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New treatment options for patients with metabolic syndrome

Nowe możliwości terapii osób z zespołem metabolicznym

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Abstract

The occurrence of metabolic syndrome is a risk factor for developing cardiovascular disease. Moreover, the size of low-density lipoprotein (LDL) particles, and liver dysfunction identified as non-alcoholic fatty liver disease (NAFLD), both represent important biomarkers for the development of cardiometabolic risk in patients with metabolic syndrome. Patients being treated with bergamot polyphenolic fraction show significant reductions in fasting plasma glucose, serum LDL cholesterol, and triglycerides along with an increase of their high-density lipoprotein cholesterol level. This effect is accompanied in the ultrasonography examination by significantly reduced NAFLD.

Key words: metabolic syndrome, bergamot polyphenolic fraction

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Definition of metabolic syndrome

Metabolic syndrome is characterised by the coexistence of metabolic risk factors for atherosclerosis and its complications. The modified definition by the National Cholesterol Education Programme Adult Treatment Panel III (NCEP-ATP III) includes:

- obesity defined as waist circumference ≥ 88 cm among women and ≥ 102 cm among men;
- fasting glucose ≥ 100 mg/dL or glucose lowering treatment;
- systolic blood pressure ≥ 130 mm Hg, diastolic blood pressure ≥ 85 mm Hg or antihypertensive treatment;
- triglycerides level (TG) ≥ 150 mg/dL (≥ 1.7 mmol/L) or lipid lowering therapy;
- high-density lipoprotein cholesterol level (HDL-C, < 40 mg/dL (< 1.0 mmol/L) among men, < 50 mg/dL (< 1.3 mmol/L) among women or lipid-modifying therapy.

According to this definition, it is necessary to identify at least three of the abnormalities described above in order to make a diagnosis of metabolic syndrome [1].

Prevalence of metabolic syndrome and its complications

The prevalence of metabolic syndrome increases with age, and is around 40% in people over 60 years of age. In the general European population, the occurrence of metabolic syndrome is estimated at 38% in men and 36% in women, with its frequency increased significantly in the diabetic population. Metabolic syndrome, even without co-existing type 2 diabetes, significantly increases the risk of developing ischaemic heart disease. The incidence of diabetes in people with central obesity, which is the main component of metabolic syndrome, increases 3–4 times compared to people with normal body weight. Hypertension and lipid

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disorders are also more common in overweight and obese people. In addition, people with metabolic syndrome are more likely to have decreased levels of adiponectin A1, insulin resistance, thrombophilia, inflammation, endothelial dysfunction, hepatic steatosis, elevated uric acid, leptin, fibrinogen, low-density lipoprotein cholesterol (LDL-C) and increased alanine transaminase.

Numerous observations have indicated that inflammation plays a key role in the pathogenesis of virtually all components of metabolic syndrome, so this may be the most important mechanism underlying this disease, second only to an abnormal lifestyle [1–4].

Therapeutic treatment in metabolic syndrome

Treatment and prevention of metabolic syndrome involve primarily a change in lifestyle. The effectiveness of such a change, which has a positive effect on all the elements of metabolic syndrome, is observed even with fairly small reductions of body weight and BMI. The beneficial role of diet has been confirmed in observational studies. Minimally processed fruits, vegetables, coarse bread, nuts and seeds, olive oil as the main source of fat in the diet, elements of the Mediterranean diet, and limited intake of dairy products, eggs and red meat, have all been seen to reduce mortality and the percentage of cardiac events, favourably affecting the various components of metabolic syndrome [4]. Due to the key role of inflammation and oxidative stress in the pathogenesis of endothelial dysfunction as the first stage of the atherosclerotic process, the basis for preventing the development of atherosclerosis in metabolic syndrome should be drugs that simultaneously inhibit both processes. Pharmacological treatment of diagnosed hypertension, diabetes mellitus and hypercholesterolemia in people with metabolic syndrome does not differ from the general principles of treatment of these disease entities in people without metabolic syndrome, but a strong focus upon the benefits and the need for lifestyle modification are always required. From the point of view of cardiovascular risk, moderate correction of several risk factors (if any) is more beneficial than focusing on just one while leaving the other factors without intervention. Although in the diagnosis of metabolic syndrome, increased LDL-C concentration does not fall within the diagnostic criteria, it should nonetheless be remembered that hypercholesterolemia is an extremely common phenomenon in the Polish population, further exacerbating the risk of cardiovascular complications [2, 4].

Natural substances in the prevention and therapy of cardiovascular diseases

In recent years, the possibility of using biologically active substances of plant origin in the prevention and treatment of 'civilization diseases' has received growing interest. Biologically active compounds of plant origin, with efficacy proven and confirmed in clinical trials, are perceived not only as cheaper but even more importantly as healthier alternatives or supplementations of traditional synthetic pharmaceuticals. The European guidelines for the treatment of lipid disorders mention, among others, the need to increase fibre intake, for functional foods enriched with sterols, and for the use of cholesterol-lowering supplements (including red fermented rice).

Numerous clinical and epidemiological studies have proved that diet being the source of polyphenolic compounds contributes to reducing the risk of occurrence of, among others, cardiovascular diseases, obesity, type 2 diabetes, and cancer. Substances with antioxidant properties are particularly valuable ingredients of plant materials. The main vegetable antioxidants include polyphenolic compounds, which are the most widespread group of antioxidant compounds in the plant world. Polyphenolic compounds accumulate in the above-ground parts of plants, *i.e.* the stems, leaves and flowers and above all in the fruits. They are also responsible for their colour, which is why fruits with intense pigmentation are characterised by a high content of these compounds. Vegetables and spices, as well as drinks such as coffee, cocoa, green tea, black tea, and red wine, are also rich sources of polyphenols [5, 6].

Composition of bergamot polyphenols

Bergamot orange (*Citrus bergamia Risso & Poiteau*), also known as bergamot, is a species of citrus plant from the Rutaceae family. It probably originated in India, although today it is almost exclusively cultivated in the region of Calabria in southern Italy. The bergamot fruit is bitter and tart and not suitable for direct consumption. The main raw material for the production of bergamot oil is thick and wrinkled orange peel containing large amounts of essential oil. Bergamot juice is characterised by a unique flavonoid profile and is particularly rich in flavanones and flavones. The composition of bergamot polyphenols has been evaluated in clinical trials in which, among others, patients with metabolic syndrome were included.

For the randomised, double-blind, placebo-controlled trial performed by Mollace et al. [7], 237 patients with hypercholesterolemia were qualified, and among this group were 59 patients with metabolic syndrome (mixed hyperlipidemia and glycaemia > 110 mg/dL). This group was divided into three subgroups, in which patients received BPF 500 mg/day, 1,000 mg/day, or a placebo, while maintaining a diet of 1,600 kcal/day.

Thirty-day BPF therapy (500 mg or 1,000 mg) resulted in a significant reduction in total cholesterol (TC) and LDL-C and a significant increase in HDL-C (Table 1) [7]. There were no significant changes in lipid parameters in the placebo group.

Table 1. Percentage changes in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) in patients with metabolic syndrome undergoing 30-day treatment with a composition of bergamot polyphenolic fraction (source [7])

Patient group N = 59	Daily intake of BPF [mg]	Average change [%]		
		TC	LDL-C	HDL-C
Metabolic syndrome	500	**–24.7** ± 2.6	**–26.8** ± 3.6	**16.5** ± 1.6
	1,000	**–28.1** ± 2.6	**–33.2** ± 3.0	**29.6** ± 1.8
	Placebo	**0.5** ± 0.5	**–0.9** ± 1.4	**2.9** ± 2.0

Table 2. Percentage changes in triglyceride concentrations (TG, triglycerides) and glucose in patients undergoing 30-day treatment with a composition of bergamot polyphenolic fraction (source [7])

Patient group N = 59	Daily intake of BPF [mg]	Average change [%]	
		TG	Glucose
Metabolic syndrome	500	**–32.7** ± 2.5	**–18.9** ± 1.2
	1,000	**–41.0** ± 2.6	**–22.4** ± 1.0
	Placebo	**0.0** ± 0.6	**–0.5** ± 0.7

Additionally, the function of the vascular endothelium was monitored by brachial artery ultrasound imaging, assessing the increase in its diameter during reactive hyperemia. Thirty-day BPF therapy (500 mg or 1,000 mg) resulted in a significant reduction in total and LDL-C and a significant increase in HDL-C (Table 1) [7]. There were no significant changes in lipid parameters in the placebo group.

A significant reduction was also observed in triglycerides (TG) (Table 2). After high-dose BPF treatment, mean baseline values were of TC 278 mg/dL, of LDL-C 188 mg/dL and of TG 267 mg/dL. These were reduced to 199 mg/dL, 126 mg/dL and 158 mg/dL respectively. LDL-C reduction was accompanied by a dose-dependent increase in HDL-C in all patients.

In 10% of people with the best response to treatment, the increase in HDL-C was extremely high: 64.6%. In addition, a significant ($p < 0.0001$) reduction in blood glucose was obtained (mean reduction of –18.9% in the BPF group at a dose of 500 mg and –22.4% in the BPF group at a dose of 1,000 mg). There were no significant changes in the glucose concentration in the placebo group (Table 2) [7].

In addition, the BPF 500 mg and 1,000 mg groups showed improvements in reactive hyperemia within the brachial artery, which would indicate a beneficial effect of BPF on the vascular endothelium in patients with lipid and carbohydrate disorders, which are important biomarkers of cardiometabolic risk. According to the authors of the study, oral BPF containing dietary supplements have hypolipemic potency comparable to low doses of strong statins. In addition, the reduction of blood glucose by 15–25% suggests the possibility of a phytotherapeutic approach to the control of pre-diabetic states in patients with metabolic syndrome. The supply of natural antioxidants, such as bergamot-derived polyphenols, has a positive effect on the modulation of cardiometabolic risk biomarkers and has additional vasoprotective potential in patients with metabolic syndrome.

Gliozzi et al. [8] conducted a study evaluating the influence of BPF on the lipoprotein subfraction profile (small dense LDL) and non-alcoholic fatty liver disease (NAFLD) in patients with metabolic syndrome. 107 people with metabolic syndrome and NAFLD were qualified for the study, and were divided into two groups: a group receiving BPF at a dose of 650 mg BD and a group receiving a placebo for 120 days. A significant reduction in TC, LDL-C, TG, glucose, transaminase, gamma-glutamyl transaminase levels, 'steato-test', morphological exponents of fatty liver on imaging and inflammatory biomarkers: high-sensitivity C-reactive protein (hs-CRP) and tumour necrosis factor α (TNF-α) was observed in the BPF-treated group (Table 3) [8].

In addition, significant changes were found in the mean size of very-low-density lipoproteins (VLDLs, LDL and HDL ($p < 0.05$). In particular, BPF reduced the concentration of intermediate-density lipoproteins (IDL) by 51%, increased the concentration of large LDL by 38%, and decreased the concentration of small LDL by 35%. Moreover, 120-day BPF therapy resulted in a 20 per cent increase in the concentration of anti-atherogenic HDL particles, mainly due to the increase in HDL concentration (Table 4) [8].

In addition, the hepatorenal index decreased from 2.8 ± ± 0.4 to 1.5 ± 0.5 ($p < 0.05$), which proved that BPF administration to patients with mild to severe NAFLD associated with metabolic syndrome can lead to the reduction of steatosis. During the study, no adverse effects associated with BPF intake were reported, which again confirmed the significant safety profile of the bergamot extract. In summary, the authors found that bergamot polyphenols administered to patients with metabolic syndrome and NAFLD led to

Table 3. Effect of 120-day treatment with a composition of polyphenols from bergamot (BPF, bergamot polyphenolic fraction) at a dose of 650 mg bis die (BD) on blood biochemical parameters, inflammatory biomarkers and ultrasound parameters in patients with metabolic syndrome and non-alcoholic fatty liver disease (source [8])

Biomarkers	Baseline	BPF
Patients receiving BPF 650 mg BD for 120 days	107	
Age (years)	56 ± 12	
Gender (M/F)	64/43	
BMI [kg/m^2]	29.4 ± 2.01	28.2 ± 1.53
Glucose [mg/dL]	118 ± 1.4	98 ± 0.8*
TC [mg/dL]	245 ± 8.3	182 ± 7.1*
LDL-C [mg/dL]	162 ± 4.3	101 ± 1.8*
HDL-C [mg/dL]	38 ± 3.8	49 ± 4*
TG [mg/dL]	232 ± 5.1	160 ± 4.8*
Steato-test	0.74 ± 0.12	0.44 ± 0.09*
ALT [U/L]	54 ± 5.4	36 ± 5.3*
AST [U/L]	52 ± 6.4	41 ± 5.2*
GGTP [IU/L]	38 ± 5.2	29.33 ± 1.1*
hs-CRP [mg/L]	1.2 + 0.8	0.94 + 0.6*
TNF-α [pg/mL]	14.4 ± 1.9	10.7 ± 1.7*
Hepatorenal index	2.8 ± 0.4	1.5 ± 0.5*

*p < 0.05 (compared to baseline); M — men; F — women; BMI — body mass index; TC — total cholesterol; LDL-C — low-density lipoprotein cholesterol; HDL-C — high-density lipoprotein cholesterol; TG — triglycerides; ALT — alanine aminotransferase; AST — aspartate aminotransferase; GGTP — gamma-glutamyl transpeptidase; hs-CRP — high-sensitivity C-reactive protein; TNF-α — tumour necrosis factor α

Table 4. Effect of 120-day treatment with a composition of bergamot polyphenolic fraction (BPF) at a dose of 650 mg bis die (BD) on the size of lipoproteins and the concentration of their individual fractions in the blood in patients with metabolic syndrome and non-alcoholic fatty liver disease (source [8])

Lipoprotein — size [nm]	Baseline	BPF
VLDL	55.3 ± 6.4	44.5 ± 5.2*
LDL	22.6 ± 1.7	18.0 ± 0.8*
HDL	7.5 ± 0.8	9.6 ± 0.9*
Lipoprotein fractions — concentration [nmol/L]		
Total VLDL	83 ± 14	54 ± 12*
Large VLDL	4.2 ± 2	1.8 ± 1.3*
Medium VLDL	31 ± 9	14 ± 8*
Small VLDL	43 ± 9	38 ± 10
Total LDL	1,477 ± 75	1,293 ± 101*
IDL	77 ± 16	38 ± 10*
Large LDL	424 ± 87	653 ± 95*
Medium LDL	986 ± 105	612 ± 98*
Total HDL	30 ± 2	36 ± 3*
Large HDL	5 ± 3	15 ± 4*
Medium HDL	7 ± 4	7 ± 3
Small HDL	18 ± 5	14 ± 4*

*p < 0.05 (compared to baseline); VLDL — very-low-density lipoproteins; LDL — low-density lipoproteins; HDL — high-density lipoproteins; IDL — intermediate density lipoproteins

improved lipid profile and glycaemic status and a significant reduction in fatty liver disease. This effect, together with a decrease in the concentration of proatherogenic small dense LDL, and an increase in the concentration of anti-cancer HDL particles, sheds new light on the potential use of bergamot extract in reducing cardiovascular risk in patients with metabolic syndrome [8].

Another aspect of the beneficial effects of bergamot polyphenols on vascular endothelium is also noteworthy. Mollace et al. [9] showed that in patients with type 2 diabetes with erectile dysfunction, sexual function improved in the group treated with BPF at a dose of 650 mg BD after a 120-day treatment. This phenomenon was not observed in the placebo group.

Mechanism of bergamot polyphenols beneficial effects

The probable mechanism of hypoglycaemic and hypolipemic flavonoids appears to be the activation of AMP-activated protein kinase (AMPK), which acts as an integrator of regulatory signals that monitor the systemic and cellular energy state of the body. As a result of the action of kinase, the synthesis of glucose, fats, proteins and cell growth is inhibited, while the uptake and oxidation of fatty acids, glucose uptake and glycolysis are stimulated. In addition, chronic activation of AMPK mimics the effect of intense physical exercise through the induction of muscle hexokinase expression and glucose transporters type 4 (GLUT-4). The activation of AMPK is, therefore, a molecular activity of many natural polyphenols and may be responsible for their numerous beneficial therapeutic properties, especially in the context of metabolic disorders like obesity, diabetes, hyperlipidemia and non-alcoholic fatty liver disease (NAFLD). Some flavonoids may induce lipolysis in adipose tissue, presumably by inhibiting phosphodiesterase (PDE) and reducing the distribution of cyclic adenosine monophosphate (cAMP). This may explain the beneficial effects on obesity of some dietary supplements rich in citrus flavonoids. CAMP signalling pathways also modulate gluconeogenesis, glycogenolysis and insulin secretion [10–13]. There are also reports on BPH pleiotropic activities such as the reduction of chronic pain transmission by affecting the reactive oxygen species (ROS) and nitrogen (RNS), which are responsible for pain progression.

The composition of bergamot polyphenols also effectively limits the effects of ultraviolet B (UVB) on keratinocytes

Table 5. Intervention strategies as a function of total cardiovascular (CV) risk and low-density lipoprotein cholesterol (LDL-C) level (source [4])

Total CV risk (SCORE) [%]	LDL-C levels				
	< 70 mg/dL < 1.8 mmol/L	70 to < 100 mg/dL 1.8 to < 2.5 mmol/L	100 to < 155 mg/dL 2.5 to < 4.0 mmol/L	155 to < 190 mg/dL 4.0 to < 4.9 mmol/L	≥ 190 mg/dL ≥ 4.9 mmol/L
< 1	No lipid intervention	No lipid intervention	No lipid intervention	No lipid intervention	Lifestyle intervention, consider drug if uncontrolled
≥ 1 and < 5	No lipid intervention	No lipid intervention	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled
≥ 5 and < 10	No lipid intervention	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
≥ 10	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention

SCORE — Systematic COronary Risk Evaluation

Figure 1. Possibilities of using a composition of bergamot polyphenolic fraction (BPF) depending on the clinical situation based on the total risk of developing cardiovascular diseases (CVD) and low-density lipoprotein cholesterol level (LDL-C) (author's modification based on [4])

Total CVD risk (SCORE) [%]	LDL-C levels				
	< 70 mg/dL < 1.8 mmol/L	70 to < 100 mg/dL 1.8 to < 2.5 mmol/L	100 to < 155 mg/dL 2.5 to < 4.0 mmol/L	155 to < 190 mg/dL 4.0 to < 4.9 mmol/L	≥ 190 mg/dL ≥ 4.9 mmol/L
< 1 LDL-C < 115 mg/dl	No intervention MS	No intervention MS	No intervention MS	No intervention MS	Lifestyle intervention, drug if uncontrolled
Class/level	I C	I C	I C	I C	IIa A
≥ 1 to < 5 Target: LDL-C < 115 mg/dl	No intervention MS	No intervention MS	Lifestyle intervention, drug if uncontrolled	Lifestyle intervention, drug if uncontrolled	Lifestyle intervention, drug if uncontrolled
Class/level	I C	I C	IIa A	IIa A	I A
≥ 5 to < 10 OR HIGH RISK Target: LDL-C < 100 mg/dl < 50–100 mg/dl	No intervention MS	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention and concomitant drug interven-	Lifestyle intervention and concomitant drug interven-	Lifestyle intervention and concomitant drug interven-
Class/level	IIa A	IIa A	IIa A	I A	I A
≥ 10 OR VERY HIGH RISK Target: LDL-C < 70 mg/dl < 35–67.5 mg/dl	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention and concomitant drug interven-	Lifestyle intervention and concomitant drug interven-	Lifestyle intervention and concomitant drug interven-	Lifestyle intervention and concomitant drug interven-
Class/level	IIa A	IIa A	I A	I A	I A

SCORE — Systematic COronary Risk Evaluation

MS — diagnosis of metabolic syndrome

BPF in people who do not require statin therapy

association of BFP with a statin in people not tolerating a higher dose of statins or combination therapy with lipid-lowering drugs

in vitro. It seems that BPF modulates the basic pathways of cellular signal transduction, which leads to anti-proliferative, anti-ageing and immunomodulatory responses. Thanks to their antioxidant and anti-inflammatory properties, polyphenols may also have a protective effect on the myocardium during chemotherapy [10–13].

Potential applications of bergamot polyphenols in clinical practice

The possibilities of using BPF go well beyond the metabolic syndrome mentioned in the title of this article, including a large population of people with low [< 1% SCORE (Systematic COronary Risk Evaluation)] or moderate (1–4% SCORE) cardiovascular risk, with a 20–40% elevation in LDL-C when there is no need for aggressive lipid-lowering therapy (Table 5). Polyphenols from bergamot may be an option in the case of pharmacological intolerance of hypolipemic drugs or in patients categorically refusing statin therapy, although in this situation, according to the clinical condition, every effort should be made to convince the patient of the benefits of statin therapy. An important feature of bergamot polyphenols, distinguishing them from monacolin, is the possibility of statin-associated administration in patients who cannot be intensified with statin therapy (additive BPF effect). Patients with metabolic syndrome and impaired carbohydrate metabolism in the form of impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), and those with metabolic syndrome and NAFLD, may benefit significantly from BPF.

Although further research is needed, it is worth remembering that BPF may also be a beneficial complement to therapy in erectile dysfunction in patients with carbohydrate disorders, and may reduce the effects of UVB radiation, as well as being cardioprotective during doxorubicin chemotherapy.

Summary

The composition of bergamot polyphenols positively affects the lipid and carbohydrate metabolism, and their strong antioxidant properties additionally have a positive effect on the vascular endothelium. The effects of nutraceutical BPF seem to be comparable to synthetic drugs at a low dose, with negligible side effects. BPF can be an important supplement, and even occasionally an alternative, to conventional drugs as an addition to pro-health lifestyle modification and conventional therapy of metabolic syndrome. The features of bergamot polyphenols, such as their multidirectional lipid-reduction, hypoglycaemic activity, and modification of endothelial function, as well as the positive results of clinical trials in patients with metabolic syndrome, justify their use in this group of patients.

In Figure 1 presents a proprietary application for BFP in different populations of people with lipid disorders.

Conflict(s) of interest

Lectures fee: USP Zdrowie.

Streszczenie

Zespół metaboliczny jest uznawany za czynnik ryzyka schorzeń układu sercowo-naczyniowego. Zarówno małe, gęste cząsteczki lipoprotein o małej gęstości (LDL), jak i dysfunkcja wątroby pod postacią niealkoholowego stłuszczenia wątroby (NAFLD) są markerami ryzyka metabolicznego u chorych z zespołem metabolicznym. U pacjentów z zespołem metabolicznym leczonych kompozycją polifenoli z bergamoty stwierdza się obniżenie stężeń glukozy na czczo, triglicerydow i cholesterolu frakcji LDL oraz zwiększenia stężenia cholesterolu frakcji lipoprotein o dużej gęstości we krwi. Towarzyszy im cofanie się cech NAFLD w badaniu obrazowym, ultrasonograficznym.

Słowa kluczowe: zespół metaboliczny, kompozycja polifenoli z bergamoty

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