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Influence of chronic coffee consumption on the risk of kidney and other organ diseases. Review of the literature and clinical studies

ABSTRACT

Due to its taste and biological properties, coffee has been a very popular drink for centuries. The average coffee consumption in Poland amounts to 3 kg per capita/year and systematically increases year by year. The most popular types of coffee grown in the world are *Coffea arabica, Coffea canephora,* and *Coffea liberica*. The chemical composition of coffee depends on many factors, mainly the type of coffee and the method of its cultivation and production. Coffee contains over 1000 different chemical compounds, the most prevalent being caffeine, chlorogenic acid, trigonelline, kahweol, and cafestol. All of these compounds are characterized by high biological activity. A number of exogenous and endogenous factors affect the rate of caffeine metabolism, which may have important clinical implications. In addition, caffeine can interact with medications in various ways, increasing the risk of side effects. Numerous studies indicate both the beneficial and unfavorable effects of coffee consumption on human health. This review paper presents the effect of coffee consumption on the risk of developing diseases of the kidney, nervous system, digestive system, cardiovascular system, and metabolic diseases.

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Key words: coffee, cardiovascular system, digestive system, kidneys, nervous system

INTRODUCTION

Besides water, coffee is the most commonly consumed beverage in the world [1, 2]. According to the US National Coffee Association (NCA), about 2.25 billion cups of coffee are brewed every day around the world. According to the data from the International Coffee Organization (ICO), the largest quantities of coffee are consumed in the Netherlands, averaging at 8.3 kg/inhabitant/year (data from 2020).

In Poland, coffee consumption amounts to around 3 kg/year per capita (average of 1 to 2 cups/day). Over the last 10 years, coffee consumption in Poland has increased significantly by more than 80% [3].

COFFEE TYPES AND PRODUCTION

Coffea is a genus of evergreen shrubs native to the tropical region and belonging to the family of *Rubiaceae* consisting of 500 genera and over 6000 species. From the commercial point of view, the main coffee types are arabica (*Coffea arabica*), robusta (*Coffea canephora*), and liberica (*Coffea liberica*) (Tab. 1) [4–6]. The largest quantities of coffee are produced in Brazil [1].

The organoleptic, physical, and biochemical properties of coffee are influenced by many factors which can be divided into two groups, namely the pre-harvest (e.g. sunlight, place of cultivation) and the post-harvest (e.g. grain proceffing method, grain roasting time) factors. It is estimated that they respectively account for about 40% and 60% of the organoleptic, physical, and biochemical properties of coffee [8].

Coffee production is a multi-stage process, with four different coffee cherry processing techniques as listed in Table 2, namely dry processing, wet processing, semi-dry (semi-wet) processing, and bioprocessing (the method used to produce kopi luwak, one of the most expensive coffees in the world) [8]. The processing methods have a significant im-

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Table 1. Characteristics of *Coffea arabica, Coffea robusta* i *Coffea liberica*. Based on [4–7]

Characteristics	Coffee type		
	Coffea arabica	Coffea canephora	Coffea liberica
Common name	Arabica	Robusta	Liberica
Main cultivation areas	Brazil, Central America, and Africa	Vietnam, Brazil, Indonesia, and Africa	Malaysia, certain regions of the Philippines, and Africa (Liberia)
Global market share	64%	35%	1%
Aroma	++	+++	+
Concentration of biological components [g/100 g]			
Caffeine	1.61	2.26	1.23
Water	8–12	8–12	11
Protein	9.8	9.5	14
Sucrose + reducing sugars	8.1	4.4	8
Polysaccharides	49.8	54.4	42
Lipids	16.2	10	12
Chlorogenic acid	6.5	10	7
Minerals	4.2	4.4	4

Table 2. Coffee cherry processing methods. Based on [8]

Dry	Wet	Semi-wet/semi-dry	Bioprocessing
Fruits are dried in the sun or using automated dryers. The dried, hardened pulp and the sheath are subsequently removed from the cherries using special mechanical devices. This is the most commonly applied method.	The fruit pulp is removed mechanically, a significant part of the process taking place in water. The remaining pulp and rinds are rinsed off in fermentation basins. Coffee beans obtained in this processing method are clean but still covered by a pectin sheath. The next stage consists in beans being dried as described for the dry method.	As in the case of wet treatment, the fruit pulp is separated from the bean while the polysaccharide mucus is not completely removed, drying out on the surface of the parchment husk. After drying, the parchment husk is removed from the bean using a machine.	Coffee cherries are fed to animals capable of digesting the pulp but not the coffee beans. After partial digestion by digestive enzymes and slight fermentation by lactic acid bacteria, the grains are excreted with the stool. Kopi luwak — collected from Asian palm civet waste. Black ivory coffee — collected from elephant waste.

pact on the organoleptic, physical, and chemical properties of coffee [8].

CHEMICAL CONSTITUENTS OF COFFEE AND ITS METABOLISM

As previously mentioned, the chemical composition of coffee depends on its type (Tab. 1) and the methods of its production (Tab. 2) and brewing (Fig. 1). It is estimated that more than 1000 chemicals are present in coffee [9].

The main biologically active constituent of coffee is a xanthine alkaloid, caffeine (1,3,7-trimethylxanthine) [1]. The chemical composition of decaffeinated coffee is similar to that of normal coffee. A small amount of caffeine (0.02 mg/mL) may be present in decaffeinated coffee [10]. After consumption, caffeine is quickly and almost completely absorbed in the digestive tract (99% after 45 minutes from consumption). Caffeine is absorbed in the stomach (20%) and small intestine (80%). The rate of absorption varies according to the food product which contains caffeine. Depending on the number of cups of coffee consumed, caffeine concentration in the plasma is in the range of 20–40 μM/L (1–3 cups of coffee) approximately one hour after consumption [1, 11]. Caffeine enters systemic fluids such as blood, umbilical blood, cerebrospinal fluid, saliva (65–85% of plasma concentration), bile, semen, and breast milk [11]. The half-life of caffeine is approximately 5 hours [1, 12]. The metabolism of caffeine is very complex (Fig. 2) [11].

In the liver, caffeine is demethylated by the 1A2 subunit of cytochrome P_{450} (CYP1A2). It is the main enzyme responsible for the metabolism of caffeine (95%). Caffeine is converted to paraxanthine (84%), theobromine (12%), and theophylline (4%) [1]. These compounds are then further metabolized by microsomal enzymes and the resulting products are filtered by the kidneys and eliminated in the urine. Caffeine reaching the kidneys is largely reabsorbed in the nephron tubules, while about 1–5% is excreted unchanged in the urine. In urine, caffeine metabolites are: dimethylxanthines, dimethyl- and monomethyl uric acids, trimethyl- and dimethylalantoin and uracil derivatives [9].

From a clinical point of view, factors that may affect the rate of caffeine metabolism are important (Tab. 3).

The second most prevalent constituent of coffee is a polyphenolic compound, namely chlorogenic acid. Phenolic compounds are thermally labile and thus susceptible to degradation upon coffee roasting. However, significant levels of chlorogenic acid are retained in the brew [1]. About 30% of chlorogenic acid content is absorbed within the small intestine, while the remaining part is absorbed within the colon. Depending on the number of cups of coffee consumed, the plasma chlorogenic acid concentration reaches the level of 0.035 μM/L (1–3 cups of coffee) approximately one hour after consumption. In contrast to chlorogenic acid, its metabolites, such as the dihydroxycinnamic acids and the sulfates and glucuronides thereof, particularly catechol, achieve significantly higher plasma concentrations. The maximum plasma level of catechol is 2.5 μM/L approximately one hour after the consumption of coffee. This is because chlorogenic acid is largely metabolized by the colonic microbiota. In clinical study was shown a 3-fold reduction in the excretion of certain metabolites of chlorogenic acid in patients subjected to ileostomy as compared to healthy individuals [1, 13].

Another common alkaloid present in coffee is a pyrimidine compound, trigonelline [1, 14–15]. As a result of bean roasting, part of the trigonelline content undergoes demethylation to nicotinic acid which is mainly found in espresso coffee (0.35 mg/mL) [1]. Following the consumption of about 350 mL of of normal coffee, trigonelline coffee, trigonelline is absorbed mainly from the small intestine and reaches the maximum plasma concentration of approximately 5.6 μM/L after about

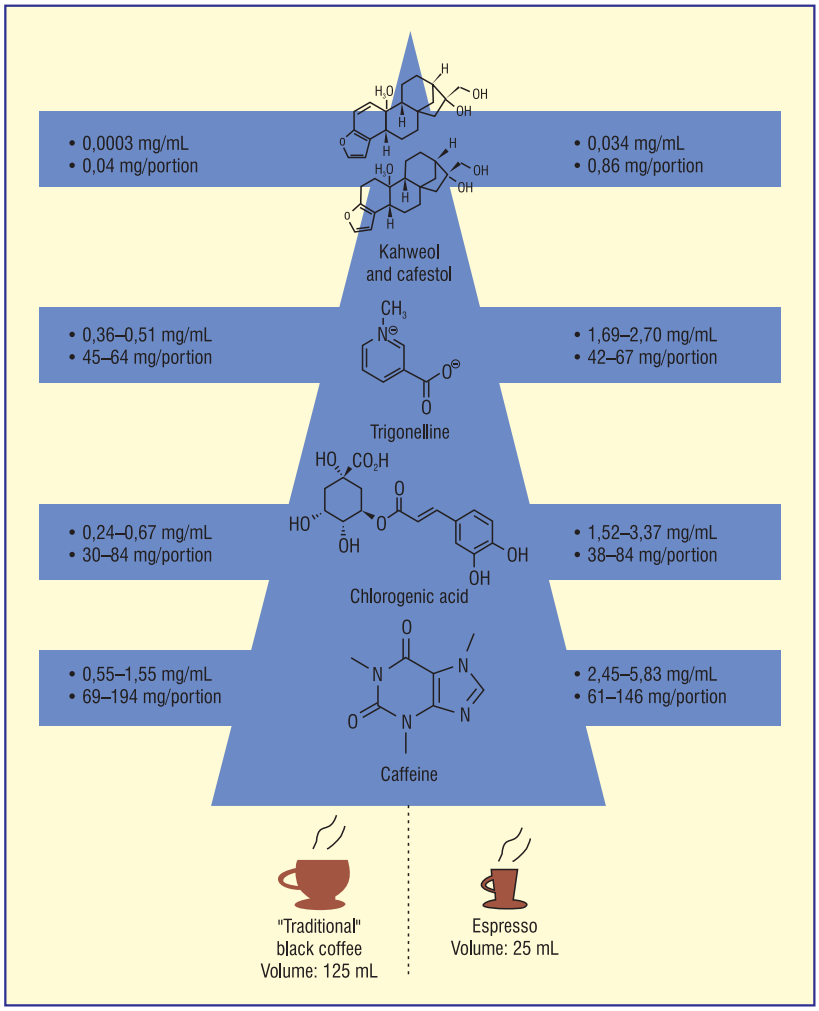

Figure 1. Main chemicals present in traditional coffee and espresso by concentration and quantity in the usual portions. Based on [1]

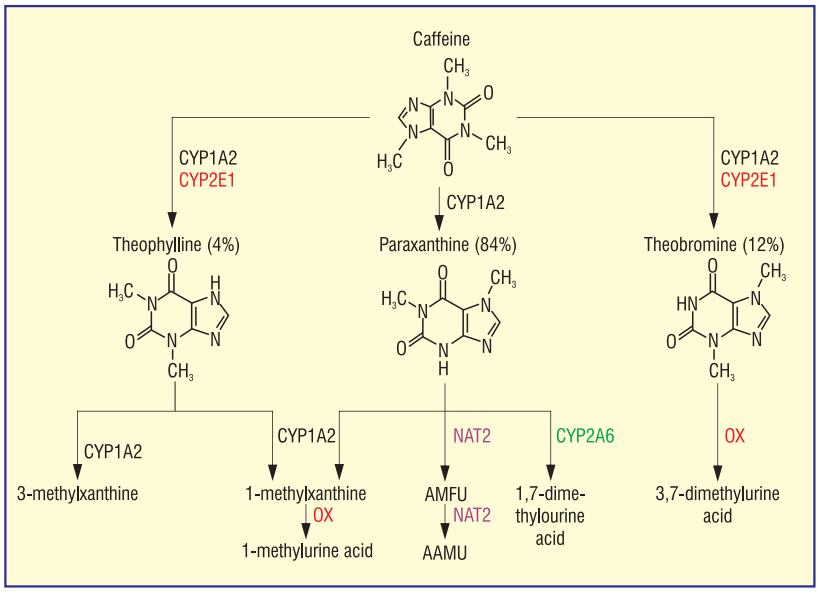

Figure 2. Caffeine metabolism. Based on [11]. AAMU — 5-acetylamino-6-amino-3-methyluracil; AMFU — 5-acetylamino-6-formylamino-3-methyluracil; CYP1A2, CYP2E1, CYP1A1 and CYP2A6 — isoforms of cytochrome P_{450}; NAT2 — N-acetyltransferase-2; XO — xanthine oxidase

Table 3. Factors affecting the rate of caffeine metabolism in the body. Based on [9, 11]

When interpreting the data in the table, a healthy adult male with caffeine half-life of approximately 5 hours should be taken as a reference.							
Physiological factor/state	**Effects on the caffeine metabolism rate**	**Medication**	**Effects on the caffeine metabolism rate**	**Medication**	**Effects on the caffeine metabolism rate**	**Other factors**	**Effects on the caffeine metabolism rate**
Age • neonates • children and adolescents • adult • elderly	 ↓* ↔/↑ ↔ ↔	quinolol antibiotics	↓*****	rofecoxib	↓	CYP1A2*1F genotype	↓
		mexiletin	↓	fluconazole	↓	Gene polymorphisms of caffeine-metabolizing enzymes (CYP2E1, CYP1A1, CYP2A6, OX and NAT2) (for more information, see Nehlig A. Pharmacol. Rev. 2018; 70: 384–411)	↓/↔/↑
		dithiazem	↓	isavuconazole	↔		
		verapamil	↓	ketoconazole	↓		
		propaphenone	↓	terbinafine	↓		
Sex • female • male	 ↓/↔ ↔	propranolol	↓	cymetidine	↑		
		triamterene	↓	lansoprazole	↔		
		warfarin	↓	omeprazole	↑		
Pregnancy	↓**	clozapine	↓	pantoprazole	↔		
OC	↓	fluvoxamine	↑	ondasetron	↓		
Smoking	↑	venlafaxine	↔	metoxalene	↑		
Obesity	↓/↔	alprazolam	↔	5-methoxypsoralen	↑		
Diabetes (types 1 and 2)	↔	olanapine	↓	furafylline	↓		
Hepatic diseases	↓***	triptamine derivatives	↓	theophylline	↓		
Coffee consumption	↑****	armodafinil	↔	St. John's wort	↔		
Grapefruit consumption	↓	Tacrine	↓	ginseng	↑?		
Vegetable-rich diet	↑/↓	zolpidem	↔	rifampicin	↓		
Alcohol consumption	↓	idrocilamide	↓	carbamazepine	↓		

OC — Oral contraception
*half-life extended up to 100 hours
**caffeine metabolism rate increased particularly in the third trimester (up to 18 hours). The rate of caffeine metabolism is normalized few weeks after the delivery
***half-life extended up to 160 hours
****regular consumption of 2–3 cups of coffee per day
*****excluding fleroxacin, ofloxacin, rufloxacin, temafloxacin, and trovafloxacin, which do not affect the rate of caffeine metabolism
↓ reduced rate; ↔ — no impact; ↑ — increased rate
(NOTE: Large amounts of coffee should not be drunk when using antiepileptic drugs, ketoprofen, methotrexate, teophylline, aminophylline, antituberculosis drugs, and moclobenide. Sporadic consumption or intake of larger quantities may reduce the reliability of the dexamethasone suppression test).

3 hours. In the liver, trigonelline is methylated by nicotinamide N-methyltransferase to N-methylnicotinamide and then oxidized to N-methyl-2-pyridone-5-carboxamide and N-methyl-4-pyridone-5-carboxamide. Like caffeine, trigonelline has a long half-life of about 5 hours [1, 12].

Thus, caffeine, trigonelline, and chlorogenic acid are characterized by high bioavailability. During moderate regular coffee consumption (2–3 cups of coffee/day), due to the long half-life, mainly caffeine and trigonelline, as well as chlorogenic acid metabolites, accumulate in the plasma [1].

Coffee also contains lipids, mainly represented by cafestol and kahweol. Both compounds are almost completely removed when drip-brewing coffee over a paper filter [16]. In addition, coffee contains theobromine and vitamin B_3 [17].

Moreover, coffee is also a source of fiber (6.5 mg/mL in espresso), mainly in the form of mannose and galactose polysaccharide chains [18].

Melanoidins are formed upon roasting, their levels in the espresso product reaching 1.75 to 3.65 mg/mL [19–20].

Other constituents of coffee include flavonoids, catechins, anthocyanins, ferulic acid, caffeic acid, p-cumaric acid, and tocopherols [9].

BIOLOGICAL EFFECTS OF SELECTED BIOLOGICALLY ACTIVE CONSTITUENTS OF COFFEE

As already mentioned, coffee is estimated to include more than 1000 chemical constituents [9]. Given that probably not all the chemicals present in coffee have been identified and that the mechanisms of action of most of the identified compounds have not been fully elucidated, the biological effects of coffee are now explained using the effects of the best-studied compounds, such as caffeine, chlorogenic acid, trigonelline, cafestol, and kahweol. The biological effects of these compounds are shown in Table 4. One should also remember that compounds formed in the course of caffeine metabolism are also biologically active. Paraxanthine stimulates lipolysis, theobromine exerts diuretic action, and theophylline relaxes the smooth muscles of blood vessels [9].

The impact of coffee on the oral and intestinal microbiota in humans is interesting from the clinical standpoint. In their cross-sectional study of 938 subjects, Peters et al. assessed the impact of coffee on the composition of oral microbiota. The researchers showed that consuming less coffee did not increase the variety of oral microorganisms (as opposed to tea consumption). Higher consumption of coffee (≥ 3 cups/day) was linked only to the higher abundance of *Granulicatella* and *Synergistetes* [29]. In their study of 147 healthy individuals, González et al. showed that regular consumption of 45 to 500 mL of coffee per day increased the *Bacteroides-Prevotella-Porphyromonas* counts. Changes in the composition of the gastrointestinal microbiota in individuals regularly consuming moderate amounts of coffee may be one of the mechanisms contributing to the clinical outcomes observed in these individuals [30].

THE EFFECT OF COFFEE ON ALL-CAUSE MORTALITY

In their meta-analysis of 39 studies covering almost 4 million individuals and more than 450000 deaths due to any or specific reasons, Kim et al. demonstrated that coffee consumption had an impact on the mortality rates. The greatest reduction in all-cause mortality rate, as high as 15%, was observed in individuals consuming 3–5 cups of coffee per day [31].

According to a conclusion from another meta-analysis, one extra cup of coffee per day was associated with mortality rates being lower by 4% [32].

The results of a multi-center study by Loftfield et al., covering a population of nearly 500000 people, are worth mentioning in this context. In the study, the effect of coffee consumption on all-cause mortality rates was assessed by considering gene polymorphisms of enzymes involved in caffeine metabolism (AHR, CYP1A2, CYP2A6, and POR). An inverse correlation between the amount of coffee consumed and the mortality rate was shown. Notably, however, the correlation was independent of the polymorphisms of genes resulting in faster or slower caffeine metabolism. In addition, the most significant effect (risk reduction of 16%) was observed in individuals consuming 6 to 7 cups of coffee per day [33].

In conclusion, moderate regular consumption of coffee seems to reduce the all-cause mortality rate independently of the gene polymorphisms of enzymes involved in caffeine metabolism.

Table 4. Mechanism of action and biological effects of the selected coffee ingredients. Based on [1, 2, 9, 11, 21–28].

Coffee constituent	Mechanism of action	Effects
Caffeine	• A_1R antagonism and reduced PDE stimulation: increased cellular cAMP levels	Systemic stimulation, increase of heart rate, bronchospasm, increased lipolysis in adipocytes, mesangial cell relaxation, reduced stimulation of macrophages, stimulation of gastric juice secretion and stimulation of glycogen degradation. Increased diuresis (reduced vasopressin secretion, increased glomerular filtration, reduced glomerulotubular auto-regulation, and reduced hepatorenal reflex), increased nitrogen oxide secretion → vasodilatation
	• $A_{2A}R$ antagonism: reduced cellular cAMP levels	Increased secretion dopamine and strengthened binding of dopamine to the D_2R receptor. This activity of caffeine contributes to neural stimulation. Stimulation of the respiratory center, relaxation of inferior esophageal sphincter. Reduced nitrogen oxide output → vasoconstriction
	• reduced stimulation of Na^+/HCO_3^- and Na^+/PO_4^{2-} co-transporters within the proximal tubules	Increased diuresis and natriuresis (antihypertensive effect) *(a likely mechanism)*
	• the bitter taste of caffeine stimulates TAS2R receptors interacting with gustducin and located within the mouth and stomach	Increased production of hydrochloric acid in the stomach
Chlorogenic Acid	• Reduced concentration of reactive oxygen species • Improved glucose metabolism • Stimulation of PPAR-α and increased adiponectin levels	Anti-inflammatory, anti-diabetic, anti-atherosclerotic, and nitrogen oxide generation-stimulating (antihypertensive) effects
Trigonelline	• Regulation of glucokinase and glucose 6-phosphatase stimulation and reduced plasma TNFα levels • Reduced absorption of glucose within the small intestine (effect on SGLT1) • Reduced activity of fatty acid synthase, increased activity of carnitine • increased superoxide dismuthase and catalase activity and increased intracellular glutathione levels • reduced stimulation of GABA receptors, stimulation of Neuronal growth, reduction in amyloid-mediated neuronal degradation	Anti-diabetic, anti-atherosclerotic, anti-oxidative, stimulatory, neuroprotective effects Antibacterial, antiviral, and antiparasitic effects of trigonelline should also be kept in mind
Kahweol and cafestol	• Kahweol is characterized by greater biological activity than cafestol • Reduced number of LDL-Rs on the surface of hepatocytes, increased plasma CETP and PLTP levels • Reduced expression of iNOS and COX2 and reduced secretion of proinflammatory cytokines • Regulation of the Bcl-2 and cyclin effects as well as the VEGFR-2 receptor pathway • Increased Nrf2 production • Stimulation of insulin secretion by pancreatic β cells and increased utilization of glucose in skeletal muscles • Reduced differentiation and stimulation of osteoclasts with simultaneous increase in differentiation of osteoblasts	Proatherosclerotic activity (in healthy individuals, cafestol was shown to increase serum triglyceride levels by 86%, while the combination of cafestol and kahweol resulted in an additional 7% increase. However, the negative effect of kahweol and cafestol on the lipid profile has been reduced with long-term consumption. Furthermore, using coffee filters reduces the levels of both compounds in the coffee, thus contributing to reduced adverse effects on the lipid profile Anti-inflammatory, anti-cancer, anti-diabetic, anti-osteoporostic activity

Bcl-2 — B-cell lymphoma 2; cAMP — cyclic adenosine monophosphate; CETP — cholesteryl ester transfer protein; COX-2 — cyclooxygenase-2; iNOS — inducible nitric oxide synthase; LDL-R — low-density lipoprotein receptor; Nrf2 — nuclear factor-erythroid 2 related factor 2; PDE — phosphodiestarase; PLTP — phospholipid transfer protein; PPAR-α — peroxisome proliferation-activated receptor α; SGLT1 — sodium-glucose linked transporter 1; TAS2R — taste receptor type 2; TNFα — tumor necrosis factor; VEGFR-2 — vascular endothelial growth factor receptor

THE EFFECT OF COFFEE ON THE RISK OF CERTAIN KIDNEY DISEASES

CHRONIC KIDNEY DISEASE

The effect of coffee on the risk of chronic kidney disease (CKD) was the subject of a meta-analysis carried out by Srithongkul and Ungprasert. The meta-analysis covered four cohort studies carried out in more than 25000 people. The risk of CKD among coffee drinkers was reduced by 13% [34]. Similar results were obtained in a randomized study by Kennedy et al. assessing the impact of coffee on kidney function. The authors showed that the consumption of an extra cup of coffee per day reduced the risk of grade 3–5 CKD and the risk of increased albuminuria by 16% and 19%, respectively. An extra cup of coffee per day was also correlated with a higher estimated glomerular filtration rate. The authors of the study concluded that coffee has a positive effect on kidney function [35]. In addition, a retrospective analysis of nearly 5000 patients with CKD showed that consumption of about

2 cups of coffee per day reduced the mortality rate by 26% in this group of patients [36]. A study of 63257 subjects aged 45–74, carried out by Lew et al., assessed the effect of coffee on the risk of end-stage renal disease (ESRD). During 16.8-years of follow-up, ESRD developed in 1143 subjects. Consumption of ≥ 2 cups of coffee per day was shown to reduce the risk of ESRD by 18%, the effect being more pronounced in males. Interestingly, consumption of black or green tea was not demonstrated to reduce the risk of ESRD [37].

The safety of coffee consumption by patients receiving hemodialysis treatment remains an important issue. In the study by Caetano et al., carried out in a group of 373 hemodialyzed patients, consumption of ≥ 3 cups of coffee per day was shown to increase the diastolic blood pressure, risk of hyperkalemia, and higher body weight between dialysis procedures. The study authors concluded that consumption of 1 to 2 cups of coffee per day could be considered safe in hemodialyzed patients [38].

Therefore, moderate regular consumption of coffee can be expected to present with nephroprotective effects and reduce the risk of disease progression and death in CKD patients. Consumption of 1 to 2 cups of coffee per day appears to be safe in hemodialyzed patients.

UROLITHIASIS

Coffee's impact on the risk of development of urolithiasis was assessed in a meta-analysis by Wang et al. of two cohort studies and four case-control studies. The authors showed that the risk of urolithiasis was significantly lower (by 30%) for high coffee consumption. Increasing the consumption of coffee by one cup a day reduced the risk of urolithiasis by 8.7% [39]. In a prospective study involving 217883 subjects, Ferraro et al. demonstrated that consumption of larger amounts of coffee reduced the risk of urolithiasis by 26–31% [40].

Thus, moderate regular consumption of coffee can reduce the risk of urolithiasis.

OVERACTIVE BLADDER

The influence of coffee on the frequency of urination in patients with overactive bladder (OAB) is interesting and important from the clinical point of view. The issue was studied by Lohsiriwat et al. in a group of 9 females and 3 males who regularly consume coffee in quantities of ≥ 3 cups a week. Subjects received a caffeine-containing drink and cystometry and uroflowmetry examinations were performed after 30 minutes. Caffeine at a dose of 4.5 mg/kg body weight was shown to enhance diuresis and reduce the urge threshold during the bladder filling phase. Thus, caffeine may increase the incidence of urgency as well as the frequency of urination. Individuals with OAB should avoid caffeine-containing products, including coffee [41].

RENAL CELL CARCINOMA AND BLADDER CARCINOMA

The impact of coffee on the risk of renal cell cancer was the subject of a meta-analysis by Wijarnpreecha et al. of 22 observational studies. A significant change in the risk of renal cell carcinoma was not observed in coffee-consuming subjects. Sex subgroup analysis revealed that the risk of renal cell carcinoma was not significantly increased in females while being reduced, albeit to a non-significant degree, in males. The authors of the meta-analysis suggest that coffee consumption is probably not a risk factor for the development of renal cell carcinoma [42].

The impact of coffee on the risk of urinary tract carcinoma remains a controversial issue. A meta-analysis of 40 studies conducted by Wu et al. showed that coffee consumption significantly increased the risk of developing bladder cancer [43]. Hashamian et al. obtained less pessimistic results in the study published in 2019. These researchers found that consumption of coffee (4 cups/day) versus not consumption was associated with a negligible increase in the risk of developing bladder cancer [44].

Thus, further studies are required on the effects of coffee on the risk of renal cell carcinoma and bladder carcinoma.

THE EFFECT OF COFFEE ON THE RISK OF CERTAIN NERVOUS SYSTEM DISEASES

HEADACHE

The relationship between coffee consumption and headache remains controversial. A review of the literature related to the treatment of tension-type or migraine headaches, as performed by Lipton et al., showed that the combination of an analgesic (paracetamol, ibuprofen, or acetylsalicylic acid) with caffeine at a dose of ≥ 100 mg increased the therapeutic efficacy of the drug [45]. However, chronic use of high doses of caffeine to reduce the intensity of migraine headaches increases the risk of addiction. The results indicate that chronic

consumption of > 450 mg caffeine per day may increase pre-existing headaches. The effect is mediated by the reactions of adenosine receptors. Chronic consumption of large amounts of caffeine results in upregulation of adenosine receptors leading to secondary hypersensitivity to adenosine. This phenomenon partly explains the development of physical dependence symptoms manifesting as overactivation of adenosine receptors in the event of the supply of caffeine being reduced or interrupted. This results in dilatation of blood vessels and a significant increase in cerebral blood flow, which is clinically manifested by headaches [46]. These findings were confirmed by Couturier et al. who observed that migraine episodes are more frequent on Saturdays and Sundays as compared to other days of the week due to the coffee consumption being lower on weekends [47]. Alstadhaug et al. assessed the impact of coffee on headaches in a literature review published in 2019. Chronic consumption of coffee was found to increase the intensity of migraine, while sporadic consumption may bring about therapeutic effects. Discontinuation of coffee consumption may intensify migraine headaches [48].

A study by Shirlow et al. carried out in a group of 4558 Australian subjects to assess the impact of about 4–5 cups of coffee per day on the risk of migraine is worth mentioning in this context. The risk of headache was found to be increased in coffee consuming subjects by a factor of 1.3 [49].

Therefore, coffee's impact on headaches remains ambiguous and further clinical studies are needed to improve knowledge in this area.

DEMENTIA AND ALZHEIMER'S DISEASE

A meta-analysis of prospective studies carried out by Liu et al. assessed the effect of coffee on the risk of cognitive impairment. Eleven prospective studies covering a population of 29155 patients were included in the meta-analysis. The study showed that high consumption of coffee was not associated with the risk of deterioration in cognitive functions. In addition, one subgroup showed an inverse relationship between high coffee consumption and Alzheimer's disease [50]. Larsson et al. performed a meta-analysis of the dose-response relationship to summarize the available data on coffee consumption and the risk of dementia and Alzheimer's disease. Eight prospective studies covering more than 7000 cases of dementia identified in nearly 330000 individuals were identified. The meta-analysis of these studies revealed coffee consumption reduced the risk of dementia to a small degree. The greatest reduction in the risk of dementia, as high as 10%, was observed in individuals consuming 2 cups of coffee per day [51].

An analysis of five studies on Alzheimer's disease revealed no link between coffee consumption and the reduced risk of Alzheimer's disease [51].

Different results were obtained in the CAIDE (Cardiovascular Risk Factors, Aging, and Dementia) study. It showed that consumption of 3-5 cups of coffee/day by middle-aged people was associated with a significant reduction in the risk of dementia and Alzheimer's disease later in life [52].

Interestingly, another study demonstrated a positive effect of regular consumption of espresso on improved cognitive function in AIDS (acquired immunodeficiency syndrome) patients who often suffer from objective deterioration in cognitive functions [53].

Thus, moderate regular consumption of coffee can reduce the risk of dementia. However, further studies are needed to assess the impact of coffee on the risk of Alzheimer's disease.

PARKINSON'S DISEASE

The relationship between the consumption of coffee and the risk of Parkinson's disease is well documented. A meta-analysis carried out by Qi et al. in a population of 901764 individuals consuming coffee revealed a non-linear correlation between coffee consumption and the risk of Parkinson's disease. The beneficial influence of coffee was most pronounced for average consumption of 4 to 7 cups per day (29% risk reduction). The observed relationship was more pronounced among male than female subjects; it was also weaker in patients from the United States as compared to those from Europe or Asia [54].

A meta-analysis of 13 studies carried out by Hong et al. assessed the effects of coffee consumption on the risk of *de novo* Parkinson's disease (four studies) and the progression of Parkinson's disease (nine studies). Healthy regular coffee drinkers were shown to have a significantly lower risk of Parkinson's disease compared to non-drinkers. Coffee-drinking Parkinson's disease patients were found to be at a significantly lower risk of progression compared to non-drinking patients [55].

Therefore moderate regular consumption of coffee seems to reduce the risk and progression of Parkinson's disease.

SLEEP DISORDERS

A systematic review of both observational and randomized controlled studies carried out by Clark et al. assessed the effects of caffeine consumption on sleep. Caffeine has been shown to increase the time to fall asleep, reduce the overall sleep time and effectiveness, as well as subjective sleep quality. In addition, caffeine was shown to have a bigger impact on sleep in older adults as compared to younger adults. Clear interindividual differences were also observed in young people, and genetic studies confirmed the existence of functional polymorphisms of genes involved in neurotransmission and metabolism of adenosine [56].

Takabayashi et al. analyzed the effects of coffee on sleep-related breathing disorders as estimated by desaturiation index. One thousand one hundred and twenty-six males aged 22–59 were included in the study. An inverse relationship between coffee consumption and desaturation has been found, indicating a lower risk of respiratory distress during sleep in coffee drinkers [57].

Thus, while coffee may have an adverse effect on sleep quality, particularly when consumed in the evening, it may simultaneously reduce sleep-related breathing disorders.

DEPRESSION

Given the scale of the phenomenon of depression, the impact of coffee on the risk of this disorder appears to be an interesting issue. A meta-analysis of 12 observational studies was carried out by Grosso et al. in a population of 346913 individuals, including 8146 depression patients, to assess the effect of coffee on the risk of depression. Individuals consuming larger quantities of coffee were shown to present with the risk of depression that is lower by 24% than individuals who consumed lower quantities. The relationship had a J-curve shape and was most pronounced at daily consumption of about 400 mL (2 to 3 cups/day) [58]. The same result (24% reduction) was obtained for the effect of coffee consumption on the risk of depression by Wang et al. in their meta-analysis of 11 observational studies. Moreover, the researchers concluded that the risk of depression was reduced by 8% for coffee consumption being increased by each subsequent cup per day [59].

Thus, the results of two meta-analyses show that moderate regular consumption of coffee can reduce the risk of depression.

BRAIN CANCER

A meta-analysis by Song et al. investigated the effects of coffee consumption on the risk of brain cancer in 11 studies. A statistically significant reduction in the risk of brain cancer by 21% was observed in coffee drinkers (average of 3 to 4 cups per day). The effect was most pronounced in Asian populations [60]. However, no impact of coffee consumption on the risk of glioma was demonstrated in the prospective study carried out by Cote et al. in more than 237000 subjects [61].

Thus, the influence of coffee on the risk of brain cancer remains unclear and requires further research.

THE EFFECT OF COFFEE ON THE RISK OF SELECTED GASTROINTESTINAL DISEASES

CARIES, ORAL CANCER, AND PHARYNGEAL CANCER

An interesting study examined the antibacterial properties of coffee in saliva samples collected from 120 healthy young individuals. Coffee containing no additives (black coffee without sugar) was shown to present with the highest anti-microbial activity against *Streptococcus mutas* (the main etiological factor of caries along with *Lactobacillus acidophilus*). The anti-caries properties of black coffee were reduced after the addition of milk and sugar [62]. The anti-caries properties of coffee were also demonstrated in the study by Namboodiripad and Kori. The study was conducted in 2000 individuals, with half of the population drinking coffee. Black coffee was shown to have an anti-caries effect, which was completely canceled by additives such as sugar and milk [63].

The issue of the impact of coffee on the risk of oral and pharyngeal cancer was the subject of a meta-analysis of 17 studies, as conducted by Miranda et al. Higher consumption of coffee was shown to be linked to a 31% reduction in the risk of oral cancer and pharyngeal cancer as compared to lower consumption. Separate analyses of the risks of oral cancer and pharyngeal cancer showed risk reductions of 18% and 28%, respectively [64].

Therefore, moderate regular consumption of coffee may reduce the risk of caries, oral cancer, and pharyngeal cancer.

GASTROESOPHAGEAL REFLUX DISEASE AND ESOPHAGEAL CANCER

In their meta-analysis of 15 clinical and case-control studies, Kim et al. assessed the impact of coffee on the risk of gastroesophageal reflux disease (GERD). No significant impact of coffee consumption on the incidence of GERD was observed [65].

The influence of coffee consumption on the risk of esophageal cancer was assessed in a meta-analysis of 24 studies by Zheng et al. High coffee consumption was shown to slightly reduce the risk of esophageal cancer as compared to low consumption [66].

Therefore, moderate regular consumption of coffee is unlikely to affect the risk of GERD while possibly slightly reducing the risk of esophageal cancer.

GASTRODUODENAL ULCER DISEASE AND GASTRIC CANCER

A meta-analysis carried out by Shimamoto et al. assessed the effects of coffee on the risk of gastroduodenal ulcer disease. Coffee consumption did not significantly increase the risk of gastroduodenal ulcer disease [67].

A meta-analysis of 13 prospective cohort studies carried out by Li et al., assessed the impact of coffee on the risk of gastric cancer. Compared to the lowest consumption group, the risk of gastric cancer in individuals who drank coffee more often was increased in a non-significant manner. The dose-response analysis showed that the risk of gastric cancer was the lowest in people consuming 1 to 2 cups of coffee per day [68].

Therefore, moderate regular consumption of coffee is unlikely to increase the risk of gastroduodenal ulcer disease and gastric cancer.

FATTY LIVER DISEASE, HEPATIC CIRRHOSIS, AND LIVER CANCER

In a meta-analysis of five studies, as carried out by Wijarnpreecha et al., the effect of coffee consumption (≥ 3 cups/day) on the risk of *de novo* non-alcoholic fatty liver disease (NAFLD) and the risk of liver fibrosis in NAFLD patients were assessed. The risk of NAFLD in coffee drinkers was significantly lower than in non-drinkers. A significantly lower risk of liver fibrosis was also observed in coffee-drinking NAFLD patients [69].

The impact of coffee on the risk of liver cirrhosis was assessed by Kennedy et al. in their meta-analysis of five cohort studies and four case-control studies carried out in 432133 subjects, including 1990 hepatic cirrhosis patients. The risk of cirrhosis was shown to decrease gradually with the increase in the number of cups consumed per day. Moreover, the risk of death due to hepatic cirrhosis was also reduced [70].

The influence of coffee on the risk of liver cancer was assessed by Yu et al. based on their meta-analysis of 20 prospective cohort studies. The risk of liver cancer in regular coffee drinkers was shown to be significantly reduced by 46% compared to occasional drinkers. Furthermore, an inverse linear correlation was found between the number of cups of coffee per day and the risk of liver cancer [71]. Similar results were obtained by Godos et al. in their meta-analysis of 13 studies [72]. As shown by another meta-analysis as carried out by Kennedy et al., the beneficial effect of coffee drinking on the risk of liver cancer did not change significantly at different stages of liver disease and in the presence of significant alcohol consumption, high body weight index, type 2 diabetes, smoking, or hepatitis B and/or C infections [73].

Thus, moderate regular consumption of coffee can reduce the risk of NAFLD, cirrhosis, and cirrhosis-related death, as well as the risk of liver cancer.

CHOLELITHIASIS AND BILE DUCT CANCER

The impact of coffee consumption on the risk of cholelithiasis is another important issue. This issue was addressed in a meta-analysis by Zhang et al. of one case-controlled and five prospective cohorts in a population of 227749 subjects, including 11477 cholelithiasis patients. Dose-dependent reduction in the risk of cholelithiasis was observed in this meta-analysis [74]. The case-control study showed no significant relationship between coffee consumption and the risk of cholelithiasis [74].

The impact of coffee consumption on the risk of bile duct cancer was the subject of a meta-analysis of five studies, as conducted by Godos et al. No significant effect of coffee consumption on the risk of bile duct cancer was observed [72].

Therefore, moderate regular consumption of coffee can reduce the risk of cholelithiasis while not affecting the risk of bile duct cancer.

PANCREATIC CANCER

In their meta-analysis of 13 cohort studies involving almost 960000 people, including

3800 pancreatic cancer patients, Li et al. observed a observed a no significant increase in the risk of pancreatic cancer in individuals consuming large quantities of coffee as compared to those who consumed lower quantities. The risk of pancreatic cancer was increased by about 6% per each coffee cup per day [75]. However, these results were not confirmed by the prospective study by Zhou et al. The study was conducted in 310000 females who drank coffee and never smoked cigarettes. Drinking as much as ≥ 5 cups of coffee per day was shown to have no significant impact on increasing the risk of pancreatic cancer. Furthermore, a meta-analysis of the results of this study along with the results of three other prospective studies also failed to demonstrate that coffee consumption (≥ 4 cups/day) increases the risk of pancreatic cancer in non-smokers [76].

Therefore, further studies are needed to assess the impact of coffee on the risk of pancreatic cancer.

COLON AND COLORECTAL CANCER

Sartini et al. carried out a meta-analysis of 23 prospective studies involving more than 3 million subjects. Coffee consumption was found to have no effect on the risk of colorectal cancer while it reduced the risk of colon cancer by 9% [77]. Another meta-analysis of nine studies conducted by Bae showed that the consumption of 1 to 3 cups of coffee per day no significantly reduced the risk of colon cancer in Asian subjects [78]. Similar results were obtained by Micek et al. in their meta-analysis of 17 studies which showed that coffee consumption has no effect on the risk of colon or colorectal cancer [79].

Therefore, moderate regular consumption of coffee is unlikely to affect the risk of colon and colorectal cancer.

THE EFFECT OF COFFEE ON THE RISK OF SELECTED CARDIOVASCULAR DISEASES

A prospective study carried out by Zhou and Hyppönen in a population of nearly 350000 subjects assessed the impact of coffee consumption on cardiovascular risk, with *CYP1A2* gene polymorphism being taken into account. Compared to consumption of 1 to 2 cups of coffee per day, no consumption, or consumption > 6 cups of coffee per day were associated with the increased risk of cardiovascular diseases by 11% and 7%, respectively. No effects of *CYP1A2* polymorphism were identified for these correlations. As shown by the results of this study, moderate regular consumption of coffee seems appears to be safe for the cardiovascular system [80].

ARTERIAL HYPERTENSION

The impact of coffee consumption on the risk and control of arterial hypertension remains a very interesting and controversial issue.

A meta-analysis of four studies as conducted by D'Elia et al. assessed the influence of coffee on the risk of arterial hypertension (AH) in a population of nearly 200000 subjects. Consumption of 1 to 2 cups of coffee per day was shown to have no impact on the risk of AH. What is more important, consumption of > 3 cups of coffee per day reduced the risk of AH by 3%, while consumption of > 6–7 reduced this risk by 14% [81]. These results were confirmed in the meta-analysis carried out by Miranda et al. who showed that the consumption of 1 to 3 cups of coffee per day reduced the risk of AH by 18%. Consumption of > 3 cups of coffee per day was shown to have no impact on the risk of AH. Notably, the authors of the meta-analysis concluded that the beneficial effect of moderate regular consumption of coffee applied only to individuals who had never smoked cigarettes [82]. In their review carried out using Mendelian randomization, van Oort et al. did not demonstrate any effect of coffee consumption on the risk of AH [83].

The impact of coffee consumption on the control of hypertension in AH also remains an important issue. This was addressed in a meta-analysis by Meas et al. who concluded that occasional consumption of about 2 cups of coffee increased the average systolic and diastolic blood pressure values by 8.1 and 5.7 mmHg, respectively. The increase in the blood pressure was observed in the first hour after consumption and was maintained for approximately 3 hours. No increase in blood pressure was observed in individuals who consumed coffee regularly and in moderate amounts. Moreover, no link was observed between moderate coffee consumption and a higher risk of cardiovascular disease in AH patients [84].

Therefore, moderate regular coffee consumption does not influence or may potentially reduce the risk of AH. This beneficial effect is significantly reduced for smokers/ex-smokers. As opposed to moderate regular consumption, occasional consumption of coffee by AH patients may lead to reduced effectiveness of antihypertensive treatment.

CARDIAC ARRHYTHMIAS

Another interesting aspect consists in the impact of coffee consumption on cardiac arrhythmias. In their examination of 57053 participants of the Danish Diet, Cancer and Health Study, Mostofsky et al. assessed the impact of coffee consumption on the risk of atrial fibrillation. Altogether, 3415 atrial fibrillation episodes were recorded in the follow-up period of 13.5 years. Coffee consumption reduced the risk of atrial fibrillation in comparison to the non-drinker subpopulation [85].

These results were partly confirmed by a prospective study involving 18960 male subjects as carried out by Bodar et al. Two thousand and ninety-eight new cases of atrial fibrillation were recorded over the follow-up period averaging at 9 years. Consumption of 2 to 3 cups of coffee per day was shown to cause the greatest reduction in the risk of atrial fibrillation by as much as 15% [86].

In their meta-analysis of seven studies, Zuchinali et al. examined the impact of caffeine on the risk of premature ventricular contractions. No increase in the risk of premature ventricular contractions was observed within 24 hours after caffeine consumption [87].

In conclusion, moderate regular coffee consumption is unlikely to increase the risk of cardiac arrhythmias.

HEART FAILURE

The impact of coffee consumption on the risk of heart failure was the subject of a meta-analysis by Krittanavong et al. of eight prospective studies in the overall population of nearly 97000 individuals, including 9355 heart failure patients. Coffee consumption classified within the top category (≥ 5 cups/day) was not shown to be associated with the risk of heart failure [88]. In an earlier meta-analysis of five prospective studies, as carried out by Mostofsky et al., the greatest reduction in the risk of heart failure, namely a reduction by 11%, was observed in people consuming 3 to 4 cups of coffee per day [89].

Thus, moderate regular consumption of coffee can reduce the risk of heart failure.

ISCHEMIC HEART DISEASE AND MYOCARDIAL INFARCTION

Another issue of importance from the clinical point of view is the influence of coffee consumption on the risk of ischemic heart disease and myocardial infarction. A meta-analysis of 21 prospective studies conducted by Wu et al. revealed that consumption of 3 to 4 cups of coffee per day reduced the risk of ischemic heart disease in women by 18%, while the impact in men was not significant [90]. Less optimistic results were provided by a meta-analysis of six cohort studies and 11 case-control studies as carried out by Mo et al. Consumption of more than 3 cups of coffee per day was found to increase the risk of myocardial infarction [91]. This positive correlation between coffee consumption and the risk of myocardial infarction was observed only in men, and not in women, which is consistent with the results obtained by Wu et al. [90].

STROKE

The impact of coffee consumption on the risk of stroke was assessed by Qian et al. in the meta-analysis of genome-wide association studies (GWAS) encompassing a population of more than 90000 coffee drinkers. No causal link was demonstrated between the consumption of both small and larger amounts of coffee and the risk of stroke [92]. In a meta-analysis of 21 studies involving more than 2.4 million people, Shao et al. found that high consumption of coffee resulted in a 13% reduction in the risk of stroke as compared to low consumption. In addition, the relationship between coffee consumption and the risk of stroke was found to follow a U-shaped curve. The greatest reduction in stroke incidence rate, as high as 21%, was observed in individuals consuming 3–4 cups of coffee per day [93].

Thus, moderate regular consumption of coffee can reduce the risk of stroke.

THE EFFECT OF COFFEE ON THE RISK OF SELECTED METABOLIC DISEASES

TYPE 2 DIABETES MELLITUS AND OBESITY

The influence of coffee on the risk of type 2 diabetes seems to be an important issue. The issue was assessed in a meta-analysis of 30 prospective studies, as conducted by Carlström and Larsson, and comprising more than one million subjects, including 53000 cases of type 2 diabetes mellitus. Consumption of 5 cups of coffee per day was found to reduce the risk of type 2 diabetes by 29% (the risk of type 2 diabetes was reduced by 6% for each cup consumed daily). Interestingly, similar results were obtained for both normal and decaffeinated coffee [94]. The impact of coffee consumption on the risk of type 2 diabetes mellitus was also assessed in the study by Kim

et al. in more than 71000 subjects. An inverse correlation between coffee consumption and the risk of type 2 diabetes was observed [95]. However, no further reduction in the risk of type 2 diabetes was observed in subjects consuming ≥ 3 cups of coffee per day. In addition, the impact of gene polymorphism on these relationship was analyzed. No significant interactions were observed between the five single nucleotide polymorphisms of interest (CDKA1 rs7756992, CDKN2A/B rs10811661, KCNJ11 rs5215, KCNQ1 rs163184, and PEPD rs3786897) and the correlation between coffee consumption and the risk of type 2 diabetes [95]. Importantly, a meta-analysis of 27 randomized trials carried out by Kondo et al. failed to demonstrate that coffee consumption reduces fasting plasma glucose levels [96].

Therefore, moderate regular coffee consumption can reduce the risk of type 2 diabetes mellitus although the detailed mechanism for this beneficial effect requires further research.

The impact of coffee on the risk of obesity was the subject of a meta-analysis of 12 observational studies carried out by Lee et al. Coffee consumption was shown to potentially reduce the risk of obesity, particularly among male subjects [97].

LIPID METABOLISM DISORDERS

Serum lipid levels are adversely affected by coffee consumption. In their meta-analysis of 12 studies covering more than one thousand subjects, Cai et al. assessed the impact of coffee consumption on serum levels of cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides. Drinking coffee for 45 days was found to increase serum levels of cholesterol, LDL cholesterol, and triglycerides by 8.1 mg/dL, 5.4 mg/dL, and 12.6 mg/dL, respectively. Increased serum cholesterol levels were higher in non-filtered coffee drinkers. There was no indication of the effect of coffee consumption on serum HDL cholesterol levels [98]. The authors of the meta-analysis suggested that these adverse effects could be reduced by brewing methods involving the use of a paper filter (reducing the concentration of kahweol and cafestol in consumed coffee) [98].

OSTEOPOROSIS

The impact of coffee consumption on the risk of osteoporosis has been addressed in a study by Hallström et al. in a population of more than 61000 women. Coffee consumption was not shown to be responsible for higher rates of bone fractures. Consumption of large quantities of coffee (≥ 4 cups/day) was associated with a 2–4% reduction in bone mineral density as compared to low consumption (< 1 cup/day), with the risk of osteoporosis increasing in a statistically insignificant manner [99]. Thus, consumption of large quantities of coffee was demonstrated to involve a slight reduction in bone density, which did not translate into an increased risk of bone fractures and osteoporosis [99].

The above results were confirmed in the meta-analysis carried out by Li et al. Their analysis of 10 prospective cohort studies showed that compared to individuals who did not drink coffee or consumed only small quantities of it, the risk of hip fractures was increased, albeit not significantly, in those who consumed the largest quantities of the beverage [100]. Therefore, evidence from prospective cohort studies failed to demonstrate any statistically significant relationship between coffee consumption and the risk of hip fracture [100]. Machado-Fragua et al. assessed the impact of moderate regular coffee consumption on the risk of falls and injuries in persons ≥ 60 years of age. The study was conducted in 2964 subjects from the *Seniors-ENRICHA* (*Study on Nutrition and Cardiovascular Risk in Spain*) cohort and 8999 subjects from the British *Biobank* cohort. Moderate regular coffee consumption was found to be associated with the risk of falling increasing by 30%. In addition, coffee drinkers also presented a reducing trend of injury during falls [101].

INFLAMMATION

The impact of coffee consumption on the blood C-reactive protein levels was assessed in a meta-analysis of 11 studies as conducted by Moua et al. and covering more than 60000 individuals. Coffee consumption was not found to be related to the concentration of C-reactive protein in the blood [102].

CONSUMPTION OF COFFEE DURING PREGNANCY AND LACTATION

The safety of coffee consumption during pregnancy is an extremely important clinical issue. According to the recommendations of the European Food Safety Authority, the safe daily dose of caffeine is 200 to 300 mg, which corresponds to 2 to 3 cups of coffee per day. The effects of coffee consumption on the risk of spontaneous miscarriage were investigated

in a meta-analysis of 27 studies as conducted by Lyngsø et al. The intake of 100 or 300 mg of caffeine per day (1-2 and 3 cups of coffee/day) was associated with the markedly increased risk of spontaneous abortion by 8% and 37%, respectively. This risk increased with each subsequent cup of coffee per day [103]. One of the reasons behind this adverse effect may consist in the rate of caffeine metabolism being reduced during pregnancy (Tab. 3) and the fact that neither the fetus nor the placenta is capable of caffeine metabolism leading to its accumulation [11]. In a study published by Kawanishi et al. assessed the impact of coffee consumption on the risk of AH-related disorders during pregnancy. The study population consisted of 85533 pregnant women. AH-related disorders were observed in 2222 subjects. A weak link was found between coffee consumption and the risk of AH-related disorders during pregnancy [104]. Therefore, caution should be exercised, and the quantity of coffee consumed in pregnancy should be limited to the greatest possible extent.

Upon breastfeeding, about 1% of maternal caffeine is consumed by the infant. Consumption of moderate quantities of coffee, i.e. 2 to 3 cups per day, seems safe for both mother and breastfed infant [105].

LIMITATIONS OF COFFEE-RELATED RESEARCH

The most important limitation of all the above studies is the lack of information on the exact nature of the coffee products used by the participants (type, blend, country of origin, bean processing method, preparation method, additives — milk and/or sugar, as well as the differences in the definitions of a cup of coffee). As shown in the first part of this article, the biological properties of coffee are influenced by numerous factors. Another limitation consists in the impact of the subjects' diet, as well as gene polymorphisms of numerous enzymes involved in the metabolism of the chemical constituents of coffee (these polymorphisms may differ between participants in the cited studies), which may cause different sensitivity of the subjects to coffee and thus the occurrence of various biological effects after its consumption. Recently, epigenetic mechanisms are pointed out to play an important role, potentially explaining different effects of coffee consumption observed in different studies (coffee consumption is linked to different levels of DNA methylation in numerous CpG sites) [106]. In addition, most meta-analyses are based on the results of observational studies making the assessment of cause-and-effect relationships impossible. As a result of the above, our ability to interpret and compare the results is limited. Furthermore, no difference in biological effects was observed in some studies between caffeine-containing coffee and decaffeinated coffee, which indicates the important role of other compounds. Perhaps, various concentrations of biologically active compounds other than caffeine might also explain the differences observed in some studies and thus limit the interpretation of results. Appropriate interventional studies would facilitate a more accurate determination of the effects of coffee on the human body.

CONCLUSIONS AND RECOMMENDATIONS REGARDING COFFEE CONSUMPTION

Coffee contains numerous biologically active substances responsible for a wide range of effects. Moderate regular consumption of coffee, i.e. 2 to 3 cups per day, is safe and can have a beneficial effect on human health [107]. Therefore, coffee has found its place in the Pyramid of Healthy Diet and Physical Activity, a collection of health promotion recommendations from the National Food and Nutrition Institute in Warsaw. Individuals who want to drink coffee should do so regularly and in moderate quantities. It is worth mentioning here that some publications appear to indicate potential benefits of moderate regular consumption of coffee in both prevention and treatment of COVID-19 (*Coronavirus Disease 2019*) [108]. It is recommended to limit the consumption of coffee during pregnancy. In 2015, the US Food and Drug Administration issued their recommendations indicating that adults should not consume more than 2 cups of coffee (2 x 125 mL) at one time and no more than 4 cups (4 x 125 mL) per day [11]. Due to the limited information on the safety of caffeine for children and adolescents, coffee consumption is not recommended in these age groups [109–110].

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CONFLICT OF INTEREST

None to declared.

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