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Review

Vascular effects of the Mediterranean diet Part I: Anti-hypertensive and anti-thrombotic effects

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ABSTRACT

This review summarizes available evidence on the beneficial effects of inorganic nitrates and the monounsaturated fatty acid (MUFA) oleic acid, largely contained in Mediterranean diet, on blood pressure and coagulation activity.

Inorganic nitrate. Normal vascular function requires NO production from the L-arginine–NO synthase (NOS) pathway. This process is defective in conditions of local hypoxia, and here nitrite can substitute for L-arginine–NOS derived NO. In this context, NO generation from the nitrate–nitrite–NO pathway mostly derived from green leafy vegetables appears to be an alternative source for NOS-dependent NO production, ensuring NO bioavailability also in situations when the endogenous L-arginine/NO synthase pathway is dysfunctional or physiologically reduced in local hypoxic conditions.

Olive oil and oleic acid. In addition to effects on lipoprotein metabolism and oxidation, the beneficial effects of oleic acid occur also on coagulation activity, namely on coagulation factor VII (FVII). Normally, a substantial increase of FVII coagulant activity (FVIIc) occurs within 2–3 h after a fatty meal and persists for several hours thereafter. When a background diet high in MUFA is consumed, a lower post-prandial increase of FVIIc takes place.

Contents

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1. Introduction

The Mediterranean diet (MeD) refers to a dietary profile commonly available in the early 1960s in the Mediterranean regions. It may be considered not one specific diet, but rather a collection of eating habits (hence the term "Mediterranean diets" preferred by some authors) traditionally followed by people bordering the Mediterranean sea, and consisting in a plant-centered diet with high intakes of vegetables and fruit, whole-grain cereals, extra-virgin olive oil, nuts, a moderate consumption of fish and poultry, a low intake of dairy products, red meat, and sweets, and a moderate consumption of red wine [1,2].

A persuasive body of evidence from observational studies [3–5] and secondary prevention trials [6,7] has now documented that adherence to a Mediterranean-style diet is consistently beneficial, compared with other dietary patterns, with respect to the risk of cardiovascular disease, cancer, Alzheimer's disease, and Parkinson disease, as well as of death from cardiovascular disease or cancer and even premature death overall.

A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease [8] has recently ranked the MeD as the most reliable dietary model to provide protection primarily from coronary heart disease. The Scientific Advisory Committee of the American Heart Association stated that the Mediterranean-style diet has impressive effects on cardiovascular disease [9].

The healthful properties of MeD have been mainly attributed to the additive or synergistic interaction of its various constituents as a whole. Despite an awareness of the high complexity of the MeD nutrient composition, basic researchers are still nowadays concentrating their efforts on single food items with the hope that such single food-focused research might eventually be exploited for specific appropriate dietary advice. Some MeD constituents have indeed been found to exert specific actions on the cardiovascular system. Such are inorganic nitrate, n−9 and n−3 fatty acids, antioxidants and polyphenols, which have been shown to exert effects particularly on blood pressure, coagulation activity and endothelial functions.

In two separate reviews we will review the effects of specific MeD constituents. In the present one we will deal with the role of MeD inorganic nitrate and saturated/monounsaturated fatty acids as to their effects on hypertension and thrombosis respectively. A second, parallel review will deal with the effects of n−3 fatty acids and polyphenols.

2. Leafy vegetables, inorganic nitrate and blood pressure: a rational basis for the anti-hypertensive effects of the Mediterranean diet

Many trials have shown that diets rich in fruits and vegetables reduce blood pressure [10,11] and the risk of cerebro- and cardiovascular events [12–15]. These benefits have previously been attributed to MeD constituents as a whole, including vitamins, minerals, fibers, and the so-called non-nutritive substances, such as flavonoids and glucosinolates as a whole. At present, other factors are clearly emerging as alternative candidates.

According to recent epidemiologic trials, the greatest protection against coronary heart disease is associated with the consumption of green leafy vegetables (e.g., spinach, lettuce, collard greens, beetroots) [14,15]. Such vegetables have a high content of nitrate (NO_3^-), and actually are the richest known source of dietary inorganic nitrate. They account for 80–85% of daily dietary nitrate exposure in the average population [16,17].

This dietary inorganic nitrate has been shown to be an important source of nitric oxide (NO). There is a consensus that dietary nitrate is essentially inert, but acquires biological activity after reduction to nitrite [16]. In particular, the reduction of dietary nitrate to nitrite is necessary for nitrate to serve as a substrate for NO production. Most if not all the beneficial effects of dietary nitrate are considered to be mediated by its reduction to nitrite and then to NO, a critical regulator of vascular homeostasis [18–23] (Fig. 1).

Dietary nitrate (NO_3^-) undergoes reduction to nitrite (NO_2^-) and then to NO through a nitrate–nitrite pathway alternative to the classical L-arginine–NO synthase (NOS) pathway for NO production in the body [24–27]. Even though 80% of the basal plasma nitrite levels derive from the oxidation of NO [28], reduction of nitrate also significantly contributes to increasing nitrite levels and, eventually, to the synthesis of NO [29,30] (Fig. 1).

2.1. NO production by eNOS in the vascular bed in physiologic conditions

The normal functioning of the human vasculature requires the presence of nitrite and NO along with the biochemical machinery necessary to respond to these important signaling molecules [25,26]. The generation of up to 70% of systemic NO is accomplished by endothelial cells through the action of the endothelial nitric oxide synthase (eNOS), one of the 3 members of the NOS family of enzymes [31]. NOS synthesizes NO from the amino acid L-arginine and molecular oxygen (Fig. 1). In the vasculature, this results in vasodilation and blood pressure regulation. The production of NO by endothelial cells is stimulated by laminar shear stress, part of the tangential shear forces generated by the flowing blood on the endothelial surface [32].

2.2. Alternative NO production by nitrate in tissues

Recently, part of NO synthesis in healthy tissues has been shown to occur independent of the L-arginine–NOS pathway [20]. In fact, at variance from the provision of eNOS-derived NO to the endothelium to regulate the vasomotor tone, NO production also occurs in other tissues, and the dietary provision of nitrate and nitrite may account for approximately half the steady state NO concentration [33].

The reduction of dietary nitrate to NO in the body involves its initial reduction to nitrite, and then to NO [24–27] (Fig. 1). There are 2 systems of reducing dietary nitrate to nitrite in mammals.

1. The first system involves the action of commensal Gram-negative bacteria on the tongue (Fig. 2). After swallowing and the absorption through the stomach wall, about 25% of consumed nitrate (NO_3^-) enters the entero-salivary circulation. The absorbed nitrate (NO_3^-) is then concentrated 10 fold in the salivary glands, and reduced to nitrite (NO_2^-) by bacterial nitrate reductases contained in facultative anaerobes present on the dorsal surface of the tongue [24,29,34]. Once swallowed into the stomach, nitrite is partly converted to NO by the local acidic conditions (Fig. 2). Nitrite and NO then diffuse into the portal circulation, and NO is oxidized to nitrite, which in turn is transported in the arterial circulation to resistance vessels, where it lowers O_2 tension and favors the reduction of nitrite to NO, which in turn causes vasodilatation and the consequent lowering of blood pressure.
2. There are also several different mammalian enzymes and metalloproteins that have nitrate reductase activity, a function previously

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