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The effect of bergamot polyphenolic fraction in patients with non alcoholic liver steato-hepatitis and metabolic syndrome

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ABSTRACT

The occurrence of metabolic syndrome (MS) represents an independent risk factor for developing cardiovascular disease states in patients suffering from type 2 diabetes mellitus. Moreover, both the size of LDL particles and liver dysfunction identified as non alcoholic steato-hepatitis (NASH) represent important biomarkers for the development of cardiometabolic risk in patients with MS. Recent evidence shows that bergamot polyphenolic fraction (BPF) in patients with MS and NASH induces a significant reduction of fasting plasma glucose, serum LDL cholesterol and triglycerides alongside with an increase of HDL cholesterol. In addition, a significant reduction of both ultrasonographic, TC scans and metabolic biomarkers of NASH as well as a significant reduction of small dense LDL particles were found after BPF treatment suggesting a beneficial effect of bergamot-extract in patients with MS and NASH. This suggests a potential preventive role of bergamot derivatives in reducing cardiometabolic risk.

Contents

1. Introduction

Evidence has been collected showing that the occurrence of metabolic syndrome (MS) is associated to increased risk of developing cardiovascular diseases and type 2 diabetes [1]. In particular, MS has been found to double the cardiometabolic risk and to enhance the risk of developing type 2 diabetes by five times [2]. Besides imbalanced glycemic control has been associated with parameters of vascular damage [3], increasing hyperglycemia in type 2 diabetes does not contribute to the cardiovascular risk to the same extent as it does in type 1 diabetes [4], pointing to the importance of nonglycemic related risk factors belonging to the MS. Numerous studies demonstrated an increased cardiovascular risk in patients with MS prior to the development of overt hyperglycemia [5,6]. Likewise, patients with type 2 diabetes or MS have an increased cardiovascular risk despite optimal control of other risk factors as low-density lipoprotein cholesterol (LDL-C) [7]. The metabolic impairment observed in these patients is often characterized also by other pathological conditions such as the hepatic manifestation of MS known as non alcoholic liver steatohepatitis (NASH) suggesting that both a healthy lifestyle

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as well as a therapeutic intervention aimed to reduce the risk of cardiovascular disease are needed.

2. LDL particles profile and cardiovascular risk

In the context of the shortcomings of commonly assessed risk factors in individuals with features of the MS, the characterization and sub-classification of LDL and high-density lipoprotein HDL particles emerged as a tool that may offer a better risk prediction. A decrease of HDL associated with an increase in small, dense LDL particles (sdLDL), class III and IV, is closely associated with an increased cardiovascular risk, independently of the traditional risk factors both in patients with [8–10] and without [11–13] diabetes or MS. Individual LDL particle profiles normally cluster into two patterns of LDL size distribution: the majority of profiles demonstrates a predominance of large or medium sized LDL particles (LDL pattern A), whereas a substantial minority exhibits the LDL pattern B with a higher proportion of smaller LDL particles [14].

Several aspects must be taken into account when evaluating the potential role of sdLDL in patients with MS. In particular, evidence has been accumulated suggesting that the formation of sdLDL particles seems to be favoured in the presence of insulin resistance and elevated triglicerydes [15,16]. Although the mechanism underlying this effect is still unknown, it is likely also that such a condition involves an increased hepatic uptake of LDL particles, possibly due to the upregulation of hepatic LDL receptor activity and/or increased clearance of LDL particles due to their altered composition and liver dysfunction.

3. Non alcoholic liver steato-hepatitis and metabolic syndrome

Recently, it has been shown that MS is associated with NASH. In particular, NASH is one of the most common causes of liver-related mortality worldwide [17,18]. NASH has been identified as the hepatic manifestation of MS [19] and the association between NASH and MS has been reported in earlier observational studies [20–22]. There are a number of common mechanisms underlying the development of NASH and MS. For example, they may have the same pathophysiological basis of insulin resistance [23]. A systematic review suggested a potential predictive effect of liver fat on the presence of MS [23]. However, no evidence was provided regarding the causal association between NASH and MS. Moreover, many compounds used for counteracting the detrimental effect of MS on cardiovascular system, such as statins, have not been found to produce beneficial effect on liver dysfunction or enhanced fat accumulation in the liver [24], as well as asymptomatic elevation of serum alanine (ALT) and aspartate amino-transferases (AST) [25].

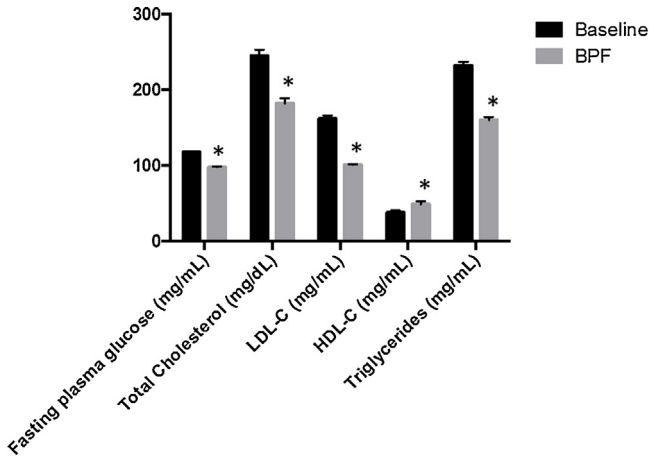

Fig. 1. Blood glucose, lipid and tryglyceride levels obtained at baseline and after treatment with BPF (650 mg twice a day for 120 consecutive days) in 107 patients suffering from MS and NASH. (Data are expressed as mean ± SD for each value; a P value of <0.05 between values at baseline and after BPF treatment was taken as significant*).

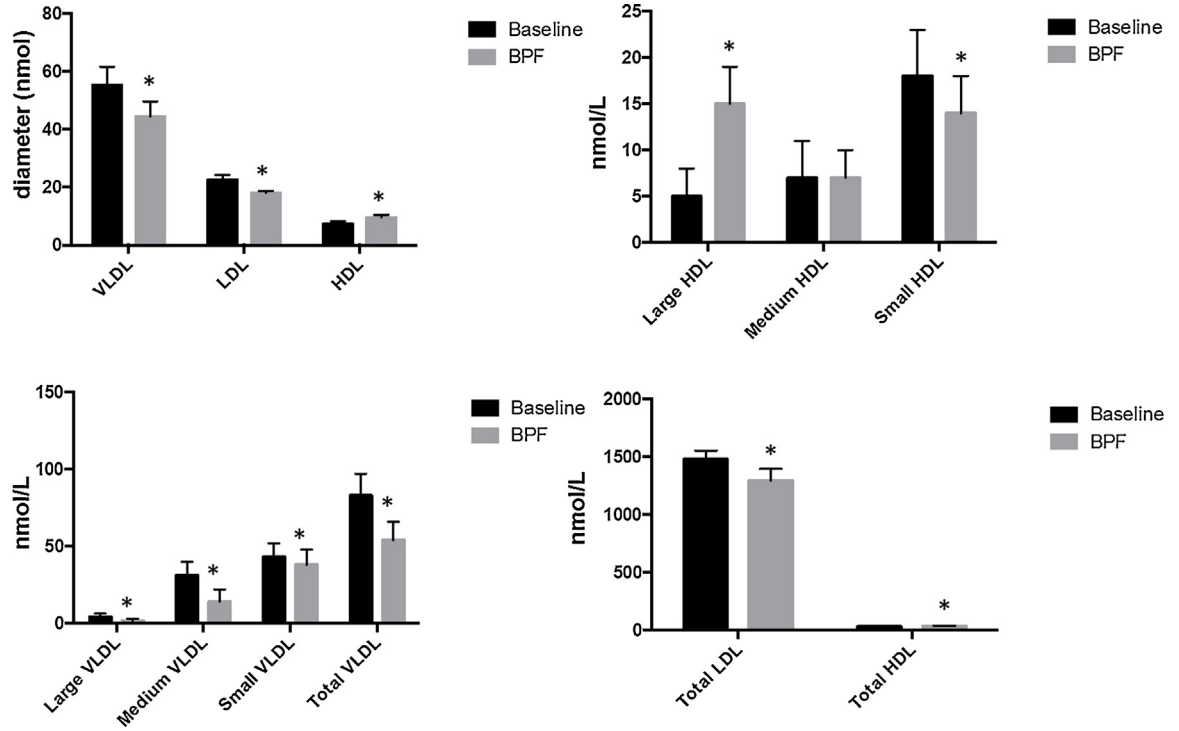

Fig. 2. Plasma lipoprotein particle size and concentration in patients with MS and NASH at the baseline and after 120 consecutive day treatment with BPF 650 mg × 2 daily. (Data are expressed as mean ± SD for each value; a P value of <0.05 between values at baseline and after BPF treatment was taken as significant*).