

# The Migraine-Metabolic Connection: Screening for and Addressing Metabolic Syndrome in Patients with Migraine

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Patients presenting with migraine may benefit from screening for insulin-related comorbidities such as metabolic syndrome. Proper assessment optimizes patient care by simultaneously addressing migraine symptoms and offering therapeutic options that can collectively benefit both conditions and improve not only quality of life but risk factors of cardiovascular disease.

## The Crisis of Cardiometabolic Conditions

The growing prevalence of chronic health conditions in Canada is alarming with a need for proficient primary care assessment and intervention. Nationwide, metabolic syndrome (MetS) and related cardiometabolic conditions contribute to 17% of all health care costs and more alarming, 43% of all deaths. According to a 2014 study, nearly 1 in 5 individuals (19.1%) meet the diagnostic criteria for MetS—and often without awareness of their risk factors or the implications thereof.<sup>1</sup> Addressing the risk factors associated with chronic health conditions can be challenging for both the patient and the clinician. Developing a therapeutic alliance where patients are informed *and* motivated can be frustrating when the modifiable outcome for patients is often an abstract and fearful endpoint in the future (i.e. mortality and the risk of heart attack or stroke). Addressing tangible symptoms can inspire patients while simultaneously decreasing their risk profile. Improving the risk factors of MetS unfortunately does not always correlate with improved symptomatology. Subtle improvement in triglycerides and blood pressure, for example, is unlikely to significantly alter daily experience. However, improving prominent symptoms that impact the patient regularly may result in therapeutic compliance and long-term success. Migraine is known to coexist with MetS and insulin resistance (IR), though the pathophysiological processes are not entirely known.<sup>2,3</sup> Patients presenting with a chief concern of chronic migraine may benefit from naturopathic medical treatment not only to alleviate the discomfort but also to screen for and address cardiometabolic conditions such as MetS.

## The Migraine-Metabolic Connection

There are multiple theoretical etiologies of migraine. A misinformed concept is the “vascular theory of migraine” that originated due to the pulsatile nature of the pain. This perspective was adopted due to certain vasodilators (e.g. nitric oxide) triggering migraines and vasoconstrictive therapies (e.g. triptans) proving to be effective abortive agents. However, clinical data has revealed that the painful pulsations have a lower frequency and are not synchronized with

cardiac rhythm.<sup>4</sup> Intracranial vessel dilation during migraine is slight and is unaffected by sumatriptan (which has also been shown to have neural effects). Though appealing, the vascular theory has been proven obsolete.<sup>4</sup> Current research suggests that migraine is more fittingly a disorder of neurological processes. Neurological hyperexcitability—an over-response to sensory stimuli—has been hypothesized as a key feature of migraine. There are several mechanisms explaining the excitatory neuronal cascades leading to migraine including metabolic influences.<sup>3,4</sup>

Insulin metabolism and activation has been implicated in migraine. A contributing factor to changes in blood glucose levels are appetite-related neuropeptide signals in the hypothalamus. Prodromal migraine symptoms (e.g. fatigue and food cravings) implicate the involvement of the hypothalamus in addition to other brain areas such as the brainstem, cortex, and limbic system.<sup>3</sup> Orexigenic (stimulating food intake and decreasing energy expenditure) and anorexigenic (inhibiting food intake and increasing energy expenditure) neuropeptides are regulators of energy homeostasis in specific hypothalamic nuclei. Neuropeptide Y (NPY) and agouti-related peptide (AgRP) are orexigenic peptides that are inhibited by peripheral insulin and leptin. Insulin levels have been found to be consistently higher in migraineurs compared with controls—implicating the role of IR in migraine. Hypoglycemia from a fasted state is a trigger associated with initiating migraine. In susceptible individuals, low insulin receptor activation—through fasting—may trigger a migraine.<sup>4</sup> Genetic polymorphisms related to insulin receptor function may be a confounding factor.<sup>5</sup> There are many metabolic pathways which have been posited as the formal mechanism linking IR and migraine.<sup>3,4</sup> Research continues to offer more details on relevant pathophysiology but more importantly shows consistent correlations that warrant judicious and novel approaches to treating migraine and comorbidities collectively.

MetS exhibits a broader range of symptoms than IR alone. Migraine with aura (MA) has a positive association with low HDL-cholesterol, hyperglycemia, and abdominal obesity. MA may contribute to a

higher risk of MetS and should undergo appropriate screening.<sup>6</sup> Obesity is not considered a risk factor for migraine but is, however, associated with higher incidence and severity of symptoms.<sup>4</sup> There is a link between medication overuse headache (MOH) and MetS. A clinic-based study revealed that comorbid analgesic overuse may be the risk factor for MetS in female migraineurs and is associated with central obesity and hypertension.<sup>7</sup> Appropriate screening and treatment of migraine necessitates a full work up and health inquiry including (1) proper diagnosis of migraine; (2) clinically relevant assessments; (3) evidence-informed treatment strategies; and (4) and a strong therapeutic alliance.

### Assessing Migraine Headaches and Screening for Metabolic Conditions

The proper assessment of migraine headache is the clinician's primary duty before considering comorbid metabolic influences. The features of migraine headache are unilateral, pulsating pain of moderate to severe intensity that lasts 4 to 72 hours and typically results in avoidance of normal physical activities (e.g. walking). Migraine is usually associated with nausea and/or vomiting as well as photophobia and phonophobia. Migraine with aura has precipitating symptoms of vision changes (e.g. scotomas), unilateral numbness or tingling, muscle weakness, or speech changes which typically occur less than 60 minutes before the onset of head pain. Migraine can be episodic or chronic.<sup>8</sup> The Migraine Screen Questionnaire (MS-Q) is a self-administered checklist consisting of a mere 5 questions and has been shown to be useful in the primary care setting for early detection and assessment of migraine.<sup>9</sup> A headache diary may be a useful tool to clarify symptoms and to determine possible triggers.<sup>10</sup> Intracranial and emergent conditions such as temporal arteritis, acute glaucoma, and meningitis must be excluded when working up acute migraine.<sup>8</sup> To ensure the safety of patients, the clinician should be satisfied with a non-emergent diagnosis of migraine before pondering specific triggers or coexisting concerns such as food sensitivities, hormonal influences, and IR. Vital signs and a focused neurological examination are non-negotiable.

If risk factors supporting a diagnosis of MetS are present, then a thorough metabolic screen is indicated. The diagnostic criteria for MetS is the presence of 3 of the following features: visceral obesity, low HDL-cholesterol, high triglycerides, hypertension, and insulin-resistance.<sup>1</sup> Evaluating MetS requires diligent observation, physical examination, and laboratory investigations. Querying current pharmacologic intervention is important as some patients exhibit normal blood pressure or lab values due to effective medication use. Medication, genetic, and lifestyle factors may contribute to features associated positively with MetS (e.g. statin medications may increase blood glucose<sup>11</sup> and idiopathic hypertension has a familial component<sup>12</sup>). Inquiry about specific analgesic medications used to treat the migraine—including dose and frequency—helps to rule out MOH as part of the differential diagnosis (recall that MOH can also increase the risk of MetS<sup>7</sup>). Additional physical exam and observations include weight tracking, body measurements, calculation of body mass index (BMI), and possibly bio-electrical

impedance analysis (BIA). Cardiopulmonary and vascular health should be examined. If there are prominent features of overt diabetes, then distal extremity, ophthalmoscopic, and nervous system assessment is needed. Laboratory investigations should include basic bloodwork (complete blood count (CBC), cholesterol panel and triglycerides, and a comprehensive metabolic profile (CMP)) to assess the presence and/or progression of MetS. Glucose metabolism can be screened with HbA1c or fasting insulin, but detailed blood insulin and glucose assessment with a 2-hour insulin tolerance test should be considered. Proactive and functional testing considerations are the Kraft Prediabetes Profile; the Protein Unstable Lesion Signature (PULS) Cardiac Test; the CardioMetabolic Profile; Advanced Lipoprotein Testing; and possibly testing that may reveal non-metabolic origins of migraine such as food sensitivity testing and comprehensive hormone analysis.<sup>13</sup>

### Naturopathic Approaches to Treatment

Treatment approaches should be evidence-informed and should emphasize development of a therapeutic alliance that is rooted in informed consent, especially when discussing the risks associated with MetS. Patients presenting with a chief concern of chronic migraine require careful management and intervention should not withhold conventional treatments if required: abortive therapies to address acute migraine (NSAID combination medications and triptans) and migraine prophylaxis. If MetS is a suspected comorbidity, then keystone interventions are preventative in nature: diet modification, sleep hygiene, medications, and exercise.<sup>8</sup> The foundations of health—breath, hydration, whole foods, social connection, movement and rest—foster balance and are proactive recommendations that may serve patients well. Therapies such as vitamins, minerals, nutraceutical formulations, herbal preparations, and physical therapies are all on the table when treating migraine and metabolic dysfunction cohesively. Though the link between metabolic conditions and migraine has been established, supporting blood sugar homeostasis does not guarantee mitigation or resolution of migraine-related symptoms. Open and honest discussion around expectations of treatment is needed.

Therapies that simultaneously address IR and migraine can be considered. Interventions include but are not limited to alpha-lipoic acid, magnesium, riboflavin, coenzyme Q10, vitamin D, and therapeutic ketosis. Alpha-lipoic acid (ALA) has evidence in improving IR and may additionally decrease the number of migraine attacks and days of treatments, a 6-month cohort study revealed.<sup>14</sup> Hypomagnesemia has been associated with migraine and IR. Intravenous magnesium significantly relieved acute migraine up to 24 hours after the initial infusion. Oral supplementation with magnesium alleviated the frequency and intensity of migraine.<sup>15</sup> In the context of IR, magnesium supplementation positively effects fasting insulin and glucose levels.<sup>16</sup>

Riboflavin (vitamin B<sub>2</sub>) has implications for prophylactic migraine therapy based on a randomized control trial (RCT)<sup>4</sup> and a Korean study showed insufficient riboflavin intake may increase the risk of

developing cardiometabolic disorders—particularly in women.<sup>17</sup> Coenzyme Q10 supplementation is indicated for migraine treatment<sup>17</sup> and may slow the progression of prediabetes to overt diabetes.<sup>19</sup> An RCT showed that the simultaneous use of simvastatin plus vitamin D resulted in improvement in migraine at 12 and 24 weeks compared to placebo.<sup>20</sup> Hypovitaminosis D can hasten the development of IR.<sup>21</sup> Therapeutic ketosis has implications for both blood sugar control and migraine. Elevated ketone bodies (specifically D-β-hydroxybutyrate) are associated with improved migraine symptoms with evidence that a ketogenic diet may be a credible treatment approach. The therapeutic benefit of ketone bodies is attributed to the influence on physiological processes such as inflammation, oxidative stress, and mitochondrial function.<sup>22</sup> Hypoglycemia from fasting is a known trigger for migraines and distinct from glucose and insulin changes in nutritional ketosis. Utilizing therapies that benefit MetS while decreasing migraine duration and frequency can improve quality of life while decreasing risk factors that contribute to morbidity and mortality.

## Conclusion

Migraine management requires thorough assessment; exclusion of life-threatening conditions; and openness to conventional therapies. It is prudent to include MetS in the differential diagnosis of migraine when applicable features are present. Though mechanisms are not entirely understood, migraine is a neurological condition that may benefit from metabolic regulation—especially when MetS is noted as a comorbid condition. 🍌

## About the Author

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