK represent important molecular nodes through which insulin resistance, mitochondrial dysfunction, and neuroinflammation may converge in migraine [32-36].

Dyslipidemia and Altered Lipid Metabolism

Dyslipidemia represents a further component of metabolic syndrome with potential implications for migraine pathophysiology. The characteristic metabolic syndrome lipid profile includes elevated triglycerides, reduced HDL cholesterol, increased remnant lipoproteins, and a greater proportion of small dense LDL particles [37]. Studies evaluating conventional lipid parameters in migraine have generated heterogeneous findings, although unfavorable lipid profiles have been reported in subsets of patients, particularly those with frequent attacks or coexisting obesity and insulin resistance. It remains uncertain whether individual cholesterol fractions directly influence migraine or primarily reflect broader systemic metabolic dysfunction. Nevertheless, lipids have biological functions extending far beyond energy storage. They form neuronal and mitochondrial membranes, regulate receptor organization, serve as precursors for signaling molecules, influence inflammation, and modulate vascular function. Disturbances in lipid metabolism could therefore alter both vascular and neuronal processes relevant to migraine [38-40].

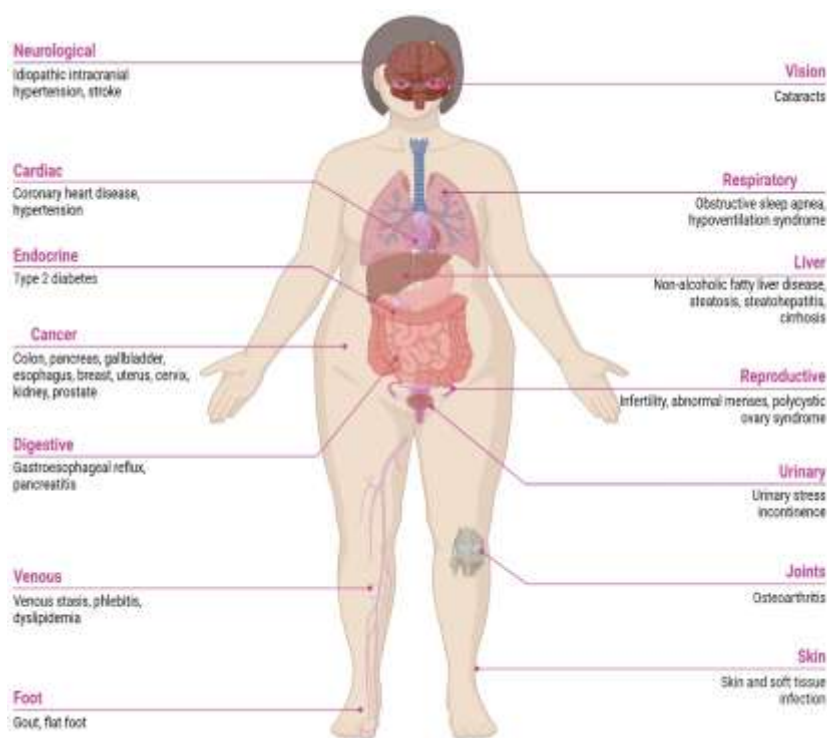


Fig: 3 Systemic Organ Complications and Comorbidities Associated with Obesity and Metabolic Syndrome

Oxidative modification of LDL represents one potential connection. Oxidized LDL promotes endothelial activation, oxidative stress, inflammatory cell recruitment, reduced nitric oxide bioavailability, and atherogenesis. These effects may exacerbate vascular dysfunction in metabolically compromised migraine patients. In parallel, biologically active lipid mediators derived from arachidonic acid and other polyunsaturated fatty acids can influence nociception and inflammation. Prostaglandins, leukotrienes, resolvins, endocannabinoid-related lipids, and other mediators can either amplify or suppress pain signaling depending on their biochemical context. Altered production or degradation of such lipid mediators may therefore influence trigeminovascular sensitization [41].

Sphingolipid biology provides an especially interesting emerging connection. Ceramides and related sphingolipids regulate membrane architecture, apoptosis, inflammatory signaling, insulin sensitivity, mitochondrial function, and endothelial responses. Ceramide accumulation is a recognized feature of metabolic stress and can interfere with insulin signaling by suppressing Akt activation. In neural tissues, excessive ceramide signaling may promote oxidative stress, mitochondrial dysfunction, inflammatory activation, and cellular injury. Conversely, sphingosine-1-phosphate can participate in vascular, immune, and neuronal signaling. Disturbances in the balance among sphingolipid species could therefore constitute a molecular link between metabolic dysfunction and migraine susceptibility [42].

Lipidomics has expanded the ability to investigate these relationships by simultaneously measuring hundreds of lipid species rather than relying only on total cholesterol or triglyceride concentrations. Emerging lipidomic approaches may identify signatures involving phospholipids, sphingomyelins, ceramides, lysophospholipids, or fatty-acid derivatives that distinguish migraine phenotypes or reflect attack state, metabolic comorbidity, or treatment response. However, this field remains exploratory. Standardization of sampling conditions, fasting status, migraine phase, medication exposure, sex, and metabolic phenotype will be essential before lipidomic signatures can be translated into reliable biomarkers or therapeutic targets [43-45].

Hypertension and Vascular Dysfunction

Hypertension is another central component of metabolic syndrome and may interact bidirectionally with migraine through vascular, endothelial, autonomic, and neurohumoral mechanisms. Blood-pressure abnormalities have been reported more

frequently in some migraine populations, although the relationship is not uniform across studies. The strongest clinical concern is not that ordinary blood-pressure fluctuations directly cause migraine, but that chronic hypertension and migraine may share biological pathways capable of promoting vascular dysfunction and headache chronification. A contemporary review concluded that endothelial dysfunction, altered CGRP signaling, blood–brain barrier abnormalities, and renin–angiotensin–aldosterone system dysregulation represent plausible links between hypertension and chronic migraine [46].

Endothelial dysfunction is particularly important because the endothelium actively regulates vascular tone, platelet function, coagulation, inflammation, permeability, and leukocyte adhesion. In metabolic syndrome, oxidative stress, insulin resistance, hypertension, and dyslipidemia impair endothelial nitric oxide production and increase pro-inflammatory and vasoconstrictive signaling. Nitric oxide normally maintains vasodilation through activation of soluble guanylate cyclase and cyclic GMP signaling. In migraine, however, NO biology is complex because excessive or dysregulated NO signaling can trigger headache and facilitate trigeminovascular activation, whereas impaired endothelial NO availability contributes to vascular dysfunction. Thus, migraine may involve compartment-specific imbalance rather than simply increased or decreased nitric oxide. Recent evidence emphasizes interactions among oxidative stress, NO signaling, endothelial injury, mitochondrial dysfunction, cortical spreading depolarization, and neuroinflammation [47].

Chronic hypertension can also increase arterial stiffness and impair vascular compliance. Reduced elasticity alters pulsatile hemodynamic transmission into the cerebral circulation and may impair adaptive responses to changes in perfusion demand. Migraine itself has been associated in some studies with altered measures of vascular reactivity and endothelial function, although findings vary according to migraine subtype and methodology. Cerebrovascular autoregulation normally maintains stable cerebral blood flow despite fluctuations in systemic arterial pressure. Metabolic syndrome may compromise this process through endothelial dysfunction, oxidative stress, autonomic imbalance, vascular remodeling, and small-vessel disease. In susceptible individuals, impaired cerebrovascular regulation could interact with cortical excitability and trigeminal activation, particularly during physiological stress [48].

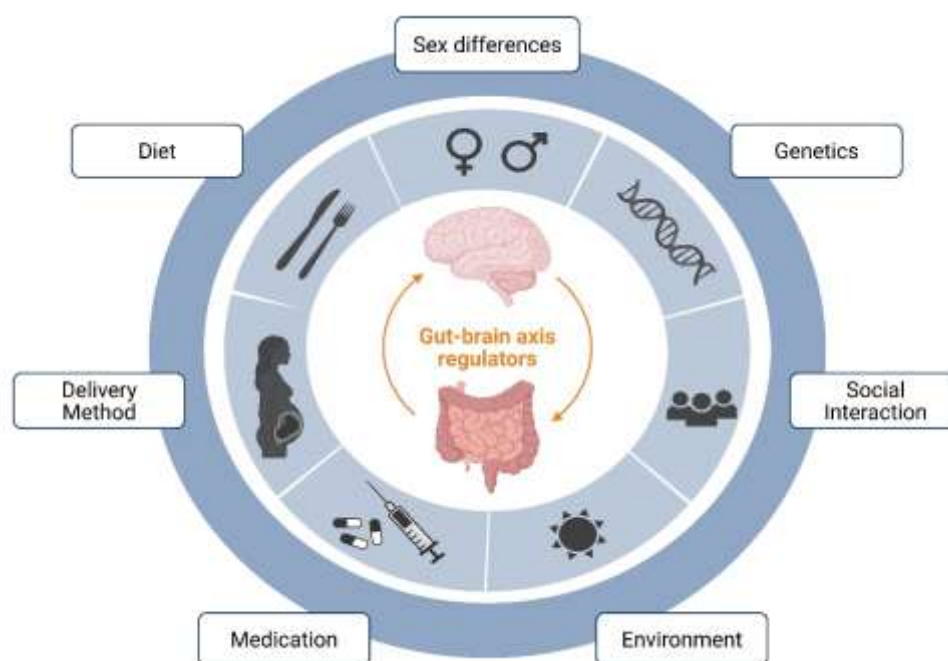


Fig: 4 Major Regulators of the Gut–Brain Axis

These vascular abnormalities have broader clinical implications because migraine, especially migraine with aura, is associated with increased risk of selected cardiovascular and cerebrovascular outcomes in particular populations. Recent cardiovascular literature continues to emphasize endothelial and vascular abnormalities as important areas for risk assessment in migraine. The coexistence of migraine with obesity, hypertension, insulin resistance, dyslipidemia, smoking, or other vascular risk

factors may therefore identify patients who warrant comprehensive cardiometabolic assessment rather than management focused exclusively on headache symptoms [49]. Importantly, this does not mean that migraine itself should be treated as equivalent to conventional cardiovascular disease. Rather, migraine and metabolic syndrome may interact through a shared network encompassing endothelial dysfunction, inflammation, oxidative stress, altered nitric oxide and CGRP signaling, insulin resistance, autonomic imbalance, and mitochondrial dysfunction. Recognition of this overlap has important therapeutic implications because improving blood pressure, body weight, insulin sensitivity, lipid profile, physical activity, sleep, and dietary quality may potentially reduce both long-term vascular risk and migraine burden. The most clinically relevant model is therefore an integrated neuro-metabolic-vascular framework in which obesity, glucose dysregulation, abnormal lipid metabolism, and hypertension collectively lower the threshold for neurovascular dysfunction and may contribute to greater migraine frequency, severity, and chronification [50].

Pathophysiological Mechanisms Linking Metabolic Syndrome and Migraine

Chronic Low-Grade Systemic Inflammation

Chronic low-grade systemic inflammation is one of the most important biological links between metabolic syndrome and migraine. Central obesity, insulin resistance, dyslipidemia, and hyperglycemia create a persistent pro-inflammatory environment in which visceral adipose tissue becomes metabolically and immunologically active. Adipocyte hypertrophy, local hypoxia, oxidative stress, and cellular dysfunction promote infiltration and activation of macrophages, resulting in increased release of tumor necrosis factor- α , interleukin-1 β , interleukin-6, and other inflammatory mediators. Obesity is also associated with increased leptin and resistin and reduced protective adiponectin signaling, producing an adipokine imbalance that further enhances inflammatory activity. These circulating mediators can act on endothelial cells, sensory neurons, vagal pathways, and trigeminal afferents, reducing nociceptive thresholds and facilitating calcitonin gene-related peptide release. Metabolic excess also activates Toll-like receptors, NF- κ B, and the NLRP3 inflammasome, reinforcing cytokine production and linking metabolic stress with nociceptive signaling. Persistent peripheral inflammation may promote microglial priming and central sensitization, thereby increasing attack frequency and contributing to progression from episodic to chronic migraine [51].

Neuroinflammation

Neuroinflammation represents a central process through which systemic metabolic abnormalities may influence migraine-generating neural circuits. Metabolic syndrome exposes the nervous system to hyperglycemia, circulating lipids, insulin resistance, inflammatory cytokines, and oxidative stress, all of which can promote microglial and astrocytic activation [52]. Reactive microglia release IL-1 β , IL-6, TNF- α , nitric oxide, prostaglandins, and reactive oxygen species, while dysfunctional astrocytes may become less effective at maintaining extracellular potassium balance and clearing glutamate. Increased extracellular glutamate enhances cortical excitability and may lower the threshold for cortical spreading depolarization. Within the trigeminovascular system, activation of trigeminal afferents promotes release of CGRP and other neuropeptides that interact with vascular, immune, and nociceptive cells. Mast cells may further contribute by releasing histamine, prostaglandins, and cytokines that sensitize trigeminal terminals. NF- κ B and NLRP3 signaling amplify this response, whereas repeated glial and trigeminal activation contributes to central sensitization in the trigeminal nucleus caudalis and thalamic pain pathways. This sustained neuroimmune activation provides a plausible mechanism for migraine persistence and chronification [53].

Oxidative and Nitrosative Stress

Oxidative and nitrosative stress form another important mechanistic bridge between metabolic syndrome and migraine. Hyperglycemia, free-fatty-acid overload, mitochondrial electron leakage, NADPH oxidase activation, and chronic inflammation increase the generation of reactive oxygen species, including superoxide, hydrogen peroxide, and hydroxyl radicals. Excess superoxide can react with nitric oxide to form peroxynitrite, producing nitrosative stress while simultaneously reducing physiologically available nitric oxide. Reactive species damage mitochondrial DNA, membrane lipids, proteins, and respiratory-chain components, further compromising ATP production. Oxidative stress also alters ion-channel activity, glutamate signaling, calcium handling, and neuronal membrane stability, thereby increasing cortical hyperexcitability. TRPA1 and TRPV1 channels on trigeminal afferents may be sensitized by oxidative products, facilitating CGRP release and nociceptive transmission. In parallel, reduced antioxidant capacity involving glutathione, superoxide dismutase, and catalase

further increases vulnerability. Oxidative stress also activates NF- κ B and NLRP3, creating a self-reinforcing inflammatory-redox cycle that links obesity, insulin resistance, dyslipidemia, hypertension, and migraine [54,55].

Table 2. Clinical and Epidemiological Studies Evaluating Metabolic Syndrome and Related Metabolic Abnormalities in Migraine

Study	Study design / population	Metabolic parameter evaluated	Major findings	Clinical interpretation
Guldiken et al., 2009	Cross-sectional study; 210 patients with metabolic syndrome	Metabolic syndrome and migraine prevalence	One-year migraine prevalence among patients with metabolic syndrome was 11.9% in men and 22.5% in women.	Demonstrated substantial coexistence of migraine and metabolic syndrome, with a higher migraine burden among women.
Bhoi et al., 2012	Clinical observational study; 135 consecutive migraine patients	Metabolic syndrome and insulin resistance	Metabolic syndrome was present in 31.9% of migraineurs and insulin resistance in 11.1%. Metabolic syndrome correlated with age, sex, number of triggers, duration of headache history, and attack duration.	Suggests that metabolic abnormalities may be particularly relevant in patients with long-standing migraine and multiple triggers.
Winsvold et al., 2013 – HUNT Study	Population-based longitudinal cohort; 19,895 participants; median follow-up 11.3 years	Development of metabolic syndrome	Migraine with aura was associated with an increased subsequent risk of developing metabolic syndrome.	Provides longitudinal evidence suggesting that the relationship between migraine, particularly migraine with aura, and metabolic dysfunction may extend beyond simple cross-sectional coexistence.
Study of hyperlipidemia in migraine, 2013	Case-control study; approximately 100 migraineurs and 100 controls	TG, total cholesterol, LDL-C and HDL-C	Migraineurs showed significantly higher triglycerides, total cholesterol and LDL-C; hypertriglyceridemia and hypercholesterolemia were also more prevalent among migraine patients.	Supports dyslipidemia as a potential cardiovascular and metabolic comorbidity of migraine.
Migraine frequency and dyslipidemia study, 2015	Cross-sectional study; 64 women with migraine	Serum lipid profile and migraine frequency	Total cholesterol and triglyceride concentrations were significantly correlated with migraine attack frequency.	Suggests that lipid abnormalities may be related not only to vascular risk but also to migraine burden.

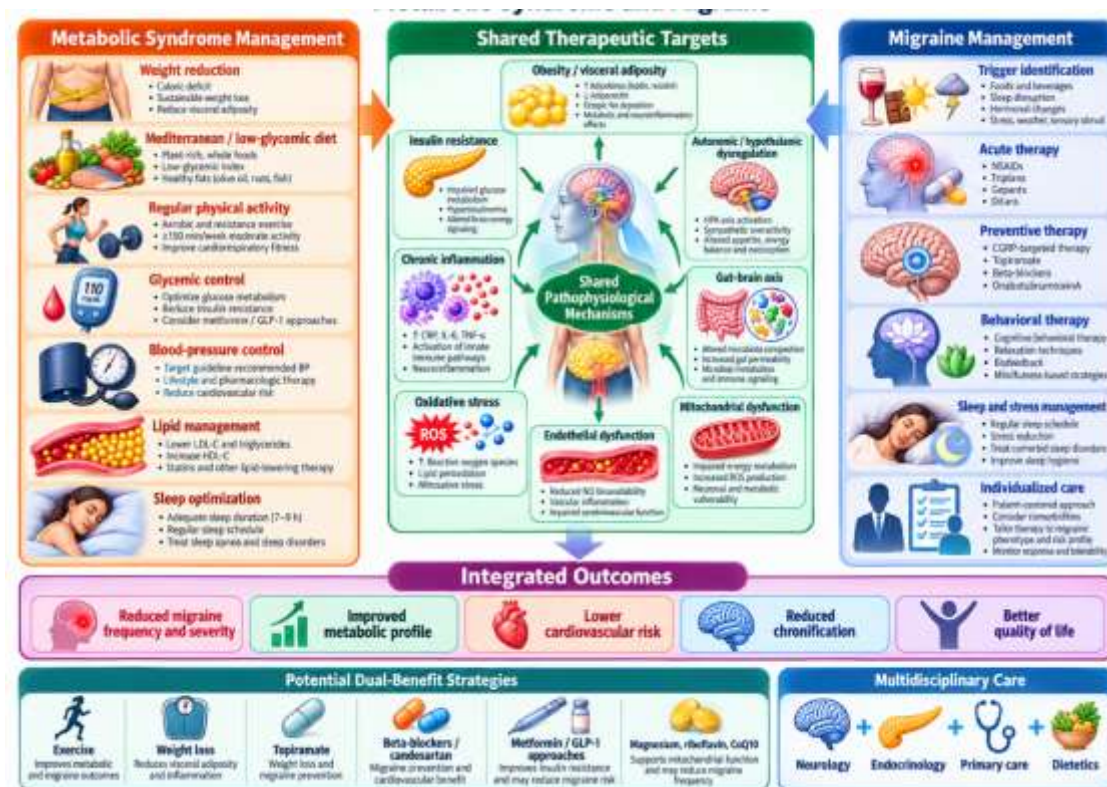


Fig: 5 Integrated Therapeutic Framework Targeting Both Metabolic Syndrome and Migraine

Mitochondrial Dysfunction and Impaired Bioenergetics

Mitochondrial dysfunction may be particularly relevant to migraine because the brain has exceptionally high energy requirements. Neurons require continuous ATP production to maintain membrane potentials, synaptic transmission, neurotransmitter cycling, and calcium homeostasis. In metabolic syndrome, insulin resistance, hyperglycemia, elevated free fatty acids, and chronic inflammation overload mitochondrial metabolism and impair oxidative phosphorylation. Reduced ATP generation compromises Na^+/K^+ -ATPase and calcium-pump function, resulting in accumulation of extracellular potassium and intracellular calcium, which enhances neuronal excitability [56]. Mitochondrial impairment also increases reactive oxygen species generation and reduces the efficiency of calcium buffering. These changes may enhance glutamatergic transmission, NMDA-receptor activity, and cortical spreading depolarization. Defective mitochondrial biogenesis and mitophagy can further worsen the problem by allowing damaged mitochondria to accumulate. AMPK, SIRT1, and PGC-1 α pathways normally regulate mitochondrial renewal and energy homeostasis, and dysfunction of these pathways may contribute to reduced metabolic resilience. This helps explain why fasting, sleep deprivation, and irregular meals can precipitate attacks in susceptible individuals [57].

Endothelial Dysfunction

Endothelial dysfunction provides an important connection between cardiometabolic abnormalities and migraine. Hyperglycemia, oxidized LDL, insulin resistance, obesity, hypertension, and systemic inflammation reduce endothelial nitric oxide bioavailability and increase oxidative stress [58]. This shifts the vascular endothelium toward a pro-inflammatory, vasoconstrictive, and prothrombotic state characterized by increased endothelin-1, angiotensin II, adhesion molecules, and vascular stiffness. Insulin normally activates the PI3K/Akt/eNOS pathway and promotes nitric oxide production, but this protective pathway becomes impaired during insulin resistance. Although migraine is no longer considered a purely vascular disorder, endothelial abnormalities can modify cerebral vascular responsiveness and interact with trigeminal sensory pathways and CGRP signaling. Chronic hypertension further damages endothelial function and promotes vascular remodeling and arterial stiffness. These processes may be especially important in migraine with aura, where vascular risk is already of clinical

concern. Thus, endothelial dysfunction may not initiate migraine independently, but it can create a neurovascular environment that favors trigeminal sensitization and increased migraine susceptibility [59,60].

Autonomic Nervous System Dysregulation

Autonomic dysfunction is common to both metabolic syndrome and migraine. Obesity, hyperinsulinemia, leptin resistance, sleep disturbance, and hypothalamic inflammation can produce chronic sympathetic activation and reduced parasympathetic tone. Persistent sympathetic overactivity promotes vasoconstriction, sodium retention, hypertension, insulin resistance, and cardiovascular stress. In migraine, autonomic involvement is reflected by nausea, vomiting, altered gastric emptying, sweating, pallor, and other cranial autonomic symptoms. Reduced vagal activity may also weaken the cholinergic anti-inflammatory reflex, permitting exaggerated cytokine production and further inflammatory activation. Altered baroreceptor sensitivity and autonomic instability can influence vascular tone and stress responsiveness, while hypothalamic dysregulation can simultaneously disturb appetite, circadian rhythm, sleep, and sympathetic output. Repeated autonomic imbalance may therefore maintain a physiologically unstable state that lowers the migraine threshold and contributes to recurrent attacks and chronification [61,62].

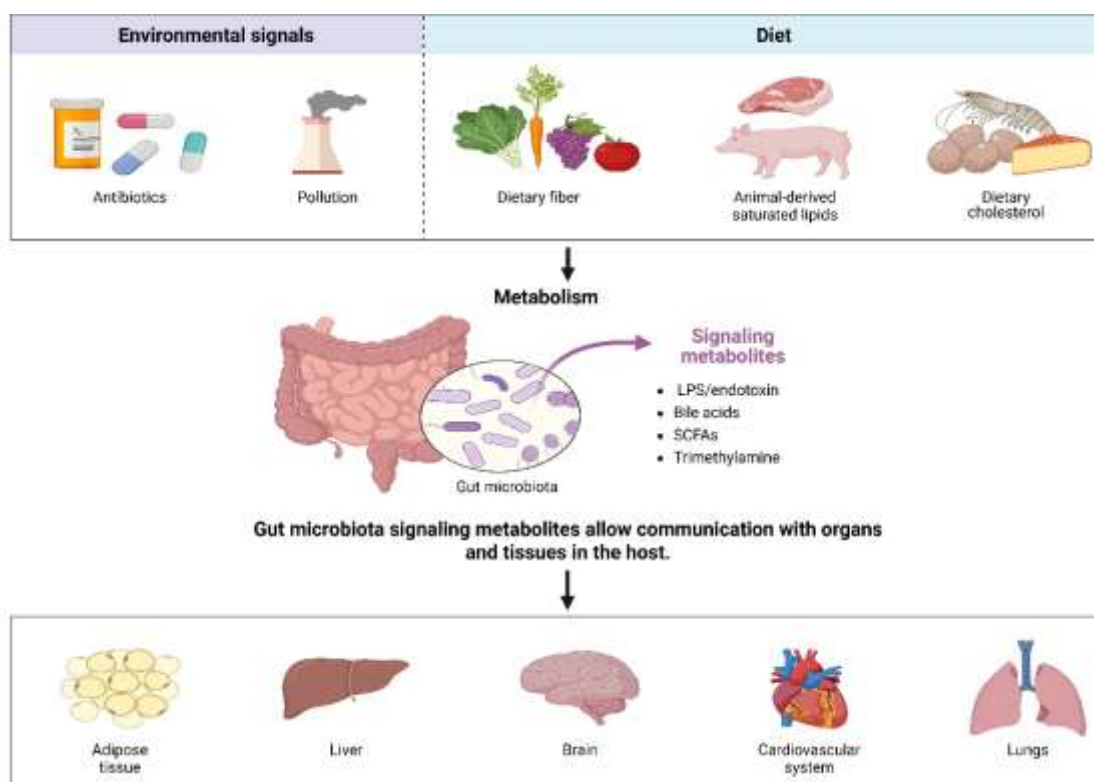


Fig: 6 Environmental and Dietary Determinants of Gut Microbiota-Derived Signaling Metabolites and Their Systemic Effects on Host Organs

Hypothalamic Dysfunction

The hypothalamus represents a major point of convergence between metabolic regulation and migraine biology because it controls appetite, energy balance, sleep, circadian rhythms, autonomic activity, stress responses, and endocrine function. Premonitory migraine symptoms such as yawning, food craving, thirst, mood changes, and fatigue suggest early hypothalamic involvement in attack generation. Obesity and insulin resistance impair hypothalamic responses to insulin, leptin, glucose, ghrelin, and fatty acids and may trigger local inflammatory signaling involving microglia and NF- κ B [63]. Disturbed orexin signaling may connect sleep disruption, fasting, and altered pain processing, while circadian dysfunction can aggravate both metabolic abnormalities and migraine susceptibility. The hypothalamic–pituitary–adrenal axis also contributes through abnormal cortisol signaling during chronic stress. Because hypothalamic regions communicate with brainstem structures

involved in trigeminal nociception, disturbed hypothalamic regulation may lower the threshold for trigeminovascular activation and explain why metabolic, sleep, and stress-related triggers frequently precipitate migraine attacks [64].

Blood–Brain Barrier Alterations

Metabolic syndrome can impair the blood–brain barrier through endothelial injury, oxidative stress, inflammation, hypertension, and hyperglycemia. Cytokines such as TNF- α , IL-1 β , and IL-6, together with matrix metalloproteinases and reactive oxygen species, can disrupt tight-junction proteins including claudins, occludin, and zonula occludens proteins. This may increase barrier permeability and disturb the transport of insulin, leptin, glucose, fatty acids, and inflammatory mediators. Increased exposure of perivascular and neural cells to circulating inflammatory signals can activate astrocytes and microglia and amplify neuroinflammation. However, generalized blood–brain barrier breakdown is not considered a universal feature of migraine; more subtle changes in neurovascular-unit function and selective permeability are likely to be more relevant. In patients with metabolic syndrome, pre-existing endothelial and barrier vulnerability may nevertheless enhance cerebral sensitivity to systemic inflammatory and oxidative stress signals, facilitating cortical and trigeminal sensitization [65].

Gut–Brain–Metabolic Axis

The gut–brain–metabolic axis provides a further link between metabolic syndrome and migraine through microbial, immune, endocrine, and neural signaling. Obesity and insulin resistance are often associated with gut dysbiosis, reduced microbial diversity, and impaired intestinal barrier integrity. Increased permeability may permit lipopolysaccharide and other bacterial products to enter the circulation, activating Toll-like receptor 4 and NF- κ B pathways and contributing to metabolic endotoxemia. Dysbiosis also alters short-chain fatty acid production, tryptophan metabolism, serotonin-related pathways, and bile-acid signaling. These changes can influence immune function, microglial activity, neuronal excitability, and vagal signaling. Altered microbial metabolites may therefore reinforce systemic and central inflammation and contribute to trigeminal sensitization. Although microbiome-targeted therapies remain investigational, the gut–brain axis provides a biologically plausible mechanism through which dietary quality and metabolic health can influence migraine expression [66].

Hormonal and Neuroendocrine Mechanisms

Hormonal and neuroendocrine pathways are particularly important because migraine exhibits strong sex- and life-stage-dependent variation. Estrogen fluctuations can modify serotonergic signaling, CGRP biology, nitric oxide production, glutamatergic neurotransmission, and endogenous pain modulation. Declining estrogen after menopause also promotes visceral adiposity, insulin resistance, dyslipidemia, and vascular dysfunction, potentially strengthening the metabolic–migraine relationship. The hypothalamic–pituitary–adrenal axis also plays an important role, because chronic stress and altered cortisol dynamics can promote visceral fat accumulation, inflammation, sleep disruption, and insulin resistance. Leptin and insulin additionally act as neuroendocrine signals regulating appetite, autonomic function, and neuronal metabolism [67]. Dysfunction in these hormonal systems can therefore simultaneously worsen metabolic homeostasis and alter nociceptive processing. Collectively, estrogen, cortisol, insulin, leptin, orexin, and hypothalamic signaling converge on neural networks that regulate energy balance, vascular function, inflammation, and trigeminal excitability, making neuroendocrine dysregulation a major contributor to migraine susceptibility and chronification. Overall, these mechanisms operate as an interconnected metabolic–inflammatory–mitochondrial–neurovascular network rather than as independent pathways. Central obesity and insulin resistance promote inflammation, oxidative stress, and mitochondrial dysfunction; these processes impair endothelial and blood–brain barrier function, alter autonomic and hypothalamic regulation, and interact with gut-derived and hormonal signals. Their convergence lowers the threshold for cortical hyperexcitability, trigeminovascular activation, CGRP release, peripheral sensitization, and central sensitization, ultimately increasing the likelihood of frequent and chronic migraine [68].

Inflammatory Signaling Connecting Metabolic Syndrome and Migraine

TNF- α

Tumor necrosis factor- α (TNF- α) represents an important inflammatory mediator connecting metabolic dysfunction with migraine susceptibility. In metabolic syndrome, visceral adipocyte hypertrophy and infiltration of adipose tissue by activated macrophages substantially increase TNF- α production. Elevated TNF- α interferes with insulin receptor signaling through inhibitory phosphorylation of insulin receptor substrates, thereby aggravating insulin resistance and promoting further

metabolic inflammation. Within the vascular system, TNF- α enhances endothelial expression of adhesion molecules, reduces endothelial nitric oxide bioavailability, increases oxidative stress, and promotes vascular inflammation. These effects are particularly relevant to migraine because endothelial and trigeminovascular abnormalities can influence nociceptive processing [69]. TNF- α may also sensitize peripheral nociceptive neurons and enhance the activity of ion channels involved in pain transmission. At the central level, TNF- α released from microglia, astrocytes, and other immune-responsive cells can alter glutamatergic transmission and increase neuronal excitability. Persistent cytokine exposure may subsequently facilitate activation of the trigeminovascular system and increase CGRP-mediated signaling. Moreover, TNF- α interacts strongly with NF- κ B and oxidative stress pathways, creating a positive feedback cycle in which inflammatory signaling generates reactive oxygen species and oxidative stress further stimulates cytokine production. In individuals with obesity, insulin resistance, and other components of metabolic syndrome, sustained elevations in TNF- α may therefore lower the threshold for migraine attacks and facilitate central sensitization. Repeated inflammatory activation may be particularly relevant to migraine chronification because persistent nociceptive input can progressively increase responsiveness of neurons in the trigeminal nucleus caudalis, thalamus, and higher pain-processing networks. Thus, TNF- α is not simply a circulating marker of metabolic inflammation but a mechanistically relevant mediator linking adipose-tissue dysfunction, insulin resistance, endothelial injury, neuroinflammation, and migraine [70].

IL-1 β and IL-6

Interleukin-1 β (IL-1 β) and interleukin-6 (IL-6) are major pro-inflammatory cytokines involved in the metabolic-inflammatory network associated with both metabolic syndrome and migraine. IL-1 β is generated primarily after activation of innate immune mechanisms such as the NLRP3 inflammasome, whereas IL-6 is released by adipocytes, macrophages, endothelial cells, skeletal muscle, and several central nervous system cell populations [71]. In obesity, expansion of visceral adipose tissue creates local hypoxia, lipotoxicity, mitochondrial stress, and macrophage activation, producing sustained elevations in these cytokines. IL-1 β can increase nociceptor sensitivity, enhance prostaglandin synthesis, stimulate inflammatory signaling in vascular and neural tissues, and amplify trigeminal activation. IL-6 has more context-dependent actions but persistent elevation during metabolic syndrome is generally associated with systemic inflammation, insulin resistance, hepatic acute-phase responses, and endothelial dysfunction. Circulating IL-1 β and IL-6 may influence the brain through endothelial signaling, vagal pathways, and regions with relatively permissive communication between blood and neural tissues. They can activate microglia and astrocytes and enhance central neuroinflammatory responses. IL-1 β may also increase glutamatergic excitability, whereas IL-6 signaling can influence neuronal activity and pain processing. Together, these cytokines promote communication between peripheral metabolic inflammation and central nociceptive networks. Persistent elevation of IL-1 β and IL-6 may therefore establish an inflammatory environment in which migraine triggers more readily activate trigeminal pathways. Their interaction with oxidative stress, NF- κ B, mitochondrial dysfunction, and endothelial abnormalities further strengthens their relevance to migraine chronification [72].

NF- κ B Signaling

Nuclear factor kappa B (NF- κ B) is a central transcriptional regulator that integrates metabolic, oxidative, immune, and inflammatory signals and therefore represents a major molecular intersection between metabolic syndrome and migraine. Under resting conditions, NF- κ B is retained in the cytoplasm by inhibitory I κ B proteins. Exposure to inflammatory cytokines, reactive oxygen species, free fatty acids, hyperglycemia, lipopolysaccharide, or Toll-like receptor stimulation activates the I κ B kinase complex, leading to degradation of I κ B and nuclear translocation of NF- κ B. Once inside the nucleus, NF- κ B promotes transcription of TNF- α , IL-1 β , IL-6, inducible nitric oxide synthase, cyclooxygenase-2, chemokines, and adhesion molecules. Metabolic syndrome chronically stimulates this pathway through adipose-tissue inflammation, insulin resistance, oxidative stress, and gut-derived inflammatory products [73]. Within the nervous system, NF- κ B activation in microglia, astrocytes, endothelial cells, and potentially neurons can promote neuroinflammation and increase sensitivity of nociceptive circuits. Activation of NF- κ B can also facilitate NLRP3 inflammasome priming, creating a mechanistic connection between inflammatory transcription and cytokine maturation. Increased inflammatory mediator production may sensitize trigeminal afferents, promote CGRP-associated signaling, and enhance central pain transmission. Because NF- κ B simultaneously worsens insulin resistance and inflammation, it establishes a self-sustaining metabolic-inflammatory loop. Persistent NF- κ B activity may consequently provide one explanation for the increased susceptibility to frequent or chronic migraine among patients with pronounced metabolic dysfunction [74].

NLRP3 Inflammasome Activation

The NLRP3 inflammasome is an intracellular multiprotein complex that acts as a sensor of metabolic and cellular danger and has emerged as an important link between metabolic inflammation and neuroinflammatory disorders. Metabolic syndrome provides numerous potential NLRP3 activators, including saturated fatty acids, cholesterol-related danger signals, hyperglycemia, mitochondrial reactive oxygen species, extracellular ATP, damaged mitochondrial DNA, and metabolic endotoxemia. NLRP3 activation promotes caspase-1-mediated processing of pro-IL-1 β and pro-IL-18 into their active forms, thereby amplifying inflammatory responses [75]. In obesity and insulin resistance, persistent inflammasome activity contributes to adipose-tissue inflammation and impaired insulin signaling. Similar mechanisms within microglia and other neural cells may promote neuroinflammation. Mitochondrial dysfunction is particularly relevant because damaged mitochondria generate ROS and release intracellular danger signals capable of activating NLRP3. This creates a feedback cycle in which metabolic stress promotes mitochondrial injury, inflammasome activation, cytokine release, and further oxidative damage. Within migraine-related pathways, increased IL-1 β signaling can enhance neuronal excitability and trigeminal nociceptive processing. NLRP3 activation may therefore contribute to the transition from systemic metabolic inflammation toward persistent neuroimmune sensitization. Although the exact clinical importance of inflammasome activation in human migraine requires further clarification, the NLRP3–IL-1 β axis provides a biologically plausible mechanism linking obesity, oxidative stress, mitochondrial dysfunction, and migraine [76].

Toll-Like Receptor Signaling

Toll-like receptors (TLRs) are pattern-recognition receptors that detect microbial molecules and endogenous danger-associated signals. TLR2 and TLR4 are particularly relevant to metabolic syndrome because saturated fatty-acid-associated signals, damaged cellular components, and circulating lipopolysaccharide can activate these innate immune pathways. Obesity-associated disruption of intestinal barrier integrity may increase the systemic availability of bacterial lipopolysaccharide, creating low-grade metabolic endotoxemia [77]. Activation of TLR4 recruits intracellular adaptor proteins and ultimately stimulates NF- κ B and mitogen-activated protein kinase signaling, increasing production of TNF- α , IL-1 β , IL-6, and additional inflammatory mediators. Within adipose tissue, this promotes macrophage activation and insulin resistance, while activation of TLR pathways in vascular cells contributes to endothelial dysfunction. In the nervous system, TLRs are expressed on microglia, astrocytes, endothelial cells, and certain neuronal populations. Their activation can therefore translate circulating metabolic danger signals into central neuroinflammation. Persistent TLR stimulation may prime microglia and increase their responsiveness to subsequent nociceptive or metabolic stress. By interacting with NF- κ B and NLRP3 signaling, TLR activation forms a major upstream component of the inflammatory cascade capable of facilitating trigeminal sensitization and migraine chronification [78].

Microglial Activation

Microglia are the resident immune cells of the central nervous system and act as highly sensitive detectors of neuronal injury, metabolic stress, inflammatory mediators, and changes in the extracellular environment. Under physiological conditions they support neuronal homeostasis, synaptic remodeling, and tissue surveillance. However, chronic exposure to obesity-associated cytokines, hyperglycemia, oxidative stress, altered lipid metabolites, and mitochondrial danger signals can shift microglia toward reactive inflammatory phenotypes [79]. Activated microglia produce TNF- α , IL-1 β , IL-6, prostaglandins, nitric oxide, and reactive oxygen species, all of which can modify neuronal excitability and pain transmission. Within migraine-associated neural circuits, microglial activation may increase responsiveness of second-order neurons in the trigeminal nucleus caudalis and contribute to central sensitization. Microglial cytokines can also alter astrocytic function and impair glutamate homeostasis, further promoting excitatory neurotransmission. Importantly, repeated inflammatory exposure may produce microglial priming, in which subsequent stimuli generate exaggerated inflammatory responses. This provides a potential explanation for how chronic metabolic inflammation may progressively reduce the threshold for migraine attacks. Microglia also interact with mitochondrial ROS, NF- κ B, and NLRP3 signaling, positioning them at the center of the metabolic-neuroimmune interface. Persistent glial activation could therefore contribute not only to attack generation but also to allodynia and transition from episodic to chronic migraine [80].

Interaction Between Peripheral and Central Inflammation

The relationship between metabolic syndrome and migraine ultimately depends on communication between peripheral inflammatory processes and central nociceptive networks. Visceral adipose tissue, liver, skeletal muscle, vascular endothelium, and circulating immune cells generate inflammatory mediators during metabolic syndrome, creating a persistent systemic inflammatory state. These signals do not need unrestricted entry into the brain to influence neural activity [81]. Cytokines can activate cerebral endothelial cells, stimulate vagal afferents, alter transport mechanisms at the blood–brain barrier, and act at circumventricular structures with greater accessibility to circulating factors. Endothelial activation subsequently produces secondary inflammatory signals capable of influencing astrocytes, microglia, and neurons. In parallel, obesity-associated gut permeability may increase circulating microbial products, further strengthening TLR–NF- κ B signaling. Central inflammatory responses can then activate trigeminal nociceptive circuits, promote CGRP release, increase glutamatergic transmission, and facilitate sensitization. Conversely, repeated migraine attacks may themselves generate stress responses, sleep disturbance, autonomic dysfunction, and behavioral changes that exacerbate systemic metabolic inflammation. The relationship is therefore bidirectional rather than linear. Peripheral metabolic inflammation primes the central nervous system, while recurrent central nociceptive activation can indirectly worsen metabolic and inflammatory homeostasis. This interconnected inflammatory network provides a coherent framework linking obesity, insulin resistance, gut dysbiosis, endothelial dysfunction, oxidative stress, and neuroinflammation with migraine frequency and chronification. In this model, TNF- α , IL-1 β , IL-6, TLRs, NF- κ B, NLRP3, and microglia function as interconnected components of a single metabolic–immune–trigeminovascular axis rather than as isolated mechanisms [82].

CGRP and Trigeminovascular Signaling in Metabolic Dysfunction

CGRP in Migraine Pathophysiology

Calcitonin gene-related peptide (CGRP) is one of the most important neuropeptides involved in migraine pathophysiology and represents a central component of trigeminovascular signaling. CGRP is abundantly expressed in primary sensory neurons of the trigeminal ganglion and is released from peripheral and central trigeminal terminals during activation of the migraine pathway [83]. Once released, CGRP acts on a receptor complex composed primarily of the calcitonin receptor-like receptor and receptor activity-modifying protein 1, leading to activation of cyclic AMP-dependent signaling. Within the meninges and trigeminovascular system, CGRP contributes to vasodilation, nociceptive transmission, neurogenic signaling, and sensitization of pain pathways. Elevated CGRP concentrations have been reported during migraine attacks in some studies, and the clinical efficacy of CGRP-targeted therapies provides strong functional evidence for its role in migraine. CGRP can enhance excitability of second-order trigeminal neurons and interact with vascular smooth muscle cells, endothelial cells, satellite glial cells, and immune-responsive cells. It may also facilitate peripheral sensitization and promote sustained signaling within the trigeminal nucleus caudalis and higher-order pain-processing regions. Importantly, contemporary understanding of migraine does not consider CGRP-mediated vasodilation alone as the cause of headache. Rather, CGRP acts as a neurovascular signaling molecule that amplifies nociceptive transmission within an already susceptible migraine network [84].

Table 3 Biomarkers Associated with Migraine and Metabolic Abnormalities

Biomarker category	Biomarker	Reported alteration / association	Relevance to migraine–metabolic syndrome link	Potential clinical significance
Neuropeptide	CGRP	Often increased during migraine attacks and implicated in chronic migraine	Links trigeminovascular activation with vascular regulation, inflammation, and metabolic signaling	One of the most established migraine-related biomarkers and a validated therapeutic target, although not yet a routine diagnostic blood test.
Neuropeptide	PACAP	Altered in migraine and capable of inducing migraine-like attacks in susceptible	Influences vasodilation, autonomic signaling, inflammation, and energy-	Emerging biomarker and therapeutic target; clinical validation

		individuals	regulating pathways	remains incomplete.
Inflammatory	TNF- α	Higher circulating levels reported in migraine compared with controls in meta-analytic data	Promotes insulin resistance, endothelial dysfunction, neuroinflammation, and trigeminal sensitization	May reflect inflammatory burden, but lacks migraine specificity.
Inflammatory	IL-1 β	Increased particularly during ictal states in some studies	Links NLRP3 inflammasome activity with neuronal excitability and nociceptive sensitization	Potential marker of attack-related inflammation.
Inflammatory	IL-6	Elevated in migraine; higher levels have also been associated with chronic versus episodic migraine	Closely associated with obesity, insulin resistance, systemic inflammation, and neuroimmune activation	May help characterize inflammatory and chronification phenotypes, but heterogeneity remains substantial.
Inflammatory	High-sensitivity CRP	Frequently elevated in inflammatory migraine phenotypes	Reflects systemic low-grade inflammation commonly associated with obesity and metabolic syndrome	Easily measurable marker of systemic inflammation, but nonspecific for migraine.
Adipokine	Leptin	Several studies report increased concentrations in migraine and chronic migraine	Connects visceral adiposity, hypothalamic regulation, insulin resistance, inflammation, and migraine	Possible marker of an obesity-associated inflammatory migraine phenotype.
Adipokine	Adiponectin	Altered concentrations reported; recent meta-analysis found higher levels in chronic than episodic migraine	Modulates insulin sensitivity, inflammation, endothelial function, and energy metabolism	One of the more promising metabolic biomarkers of chronic migraine, although molecular isoforms and confounding factors complicate interpretation.
Adipokine	Resistin	Associations with migraine are less consistent than for leptin or adiponectin	Links adipose inflammation with insulin resistance and endothelial activation	Currently an exploratory rather than established migraine biomarker.
Glucose metabolism	Fasting glucose / HbA1c	May be abnormal in migraine patients with metabolic syndrome, prediabetes, or diabetes	Reflects impaired glucose regulation and chronic glycemic exposure	Useful for identifying metabolic comorbidity rather than migraine itself
Insulin resistance	Fasting insulin / HOMA-IR	Increased insulin resistance has been reported in subsets of migraine patients	Connects hyperinsulinemia with mitochondrial dysfunction, inflammation, altered vascular tone, and	Potential metabolic risk-stratification marker in migraine patients with obesity or metabolic syndrome

			neuronal energy instability	
Lipid metabolism	Triglycerides	Higher levels reported in some migraine cohorts	Hypertriglyceridemia reflects insulin resistance, excess fatty-acid availability, and vascular risk	Useful for cardiometabolic profiling; not migraine-specific
Lipid metabolism	LDL-C / oxidized LDL	Elevated LDL-C or adverse lipid patterns reported in some studies	Oxidized LDL promotes endothelial inflammation and oxidative stress	May identify migraine patients with increased vascular-metabolic burden
Lipid metabolism	HDL-C	Reduced HDL-C may accompany metabolic syndrome in migraine patients	Low HDL-C indicates impaired reverse cholesterol transport and greater cardiometabolic risk	Useful as part of metabolic syndrome assessment
Oxidative stress	Malondialdehyde (MDA)	Increased lipid-peroxidation markers have been described in migraine	Reflects ROS-mediated membrane damage, mitochondrial stress, and inflammatory activation	Experimental marker of oxidative burden; insufficient standardization for routine practice
Antioxidant defense	Glutathione, SOD, catalase	Reduced antioxidant capacity has been reported in some migraine studies	Indicates impaired ability to neutralize metabolic and mitochondrial ROS	Potential mechanistic biomarkers; clinical utility remains investigational
Nitrosative stress	Nitric oxide-related metabolites	Dysregulated NO signaling has been associated with migraine	Links endothelial function, vascular regulation, oxidative stress, and trigeminal activation	Mechanistically relevant but highly variable and technically difficult to interpret
Endothelial	Pentraxin-3	Investigated as an endothelial/inflammatory marker in migraine	Reflects vascular inflammation and endothelial activation	Promising research biomarker but not clinically validated.
Neuroexcitatory	Glutamate	Altered circulating or central glutamate has been reported, particularly in chronic migraine	Reflects excitatory neurotransmission, cortical hyperexcitability, and impaired energy metabolism	Considered among the more promising chronic migraine biomarkers alongside CGRP and adiponectin.
Metabolic/redox	Uric acid	Relationship appears context-dependent	May act as an extracellular antioxidant but can promote oxidative and inflammasome signaling under some conditions	Emerging marker in proposed CGRP–redox–metabolic frameworks; evidence remains exploratory.

Metabolic Effects of CGRP

Beyond its established role in migraine, CGRP also participates in metabolic and cardiovascular regulation. CGRP receptors are expressed in multiple tissues, including the pancreas, gastrointestinal tract, adipose tissue, skeletal muscle, vasculature, and central nervous system. CGRP can influence insulin secretion, glucose handling, energy expenditure, vascular tone, and

gastrointestinal function, although its effects vary according to tissue, concentration, and physiological context. Experimental studies suggest that CGRP may modulate pancreatic β -cell function and insulin release, while chronic alterations in CGRP signaling may affect glucose tolerance and insulin sensitivity. CGRP is also a potent vasodilator and can act as a compensatory protective peptide during vascular stress, particularly in hypertension and endothelial dysfunction. In adipose and metabolic tissues, CGRP signaling has been linked with regulation of lipolysis, thermogenesis, and energy balance. These broader physiological actions create an important conceptual overlap between migraine and metabolic syndrome. In individuals with obesity, insulin resistance, or hypertension, altered CGRP activity may represent both a response to metabolic stress and a factor capable of modifying metabolic homeostasis. Therefore, CGRP should be considered not only as a migraine-associated neuropeptide but also as part of a wider neuroendocrine and cardiometabolic regulatory system [85].

Obesity, Insulin Resistance, and CGRP Signaling

Obesity and insulin resistance may alter CGRP signaling through several interconnected mechanisms. Visceral adiposity promotes chronic low-grade inflammation, oxidative stress, hyperinsulinemia, and dysregulated adipokine secretion. These abnormalities can influence sensory neurons and increase responsiveness of trigeminal pathways. Pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6 may enhance neuronal excitability and indirectly facilitate CGRP synthesis or release. Hyperinsulinemia and impaired insulin signaling can also alter autonomic and vascular regulation, thereby modifying the environment in which CGRP acts [86]. In addition, obesity-associated leptin excess, reduced adiponectin activity, and mitochondrial dysfunction may increase oxidative stress within sensory and central neural pathways, lowering the threshold for CGRP-mediated nociceptive activation. Experimental data suggest that CGRP itself may influence insulin action and metabolic regulation, raising the possibility of a bidirectional relationship. Thus, obesity may enhance migraine susceptibility through increased inflammatory and metabolic priming of CGRP-sensitive pathways, while chronic alterations in CGRP signaling may also influence glucose and vascular homeostasis. This bidirectional interaction is particularly relevant to patients with metabolic syndrome, in whom migraine frequency and chronification may be shaped by the combined effects of adiposity, insulin resistance, and persistent neuropeptide signaling [87].

Trigeminal Neurovascular Activation

The trigeminovascular system consists of trigeminal sensory afferents innervating meningeal and cerebral blood vessels, central projections to the trigeminal nucleus caudalis, and ascending pathways to the thalamus and cortex. Activation of this system is a defining event in migraine pain. Metabolic and inflammatory disturbances can increase susceptibility to trigeminal activation by altering neuronal excitability, endothelial function, mitochondrial energy balance, and inflammatory signaling. Once trigeminal terminals are activated, they release CGRP and other neuropeptides that interact with meningeal vessels and surrounding cells. CGRP enhances nociceptive transmission and can promote sensitization of trigeminal neurons, while prolonged activation may contribute to central sensitization and cutaneous allodynia. Peripheral sensitization increases responsiveness of meningeal afferents, whereas central sensitization enhances activity within the trigeminal nucleus, thalamus, and cortical pain networks. In metabolic syndrome, oxidative stress, endothelial dysfunction, hyperglycemia, and systemic inflammation may facilitate both stages of sensitization. As a result, patients with metabolic abnormalities may develop a lower threshold for trigeminovascular activation and more frequent or severe migraine attacks [88].

Substance P and Other Neuropeptides

Although CGRP is the dominant neuropeptide in current migraine therapeutics, other neuropeptides also contribute to trigeminovascular and nociceptive signaling. Substance P is co-localized with CGRP in subsets of sensory neurons and acts primarily through neurokinin-1 receptors. It can increase vascular permeability, promote inflammatory signaling, activate immune cells, and enhance nociceptive transmission [89]. However, unlike CGRP, targeting substance P pathways has not produced comparable therapeutic success in migraine, indicating that its role may be supportive rather than central. Neurokinin A, pituitary adenylate cyclase-activating polypeptide, vasoactive intestinal peptide, and amylin-related peptides have also been implicated in headache biology. PACAP is especially relevant because it can provoke migraine-like attacks in susceptible individuals and interacts with autonomic, vascular, and inflammatory pathways. These neuropeptides may act in parallel with CGRP and contribute to heterogeneity in migraine mechanisms. In metabolically compromised patients, altered inflammatory and neuroendocrine states may further influence peptide release and receptor sensitivity [90].

Implications for CGRP-Targeted Therapies

The development of monoclonal antibodies against CGRP or its receptor and small-molecule CGRP receptor antagonists has transformed migraine prevention and acute treatment. These therapies validate CGRP as a major therapeutic target and are particularly valuable in patients who do not tolerate or respond adequately to conventional preventive drugs. However, because CGRP also participates in cardiovascular and metabolic homeostasis, its long-term inhibition warrants careful consideration in patients with metabolic syndrome, hypertension, obesity, or vascular disease [91]. CGRP has protective vasodilatory functions and may help counteract excessive vascular resistance under conditions of cardiovascular stress. Therefore, sustained blockade could theoretically modify compensatory vascular responses, although current clinical use has generally demonstrated favorable safety profiles. The metabolic consequences of long-term CGRP inhibition remain less clearly defined and require continued investigation, particularly regarding insulin sensitivity, glucose regulation, body weight, and vascular risk. In patients with metabolic syndrome, individualized treatment should therefore consider both migraine burden and underlying cardiometabolic status. Future studies should determine whether specific metabolic phenotypes predict treatment response or adverse effects and whether CGRP -targeted therapy influences the broader metabolic-inflammatory network associated with migraine [92].

Mitochondrial Dysfunction and Oxidative Stress

Mitochondrial Dysfunction in Migraine

Mitochondrial dysfunction is increasingly recognized as an important contributor to migraine because the brain has exceptionally high energy requirements and depends heavily on oxidative phosphorylation for continuous ATP generation. Neurons require substantial energy to maintain membrane potentials, synaptic transmission, neurotransmitter recycling, and ionic gradients, and even modest impairment of mitochondrial function can alter neuronal excitability. In migraine-prone individuals, reduced mitochondrial metabolic reserve may make cortical and trigeminal neurons more vulnerable to physiological stressors such as fasting, sleep deprivation, intense sensory stimulation, and hormonal fluctuations. Impairment of the electron transport chain can reduce ATP production while simultaneously increasing electron leakage and reactive oxygen species formation. This energetic deficiency can compromise Na^+/K^+ -ATPase and calcium-pump activity, leading to membrane depolarization, intracellular calcium accumulation, and enhanced glutamatergic transmission. Such changes may lower the threshold for cortical spreading depolarization, particularly in migraine with aura, and can facilitate activation of trigeminovascular pathways. Mitochondrial dysfunction may therefore contribute to migraine not simply by reducing cellular energy availability but also through its effects on oxidative stress, calcium handling, inflammatory signaling, and neuronal hyperexcitability [93].

Metabolic Syndrome-Associated Mitochondrial Abnormalities

Metabolic syndrome can intensify mitochondrial dysfunction through the combined effects of insulin resistance, chronic hyperglycemia, excess circulating free fatty acids, dyslipidemia, and systemic inflammation. In insulin-resistant tissues, impaired glucose utilization and increased fatty-acid delivery place a substantial metabolic burden on mitochondria. Excessive influx of substrates into the tricarboxylic acid cycle and electron transport chain increases the mitochondrial membrane potential and promotes electron leakage, particularly from respiratory complexes I and III. Lipid oversupply also favors accumulation of toxic intermediates such as ceramides and diacylglycerols, which further disrupt insulin signaling and mitochondrial function. Hyperglycemia promotes advanced glycation end products, protein kinase C activation, and oxidative injury, while inflammatory cytokines such as $\text{TNF-}\alpha$ and $\text{IL-1}\beta$ can impair mitochondrial biogenesis and respiratory efficiency. At the same time, defects in mitochondrial quality-control mechanisms, including mitophagy and biogenesis, allow damaged mitochondria to accumulate. Regulatory pathways involving AMP-activated protein kinase, sirtuin-1, and $\text{PGC-1}\alpha$ normally maintain mitochondrial turnover and metabolic flexibility, but these pathways may become impaired in obesity and insulin resistance. Consequently, metabolic syndrome can create a state of mitochondrial inflexibility in which cells are less capable of adapting to fluctuations in energy demand, potentially increasing the vulnerability of migraine-related neural circuits [94,95].

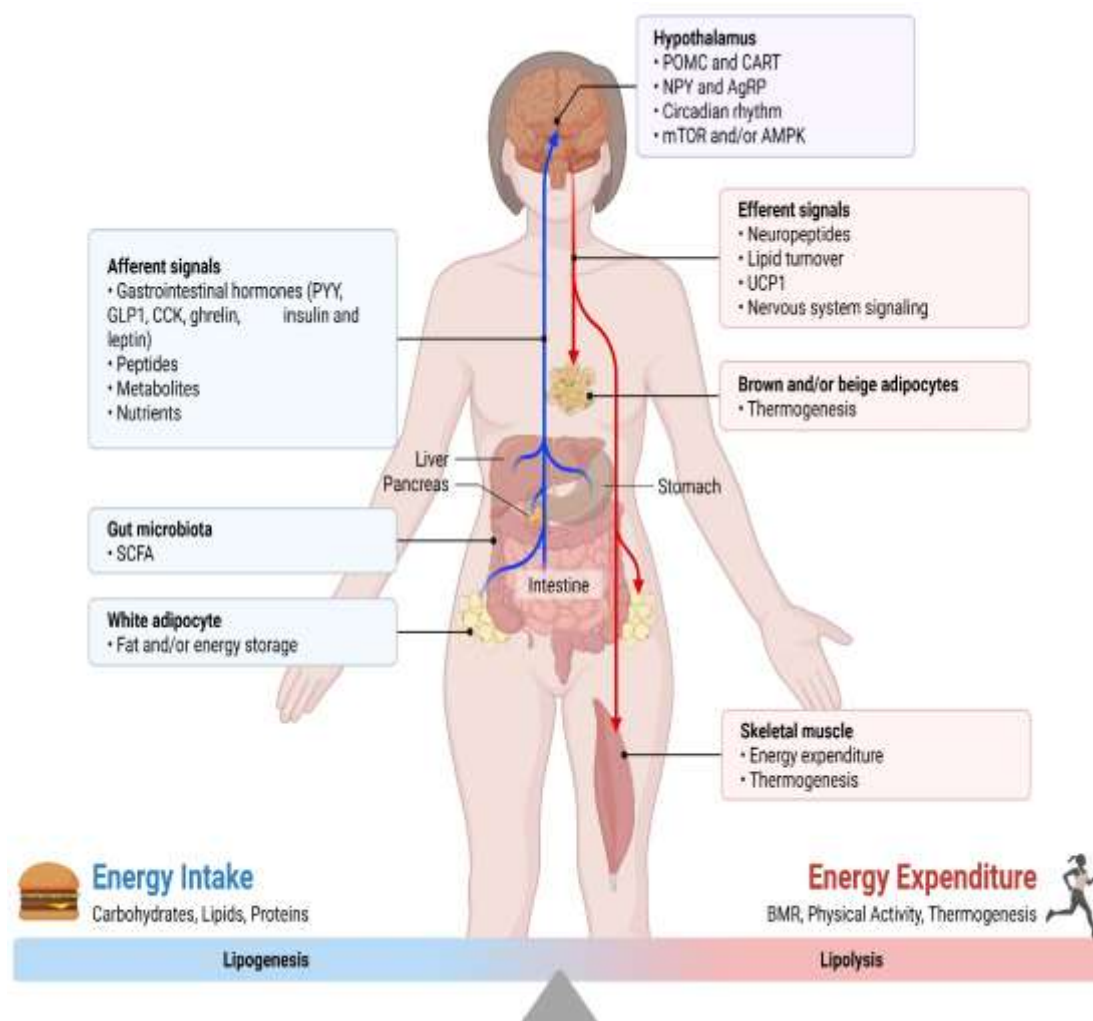


Fig: 7 Hypothalamic regulation of energy intake and expenditure through gut–brain, adipose, hormonal, and neural signaling pathways. Peripheral afferent signals, including gastrointestinal hormones, insulin, leptin, nutrients, metabolites, and gut microbiota-derived short-chain fatty acids, converge on hypothalamic circuits regulating appetite, circadian rhythm, and metabolic signaling. Hypothalamic efferent pathways subsequently modulate adipose tissue, skeletal muscle, thermogenesis, lipid turnover, and systemic energy expenditure.

Reactive Oxygen Species Generation

Reactive oxygen species generation is a major consequence of mitochondrial and metabolic dysfunction and provides a direct biochemical link between metabolic syndrome and migraine. Superoxide is produced when electrons escape from the mitochondrial respiratory chain and prematurely reduce molecular oxygen. Superoxide can subsequently be converted into hydrogen peroxide and, in the presence of transition metals, highly reactive hydroxyl radicals. Additional ROS arise from NADPH oxidases, xanthine oxidase, uncoupled nitric oxide synthase, and inflammatory immune cells. In metabolic syndrome, hyperglycemia, fatty-acid overload, angiotensin II, oxidized LDL, and inflammatory cytokines all promote these ROS-generating systems. Excessive ROS damage mitochondrial DNA, membrane phospholipids, respiratory proteins, and antioxidant enzymes, thereby worsening mitochondrial dysfunction and creating a self-perpetuating oxidative cycle. In sensory neurons, oxidative products can activate or sensitize TRPA1 and TRPV1 channels, resulting in enhanced release of CGRP and other neuropeptides from trigeminal afferents. ROS also stimulate NF- κ B and NLRP3 inflammasome signaling, thereby linking oxidative stress with neuroinflammation. Furthermore, superoxide reacts with nitric oxide to generate peroxynitrite, decreasing physiological nitric oxide availability while increasing nitrosative injury. Through these interconnected actions,

excessive ROS can simultaneously impair vascular function, increase neuronal excitability, and enhance trigeminal nociceptive signaling [96,97].

Impaired Antioxidant Defense

Oxidative stress develops when reactive species generation exceeds the capacity of endogenous antioxidant defense systems. Major protective mechanisms include superoxide dismutase, catalase, glutathione peroxidase, glutathione, thioredoxin, and several non-enzymatic antioxidants. Superoxide dismutase converts superoxide into hydrogen peroxide, which is subsequently detoxified by catalase and glutathione peroxidase. Reduced glutathione is particularly important for protecting mitochondrial proteins and membranes against oxidative damage. In metabolic syndrome, persistent substrate excess and inflammation can overwhelm these systems and may reduce antioxidant enzyme activity or glutathione availability. A similar redox imbalance has been reported in migraine populations, although findings vary across studies and disease stages. Reduced antioxidant reserve may increase vulnerability to common migraine triggers because the nervous system becomes less capable of neutralizing the oxidative burst associated with increased neuronal activity. Oxidative stress can also oxidize membrane lipids and proteins that regulate ion channels and receptors, modifying their functional properties. The resulting increase in excitability can reinforce mitochondrial dysfunction and inflammation. This biochemical rationale has contributed to interest in agents such as riboflavin, coenzyme Q10, magnesium, and other mitochondrial-supportive strategies in migraine prevention, although their clinical effectiveness varies among patients [98,99].

Mitochondrial Calcium Homeostasis

Mitochondria play a central role in intracellular calcium homeostasis by temporarily taking up calcium during neuronal activity and releasing it when demand decreases. This buffering function is closely integrated with ATP production because moderate mitochondrial calcium uptake stimulates enzymes of the tricarboxylic acid cycle and helps match energy production with cellular demand. During mitochondrial dysfunction, however, calcium regulation can become profoundly disturbed. Excessive cytosolic calcium may enter mitochondria through the mitochondrial calcium uniporter, leading to mitochondrial calcium overload, increased ROS formation, loss of membrane potential, and potentially opening of the mitochondrial permeability transition pore. In neurons, elevated intracellular calcium enhances glutamate release and activates calcium-dependent enzymes that may damage cellular membranes and proteins. Impaired calcium handling also favors activation of NMDA receptors and can facilitate cortical spreading depolarization. In metabolic syndrome, oxidative stress and insulin resistance may further disrupt calcium signaling in neurons, endothelial cells, and vascular smooth muscle. Because trigeminal neurons rely on calcium-dependent exocytosis for CGRP release, disturbances in intracellular calcium handling may also directly influence neuropeptide secretion. Mitochondrial calcium dysregulation therefore connects energy failure with oxidative stress, excitotoxicity, and trigeminovascular activation [100].

ATP Depletion and Neuronal Hyperexcitability

Reduced mitochondrial ATP generation can profoundly alter the electrical stability of migraine-related neural networks. ATP is required for the Na⁺/K⁺-ATPase to restore sodium and potassium gradients following action potentials and for calcium pumps to maintain low cytoplasmic calcium concentrations. When ATP availability declines, extracellular potassium can accumulate and intracellular sodium and calcium concentrations increase, shifting neurons closer to their firing threshold. Astrocytic uptake of extracellular potassium and glutamate is also energy dependent, meaning that metabolic deficiency can simultaneously weaken several mechanisms that normally suppress excessive excitation. Accumulation of extracellular glutamate enhances activation of NMDA and AMPA receptors and promotes additional calcium entry into neurons. This creates a positive-feedback cycle in which energetic deficiency enhances neuronal activity, while increased neuronal activity further increases ATP demand. Within the cerebral cortex, this imbalance may facilitate initiation and propagation of cortical spreading depolarization. Within trigeminal pathways, reduced metabolic reserve can enhance sensitivity to nociceptive triggers and promote CGRP release. These processes help explain why fasting, skipped meals, sleep deprivation, prolonged physical stress, and other conditions that disturb energy balance frequently precipitate migraine in susceptible individuals. Metabolic syndrome may intensify this vulnerability because insulin resistance limits efficient substrate utilization and reduces metabolic flexibility [101].

Therapeutic Potential of Mitochondrial Targeting

Targeting mitochondrial dysfunction represents a potentially valuable therapeutic approach because it could simultaneously influence energy metabolism, oxidative stress, inflammation, and neuronal excitability. Riboflavin functions as a precursor of flavin adenine dinucleotide and flavin mononucleotide, cofactors required for mitochondrial electron transport and oxidative metabolism, and has therefore been investigated for migraine prevention [102]. Coenzyme Q10 participates in electron transfer within the respiratory chain and also functions as a lipid-soluble antioxidant, while magnesium is required for numerous ATP-dependent reactions and influences NMDA receptor activity. Lifestyle interventions may be equally important. Regular aerobic exercise can activate AMPK and PGC-1 α , enhance mitochondrial biogenesis, improve insulin sensitivity, and strengthen endogenous antioxidant defenses. Weight reduction and dietary improvement can reduce mitochondrial lipid overload and systemic inflammation [103,104]. Ketogenic strategies have attracted interest because ketone bodies provide an alternative neuronal fuel and may improve mitochondrial energetic efficiency, although such interventions require appropriate clinical selection and additional long-term evidence. Newer experimental approaches include activation of SIRT1, enhancement of mitophagy, modulation of mitochondrial calcium transport, and development of mitochondria-targeted antioxidants. The strongest therapeutic rationale is therefore not merely to scavenge reactive oxygen species, but to restore mitochondrial quality, substrate flexibility, ATP production, and redox homeostasis. In metabolically compromised patients with migraine, correcting mitochondrial dysfunction could potentially interrupt the cycle of insulin resistance, oxidative stress, inflammation, neuronal hyperexcitability, and trigeminovascular activation, making mitochondrial biology an important target for future mechanism-based migraine therapy [105].

CONCLUSION

The relationship between metabolic syndrome and migraine extends beyond simple epidemiological coexistence and is increasingly supported by a broad network of shared pathophysiological mechanisms. Central obesity, insulin resistance, dyslipidemia, and hypertension generate a metabolic environment characterized by adipokine imbalance, chronic low-grade inflammation, oxidative stress, endothelial dysfunction, and impaired cellular bioenergetics. These abnormalities can converge on migraine-related neural pathways by promoting trigeminovascular activation, CGRP release, cortical hyperexcitability, neuroinflammation, and central sensitization. Pasted text Inflammatory mediators such as TNF- α , IL-1 β , and IL-6, together with NF- κ B, TLR, and NLRP3 signaling, appear to provide an important bridge between peripheral metabolic inflammation and central nociceptive processing. Pasted text Mitochondrial dysfunction further reinforces this interaction through reduced ATP generation, excessive reactive oxygen species production, impaired antioxidant defense, disturbed calcium homeostasis, and enhanced neuronal excitability. The association is also likely to be bidirectional. Metabolic dysfunction may increase migraine susceptibility and chronification, whereas recurrent migraine can contribute indirectly to physical inactivity, sleep disturbance, psychological stress, medication-related weight changes, and worsening cardiometabolic health. Pasted text Gut dysbiosis, hypothalamic and autonomic dysfunction, hormonal changes, and altered neuroendocrine signaling further expand this interaction into a broader neuro-metabolic framework. From a clinical perspective, patients with migraine—particularly those with obesity, hypertension, insulin resistance, dyslipidemia, or migraine with aura—may benefit from systematic cardiometabolic assessment alongside conventional neurological management. Future research should prioritize longitudinal studies, standardized metabolic phenotyping, biomarker validation, multi-omics approaches, and mechanism-based clinical trials. An integrated strategy combining weight control, dietary improvement, exercise, sleep optimization, cardiometabolic risk reduction, and appropriate migraine-specific therapy may offer the greatest potential to reduce both migraine burden and long-term metabolic and vascular risk.

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