REVIEW

Food-derived caffeine in human nutrition

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Summary
Caffeine, a substance discovered in plant raw materials over 200 years ago, has been extensively studied. However, many of the mechanisms of its influence on the human body have not yet been elucidated or have given contradictory results in experiments. The aim of this paper was to review and systematize current knowledge on caffeine and its impacts on the human body. A combined physiological and psychological effect of caffeine consumption has been shown to depend mainly on individual genotype and the frequency as well as degree of exposure to the substance. An example of this is the effect of caffeine on sports results, depending on the genotype as well as the effect on the cardiovascular system. People who regularly consume large amounts of coffee or tea do not have increased blood pressure, in contrast to occasional users. Caffeine has many positive properties, which include a slight increase in energy expenditure by increasing basal metabolic rate and promoting less fat gain, by potential reduction of the expression of genes associated with obesity, which can help maintain correct normal body weight and help its normalization.

Keywords
caffeine; coffee; tea; nutrition

Coffee and tea, as beverages popular for many years, have always been eagerly drunk due to their taste and physiological effects causing stimulation and mood improvement. Equally often, coffee and tea aroused controversy in the society regarding the impact on human health. The main reason for the controversy was the content of caffeine and other alkaloids present in these infusions, which classified them as stimulants. Caffeine itself is labelled a "legal drug" because of its stimulant and psychoactive properties. Cultural norms allow the substance to be accepted in the diet, despite its potentially addictive properties, mainly due to its widespread use around the world and the lack of negative effects of its consumption in the form of desocialization or propensity to crime or other inappropriate behaviour. On the other hand, we know today that coffee and tea, which for many years were considered only stimulants, also bring health benefits. The main health benefits of these beverages include high antioxidant potential protecting the body's cells from damage [1]. The result is a preventive effect against many diseases, including atherosclerosis, heart attack and malignant tumours [2]. Scientists' attention is also drawn to promising research on the potential effects of coffee in preventing the development of Alzheimer's and Parkinson's diseases [3]. Along with the development of science, popular sources of caffeine in the diet (such as coffee, tea or cocoa) have been the subject of many studies, thanks to which these raw materials and their properties are now much better known.

The aim of the study was to systematize the results of scientific research on caffeine, in particular its sources and impact on human health in the context of the prevention of selected non-communicable diseases such as obesity, cardiovascular diseases, osteoporosis, nephrolithiasis or diabetes. Caffeine is also discussed as a psychoactive substance, regarding its effects on physical activity and on pregnant women.

Caffeine

Caffeine is the commonly used name for a compound with the molecular formula $C_8H_{10}N_4O_2$ and the systematic nomenclature (IUPAC) of 1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione,

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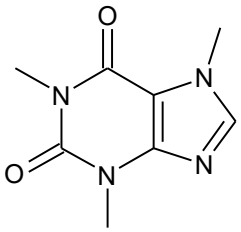

Fig. 1. Structural formula of caffeine.

also often referred to as 1,3,7-trimethylxanthine. The structural formula of caffeine [4] is shown in Fig. 1. It belongs to methylxanthines, a group of central nervous system stimulants commonly found in the daily diet of people. Its structure contains nitrogen rings and belongs to the group of purine alkaloids. It naturally occurs, among others, in the fruit of the coffee tree (mainly *Coffea arabica* and *C. canephora*), cocoa beans (*Theobroma cacao*), tea leaves (*Camellia sinensis*) and Paraguayan holly (*Ilex paraguariensis*). Other names of this organic compound are 7-methyltheophylline and 1-methyltheobromine and, depending on the source, theine (when in tea), guaranine (when in guarana) and mateine (when in yerba mate) [5, 6]. Although the names are different, they mean the same substance. Though it can be found naturally in over 60 plant species that use it as a natural pesticide against insects, it is also obtained synthetically in a technological process and used as an additive to certain products, such as the so-called soft drinks (e. g. cola drinks), the so-called energy drinks and dietary supplements, as well as drugs, e. g. from the group of painkillers. There is no chemical difference between synthetic and naturally obtained caffeine [5]. As a chemical compound, it dissolves well in boiling water and its solubility is increased by the addition of acids such as benzoate, citrate or salicylate, and the formation of complexes at high temperatures [7].

History of caffeine research

The medical works of Persian physicians, such as the Manuscripts of Rhazes (AD 850–922) and the "Canon of Medicine" written by Avicenna in 1025, are the first documents to mention the fruits of the Arabian coffee bushes as stimulants and healing agents. They testify to the possible health benefits of their use in the treatment of various diseases, including kidney stones, gout, smallpox, measles and cough [8, 9]. However, it took many years to study the composition of this plant, as caffeine was first extracted in relatively pure form from green coffee beans in 1819 by the chemist Friedrich Runge. In 1826, Theodore von Martius isolated from guarana a substance that he called "guaranine" and a year later Oudry discovered "theine" in tea. After 11 years, it was shown that theine and guaranine are the same chemical compound as caffeine. Then in 1843, caffeine was discovered in mate tea prepared with Ilex paraguayensis and called "mateine" and in 1865 in kola nuts (*Cola* sp.) [7, 9].

Caffeine as a food ingredient has been regulated by the US Food and Drug Administration (FDA) since 1958, when it was listed as a commonly used substance, recognized by experts as safe due to its intended use in cola beverages at levels not exceeding 0.02 % [10]. Data on the health properties of caffeine, with particular emphasis on carcinogenicity, were published in a monograph of the International Agency for Research on Cancer (IARC) in 2016 [11]. The final assessment concluded that there is insufficient evidence of carcinogenicity of caffeine in humans and, therefore, is classified in Group 3. This means that the extensive scientific literature does not show an association between caffeine consumption in coffee and cancer. It was re-examined in 2016, but no clear link was found, and some studies even suggested a link between coffee drinking and a lower risk of certain cancers, including breast, pancreatic, colon, endometrial, oesophageal and prostate cancer [12].

So far, the recommended level of caffeine intake has not been estimated because it is not included in the nutritional requirements of the diet [13]. Besides, its acceptable daily intake (ADI) has not been established [14]. Although the consumption of caffeine from natural sources and energy drinks is not regulated by law, its excessive supply can be dangerous [13].

Metabolic pathway of caffeine and its toxicity

Absorption of caffeine after oral administration is rapid and almost complete, its bioavailability is practically 100 %. In principle, 20 % of absorption takes place in the stomach and 80 % takes place in the small intestine. In general, it reaches its maximum plasma concentration within 30–120 min after consumption, depending on the presence of food in the stomach. It is lipophilic enough to easily pass the blood-brain barrier and the placental barrier. It penetrates all body tissues and fluids, such as blood plasma, cerebrospinal fluid, saliva, bile, semen, milk and all organs [14, 15].

The metabolic pathway of caffeine occurs almost completely in the liver, where it is demethylated and oxidized successively, through the hepatic system of microsomal enzymes. Only up to

2 % of the consumed amount is excreted in the primary form in urine. The major enzyme responsible for biotransformation of caffeine is cytochrome P450 1A2 (CYP1A2), which accounts for approximately 95 % of caffeine clearance. Its major metabolites in the demethylation process paraxanthin (84 %), theobromine (12 %; in co-operation with CYP2E1) and theophylline (4 %). These are 1,7-dimethylxanthine, 3,7-dimethylxanthine and 1,3-dimethylxanthine, respectively, which are also pharmacologically active [15]. In a further complex biotransformation process, approximately 60 % of paraxanthin is excreted unmodified and the remainder undergoes metabolism by two parallel pathways. The product of the first pathway is 8-hydroxyparaxanthin and the second one, which is 7-demethylated paraxanthine, produces three metabolites: 1-methylxanthine, 1-methyluric acid and 5-acetylamino-6-formylamino-3-methyluracil. The latter, by the N-acetyltransferase-2 enzyme, is converted into a stable form, which is 5-acetylamino-6-amino-3-methyluracil. Approximately 50 % of theobromine is excreted unchanged. Its action includes the induction of diuresis, stimulation of the cardiovascular system and relaxation of smooth muscles. The isoenzymes CYP1A2 and CYP1A1, together with xanthine oxidase, are involved in further breakdown of theobromine and theophylline, the subsequent breakdown products are 3,7-dimethyluric acid and 3-methylxanthine. The resulting end metabolites are actively transported in the renal tubules [8].

The half-life of caffeine in the average person over nine years of age is on average 5 h (2–12 h), in men it is 20–30 % longer than in women. This time may vary due to inter-individual variability in absorption and metabolism, influenced by many exogenous and endogenous determinants, such as genetic determinants, age (younger people are less sensitive to the effects of caffeine), pregnancy, diet, lifestyle, smoking, environmental agents, drugs or diseases. When the levels of the ingested dose are higher, prolonged duration of action may be observed, possibly due to a delay in caffeine clearance resulting in accumulation of paraxanthin and other xanthines. Besides, liver diseases, contraceptives and certain food products such as grapefruit juice, alcohol or curcumin can inhibit the activity of CYP1A2 and thus increase the half-life of caffeine. In the case of grapefruit juice, the half-life of caffeine in the human body can be up to 31 % longer. Smokers are characterized by a faster metabolism of caffeine than non-smokers because cigarettes contain polycyclic aromatic hydrocarbons that promote the greater activity of liver enzymes, thus speeding up the metabolism. People who choose to quit smoking will have increased levels of caffeine in their body with the same consumption of caffeine as before, which is why such people often report that they „tolerate coffee less well“. Factors such as high vitamin C intake or the presence of broccoli and other cruciferous vegetables in the diet may also increase caffeine clearance [8, 15, 16].

The usual consumption of caffeine in a dose of up to 400 mg (i. e. approximately 5.7 $mg \cdot kg^{-1}$ body weight for a person weighing 70 kg) per day does not give rise to health safety concerns for non-pregnant adults [16]. The toxicity of caffeine is defined by the specification of the symptoms that arise as a direct consequence of the consumption of this alkaloid. Common features of caffeine intoxication, also known as “caffeinism” (i. e. a state of chronic toxicity due to excessive caffeine consumption), include anxiety, agitation, restlessness, insomnia, gastrointestinal disturbances, tremors, tachycardia, psychomotor agitation and, in some cases, death [8]. Caffeine poisoning is a recognized clinical syndrome included in the classification of mental disorders (DSM-5) of the American Psychiatric Association [17] and the International Classification of Diseases and Related Health Problems of the World Health Organization (ICD-11) [18]. Generally, it has been noted that toxicological symptoms (i. e. irritability and nervousness, but also potentially palpitations, nausea, tremors, sweating and paraesthesia) often start when the concentration in the blood is above 15 $mg \cdot l^{-1}$, a concentration of 50 $mg \cdot l^{-1}$ is considered to be “toxic” and concentrations of 80 $mg \cdot l^{-1}$ or greater are considered lethal and generally relate to the ingestion of caffeinated drugs and dietary supplements rather than caffeinated foods and beverages [19]. Acute fatal overdose in humans is induced by a dose of approximately 10–14 g of caffeine (corresponding to 150–200 $mg \cdot kg^{-1}$ body weight) and is comparable to the consumption of about 100 cups of coffee or more than 200 bars of chocolate [20].

Caffeine in food

The amount of natural caffeine consumed in drinks varies greatly and depends on the method of preparation of the infusion and brewing time (the longer the time, the more caffeine will be released), the type of plant from which the infusion is made and even its growing conditions or part of the plant from which the raw material was obtained (usually the lower parts of the plant contain a higher amount of the alkaloid). For example, green coffee beans of *C. canephora* (robusta) species contain on average 24–28 $g \cdot kg^{-1}$ caffeine,

while *C. arabica* (arabica) species contain only 10–15 $g \cdot kg^{-1}$ caffeine [21]. The content of caffeine does not change significantly during roasting of coffee due to its thermal stability, although slight losses due to sublimation may occur [7]. The concentration of the alkaloid in this type of infusion, prepared from coffees available on the Polish market, was measured by Jarosz et al. [21]. They established that a volume of 160 ml of coffee infusion may contain from 28.1 mg to 136.6 mg of caffeine.

Regarding the instant coffee, production typically involves treating the roasted ground coffee with hot water at high pressure to extract water-soluble compounds, followed by drying. While in Western countries commercially ground roasted coffee generally consists only of seeds of *C. arabica* or a blend with a small percentage of *C. canephora*, in some countries a high proportion of robusta are used to produce instant coffee due to the higher yields of more soluble solids in the infusion. This explains the higher caffeine content often observed in instant coffees from Brazil [7].

In fresh tea leaves, content of caffeine is up to 45 $g \cdot kg^{-1}$, while in Paraguayan mate leaves it is up to 18 $g \cdot kg^{-1}$. Tea contains more caffeine than coffee on a dry weight basis but generally less of it is used for brewing. In addition, the concentration of the alkaloid decreases after the preparation of the tea infusion. This is due to the catechin tannins released during the brewing process. It is estimated that the extraction efficiency of caffeine from tea leaves for infusion is approximately 86 % [5, 22]. According to the research carried out by Jarosz et al. [21], a 5-minute infusion of tea contains on average less than 40 mg in 200 ml of tea (usual serving).

Caffeine content in coffee brewed using various methods

It is very difficult or even impossible to determine how many milligrams of caffeine contains an average cup of coffee. It is very tough to truly evaluate caffeine daily consumption by consumers because the contents of caffeine in cups can be different. This is due to the many factors that cause that even the same coffee, prepared by the same person in the same way, may have a different concentration of this alkaloid. In addition to the factors that were mentioned in the previous section, the grind size of the coffee grains, which varies depending on the preferred method of filtration and brewing or the pressure at which the extraction will be carried out, affect significantly the final chemical composition of a cup of infusion. Based on the huge amount of research and results that can be found in the literature, it becomes impossible to answer a simple question: how much caffeine is delivered to the body in one cup of coffee, if we do not measure this amount in a chemical analysis before consumption. All we can do is to indicate range of such content – a volume of 100 ml of coffee infusion may contain from 42 mg to even 253 mg of caffeine, depending on the preparation method used and the composition of the bean mix [7].

Methods of obtaining caffeine

Caffeine obtained from decaffeination processes is used mainly by the pharmaceutical industry and by producers of non-alcoholic cola drinks as well as by the cosmetic industry. Potentially, pure caffeine can be obtained from any plant that contains it but, in practice, coffee beans are the main source of this alkaloid as a by-product of decaffeinated coffee production [6]. In the beginning, many unsuccessful attempts were made to extract caffeine from natural sources, often using harmful to health chemical solvents, e. g. benzene, which is now recognized as carcinogenic [23]. The breakthrough came when Ludwig Roselius, the founder of Kaffee HAG in Germany, applied an additional preliminary process, assuming that first green beans should be conditioned with water or steam. This causes their swelling, doubling the surface area, which facilitates the entire process and increases its efficiency. In 1908, Meier, Roselius and Wimmer patented their first useful method of decaffeination (US patent 897763) [24]. At the end of the process, the initial water content of the beans has to be restored by drying and the isolated caffeine is refined [24]. There are currently three main methods of decaffeination in use, each of which includes a preliminary Roselius process and final drying. These are methods using methylene chloride or ethyl acetate as organic solvents, liquid carbon dioxide in a supercritical state or water and a carbon filter [25]. Following various national and international laws and regulations, decaffeination processes should lower the concentration of methylxanthine by 97–99.9 % in roasted coffee and 97 % in soluble coffee, without affecting other naturally present compounds. A more restrictive standard is mandatory in European Union countries, where decaffeinated coffee must be 99.9 % alkaloid-free [7].

When a chemical solvent is used, directly or indirectly, its molecules bind selectively with caffeine molecules in the beans and the aqueous solution. The resulting mixture is then heated to a temperature around the boiling point of the

used extractant so that it evaporates and is separated from caffeine. The solvent should isolate the caffeine without damaging the beans. One of the solvents applied in this process is methylene chloride. The advantage of methylene chloride is its relatively low boiling point (less than 40 °C). This makes it easier to remove its residues from the raw material through evaporation during roasting of coffee beans, which takes place at temperatures exceeding 200 °C [23, 26].

The second method of decaffeination with water and without the use of chemical solvents is the so-called "Swiss water process" introduced by the company Coffex (Brunswick, Australia). The method is used almost exclusively for decaffeination of organic coffee. It is not very popular, mainly because the process is expensive [24, 25, 27].

The third method uses liquid carbon dioxide (CO_2 in the supercritical state). It was developed in 1970 by Kurt Zosel, who used this compound instead of typical chemical solvents [25]. In the first stage, the wet grains are placed in an extractor (a sealed stainless steel container), into which liquid CO_2 is injected under very high pressure to keep it in a supercritical state, i.e. in a state between the liquid and the gas. It is in contact with the raw material until 97 % of the extracted component is recovered [25, 28].

Caffeine can also be chemically synthesized by various procedures, using, for example, theophylline, uric acid or uracil as starting molecules [29, 30].

Caffeine as a psychoactive substance

Caffeine belongs to the group of central nervous system stimulants and is the most consumed psychoactive substance in the world, although overall this is not related to its potentially harmful effects. As a strong stimulant of the central nervous system, it is most often used to alleviate the symptoms of drowsiness and physical fatigue as well as to stimulate mental activity, increase concentration and improve general well-being [31]. Many occupations, including military service, health work, shift workers and professional transport drivers, as well as others engaged in long and monotonous activities, require optimal levels of concentration, focus and agitation to be maintained for many hours to ensure safety and efficiency in the workplace. Many studies show that such people can achieve beneficial effects with doses of 200 mg of caffeine. In situations that additionally involve reduced sleep or its deficit, caffeine in the range of 200–600 mg is an effective means to maintain these functions at an optimal level for a longer period and prevent the manifestations of physiological sleepiness [32].

There are three main mechanisms of action of caffeine on the central nervous system. These include antagonism (blockade) of adenosine receptors, mainly A_1 and A_{2A} (related to brain functions influencing, inter alia, sleep and cognitive processes), mobilization of intracellular calcium ion storage and inhibition of specific phosphodiesterase enzymes. The last two occur only at high non-physiological concentrations of caffeine, therefore most of the effects occur through the first mechanism, which is the only application in the assessment of the effects of caffeine on the human body at standard doses [19].

Adenosine is a compound produced in the body that is involved in numerous biochemical pathways, mainly energy transfer in the form of adenosine triphosphate and in transmission of signals. It is a neuromodulator that, by engaging adenosine receptors, can inhibit the release of various compounds to the brain and slow down certain processes that influence the reduction of energy levels and promote sleep or rest of the body [13, 32]. The chemical structure of caffeine is very similar to that of adenosine, so it can easily replace it and bind to adenosine receptors without activating them. This results in a temporary lack of signal transmission to the brain when someone is, for example, tired. A_1 receptors can be found in almost all areas of the brain. Their greatest amount is found in the cerebral cortex, the cerebellum and the hippocampus [8], and their occupation by caffeine causes vasodilation and greater release of neurotransmitters such as acetylcholine, noradrenaline, dopamine or glutamate. On the other hand, the greatest number of A_{2A} receptors is found in dopamine-rich brain regions [7, 8]. By antagonizing these receptors, caffeine promotes the activity of dopamine and its more effective binding with the D_2 receptor [5]. As a result, caffeine increases the response of dopaminergic receptors, stimulating psychomotor properties and improving behavioural functions such as mood and well-being, physical agitation and give effects related to greater concentration and attention, better memory, faster information processing speed and faster reaction time [7].

The consequences of caffeine consumption in humans are dependent on the dose and individual body tolerance. They fall into two broad categories: at lower concentrations, caffeine stimulates motor activity, at higher concentrations, it produces anxiety-like effects that are well documented in both humans and animals [8]. Meta-analyses showed that doses of 0.5–4.0 $mg \cdot kg^{-1}$ body weight (corresponding to 40–300 mg) may improve the

functions of cognitive processes in well-rested people [32].

Regular consumption of caffeine increases the number of adenosine receptors in the central nervous system. The prolonged use of caffeine-containing beverages causes development of tolerance to caffeine, requiring higher doses to be taken to obtain the desired stimulatory effect. However, it has been shown that tolerance develops in peripheral blood pressure but not in cerebral blood flow, which is where the performance benefits are likely to stem from. This suggests that some of the positive aspects of caffeine intake may be persistent and independent of tolerance. Reducing the consumption of caffeine from high doses to moderate or low doses results in a decrease in the number of adenosine receptors, returning to their original number. This takes several days [33].

Sudden stopping caffeine consumption can cause a phenomenon called withdrawal syndrome. Its characteristic symptoms include headache, drowsiness, fatigue, difficulty at work (decreased motivation to work and impaired concentration), depressed mood (including decreased self-confidence and increased irritability), drop in blood pressure [7] and flu-like symptoms that may begin 12–24 h after the last dose and last up to about a week, peaking after 20–48 h. After long-term use of high doses of caffeine, withdrawal disorders may be more intense [13]. Although studies indicate a deterioration of mood even after discontinuation of relatively small amounts of previously consumed caffeine, they do not show a tendency to worsen other effects, such as psychomotor performance [33]. Controlled discontinuation of caffeine using a placebo among coffee drinkers showed that 20–50 % of them experienced headaches and approximately 10 % experienced psychological symptoms. Ailments related to this type of pain appearing on weekends and caused by high consumption of caffeine on weekdays (drinking coffee at work) and much lower consumption on days off from work are relatively common. Also, unintentional abandonment of drinking coffee or other caffeinated drinks, for example in connection with hospital stay, can cause severe headaches, the cause of which may be misinterpreted. Caffeine withdrawal syndrome can be avoided if consumption is reduced gradually [31].

Despite the described withdrawal symptoms and documented specific addictive potential, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnostic criteria for mental disorders, caffeine is not classified as a typical addictive substance [7]. As a substance causing „addiction“, it is recognized by the International Statistical Classification of Diseases and Health Problems (ICD-11) of the World Health Organization [18]. It can be found in the chapter on mental and behavioural disorders resulting from the use of psychoactive substances.

Another issue that is often discussed in the literature is the effect of caffeine on sleep. Scientists find that feeling tired in the morning leads to high caffeine consumption, which in turn is associated with impairment of subsequent sleep patterns. In human studies, the results indicated that doses of 400 mg of caffeine administered 6 h before bedtime disturbed its quality and caused some problems to fall asleep. The perception of caffeine as a substance that can reverse fatigue deficits means that it is often consumed by people with low energy levels, while research suggests that it is itself associated with causing fatigue [33].

Overall, caffeine, like other psychoactive substances, can be easily abused. According to the World Health Organization, it can also be addictive, although its effects of addiction differ significantly from those caused by other substances in this group [34]. Moreover, like alcohol and tobacco, it is legally used by adults and even adolescents, but unlike the last two, its sale in the form of beverages or dietary supplements is not controlled or limited.

Caffeine and obesity

Recent scientific reports indicate the positive effect of caffeine in the prevention of obesity, as well as the normalization (reduction) of body weight. It seems that caffeine has a beneficial effect on the energy balance, e. g. by increasing thermogenesis through various mechanisms. In humans, the thermogenic effect lasts about 150 min after consuming a single dose of caffeine but may be longer and stronger in people who consume caffeine less frequently and in smaller amounts, thus suggesting the possibility of long-term insensitivity to caffeine after its high and prolonged consumption. In human studies, an increase in energy expenditure was noted from 6 % (after consuming 50 $mg \cdot kg^{-1}$ of caffeine) to 7 % (after consuming 200 $mg \cdot kg^{-1}$ of caffeine). In a pilot study, consumption of 1 cup of green coffee infusion (containing 6 $mg \cdot kg^{-1}$ of caffeine per kilogram of lean body mass, approximately 215–280 $mg \cdot kg^{-1}$ totally) increased resting energy expenditure by 6.4 % after 30 min and by 2.2 % after 180 min [35].

A possible mechanism of the action of caffeine in energy expenditure is also intensification of the secretion of catecholamines, such as adrenaline,

noradrenaline or dopamine. Catecholamines bind to adipocytes, causing an increase in thermogenesis by increasing the expression of thermogenic genes and the release of free fatty acids, which in turn increases the uncoupling protein (UCP) that produces heat in mitochondria. Caffeine also increases the excitability of the sympathetic nervous system. Its activation has been shown to suppress hunger, increase satiety and stimulate energy expenditure, in part by increasing lipid oxidation [36].

Summing up this part, caffeine is associated with an increased resting metabolic rate, therefore it has been suggested that the combination of moderate amounts of caffeine with a reduced-calorie diet may effectively support the loss of excess body fat, with slight changes in the resting metabolism. Besides, caffeine can effectively influence patients' better tolerance to the new diet. This conclusion was supported by a study showing that people who maintain weight loss consume more coffee and caffeinated beverages compared to the general population sample [36].

Caffeine and cardiovascular diseases

It is a common belief that the caffeine present in coffee negatively affects the cardiovascular system due to its ability to raise blood pressure. Meta-analyses did not show a significant effect of coffee drinking on the risk of hypertension. Controlled studies showed a substantial increase in both systolic and diastolic blood pressure caused by caffeine. This suggests that caffeine increases blood pressure but coffee probably does not significantly affect its values. There is no definitive consensus on the mechanism that would explain the poorer effects when coffee is consumed over a long period. It is biologically likely that chronic consumption of caffeinated beverages may induce tolerance and then it has no significant vascular effects [37].

The current guidelines of the Working Group of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) for the management of hypertension [38] do not mention the need to exclude drinking coffee from the diet. In the arguments of both organizations it can be read that despite the short-term effect of raising blood pressure, significant benefits of coffee consumption on the cardiovascular system were observed in a cohort study of over a million participants. Moreover, these institutes indicate that black and green teas may even contribute to a slight blood pressure-lowering effect, although they also contain caffeine.

Cholesterol is mainly responsible for the development of atherosclerosis, which is deposited in the artery walls, specifically the low-density lipoproteins (LDL) fraction [39]. Excessive coffee drinking can increase cholesterol and homocysteine levels in the body and thus contribute to the development of ischemic heart disease. However, the responsible factor is not caffeine but other compounds in the infusion [2, 40].

In the case of arrhythmia, often coexisting with the aforementioned cardiovascular conditions, caffeine is considered as one of the possible causes of physiological sinus tachycardia. ESC states that this type of arrhythmia is treated only by identifying and possibly eliminating the cause [41]. When an unequivocal diagnosis of tachycardia is not established, the influence of consumption of caffeinated beverages on the required effective dose of the drug is questioned. Currently, there are reports in population studies [42] indicating a lower risk of atrial fibrillation in men who reported drinking 1–3 cups of coffee per day. Their mean age was 66 years, the study lasted 9 years and included 18 960 participants. Recent meta-analysis showed that caffeine or coffee are not associated with the occurrence of atrial fibrillation as the most common symptom of arrhythmia and its effect is described as neutral [43].

The currently available evidence about coffee consumption and its overall cardiovascular effects is predominantly calming. It can be included as part of a health-promoting diet for both the general population and those at risk or diagnosed with cardiovascular disease [44].

Effect on kidney stones and osteoporosis

The important role in the prevention of kidney stones is limiting products rich in oxalic acid, which also contain caffeine such as coffee, tea and cocoa. The current recommendations suggest limiting these products because they can increase the excretion of calcium in the urine [39]. However, recent data from three extensive cohort studies (combined participation of over 200 000 people) analyzed by Peerapen and Thongboonkerd [45] showed 26 %, 16 %, and 11 % lower risk of developing oxalate stones in those who consumed regular coffee, decaffeinated coffee, and tea, respectively. Moreover, in an in vitro study, Peerapen and Thongboonkerd [46] demonstrated the mechanisms underlying the preventive action of caffeine in the formation of kidney stones. They found that caffeine did not affect the overall crystallization and growth of calcium oxalate crystals. Caffeine could reduce intracellular calcium storage by increasing calcium excretion, leading to translocation of the calcium oxalate crystal-binding protein annexin A1 from the apical membrane

into the cytoplasm. That results in a reduction in the binding capacity of calcium oxalate crystals by renal tubular epithelial cells. However, the authors state that, based on the evidence from in vivo and in vitro studies, more detailed information is still needed to conclude the preventive effects of caffeine in the pathogenesis of kidney stones. Moreover, the fact that decaffeinated coffee also showed a positive effect leads to another hypothesis that other bioactive compounds in coffee (e. g. trigonelline) may also exert similar protective effects against kidney stones [47].

Research results concerning the influence of caffeine on the human skeletal system are inconclusive. Opinions that caffeine reduces calcium absorption and causes short-term increased excretion of calcium in the urine seem insignificant when the possible loss of calcium can be fully compensated with just 1–2 tablespoons of milk for each cup of coffee. Some later studies reported that high coffee consumption of more than four cups a day by women resulted in 2–4 % lower bone mineral density but this did not cause an increased risk of osteoporotic fractures. In another study, it was estimated that the consumption of eight cups a day increased the risk of bone fractures in women by 14 %. In contrast, the meta-analysis carried out by Wikoff et al. [48] showed that consumption of caffeine in the general population up to 400 mg per day did not adversely affect bone mineral density, risk of fractures or calcium metabolism. There is no evidence that this amount of caffeine has any detrimental effect on bone health or calcium management in people who consume the recommended daily intake of calcium [48, 49].

Caffeine and pregnancy

Researchers have different, often contradictory, opinions on the harmfulness of caffeine before pregnancy, during pregnancy and during breastfeeding. The limited possibilities of conducting research among the population of pregnant women are of great importance in the interpretation of the results of scientific research. Most conclusions are made based on questioning mothers-to-be and observations of children [50, 51], reviewing epidemiological data [52] or on animal studies [53]. It is certain that the effect of caffeine, like other stimulants, is not indifferent to the human body and the effects depend on the dose and many other factors. Caffeine is absorbed quickly, entering blood after approximately 20 min. It freely crosses the placenta from approximately 7–8 weeks of pregnancy. The concentration of methylxanthine in maternal blood and the fetus in this period is comparable, it enters the developing organism along with the amniotic fluid. The placenta and the fetus do not have enzymes involved in the metabolism of caffeine. The still not fully developed organs of the child, including the liver, are unable to carry out transformation of caffeine and, therefore its frequent consumption by the woman leads to accumulation in the fetus [54]. The increase in the concentration of catecholamines (adrenaline, dopamine, and serotonin) caused by caffeine may disrupt blood flow by narrowing the placental vessels and impede the transport of oxygen and nutrients to the fetus, which may result in lower birth weight of the newborn [55]. The mean half-life of caffeine in the woman's body with the development of pregnancy increases almost five times. It is up to 18 h and, in the case of the fetus, as is approximately 150 h. The reason for this is that caffeine is converted to theophylline by demethylation, which is again methylated to caffeine, while in adults, the major metabolic pathway involves oxidative reactions, namely demethylation, and oxidation. This process causes hypercaffeinemia, seen in the first days of life in premature babies whose mothers consumed large amounts of caffeine during pregnancy [5].

The first guidelines recommending limitation in the daily intake of caffeine by pregnant women were issued by the FDA in 1980 [56]. Their implementation was due to the results of studies on unfavourable pregnancy outcomes in women consuming large amounts of this substance [54]. European Food Safety Authority currently reports that up to 300 mg of caffeine per day by pregnant women appears to be safe for the fetus, but a dose of 200 mg per day should not be exceeded [57]. Likewise, single doses of caffeine and normal doses of up to 200 mg consumed by breastfeeding women do not raise concerns about the infant health [16]. Limiting the dose to 200 mg is also currently recommended by American Institute of Medicine for pregnant and lactating women [58]. It can be concluded that caffeine is a chemical compound, among a long list of drugs and other chemicals, that has the potential to be detrimental to fetal growth and the normal course of pregnancy if used in significant excess. However, the usual extent of exposure of women to caffeine from food and drinks before or during pregnancy is generally below a threshold dose that would cause adverse health, development, teratogenic or reproductive effects. FDA recommendations seem to be a reasonable limit, it is worth encouraging women to limit their consumption of this drug for the safety of the child's health, however, it is not necessary to completely give up drinking coffee or tea.

Caffeine, diabetes and glycemic control

Dose-dependent, statistically significantly lower risk of developing type 2 diabetes due to regular consumption of coffee in moderate amounts was confirmed. This effect is seen in both natural and decaffeinated coffee. Meta-analyses show that daily consumption of two cups of coffee containing caffeine reduces the incidence of type 2 diabetes by 12 %, and decaffeinated coffee reduces the risk by 11 % [59]. Despite the large amount of research on coffee containing caffeine and its health effects, there is currently no reliable documented mechanism explaining the protective effect of coffee against type 2 diabetes. Paradoxically, most evidence indicates that caffeine adversely affects glucose metabolism. Many studies showed that administration of caffeine to healthy (non-diabetic) adults caused a sharp increase in insulin resistance or impaired glucose tolerance, which is an effect that may contribute to the development of diabetes in susceptible individuals. Research conducted on coffee drinkers already suffering from this metabolic disease showed that caffeine caused a greater increase in blood glucose after carbohydrate consumption, which was not observed with decaffeinated coffee. This effect may be explained in part by the direct inhibition of glucose uptake in adipocytes and skeletal muscles caused by the antagonism of adenosine receptors. The second hypothesis is that it is a result of elevated plasma adrenaline levels [60, 61]. Since in epidemiological studies similar beneficial results in the prevention of this disease are observed at consumption of natural and decaffeinated coffee, this means that while the former may induce an increased glycemic response, other bioactive compounds present in coffee, such as chlorogenic acid, phenolic compounds, magnesium or trigonelline, can counteract the decreased glucose tolerance by altering its hepatic absorption and subsequent use, "offsetting" the adverse effects of caffeine in the long term [59, 62].

Caffeine, exercise and sport

The effect of caffeine on increasing physical performance has been studied for over 100 years. The first known study on this topic was published in 1907 [63]. Since then, there have been many studies that have not always come up with consistent conclusions. Currently, the vast majority of meta-analyses and reviews recommend a moderate dose of caffeine, 3–6 $mg \cdot kg^{-1}$ body weight, 30–90 min before exercise, to maximize the effects of exercise. Such dosing can improve sustained maximum endurance, performance and recovery during endurance tasks. Higher doses of caffeine do not increase performance and can cause very undesirable effects, including gastrointestinal upset, nervousness, confusion and sleep disturbances. However, with daily consumption of caffeine, performance benefits begin to decline after approximately 15–18 days and may wear off after four weeks [64].

A frequently emerging question is whether the use of caffeine in exercise under high-temperature conditions (e. g. heat) is safe because of its ability to induce mild diuresis and thermogenic effects. This could potentially be associated with a greater risk of electrolyte loss and dehydration, adversely affecting exercise performance. On this point, the research review gives a clear position. There is no evidence to support the hypothesis that regular consumption of caffeine in doses up to 700 mg (or 9 $mg \cdot kg^{-1}$ body weight), which is much higher than the recommended level, causes altered water and electrolyte balance or body hydration in a high-temperature environment [32].

When professional athletes consider the role of caffeine in their diet, they should take into account the variability of the CYP1A2 gene, which affects caffeine metabolism and thus its erogenous effects. GUEST et al. [65] showed that a dose of 4 $mg \cdot kg^{-1}$ improved endurance by male performance athletes during 10 km of cycling, improving the cycle time score by 6.8 %, but only in "fast metabolizers" who are of the CYP1A2 AA genotype (rs762551). In the group of men with the CC genotype (referred to as the "slow metabolizers"), the same dose reduced performance by 13.7 %. In the group of people heterozygous for the A allele (genotype AC), the dose of 2 mg or 4 mg caffeine per kilogram of body weight had no significant effect. Before 2004, caffeine was on the World Anti-Doping Agency (WADA) list of banned substances, with a legal concentration in urine of 12 $\mu g \cdot ml^{-1}$ [66]. However, the compound was later removed from the list, which allowed the athletes competing in WADA-compliant sports to consume caffeine as part of their basal diet or for specific sports purposes. Contrary to WADA, National Collegiate Athletic Association (NCAA) has a urine limit of 15 $\mu g \cdot ml^{-1}$, so NCAA athletes must consider that caffeine is still on the list of controlled substances [8].

CONCLUSIONS

In this review, it was possible to show that the combined physiological and psychological impact of caffeine consumption depends mainly on the individual human genotype as well as the fre-

quency and degree of exposure to the substance. Caffeine has many positive properties, which include a slight increase in energy expenditure by increasing resting metabolism and promoting less fat gain (caused by an improper diet), by potentially reducing the expression of obesity-related genes, which can help maintain normal body weight. In most cases, delivering caffeine to the body as a single ingredient appears to be less beneficial than consuming it in the form of natural caffeine beverages, where additional benefits come from the phenolic content of tea and coffee infusions. In addition, in case of glycemic control, polyphenols and other ingredients in these beverages seem to counteract any adverse effects of caffeine on the body. Future studies should include separating the consumption of regular coffee from decaffeinated coffee, since it is critical to determine whether benefits are due to caffeine or other components, such as e. g. chlorogenic acid. Interventions taking into consideration genetic variation in human caffeine metabolism can strengthen the associations and conclusions. Due to the lack of a drug for Alzheimer's and Parkinson's disease, it seems particularly important to increase the research on neurodegenerative diseases in which caffeine may have a potential therapeutic effect.

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