The Mediterranean diet: an epigenetic diet model for MEN1 patients?

Monica Marinari [1], Francesca Marini [2], Francesca Giusti [3], Maria Luisa Brandi [2,4]

[1] Department of Pharmacy, University of Pisa, Pisa, Italy; [2] F.I.R.M.O., Italian Foundation for Research on Bone Diseases, Florence, Italy; [3] Department of Experimental and Clinical Biomedical Sciences, University of Florence, Florence, Italy; [4] Donatello Bone Clinic, Villa Donatello Hospital, Sesto Fiorentino (FI), Italy

ABSTRACT

MEN1 is a rare congenital cancer syndrome that involves multiple neuroendocrine tissues and is caused by heterozygous germline loss-of-function mutations of the MEN1 oncosuppressor gene. MEN1 syndrome is characterized by the absence of correlation between the specific MEN1 mutation and the clinical presentation of the disease; the clinical phenotype differs between members of the same family and even between homozygous twins. The lack of genotype-phenotype correlation could be due to epigenetic factors, which act as genetic mutation cofactors in driving individual MEN1 tumorigenesis. This prompts an important reflection on the role that epigenetics, viewed from a dietary and nutritional perspective, may play in MEN1 patients, thus opening, at the same time, a window on the role of nutrition as primary prevention. A healthy diet rich in antioxidants, together with an active lifestyle, should be seen by patients as a means to improve their well-being and maintain a state of good health. Indeed, several studies show that certain nutrients are also able to directly interact with and regulate key epigenetic mechanisms, modulating gene transcription. The interconnections between diet and epigenetic changes, on the one hand, and between epigenetic changes and cancer, on the other, are well supported by relevant observational studies both in humans and in animal models. This short review aims to outline how nutrients could influence epigenetic factors and intervene in tumour prevention. It focuses specifically on nutritional indications for MEN1 patients, serving to promote appropriate dietary habits for reducing/postponing tumour development.

KEYWORDS

Multiple endocrine neoplasia type 1 (MEN), nutrition, dietary habits, Mediterranean diet, epigenetic factors.

Introduction

Multiple Endocrine Neoplasia type 1 (MEN1) is a rare, highly penetrant, autosomal dominant endocrine tumour syndrome caused by a heterozygous germline inactivating mutation of the MEN1 oncosuppressor gene, encoding the nuclear protein menin. MEN1 germline inactivating mutation, followed by loss of the second wild-type allele at somatic level, results in loss of menin tumour suppressor activity, leading to the development of multiple tumours in specific neuroendocrine tissues [1,2].

MEN1 syndrome is mainly characterized by the presence of hyperplasia or adenomas of the parathyroid glands (resulting in primary hyperparathyroidism), tumours of neuroendocrine cells of the duodenum and pancreas, and/or adenomas of the anterior pituitary gland (adenohypophysis). Variable combinations of more than 20 endocrine and non-endocrine tumours have been described. The clinical phenotype differs between members of the same family and even between homozygous twins [3]. More than 1,300 different somatic and germline mutations of MEN1 and 20 benign polymorphisms have been reported but without a clear genotype-phenotype correlation. It has, therefore, been suggested that epigenetic mechanisms triggered by environmental factors, including diet, may influence the disease phenotype in patients carrying MEN1 mutations. Indeed, menin has been shown to be involved, directly or indirectly, in the regulation of epigenetic factors, and alteration of epigenetic mechanisms, consequent to loss of menin activity, seems to play a key role in the development and progression of MEN1 neuroendocrine tumours [4]. In the last decade, research on epigenetics has proceeded at a very rapid pace. It has been shown that the epigenome is very plastic and that it changes during development, but also, and in different ways, when exposed to external environmental stimuli [5].

A growing number of studies [6-8] are investigating the role that a healthy diet and an active lifestyle can play in general health, especially in the light of recent discoveries in epigenetics. Several bioactive dietary components have been identified that appear to have the potential to prevent disease and promote overall health [9]. Among dietary habits, the Mediterranean diet, rich in active nutrients, has been shown to be a dietary model capable of reducing the onset of various diseases, as demonstrated in several studies [10-12], and could, therefore, be con-

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Contact
Maria Luisa Brandi; marialuisa@marialuisabrandi.it
F.I.R.M.O., Italian Foundation for Research on Bone Diseases
Via San Gallo 123 - 50129 Florence, Italy

sidered as a dietary model to be adopted from birth to try to prevent/reduce the occurrence of diseases, including sporadic or inherited tumours, such as MEN1. This concise review aims to highlight current knowledge on how a diet rich in nutrients capable of interacting with key epigenetic mechanisms may benefit patients with cancer, including cases of inherited forms of syndromic and non-syndromic tumours.

Epigenetic mechanisms

The term epigenetics generally refers to heritable changes in gene expression that occur without altering the DNA sequence. Epigenetic modifications, including DNA methylation, histone post-translational modifications (acetylation, methylation, phosphorylation and other amino acid modifications), and non-coding RNAs [long non-coding RNAs (lncRNAS), and microRNAs (miRNAs)], can occur through external factors and are widely known to be reversible [5,13].

Epigenetic modifications, causing transcriptional deregulation, are involved in the alteration of cell proliferation, differentiation and survival, and, thus, in both tumour development and progression [14]. Indeed, epigenetic modifications may result in inappropriate expression or activation of oncogene-associated transcription factors and/or non-expression of genes responsible for tumour suppression. Furthermore, the impact of epigenomic processes in cancer is evident from the finding that in human tumorigenesis at least half of all known oncosuppressor genes is inactivated through epigenetic mechanisms [15].

Knowledge of the causes of these epigenetic modifications and the underlying control mechanisms is essential to prevent the proliferation and abnormal cell function that can lead to neoplasia. Since epigenetic alterations, unlike gene mutations, are reversible, they offer the therapeutic opportunity of reversing them through specific drugs that can block or enhance enzyme activity or critical interactions of epigenetic regulators [4].

MEN1 and epigenetics

In recent years, various studies [8,16,17] have identified several epigenetic changes that specifically characterised tumour tissues with respect to corresponding healthy tissues, and that could, thus, have a direct role in driving MEN1 tumorigenesis.

Menin interacts with histone-modifying proteins [4], thus, loss of menin activity results in alteration of histone modifications, mainly histone methylation on lysine residues. Loss of H3K4me3, H3K9me3 and H4R3me2, as well as increase of H3K27me3 were reported in MEN1 neuroendocrine tumours of the pancreas, associated with increased growth of beta cells [18].

Hypermethylation of CpG sites, a condition associated with gene silencing, was reported in MEN1 tumour specimens; global DNA hypermethylation was detected in parathyroid tumours and pancreatic neuroendocrine nonfunctioning tumours (pNETs) in MEN1 patients. Furthermore, promoter hypermethylation was observed as a frequent occurrence in MEN1-associated advanced pNETs [19]. A regulatory feedback loop between MEN1, miR-24a and menin was demonstrated in parathyroid tumour tissues resected from MEN1 patients and in cell lines of neuroendocrine pancreas [20].

The Mediterranean diet as an epigenetic diet model

A growing body of evidence suggests that certain nutrients in the human diet may influence epigenetic processes and are involved in processes such as the reactivation of oncosuppressor genes, initiation of apoptosis, repression of cancer-related genes and activation of cell survival proteins in several cancer types [9,12]. The precise molecular mechanisms by which diet influences epigenetic changes are not yet fully known. Foods such as folate, B vitamins, choline, betaine and other components may influence the methyl donor pool and, consequently, DNA and histone methylation levels [8,21].

Furthermore, more and more studies have shown that dietary phytochemicals, such as tea polyphenols, genistein, sulforaphane, resveratrol, curcumin and others, may be effective agents against cancer and act through epigenetic mechanisms [9,22-24]. These bioactive nutritional factors are thus capable of both reducing oxidative stress and modifying the epigenome, resulting in a dietary regimen that can be used for preventive purposes. Epigenetic modifications can also delay the ageing process and exert several health benefits by activating numerous intracellular pathways. The above theory is more commonly referred to as the 'epigenetic diet' since it introduces bioactive compounds that help delay the onset of ageing and age-associated disease processes [7,12]. Numerous studies [9-12] have shown a strong correlation between the Mediterranean diet and longevity; individuals who adhere to such a nutritional style have a longer life expectancy. The Mediterranean diet also prevents many diseases, such as metabolic, cardiovascular and neurodegenerative diseases, insulin resistance and several types of cancer.

In this context, the Mediterranean diet as an epigenetic diet is characterised by high consumption of whole grains (about 50-60% of the total calorie intake), and high consumption of fruit, vegetables and legumes; use of extra virgin olive oil to cover about 70% of the lipid intake; regular consumption of fresh fish (especially oily fish); regular but moderate consumption of red wine at main meals, with an optimal intake of omega-3. This type of diet is associated with low mortality from all causes [12]. For these reasons the Mediterranean diet could represent a valid dietary model for the MEN1 patient.

The main characteristics and benefits for human health of nutrients found in the Mediterranean diet and known to exert one or more epigenetic activities are summarised in Table I.

Conclusions

In conclusion, it is important to emphasise that adherence to a healthy, balanced diet, such as the Mediterranean diet, and an active lifestyle can benefit human health and cancer patients, including those with inherited tumours such as MEN1 patients. Diet can be a determining factor in the prevention of certain

Table I Main characteristics and benefits for human health of nutrients of the Mediterranean diet.

NUTRIENT FAMILY/ GROUP	NUTRIENT	FOODS	BIOLOGICAL EFFECTS IN THE HUMAN BODY	EPIGENETIC ACTIVITY	REPORTED BENEFITS FOR HEALTH	EFFECT OF NUTRIENT DEFICIENCY	REFERENCES
Group B vitamins	Folic acid (folate; vitamin B9)	Many varieties of beans, fortified breakfast cereals, pasta and green vegetables	Coenzyme or cosubstrate in single-carbon transfers in the synthesis of nucleic acids (DNA and RNA) and metabolism of amino acids Antioncogenic action by preventing alterations to DNA	Methyl group donor	Improvement of heart health and reduction of the risk of heart disease Building of normal red blood cells and prevention of anaemia	Induction of a state of DNA hypo-methylation that has been associated with increased tumorigenesis (i.e., breast, cervical, ovarian, brain, lung and colorectal cancers)	Reff. 25,26
Polyphenols	Resveratrol	Coarse cereals, potatoes, beans, berries (i.e., blueberries, mulberries), fruit (i.e., plums, grapes), nuts (i.e., peanuts, pistachios), red and white wine	Mitigation of oxidative stress: - enhancement of endogenous antioxidant enzymes - decrease of reactive oxygen species and reactive nitrogen species - direct elimination of free radicals Anti-inflammatory effects Antibacterial and antifungal properties	Reduction of DNA methyltransferase activity Inhibition of histone deacetylase Potent inhibitory effect on lysine-specific demethylase-1	Reduction of inflammatory-derived symptoms of arthritis, and skin inflammation Protective effects on heart, brain and body against oxidative stress Help in treating urinary and digestive tract infections	Not applicable	Ref. 27
	Curcumin	Plants of the species *Curcuma longa*	Anti-inflammatory and anti-proliferative effects by inhibiting the nuclear factor kB (NFkB) transcription factor Strong antioncogenic activity: - inhibits cancer cell proliferation migration and metastasis - hinders tumour angiogenesis	Inhibition of DNA methyltransferases Inhibition of histone deacetylases	Help in managing inflammatory and degenerative conditions Adjuvant treatment in adrenocortical, breast, prostate, pancreas and colorectal cancers: - prevents tumour growth - slows the spread of cancer cells Reverses multidrug resistance in cancer cells	Not applicable	Reff. 28,29
	Epigallocatechin -3-gallate (EGCG)	Green, white and black tea, berries (i.e., cranberries, strawberries, blackberries), fruit, (i.e., kiwis, cherries, pears, peaches, plums, apples, avocados), and nuts (i.e., pecans, pistachios, walnuts, hazelnuts)	Strong antioxidant and anti-inflammatory effects Multiple antioncogenic activity - antiproliferative, anti-angiogenic and anti-metastatic properties - inhibition of cell cycle, induction of cell differentiation or apoptosis - inhibition of telomerase activity	Inhibition of DNA methyltransferases Inhibition of histone deacetylases	Positive correlation between EGCG consumption and inhibition of cancers of the oral cavity, breast, prostate, gastric tract, ovary, oesophagus, colorectum and pancreas Positive cardiovascular effects (i.e., reduction of blood pressure, cholesterol, and of the accumulation of plaque in blood vessels)	Not applicable	Reff. 30-32

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NUTRIENT FAMILY/ GROUP	NUTRIENT	FOODS	BIOLOGICAL EFFECTS IN THE HUMAN BODY	EPIGENETIC ACTIVITY	REPORTED BENEFITS FOR HEALTH	EFFECT OF NUTRIENT DEFICIENCY	REFERENCES
Polyphenols	Quercetin	Capers, some vegetables (i.e., red onions, cruciferous vegetables, celery, lettuce, asparagus tomatoes, shallots), berries, fruit (i.e., pomegranate, black grapes, citrus fruits, apples), nuts (i.e., pistachios), green tea and propolis	Antioxidant, anti-inflammatory, anti-allergic, anti-platelet and anti-thrombotic actions Suppression of cancer cell growth and induction of apoptosis	Reduction of expression and activity of DNA methyltransferases Inhibition of histone deacetylase HDAC1 Regulation of expression of some miRNAs (i.e., miR-146, miR-16, miR-27a)	Lowers blood pressure, improves artery health and helps prevent heart disease Provides allergy symptom relief Helps protect against degenerative brain disorders, such as Alzheimer's disease and dementia Helps protect against tumours	Not applicable	Ref. 33
	Genistein	High concentrations in soya beans	Having a chemical structure very similar to that of oestrogen, it is able to bind oestrogen receptors, through which it may play important roles in cognitive functions, heart health, menopausal symptoms and premenstrual syndrome	Inhibition of DNA methyltransferase activity (lower global DNA methylation) Reduction of the activity of histone deacetylases and histone methyltransferases	Alleviation of premenstrual syndrome and postmenopausal symptoms Inhibitory effects on multiple types of cancer (i.e., prostate, oesophageal and colon cancer)	Not applicable	Ref. 34
	Anthocyanins	Red and purple berries, black grapes, aubergines, red beetroot, mallow, cherries, apples, plums, cruciferous citrus fruits, pomegranate	Antioxidant and anti-inflammatory activity, by acting as free radical scavengers against reactive oxygen and nitrogen species	Regulation of the H3K4me3 affecting different pathways like the integrin-like kinase signalling, involved in inflammation, and metabolism of pyruvate and amino acids	Cancer prevention Help in regulating hypertension (reduction of blood pressure) and high cholesterol levels, and in preventing cardiovascular diseases Improvement of visual and neurological health Anti-diabetes activity	Not applicable	Reff. 35-37
Isothiocyanates	Sulforaphane	Cruciferous vegetables (broccoli, cauliflower, kale)	Inhibition of cell cycle Induction of apoptosis Antioncogenic activity through the epigenetic regulation of cancer-related genes	Modification of the degree of DNA methylation of CpG, impacting both global DNA methylation and site-specific demethylation Inhibition of histone deacetylase	Reduction of the risk of cardiovascular disease Reduction of the incidence of a wide variety of cancer types (i.e., breast, lung, prostate and colorectal cancers)	Not applicable	Reff. 32, 34, 38, 39

types of cancer; many studies have shown that adherence to the Mediterranean diet is associated with a lower probability of incurring many types of cancer, when it is followed not as an occasionally adopted dietary pattern, but as a regular and constant lifestyle choice. A diet, like the Mediterranean diet, that is rich in fresh fruit and vegetables and whole grains, and low in fat, can benefit oncological patients, as it is rich in nutritional factors that can interact with main epigenetic mechanisms, whose deregulation is now well known to be involved in tumour development and progression. From this point of view, the Mediterranean diet can be regarded as a model of an epigenetic diet, capable of modulating epigenetic mechanisms and reversing the epigenetic alterations responsible for inactivation of various oncosuppressor genes in cancer cells, and, thus, of preventing or blocking tumorigenesis. Indeed, unlike genetic alterations, some epigenetic alterations can be reversed

through dietary phytochemicals. Given the fact that deregulation of epigenetic mechanisms has been shown to be an important component of MEN1 tumorigenesis, constant adherence to an epigenetic diet, such as the Mediterranean diet, could play an active role in helping to maintain a state of well-being and improving the patient's quality of life. In the light of this, it might be interesting to conduct prospective studies in MEN1 patients to evaluate how dietary habits and lifestyle may affect the occurrence and manifestation of MEN1-related tumours and positively influence their quality of life.

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