Review

Linking Migraine To Gut Dysbiosis And Chronic Non-Communicable Diseases

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Linking Migraine to Gut Dysbiosis and Chronic Non-Communicable Diseases

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Abstract: In the world, migraine is one of the most common cause of disability in adults. To date, there is no a single cause for this disorder, but rather a set of physio-pathogenic triggers, in combination with a genetic predisposition. Among factors related to the migraine onset, a crucial role seems to be played by gut dysbiosis. In fact, it has been demonstrated how the intestine is able to modulate the central nervous system activities, through the gut-brain axis, and how gut dysbiosis can influence neurological pathologies, including migraine attacks. In this contest, in addition to migraine conventional pharmacological treatments, attention has been paid to an adjuvant therapeutic strategy based on different nutritional approaches and lifestyle changes able to positively modulate the gut microbiota composition. In fact, the restoration of the balance between the different gut bacterial species, the reconstruction of the gut barrier integrity and the control of the release of gut-derived inflammatory neuropeptides, obtained through specific nutritional patterns and lifestyle changes, represent a possible beneficial additive therapy for many migraine subtypes. Herein, this review explores the bi-directional correlation between migraine and the main chronic non-communicable diseases, like diabetes mellitus, arterial hypertension, obesity, cancer and chronic kidney diseases, whose link is represented by gut dysbiosis.

Keywords: migraine; chronic non-communicable diseases; gut microbiota; nutritional approaches; lifestyle changes

1. Introduction

Migraine is a complex neurological disorder that triggers a particular type of headache, characterized by unilateral, pulsating and moderate-severe pain, which generally worsens with physical activity and is associated with other symptoms such as nausea, vomiting and photo-phonophobia [1]. With an estimated global prevalence of 14.7% [2], World Health Organization (WHO) listed migraine among the top ten causes of disability worldwide [3], at the first place if we consider the under 50s people [4]. Women are 3-4 times more affected than men and show more disabling and drug-resistant attacks and this consequently provokes a great socio-economic burden [5–7]. About 3% of the patients, suffering from episodic migraine, evolves every year towards a more complex clinical picture of chronic migraine. In this latter condition, patients should suffer a monthly migraine of about 15 or more days, in the last three months [8].

The main trigger factors of this migraine progression are hormonal pathways, psychological syndromes, drugs assumption, environmental factors and nutritional habits (Figure 1).

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Figure 1. Common trigger factors for migraine development and chronicization.

In women, migraine can be linked to the fluctuations of sexual reproductive hormones. In fact, decreased estrogens in the late luteal phase of the menstrual cycle lead to an increased permeability of blood vessels to prostaglandins, becoming a migraine trigger [9]. On the contrary, elevated estrogen levels are associated with more frequent pain attacks, especially with aura [10]. For this reason and for a higher stroke risk, associated with aura, the use of oral contraceptives is still restricted by current guidelines in those women affected by this headache subtype [11]. The most frequently psychological factor associated with this pathological condition are: (i) anxiety, which seems to have a shared genetic basis with migraine [12,13]; (ii) depression [12,14], characterized by a low availability of 5-hydroxytryptamine (5-HT), an increased sensitivity of trigeminovascular pathways [15], a hypofunction of the dopaminergic system [14], a down-regulation of the GABAergic system and decreased estrogen levels; (iii) stress [16], namely previous and recurrent stressful events which have been shown correlated with migraine onset and its chronicization [17]; (iv) excessive fear of migraine attacks, that refers to the fear of a headache occurring and which can worsen the disease course [18]. Even the use of some psychoactive drugs can be an important provoking agent for migraine generation, including nitroderivates, histamine, reserpine, hydralazine, and ranitidine as well as cocaine and marijuana [19–23].

Notably, the overuse of analgesic or other abortive pain medications (i.e. triptans) is the major clinical factor of migraine worsening, inducing a particular condition, known as "medication overuse headache" [24]. Among the environmental factors that can lead to the migraine development figure: high altitudes, changes in atmospheric pressure, temperature, light and precipitation, humidity, air pollution, sensory stimuli, such as olfactory and visual ones [25]. Impaired sleep patterns can also promote migraine attacks, particularly in young adults [26]. Other important migraine triggers are the nutritional habits and certain foods consumption like: fasting, caffeine, natural sweeteners (such as aspartame), nitrites of preserved meats, biogenic monoamines of alcohol, chocolate and dairy products (such as cheese and yogurt) and monosodium glutamate [25].

Migraine is frequently associated with chronic non-communicable diseases (CNCDs), like diabetes mellitus (DM), arterial hypertension (AH), obesity, cancer and chronic kidney disease (CKD). Moreover, CNCDs are themselves both cause and consequence of a negative change in the gut microbiota composition, called “dysbiosis” [27–29].

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At this regard, in addition to pharmacological treatments, a new adjuvant therapeutic strategy able to counteract migraine, could be represented by different nutritional approaches able to modulate the gut microbiota composition and the gut-brain axis [30].

The term "microbiota" means a very wide community consisting of bacteria, viruses, fungi, Archea and eukaryotes unicellular. The term "microbiome" instead, indicates the set of the genetic patrimony of the microorganisms, which constitute it [31].

The microbial component and its genetic patrimony are affected by lifestyle, dietetic habits and other external factors as the environment. Therefore, the gut microbiota is a dynamic system that is in constant evolution [32] and is also composed by the vascular gut-barrier [33]. The latter is a fundamental coating system able to control the epithelium permeability and the passage of potentially pathogenic molecules and bacteria into the bloodstream [34,35]. Therefore, the microbiota can be defined as a "meta-organ", namely it is a structure that anatomically is not a part of the organism, but it accompanies the human phylogenetic evolution [36,37].

The aim of this review is to analyze the possible correlation between migraine and gut microbiota dysbiosis and the possible relationship between migraine and CNCDs. Moreover, we examined the possible nutritional approaches and lifestyle changes able to positively modulate the gut microbiota composition, reducing the migraine frequency and intensity.

2. Materials and Methods

In order to achieve the review aim, a literature search was conducted using three databases (PubMed, Scopus, and Cochrane Library), until August 2023. The search was limited to peer-reviewed journals, written in the English language and the search terms were "migraine" in combination with "gut microbiota", AND "chronic degenerative non communicable diseases" , AND "diabetes mellitus", AND "Arterial Hypertension", AND "obesity", AND "cancer", AND "chronic kidney disease", AND "Mediterranean Diet", AND "Ketogenic Diet", AND "probiotics", AND "physical exercises", AND "vitamins", AND "iron", AND "polyphenols", AND "electrolytes" AND "histamine".

3. The gut microbiota physiological composition

The first studies related to the discovery of the microbiota date back to the beginning of the XX century, when a student of Pasteur, Elie Metchnikov [38] deepened the theme of the symbiotic bacteria in organism, unlike Pasteur who focused his attention mainly on pathogenic ones. Metchinikov described the beneficial effects of lactic ferments on the bacterial flora and health host [38]. Subsequent studies have pointed out the presence of these bacteria that are involved in the absorption of nutrients as well as in the immune system modulation [39,40]. In the 90s for the first time the "gut-brain axis" was highlighted, namely how the microbiota exerts a physiological role in the maintenance of the host health [41].

The human microbiota is characterized by a high bacterial density, with a metagenome that in the adult is 150 times larger than the overall human genetic pattern [42]. It is an ecosystem composed by a set of ecological niches in close contact with the intestinal mucosa, forming an area of 250-400 m^2 [37]. A more precise view of the complexity of the gut microbiota has been made in recent years thanks to metagenomic data.

Although there is a wide variety of symbiotic microorganisms, among the 160 species present in the human intestine, of which at least 57 are common to all individuals, the most widespread microbial phyla are only 4: Bacteroides, Firmicutes, Actinobacteri and Proteobacteria. The first two are present in greater quantity; in fact, they constitute about 90% of the human gut microbiota [43,44].

The microbiota is an extremely heterogeneous and complex system, strongly modulated by external factors (Figure 2).

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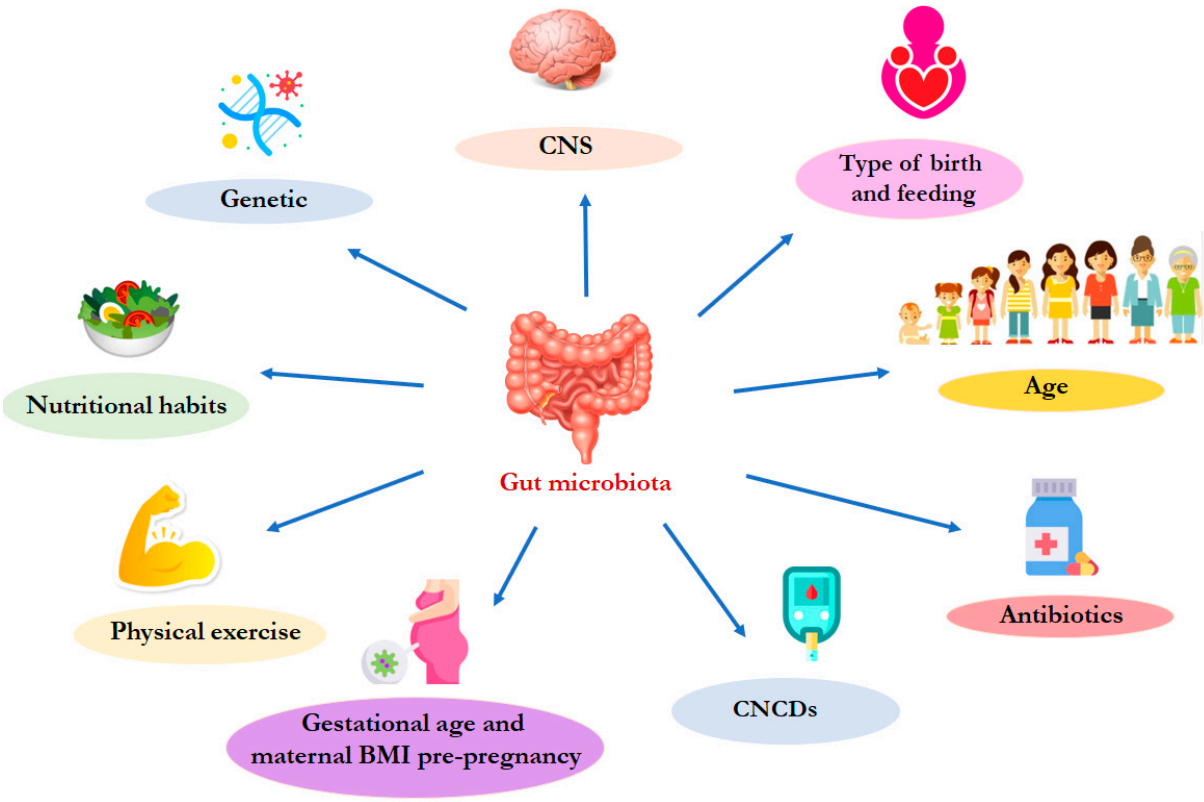

Figure 2. Main factors that can influence the gut microbiota composition. Abbreviation: BMI, Body Mass Index; CNCDs, Chronic Non-Communicable Diseases; CNS, Central Nervous System.

The composition of gut microbiota changes in relation to age. In fact, recent studies reported that the microbiota begins to colonize the intestinal tract since the intrauterine life [45,46]. At this regard, it has been demonstrated that placental microbiota can influence, already during the pregnancy, the correct fetus psychophysical development [47]. The maintenance of a correct placental eubiosis is influenced by the nutritional habits of the mother, during pregnancy. In particular, a diet rich in fats may induce the placental dysbiosis that has been associated with a high risk to develop metabolic syndrome in adult [48]. Moreover, the placenta dysbiosis can damage the maternal hypothalamic-pituitary-adrenal axis (HPA) and can influence the circulating levels of 5-HT, inducing a possible damage to the fetal neuronal development [49]. In the child gastrointestinal (GI) tract, Bifidobacteria are the most numerous bacteria [50]. In adulthood, the bacterial composition appears to be larger both in terms of the number of microorganisms and of the diversification of taxa (called α-diversity). The gut microbiota α-diversity reflects the variability of species within the human intestine. Recent studies have highlighted how it is directly related to host health and how a poor α-diversity is associated with various CNCDs [51,52]. The gut microbiota changes that are observed in relation to age are mainly due to the switch from a liquid to a solid diet. This switch causes the enrichment of bacterial flora, especially about the families of *Lachnospiraceae* and *Ruminococcaceae* [43]. Throughout the life, the dietary habits influence the composition of the gut microbiota. Scientific studies report that bacteria belonging to the genus Clostridium (the main producers of butyrate, a short chain fatty acid- SCFA) are more present in subjects following a Mediterranean diet (MD), while the subjects that follow a Western diet show fewer bacteria responsible for the degradation of fibers, such as Prevotella and Succinivibrio [53,54]. In the elderly, the gut microbiota composition is less variable due to the reduction of the foods variety in the diet and to the reduction of the fiber intake, which results in a decrease of the Firmicutes, (among these *Clostridium* cluster XIVa and *Feacalibacterium prausnitzii*, involved in saccharolytic fermentation), and in an increase of the Proteobacteria [55]. This induces a SCFAs reduced availability, that in turn contributes to the aging and to the increased of proteolytic fermentation [56]. This phoenomenon induces an enhanced production of gut derived

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toxins, like trimethylamine N-oxide (TMAO), p-cresyl sulfate (p-CS), indoxyl sulfate (IS) and indole-3 acetic acid (IAA). Moreover, an increase of proteolytic fermentation triggers the low-grade chronic systemic inflammation, factor related to the onset and the progression of CNCDs and sarcopenia [27,57,58].

Other factors that influences the gut microbiota qualitative and quantitative composition are: (i) gestational age; (ii) antibiotic therapy, above all in perinatal period; (iii) mode of childbirth (vaginal or cesarean); (iv) type of feeding (breast feeding, artificial or mixed, composition and timing of complementary feeding); (v) body mass index (BMI) pre-pregnancy and maternal body weight increase during pregnancy [59,60].

i) *Gestational age.* An interesting study analyzed the gut microbiota possible differences in full-term and in pre-term delivery. Full-term infants are characterized by a greater abundance of *Bacteroides,* while pre-term infants show a greater abundance of *Lactobacillus* [61].

ii) *Antibiotic therapy, above all in perinatal period.* Antibiotics, especially broad-spectrum ones, alter qualitatively and quantitatively the gut microbiota composition [62]. Studies conducted on mice suggested complex mechanisms (endocrine and neurocrine) involved in the signaling between gut microbiota and brain, that are induced by an excessive use of antibiotics, especially in children [63]. In fact, an excessive use of antibiotics promotes the gut colonization of *Clostridium difficile [64]*, an opportunistic pathogen that can cause diarrhea, specifically in the case of simultaneous intake of drugs that reduced the gut microbiota α-diversity [65,66].

iii) Mode of childbirth. It has been shown that the microbiota of natural births is dominated by bacterial genera such as *Bacteroides* (Bacteroidetes), bifidobacteria (Actinobatteria), lactobacilli (Firmicutes) and enterobacteria (Proteobacteria). On the contrary, the microbial pattern of Caesarean births is instead characterized by a qualitative-quantitative alteration of the gut microbiota composition [67]. In the detail, Caesarean births lack Bacteroides species until 18 months, due to non-exposure to the maternal vaginal microbiota [68].

iv) Type of feeding. The α-diversity would appear to be lower in breastfed infants compared to formula-fed infants and the gut microbiota composition shows differences. *Bifidobacterium* and Bacteroides are more abundant in breastfed infants, while Streptococcus and Enterococcus are more abundant in formula-fed infants *[69].*

v) Body mass index (BMI) pre-pregnancy and maternal body weight gain during pregnancy. A recent study pointed out differences in maternal gut microbiota composition based on pre-pregnancy weight and gestational weight gain. In fact, mothers overweight/obese, before pregnancy, are characterized by the presence of some taxa, like family *Christensenellaceae*, the genera *Lachnospira, Parabacteroides, Bifidobacterium* and *Blautia.* Moreover, mothers overweight or obese before pregnancy show a lower α-diversity compared to non-overweight/non-obese subjects. This gut microbiota maternal pattern seems not to be related to global differences in the infant gut microbiota within the first two years of life [70].

Recent studies demonstrated that also physical activity is able to modulate the gut microbiota, in terms of composition and function [71]. On the contrary, physical inactivity has been repeatedly associated with alterations in the bacterial composition of the gut microbiota [72,73]. In particular, as described in the following paragraph, the physical exercise is able to improve the body composition, positively modulating the gut microbiota pattern and stimulating the SCFAs production [74]. Nevertheless, the benefits obtained during a period of continuous physical activity are lost if you return to a sedentary condition [75].

Furthermore, as previously described, the CNCDs are, in the same time, both cause and consequence of gut microbiota dysbiosis [32,76] . For example, in CKD patients there is an alteration of gut permeability, which allows the passage of bacteria and bacterial material from the gut to the bloodstream. This phenomenon induces a chronic inflammatory state that exacerbates CKD itself. In CKD patients, it can be observed an accumulation and an increased production of gut-derived toxins (like IS, TMAO, p-CS, IAA). These toxins are associated with an increase of the cardiovascular (CV) risk [27].

4. Migraine and gut dysbiosis

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In recent decades, literature demonstrated that gut microbiota is involved in the central nervous system (CNS) activities [77]. Over time, several studies have investigated and defined some of the mechanisms through which the brain is able to connect itself to gut, defining the "gut-brain axis" [78].

The importance of this axis has been mainly highlighted in the studies that evaluated the causes underlying neurodegenerative and psychiatric diseases and neurodevelopment [79,80]. In particular, the CNS can influence the gut environment impacting on some intestinal functions, such as the regulation of gut movements, the excretions and immunity system [81]. The interaction between the intestine and the brain is confirmed by the gut microbiota modification which can impact on CNS different functions [63,82].

The brain communicates with the intestine through numerous "roads" [63] such as: (i) the immune system; (ii) the SCFAs; (iii) the autonomic nervous system (vagal nerve); (iv) the tryptophan metabolism, precursor of the neurotransmitter serotonin; (v) the neurotransmitters; (vi) the gastric peptides produced by specialized endocrine cells, whose release is influenced by the microbiota itself; (vii) the HPA axis [30,83].

Therefore, the intestine can be considered the "second brain", as it produces a series of neurotransmitters, such as serotonin and histamine [84]. Several studies demonstrated that low levels of cerebral serotonin are strongly associated with migraine. In particular, migraineurs have higher levels of cerebral serotonin during an acute pain attack compared with the periods between attacks [85,86]. At this regard, a symptomatic migraine-specific class of drugs commonly used in the clinical practice are triptans, serotonin receptor agonists that can "recreate" an optimal brain neurotransmitter concentration, by reducing the inflammation and, consequentially, the pain. Unfortunately, these medications are characterized by several side effects, such as cardiovascular dysfunction, GI disorders, muscle aches, drowsiness, tingling and dermatological disorders [87].

Moreover, it was demonstrated that patients with chronic headache present higher histamine concentrations than healthy subjects, either during or between migraine attacks [88]. Previous studies have been focused on the effects of antihistamines in the pain treatment behind the proven histamine's role as a potent migraine trigger. However, this evidence is of poor quality and often limited by frequent undesirable adverse events (i.e. excessive somnolence). Although there are positive reports about the histamine H3 receptor agonists (H3R) that seem to effectively inhibit the histamine release in the CNS, they are not very credible because based on subtherapeutic analgesic dosages [89,90].

As previously described, nausea and vomiting are symptoms commonly associated with migraine. Moreover, patients with frequent migraine attacks often present GI symptoms, such as reflux, diarrhea and constipation [91]. Starting from this observation, Camara-Lemarroy et al., have highlighted a relationship between migraine and GI disorders [92]. This statement is strengthened by the fact that inflammatory bowel diseases patients often suffer from migraine [93]. Gut dysbiosis would seem to play a key role in the pathogenesis of migraine, since this intestinal alteration would seem to induce an increased production of gut-derived inflammatory cytokines that can modulate the HPA axis [94]. Furthermore, these gut-derived inflammatory cytokines would, in turn, appear to be involved in the modulation of the vagus nerve activity which, among other functions, innervates the intestinal free fatty acid receptor 3. This receptor seems to be involved in the metabolic pathway of SCFAs [95]. Therefore, the mechanisms underlying the interaction between the gut microbiota and migraine are supported by several studies that have highlighted direct and indirect evidences [96]. The former includes the fact that gut dysbiosis, associated with impaired production of SCFAs, induces the release of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α. The latter, in animal models, seems to regulate the migraine-like pain [97]. The second ones are deduced from scientific studies that have suggested that nutritional approaches, use of probiotics, stimulation of the vagus nerve can represent a new therapeutic strategy for migraine, based on the gut microbiota modulation [98–100]. Therefore, it is evident that there is a correlation between the gut microbiota and the migraine. In fact, numerous studies both conducted on animal models and clinical trials have highlighted a gut microbiota alteration in migraine patients compared to healthy subjects. At this regard, it is important to understand whether the possible comorbidities (such as CNCDs) inducing

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dysbiosis can be a trigger for migraine, and at the same time, whether specific nutritional approaches or lifestyle changes can represent a valid and innovative adjuvant therapy for the treatment of migraine.

5. Migraine and its correlation with chronic non-communicable diseases

5.1. Diabetes mellitus and migraine

The correlation between DM and migraine is currently controversial [101]. Some epidemiological studies suggest that migraine can be considered a non-traditional risk factor for the DM onset and its progression (Figure 3) [102]. In particular, it has been highlighted that migraine is able to increase the CV risk in DM patients, worsening their outcomes, especially in the presence of aura [103]. Moreover, the insulin resistance condition has been associated with the migraine development. In particular, the insulin resistance seems capable of significantly prolonging the migraine attack, but not its severity [104]. A possible explanation could be related to the fact that insulin resistance, at the brain level, can lead to impaired release of neurotransmitters and to the onset of an inflammatory response to insulin, factors that are crucial for migraine origin [105].

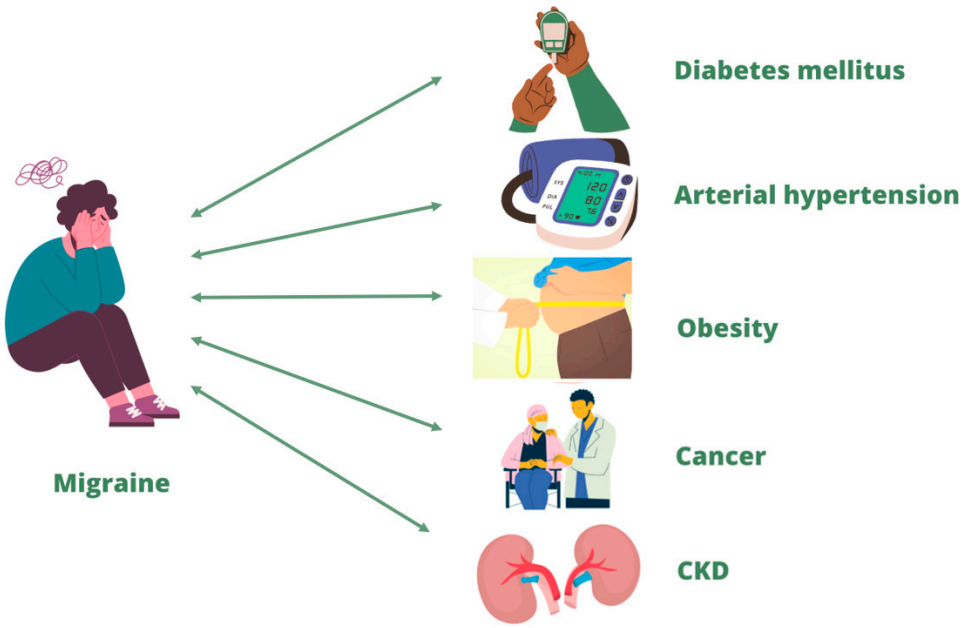

Figure 3. Correlation between migraine and chronic non-communicable diseases. Abbreviation: CKD, Chronic Kidney Diseases.

Other studies show an inverse correlation between these disorders, considering type 1 DM a protective factor against migraine. Although the exact mechanisms which underline this relationship have not yet sufficiently elucidated, it has been proposed that similarities in genetic, biochemical, and lifestyle-related pathways could account for this association [106–108].

A recent epidemiological study conducted on over 70,000 French women has highlighted a lower risk of developing type 2 DM in women with migraine compared to those without a migraine history [109]. A further study suggests, however, that migraine attacks in DM patients may be related to the episodes of hypoglycemia that these patients often manifest, suggesting that the reduction of these episodes could probably decrease the risk of migraine onset [101].

5.2. Arterial hypertension and migraine

AH and headaches have been linked in medical literature [110]. In fact, it is well-known how hypertensive crisis, namely sudden increase in blood pressure, can occur with abrupt headaches [111]. Migraine and AH may share common mechanisms, like endothelial dysfunction (ED),

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deficiency of autonomic CV regulation and renin- angiotensin- aldosterone system (RAAS) involvement [111]. Preventive anti-migraine effects were described for several antihypertensive drugs, such as the beta-blockers, angiotensin-converting-enzyme inhibitors and angiotensin II receptor blockers [112]. ED may be both one of the factors that increase the cerebrovascular and CV risk in migraine subjects and a determinant cause of AH development [113]. Nitric oxide (NO) plays a pivotal role in the pathogenesis of migraine, in fact it is involved in the regulation of cerebral and extra-cerebral cranial blood flow and of arteries size. In migraineurs, the arteries are hypersensitive to NO and it was hypothesized that this phenomenon is one of the main trigger of migraine attack [114].

Moreover, the RAAS could be another factor responsible for the clinical correlation between migraine and AH [115]. This might explain because some angiotensin-converting-enzyme inhibitors and angiotensin II receptor blockers are effective in preventing migraine, regardless of the presence or not of AH [116]. Notably, the presence of AH in a migraine patient increases the CV risk [117].

5.3. Obesity and migraine

The WHO defines obesity as a condition characterized by an excessive presence of adipose tissue in the human body, that induces a significant increase of CV mortality and morbidity, in both sexes [118]. Obesity is commonly considered a consequence both of the excessive calorie intake, compared to energy expenditure, and of the decrease in physical activity, very common habits in Western societies [119].

Clinical evidence showed that obesity could intensify the risk of episodic and chronic migraine and that the body weight reduction in obese subjects can decrease the intensity, the frequency, and the duration of migraine attacks [120].

The link between obesity and headache is attributed to shared pathophysiological features [121]. For example, adult obese subjects show increased calcitonin gene-related peptide (CGRP) plasma levels, which are also elevated in migraine patients [122]. Furthermore, a rise in proinflammatory cytokines, such as interleukin (IL)-6 and TNF-α was reported in obese individuals and in the acute headache phase [123].

5.4. Cancer and migraine

For most cancer types, there is no evidence to support a link between increased oncological risk in migraineurs [124], except for tumors of neurological origin of which migraine can often represent the onset symptom. In contrast, it has been described a lower prevalence of GI cancers in subjects with migraine, compared to those without migraine [125].

Moreover, cancer patients may present an amplified risk of developing migraine. It is very important to recognize the migraine causes in order to treat it promptly and exclude the presence of secondary headache causes (i.e. brain metastasis) [126]. Migraine induces a negative impact on the quality of life of cancer patients and, showing a very broad etiology, makes its diagnosis difficult [127]. For cancer patients, any change in pharmacological treatment, including chemotherapy, can trigger headaches [128].

5.5. CKD and migraine

Several epidemiological studies have highlighted a direct correlation between CKD and the migraine onset, even if the mechanisms underlying this correlation remain partially known. A study conducted by Wang et al, evaluated the CKD incidence in a group of subjects with normal renal function suffering from chronic migraine, compared to a group of subjects without migraine. The authors showed that the CKD incidence was higher in subjects suffering from chronic migraine than in the control group. In particular, male gender, age and the nonsteroidal anti-inflammatory drugs (NSAIDs) abuse would appear to be independent risk factors for the CKD onset [129]. This correlation seems to be associated with ED secondary to migraine, which would increase the risk of developing CKD [130]. Other factors that could lead to the CKD onset in chronic migraine patients are blood

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pressure fluctuations and coexisting comorbidities [131]. A study evaluated the possible genetic link between the two pathological conditions; although no overall genetic correlation was found, four specific genomic regions were identified that appear to be related to common pathogenic mechanisms underlying both migraine and CKD. These mechanisms appear to involve the cardiovascular system and endothelial function [130].

Hemodialysis-related migraine has been described in the literature. In fact, hemodialysis patients often suffer from headache during or after hemodialysis (HD) treatment. The headache usually occurs in the first hour of HD session and it resolves after a maximum of 72 hours after HD treatment [132]. This phenomenon could be related to the electrolyte imbalance and blood pressure fluctuations that occur during dialysis treatment [133].

6. Possible nutritional approaches and lifestyle changes to counteract migraine

Proper nutrition patterns and healthy lifestyle are useful to prevent and alleviate the headache symptoms. This issue has a very ancient origin [134]. In fact, Ippocrate was aware of the relationship between assumption of some foods and the onset of migraine [135]. Indeed, there are many foods that can cause pain attacks because they contain substances that are able to alter the intracranial blood circulation [136], inducing vasodilation-vasoconstriction imbalance and consequent headache. In this context, a healthy diet may represent a valid preventive therapeutic strategy for the migraine [137].

6.1. Mediterranean Diet

The MD can be defined as a model of dietary habits adopted by the populations living in the Mediterranean area [138]. It is characterized by a high consumption of fresh fruit and vegetables, legumes, complex carbohydrates, accompanied by a moderate consumption of seafoods and extra virgin olive oil (EVOO), as the main source of fats, and by a moderate consumption of wine [138]. There are numerous clinical studies that highlight how MD is able to reduce the risk of onset and to slow down the progression of CNCDs [139]. MD may also be considered an adjuvant approach to fight migraines in this patient population [140].

A meta-analysis highlighted the potential role of the MD in the fight against major neurodegenerative diseases [141]. This diet is rich in polyunsaturated fat acids (PUFAs) and monounsaturated fat acids (MUFAs) that seem to prevent the onset of Alzheimer's and Parkinson's diseases [142]. Moreover, the intake of PUFAs and specifically of eicosapentaenoic acid (EPA) seem to have antidepressant effects [143]. A recent meta-analysis analyzed 26 randomized double-blind placebo-controlled trials, highlighting beneficial effects on the depression symptoms of EPA intake, at a dosage of ≤1 g/day, compared to placebo [144]. Furthermore, as PUFAs are the main lipid forming cerebral cortex, they are able to exert an important role in higher cognitive processes and in learning [145].

Moreover, the MD is rich in polyphenols, vitamin C, E, B12, B9 and carotenoids, and it is therefore able to counteract the oxidative stress (OS) and the lipid peroxidation, exerting a cardioprotective and neuroprotective effects [146].

MD seems to reduce the chronic migraine symptoms [140]. In fact, a recent clinical study conducted on subjects, aged between 18-64 years, who suffered from chronic migraine, highlighted how those who had a poor adherence to MD developed more severe and frequent migraine attacks, compared to those who had a high adherence to MD [147]. This symptoms reduction appears to be associated with the systemic inflammation decrease, mediated by MD typical foods. A Western diet, on the other hand, rich in pro-inflammatory foods, would seem to be associated with an increase in migraine symptoms [148,149]. These associations would seem to be related to the gut microbiota modification induced by the different nutritional patterns. In fact, it is known that the Western diet, characterized by a high dietary intake of salt, increases the *Firmicutes*/*Bacteroidetes* ratio, providing the conditions for gut dysbiosis. The latter induces a reduction of SCFA-producing bacteria, losing their important beneficial functions for the host [54]. On the other hand, MD would seem capable of positively modulating the gut microbiota by increasing its α-diversity [150].

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The Western diet, rich in saturated fatty acids, is characterized by increased of proteolytic fermentation, which leads to the production of gut-derived toxins, as previously described. Instead, the MD is characterized by an enhancement of saccharolytic fermentation, that stimulates the SCFAs production [27].

6.2. The ketogenic diet

The ketogenic diet (KD) was initially used as adjuvant treatment for drug-resistant epilepsy and to date it is also widely used for rapid weight loss [151]. Its effects on neurodegenerative diseases, cognitive functions and the autistic spectrum disorders have also been studied. This nutritional approach is characterized by a high lipid intake, right amounts of proteins and low energy intake from carbohydrates. The objective of KD is to reduce glycolysis and to stimulate the formation of endogenous ketones through the oxidation of fatty acids [152].

The increased concentration of ketones leads to a state of ketosis, so that these molecules take the place of glucose and can be used as the primary energy source by the brain. The KD can protect the brain from OS and can normalize the neuronal bioenergetics through the stimulation of mitochondrial biogenesis and the stabilization of synaptic functions [153].

The first evidence that the KD was able to alleviate the symptoms of migraine dates back to the beginning of the last century. Since then, numerous clinical studies have been conducted on patients suffering from chronic headache. These studies have shown that, through different mechanisms, the KD is able to reduce the systemic inflammation [154] and the OS [155] at the level of the CNS, and to positively modulate the gut microbiota [156], reducing the symptoms of migraine [157–159].

6.3. Probiotic and prebiotic supplementation

The WHO has defined probiotics as "living micro-organisms" capable of bringing benefits to human health when administered in adequate quantities [160]. The main prebiotics belong to genera Lactobacilli and Bifidobacteria and their effects depend on the species and the strain: for example, the *Lactobacillus rhamnosus* seems to be very effective in the treatment of GI disorders, such as infectious diarrhea in children, or in the prevention of antibiotic-induced diarrhea [161,162].

Probiotic integration can modulate the chronic migraine symptoms [32,163]. The possible mechanisms of action are unclear and may include the stimulate of the SCFAs production, the improvement of the gut epithelial integrity and the decrease of inflammation by suppression of the kappa-B nuclear factor (NF-κB) pathway, lowering the levels of proinflammatory cytokines [164]. Probiotics could also increase the rate of gastric emptying and attenuate the gastric stasis, a GI disorder commonly present in patients with migraine [165]. Several studies have shown that the probiotics assumption can rebalance the gut microbiota composition, can improve the gut permeability and can prevent the onset of neurological disorders, such as migraine [166].

In some subjects, even some food allergies and intolerances can trigger migraine attacks. Conversely, a decrease in gut permeability can give relief from migraine. Probiotics, therefore, thanks to an improvement of the gut barrier functions, could also have a beneficial effect in patients with headache. New clinical studies are necessary to confirm this hypothesis [121,167].

Prebiotics are described as undigested substances capable of selectively stimulating the growth and/or the activity of one or a limited number of symbiotic intestinal bacteria. The prebiotics supplementation is able to restore the gut eubiosis and could favour the reduction of migraine attacks [168]. Many studies have focused on the effects induced by the two main prebiotics, galactogosharides (GOS) and fructooligosaccharides (FOS), demonstrating how these organic substances were able to reduce the neuroinflammation and the brain OS [169,170]. GOS and FOS seem to stimulate the brain functions and synaptic plasticity, towards the brain neurotrophic factor and receptors for N-methyl-D-aspartic acid (NMDA) [171].

6.4. Physical activity

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Physical activity, at the doses recommended by the WHO, seems to improve the quality of life. In particular, the WHO recommends for adults a daily moderate-intensity aerobic physical activity of at least 150-300 minutes or 75-150 minutes of vigorous-intensity aerobic physical activity [172]. This physical activity seems to improve muscle mass, cardiorespiratory fitness and bone health and it appears to reduce the risk of AH, CV diseases, DM, various types of cancer (including breast cancer and colon cancer) and depression [173]. Regarding this last aspect, the mechanisms whereby physical exercise exerts its beneficial neurological effects are numerous, among which the regulation of HPA axis, the promotion of an anti-inflammatory state and the increase of neuroplasticity [174]. It is interesting to note that the physical exercise can determine changes in gut microbiota composition, restoring the homeostasis and regulating the energy expenditure [175]. Low-intensity physical exercise can affect the GI tract functions, reducing intestinal transit time and thus, the contact time between pathogens and the GI mucus layer [176].

Adapted physical activity could represent a valid non-pharmacological strategy for the clinical management of patients affected by CNCDs [177]. In fact, these patients, as previously illustrated, present an alteration of the gut microbiota, which induces and amplifies the chronic inflammatory state, which is, in turn, responsible for the CNCDs progression [178]. Numerous studies suggested that adapted physical activity in CNCDs patients is able to modulate both qualitatively and quantitatively the gut microbiota composition, exerting important benefits on the patient's quality of life and reducing the CV risk [73]. Physical activity increases the abundance of gut microbiota bacteria and improves its quality (Figure 4) [179]. Studies on animal models suggest that physical activity is able to increase the abundance of the genus *Bacteroidetes* and decrease the genus *Firmicutes*, with a consequent reduction of the *Firmicutes*/*Bacteroidetes* ratio, improving the quality of the gut microbiota composition [73].

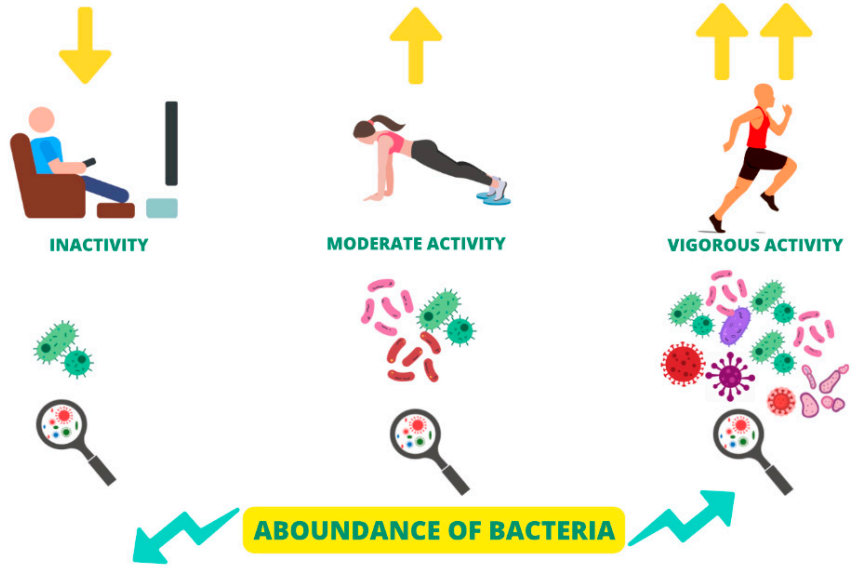

Figure 4. Modulation of gut microbiota composition and α-diversity by the physical activity degree.

Thanks to the positive modulation of the gut microbiota by the physical exercise, the latter, especially the aerobic type, would seem able to prevent the onset of chronic migraine, rather than being able to reduce the symptoms of chronic headache already existing. Several clinical studies, in fact, have highlighted how sedentary subjects were more likely to develop chronic migraine compared to active subjects [180]. On the other hand, other clinical studies showed that in subjects who already suffered from migraine, the intense physical exercise led to the exacerbation of this disorder [181].

6.5. Vitamin D supplementation

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As is known, vitamin D deficiency is associated with chronic pain, depression and some neurological disorders [182]. The brain is characterized by the abundance of receptors for vitamin D and there is evidence of a non-skeletal role of vitamin D in the mechanisms that regulate the inflammation, the immunity and the neurotransmitters metabolism [183]. Vitamin D blood levels are related to sun exposure (depending on latitude, outdoor activity), dietary intake and genetic components [184]. Migraine patients tend to avoid sunlight because of photophobia during migraine attacks. Moreover, it is known that a reduced physical activity and a sedentary life, conducted indoors, greatly increase the risk of vitamin D deficiency [185].

Several studies have reported that vitamin D low serum levels may be associated with an increased risk of migraine/headache [186]. In addition, it has been suggested that the prevalence of deficiency/insufficiency of vitamin D may be greater in patients suffering from migraine/headache when confronted with subjects without headache [187].

6.6. Other vitamins supplementation

In patients with very intense migraine, it is often observed a lack of vitamin B12 [188]. Vitamin B12 deficiency in association with hyperhomocysteinemia causes damage to endothelial cells, increasing free radicals levels, which may be related to migraine episode generation [189]. Recent studies suggested that the vitamin B12 deficiency in chronic migraine can be induced by the frequent use of analgesics, that may alter the vitamin B12 absorption [190].

Furthermore, studies on riboflavin have shown that the intake of this vitamin is effective in prophylaxis of migraine, thus reducing the frequency of attacks [191].

Emerging evidence pointed out a statistically significant role of thiamine (vitamin B1) in migraine mitigation [192,193]. Thiamine has been shown to be particularly important in the regulation of brain levels of serotonin; abnormalities in the function of serotonin seem to be directly involved in the pathophysiology of migraine [85].

Vitamin K2 supplementation could also play a potential role in patients with migraines [194].

6.7. Iron supplementation

Dietary iron is the primary source of iron in the body [195]. Dietary iron intake has different effects on migraine in women of different ages, and these different effects may be due to age-related menstrual changes [196]. Ferritin higher serum levels in women over 50 years of age may have a protective effect against migraine [197]. The recommended dietary allowance (RDA) for iron is 18 mg/day in female, but as evidenced by numerous scientific studies, the average dietary intake of iron for women aged from 20 to 50 years is lower than RDA [198].

To verify the frequency of migraine attacks in patients with iron deficiency anemia, a study was conducted on 127 subjects who underwent validated tests on migraine, anxiety, depression and quality of life. The results obtained showed that almost 80% of patients suffered from recurring headaches and that they were often smokers and showed low hemoglobin levels and low mean corpuscular volume values. Moreover, most patients with iron deficiency presented depression, anxiety and a poor quality of life [199].

6.8. Polyphenol-rich foods assumption

Polyphenols are important constituents of plant-based food, closely related to the main sensory and beneficial properties of fruit, vegetables and their derivatives. Polyphenols can be classified into 4 main categories (flavonoids, phenolic acids, stilbenes and lignans) based on the number of phenolic rings and on other structural elements that bind these rings together [200]. A diet rich in polyphenols, especially flavanones and lignans, has been associated in the literature with reduced migraine severity. A lower intake of phenols and flavonoids, on the other hand, would seem to correlate with more severe migraine attacks. Encouraging the consumption of polyphenol-rich foods, such as fruit, vegetables and EVOO, could represent a valid adjuvant strategy to counteract migraine [201]. The beneficial analgesic action of polyphenols would seem to be mainly exerted by their antioxidant

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properties. Indeed, literature studies suggest that OS may play a significant role in the pathogenesis of migraine. The antioxidant compounds contained in foods would seem able to prevent OS, by inhibiting initiation and propagation of the oxidative chain reaction, which is at the basis of the migraine attack [202].

One of the most controversial polyphenol-rich food related to the migraine onset is chocolate (rich in catechins, flavonols, anthocyanins and procyanidins). Numerous studies have evaluated the possibility that the consumption of chocolate can stimulate the migraine attack onset in subjects who are predisposed to it; however, the pathophysiological mechanisms underlying this correlation have not been elucidated and there is currently insufficient evidence to establish if chocolate is a real migraine trigger [203].

6.9. Magnesium supplementation

Magnesium is an essential mineral that plays an important role in nerve function [204]. Recent studies have shown for the general population a lower average magnesium assumption than dietary recommendations, suggesting that a low intake of magnesium may be associated with migraine and that a good percentage of migraine subjects may suffer from a magnesium deficiency [205]. Magnesium inhibits neuronal overexcitation and vasospasm, reduces the formation of inflammatory substances and improves mitochondrial oxidative phosphorylation and serotonin receptor transmission [206]. Currently, most studies on magnesium as a possible preventive treatment of migraine are limited to oral food supplements, not considering magnesium-rich foods [205]. However, most of these oral food supplements have several limitations and side effects, such as GI disorders, nephrolithiasis and increased risk of CV disease [207].

6.10. Abstention from the histamine-rich foods consumption

Histamine (2-[3H-imidazol-4-yl]ethanamine) activation causes a number of vascular phenomena, which can result in a migraine attack [89,208]. Histamine is a substance that is regularly produced by our body within immune cells [209]. It's a chemical mediator within our body that performs two important functions: mediator of inflammatory and allergic reactions and neurotransmitter [209]. Several host factors, in addition to genetic factors, may influence histamine/receptor effects, including the gut microbiota composition, gender, ageing, autoimmune diseases, cancer and pulmonary diseases [210].

Histamine is also a biogenic amine that can be found in many foods; in particular, it may be present in high amounts in those foods, often referred to as triggers of migraine in susceptible individuals [211]. The relationship between diet and migraine has long been controversial and it has been based on the association between the consumption of certain foods and the appearance of migraine pain [212]. Many of the foods in question are potentially rich in biologically active amines: histamine, tyramine and others [213]. Because of a genetic origin, some subjects produce low amounts of diaminossidase (DAO) and this means that the excess of histamine is not neutralized and it causes, among other annoyances, migraines [214]. Mutations involving genes responsible for producing DAO (AOC1 on chromosome 7) can increase the susceptibility to histamine intolerance development [215]. Some drugs, including NSAIDS, antidepressants, immunomodulators, antiarrhythmics and other substances (e.g. acetylcysteine, clavulan acid, metoclopramide, verapamil), may decrease the threshold of tolerance to histamine [216]. The alcohol consumption, in particular red wine, is a powerful inhibitor of DAO because it contains, in addition to high amounts of histamine, also other classes of biogenic amines, such as tyramine and sulfites, that compete with histamine for binding to the active site of the enzyme [217].

7. Conclusions

The migraine development seems partially to be related to a condition of gut dysbiosis. In fact, gut dysbiosis can lead to the reduction of the SCFAs production and to the concomitant increase of the gut-derived inflammatory cytokines, which can influence the CNS activities and, in turn, cause

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migraine. Moreover, there is a bi-directional correlation between the migraine and the risk of CNCDs onset and progression, in which the gut microbiota plays a pivotal role.

Numerous studies highlighted an association between specific nutritional patterns and lifestyle, related to the gut eubiosis restoration, and the prevention of migraine attacks. Therefore, healthy nutritional habits (like a MD), an appropriate choice of foods, both in quantitative and qualitative terms, an oral food supplements administration and a constant physical exercise seem to be an effective adjuvant strategy for migraine prevention.

Abbreviations:

5-HT	5-hydroxytryptamine
AH	Arterial Hypertension
BDNF	Brain Neurotrophic Factor
BMI	Body mass index
CGRP	calcitonin gene-related peptide
CKD	Chronic Kidney Disease
CNCDs	Chronic Non-Communicable Diseases
CNS	Central Nervous System
CV	Cardiovascular
DAO	Diaminossidase
DM	Dibetes Mellitus
ED	Endothelial Dysfunction
EPA	Aicosapentaenoic acid
EVOO	Extra Virgin Olive Oil
FOS	Fructooligosaccharides
GI	Gastrointestinal
GOS	Galactogosharides
HPA	Hypothalamic-Pituitary-Adrenal
IAA	Indole 3 Acetic Acid
IL	Interleukin
IS	Indoxyl Sulphate
KD	Ketogenic diet
MD	Mediteranean Diet
MUFAs	Monounsaturated Fat Acids
NF-κB	Kappa-B Nuclear Factor
NMDA	N-methyl-D-aspartic Acid
NO	Nitric Oxide
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
OS	Oxidative Stress
PUFAs	Polyunsaturated Fat Acids
RAAS	Renin- angiotensin- aldosterone system
RDA	Recommended Dietary Allowance
SCFAs	Short Chain Fatty Acids
TMAO	Trimethylamine N-Oxide
TNF	Tumor Necrosis Factor
WHO	World Health Organization

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