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REVIEW

Coffee consumption, obesity and type 2 diabetes: a mini-review

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Abstract
Purpose The effects of regular coffee intake on weight gain and development of diabetes are reviewed. The pathophysiology of obesity and type 2 diabetes as well as the necessity of preventive options based on the increasing prevalence of these two disorders worldwide is briefly discussed. The relationship between weight gain and development of diabetes is also presented. The two major constituents in the brewed coffee, chlorogenic acids and caffeine, are responsible for many of the beneficial effects suggested by numerous epidemiological studies of coffee consumption and the development of diabetes.
Methods A wide search of various databases, such as PubMed and Google Scholar, preceded the writing of this manuscript, focusing on key words that are part of the title. It was selected mainly review papers from in vivo, ex vivo, in vitro experimental studies in animals and human tissues as well as wide population-based epidemiological studies in the last 10 years.
Conclusion As of today, there are mounting evidences of the reduced risk of developing type 2 diabetes by regular coffee drinkers of 3–4 cups a day. The effects are likely due to the presence of chlorogenic acids and caffeine, the two constituents of coffee in higher concentration after the roasting process.

Keywords Coffee · Obesity · Diabetes · Chlorogenic acid · Caffeine

Introduction

This abbreviated review on the effects of coffee on weight gain and development of type 2 diabetes mellitus (T2DM) is a collection of the latest data of experimental studies in vitro and in vivo, as well as large epidemiological studies during the last decade. It starts by discussing the importance of those two pathological disorders, obesity and diabetes, and its growing prevalence in the worldwide population. It proceeds with a brief review on the pathophysiological mechanisms that link those two disorders and provides an overview of the necessary conditions for the development and diagnosis of T2DM. The main body of the review is summarized in Fig. 6 where the possible mechanisms of coffee preventive effects on weight gain and T2DM are presented. The mechanisms are displayed according to their relationship with metabolism of carbohydrates and lipids. Other mechanisms that are not specifically affecting one of those metabolisms, but involving major pathways, such as activation of AMPK, hormonal regulation and the role of sex-hormone-binding globulin, are also presented. It closes with a recent mechanism possibly involving the contents of chlorogenic acids in the coffee. It is based on the fact that chlorogenic acids increase the levels of a major adipocytokine secreted by adipose tissue. These elevated plasma levels are consistently inversely related to the occurrence of diseases such as diabetes, metabolic syndrome and cardiovascular disorders.

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Obesity and type 2 diabetes

Obesity may be defined as accumulation of fat to an extent that the health of the individual is impaired [1]. Truncal obesity, which is fat mainly distributed around abdomen and viscera, is particularly correlated with the prevalence of diabetes and cardiovascular diseases [1–6]. Diabesity [3, 7–9]—the term used to describe the coexistence of T2DM and obesity—is responsible for more than 90 % of the world's 382 million people with T2DM, and this number is set to rise beyond 592 million in less than 25 years. Yet, with 175 million cases currently undiagnosed, a vast amount of people with diabetes is progressing unaware toward complications. Moreover, with 80 % of the total number affected living in low- and middle-income countries, the epidemic is gathering pace at alarming rates (Figs. 1, 2) [10, 11]. Still, according to International Diabetes Federation (IDF) Atlas 6th edition, type 2 diabetes is the fourth to fifth leading cause of death in most high-income countries, with almost 50 % of the people with diabetes ranging from 40 to 59 years of age. Spending on diabetes accounts for 10.8 % of total health expenditure worldwide and caused 5.1 million deaths in 2013. This means that every 6 s a person dies from diabetes. In addition, more than 21 million live births were affected by diabetes during pregnancy in 2013. Another important source of information on the prevalence of diabetes in USA is The Behavioral Risk Factor Surveillance System (BRFSS), the largest ongoing telephone health survey in the world. It is a state-based system of health surveys established by the Centers for Disease Control and Prevention (CDC) in 1984. The most recent report shows the age-adjusted prevalence of obesity and the number of diagnosed diabetes among adults in USA with data from 2013 (Fig. 3) [12]. Therefore, we can conclude that diabetes is the one most common non-communicable disease, and it is epidemic in many economically developing and newly industrialized countries.

There are four main tools to measure obesity: (1) body mass index (BMI), (2) waist-to-hip ratio (WHR)—showing a more precise correlation with the prevalence of diabetes (Tables 1, 2 [1]), (3) measurement of the waist circumference (WC) and (4) waist-to-height ratio (WHtR). A waist circumference of over 94 cm in men (37 in.) and 80 cm in women (31.5 in.) predicts a BMI greater than 25 with 96 % of specificity [13]. A systematic review and meta-analysis of studies involving more than 300,000 adults in several ethnic groups shows the superiority of WHtR over WC and BMI for distinguishing adults with hypertension, type 2 diabetes, dyslipidemia, metabolic syndrome and general cardiovascular outcomes [14, 15]. The distribution of fat is itself a critical determinant of insulin sensitivity. A more peripheral distribution of fat (subcutaneous tissue deposit) found in lean individuals is considered a normal adiposity and a physiological fat storage.

Adipocytes regulate fat mass, nutrient and energy homeostasis by releasing fatty acids in the circulation through the breakdown of triglycerides in exchange of glucose, when the latter is limited [3, 15]. In the presence of insulin resistance, the extra-energy is not channeled into insulin-sensitive subcutaneous adipose tissue, but rather into

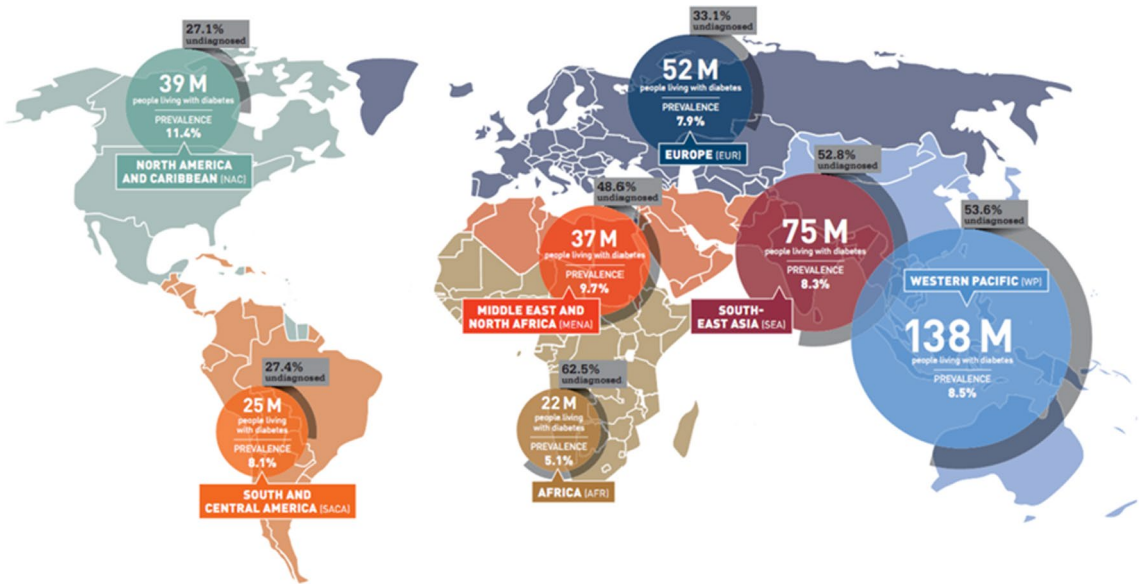

Fig. 1 Estimated number of people with diabetes worldwide and per region in 2013. After International Diabetes Federation. IDF Diabetes Atlas, 6th edn. Brussels, Belgium: International Diabetes Federation, 2013. http://www.idf.org/diabetesatlas

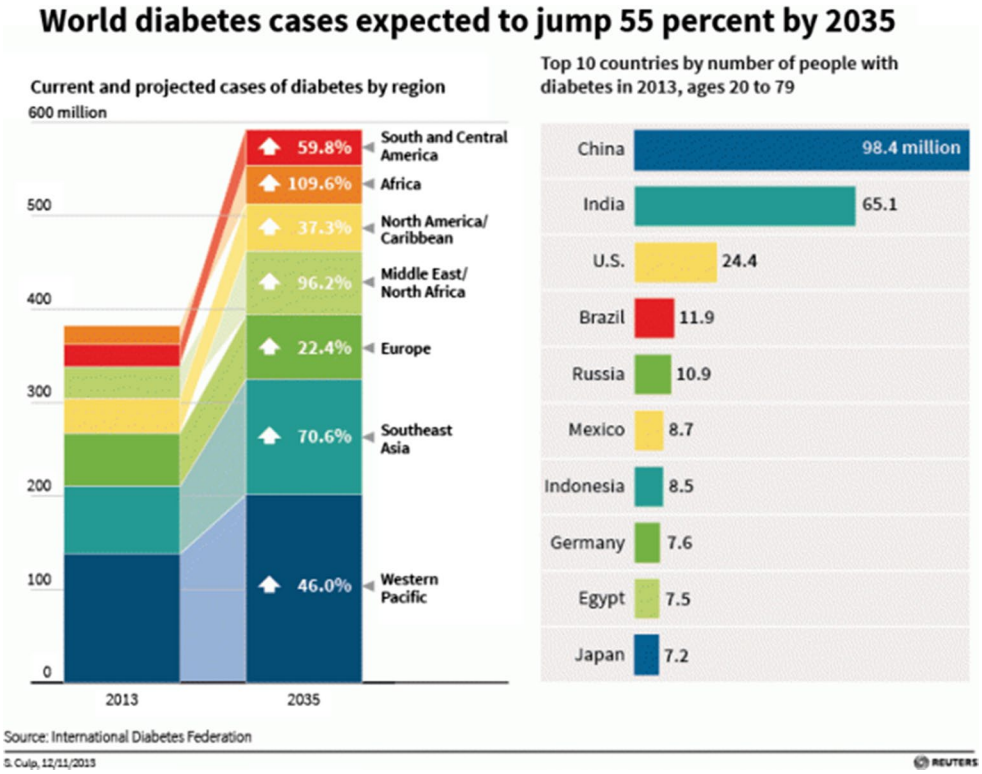

Fig. 2 World diabetes expected cases by the year of 2035. After International Diabetes Federation. IDF Diabetes Atlas, 6th edn. Brussels, Belgium: International Diabetes Federation, 2013. http://www.idf.org/diabetesatlas

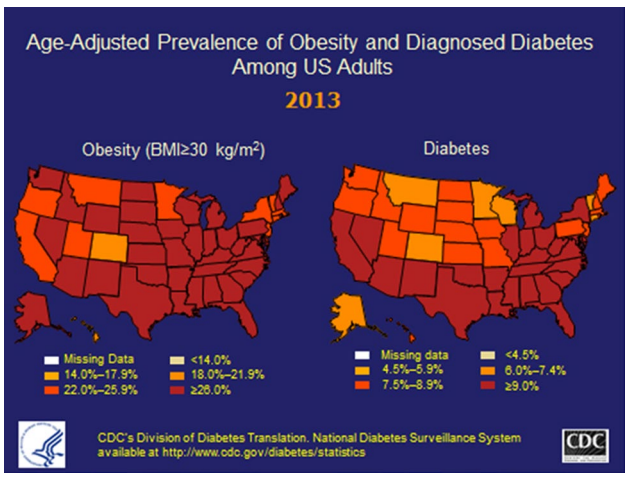

Fig. 3 Age adjusted prevalence of obesity and diagnosed diabetes among US adults. After CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at http://www.cdc.gov/diabetes/statistics. Maps of trends in diabetes and obesity. Power Point Slides on Diabetes

undesirable sites such as the liver, the heart and the skeletal muscle as a visceral adipose tissue, known as fat ectopic deposition [3, 15]. The consequences of this distorted distribution of fat are: visceral obesity, insulin resistance, atherogenic dyslipidemia and a prothrombotic inflammatory profile—the defining features of what is known as metabolic syndrome [3–5, 15].

Figure 4 shows the mechanism of how fat induces insulin resistance. Hypertrophied intra-abdominal adipocytes are characterized by a hyperlipolytic state that is resistant to the antilipolytic effect of insulin [3, 16]. Non-esterified fatty acids (NEFAs) are released in the circulation as a product of lipolysis. The increased flux to the liver and muscle will promote lipotoxicity with the corresponding consequences of altered insulin actions leading to insulin resistance and deterioration of glucose homeostasis.

Obesity and type 2 diabetes are both linked to insulin resistance, but for obesity and insulin resistance to be associated with type 2 diabetes another factor needs to be present—beta-cells dysfunction. In other words, beta-cells must be unable to fully compensate for decreased insulin sensitivity [2, 5].

Insulin resistance is manifested by hyperinsulinemia, increased glucose production in the liver and decreased glucose disposal. In the adipocytes, insulin triggers an increased release of hormone-sensitive lipase (HSL), resulting in an increase in NEFAs that can be delivered to the liver where they will have three destinies: (1) conversion into ATP in the mitochondria; (2) conversion back to triglycerides and incorporation into very-low-density lipoprotein (VLDL); and (3) storage. Also, the increased levels of glucose in the liver favor the conversion of the excess of glucose into fatty acids. The fatty acid synthesis, in turn, increases the levels of malonyl CoA, which then inhibits carnitine palmitoyltransferase 1 (CPT-1). Thus, blocking

Table 1 Risk of comorbidity according with BMI

Classification	BMI	Risk of comorbidity
Normal	18.5–24.5	Average
Pre-obese	25.0–29.9	Increased
Obese, class I	30.0–34.9	Moderate
Obese, class II	35.0–39.9	Severe
Obese, class III	>40.0	Very severe

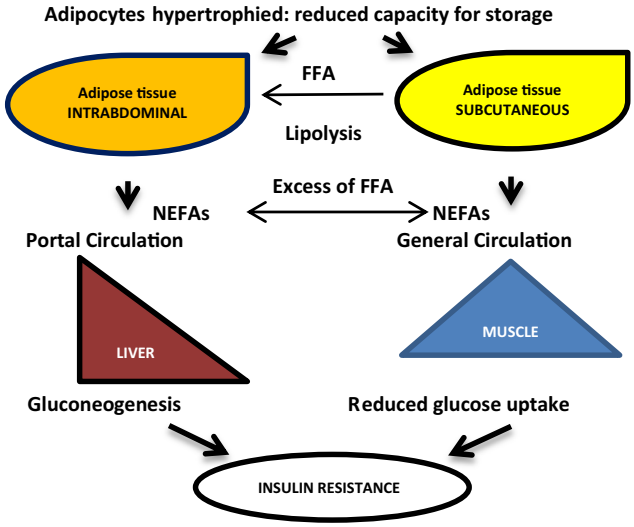

Fig. 4 Possible mechanisms through how fat induces insulin resistance

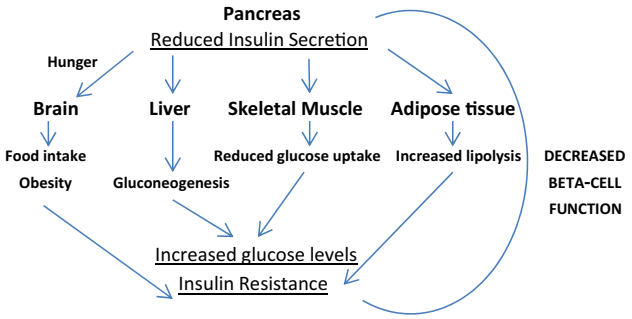

Fig. 5 Possible mechanism showing the link between obesity, insulin resistance and type-2 diabetes

Table 2 Risk of comorbidity according with WHR. Adapted from sHayward VH. Stolarcyzk LM: Applied Body Composition Assessment. Champaign IL, Human Kinetics, 1996, p82

Gender	Age	Low	Moderate	High	Very high
Disease risk related to obesity					
Male	20–29	<0.83	0.83–0.88	0.89–0.94	>0.94
	30–39	<0.84	0.84–0.91	0.92–0.96	>0.96
	40–49	<0.88	0.88–0.95	0.96–1.00	>1.00
	50–59	<0.90	0.90–0.96	0.97–1.02	>1.02
	60–69	<0.91	0.91–0.98	0.98–1.03	>1.03
Female	20–29	<0.71	0.71–0.77	0.78–0.82	>0.82
	30–39	<0.72	0.72–0.78	0.79–0.84	>0.84
	40–49	<0.73	0.73–0.79	0.80–0.86	>0.86
	50–59	<0.74	0.74–0.81	0.82–0.88	>0.88
	60–69	<0.76	0.76–0.83	0.84–0.90	>0.90

the transport of the fatty acids into the mitochondria, thereby increasing further the levels of triglycerides, ultimately released as VLDL [17].

A possible mechanism to explain the link between obesity, insulin resistance and type 2 diabetes could be what is depicted in Fig. 5 [5]. A crucial defect in the beta-cells reduces the amount of insulin secretion. In consequence, this signals the brain to increase food intake (hunger), which determines an increased need of insulin and to insulin resistance. The insulin-sensitive tissues such as liver, muscle and fat will increase the glucose production through activation of glycogenolysis and gluconeogenesis, and beta-oxidation of lipids and lipolysis, respectively. Consequently, the increased levels of NEFAs lead to an increase in the synthesis of triglycerides and eventually transformed them into VLDL or stored in the liver. Ultimately, this will promote dyslipidemias and cardiovascular disorders such as hypertension, angina and thrombosis.

Coffee consumption and bioactive components

Coffee is a complex mixture of chemical compounds, and its composition varies according to: (a) coffee bean species (*Coffeea arabica and Coffea canephora var. robusta*), (b) roasting process (speed, time and temperature) and brewing process (water-to-coffee grounds ratio, coffee grind size, water temperature, duration and methods) [18].

The composition of the green coffee includes, but not limited to: phenolic compounds, mainly chlorogenic acids or CGAs (6.5–10 %), carbohydrates (45–52 %), proteins (11 %), minerals (4.2–4.4 %), caffeine (1.2–2.2 %), trigonelline (0.7–1.0 %) and lipids (10–16 %) in special diterpenes such as cafestol and kahweol [19]. The roasted coffee has a somewhat different composition due to chemical transformations during the roasting process, which results in the

development of its characteristic aroma, flavor and color [20]. The most important chemical transformations are: conversion of CGAs to 1–5 γ-quinolactones or quinides (CGLs), mainly 3- and 4-caffeoyl-1,5-quinides (3CQL and 4 CQL); and the formation of melanoidins by the combination of sugars and amino acids through the Maillard reaction of caramelization of carbohydrates [21, 22]. Consequently, roasted coffee is composed of carbohydrates (38–42 % dry basis), which are responsible for the 'body' of the coffee; melanoidins (23 %), responsible for the color of the coffee; and lipids (11–17 %), protein (10 %), minerals (4.5–4.7 %), CGAs (2.7–3.1 %), caffeine (1.3–2.4 %) as well as hundreds of volatile compounds that contribute to the coffee aroma [23]. The total CGA content in commercial ground roasted coffee ranges considerably, varying from 0.3 to 3.5/100 g. Decaffeination may increase or decrease the CGA content in about 10 %, depending on the method used for this purpose [18].

Caffeine

The development of T2DM in overweight patients (BMI > 25) is highly prevalent, and as a consequence, diet and exercise are always part of any antidiabetic treatment. Caffeine causes weight loss in patients with diabetes by increasing thermogenesis [24–29], which means increased production of energy (ATP); and by its ergogenic properties [30–34]. In other words, caffeine enhances endurance and exercise strength, by the ability to increase physical exercise without a concomitant increase in effort sensation.

Chronic caffeinated coffee consumption in a mouse model of obesity and T2DM demonstrated that equivalent doses of caffeine in the coffee administered to mice diminished weight gain in high-fat-diet-fed mice and abolished weight gain in normal-diet-fed mice [35].

Cafestol and Kahweol

Cafestol and kahweol are diterpenes from coffee that poorly pass the cellulose paper filter. A cup of unfiltered coffee has levels around 6–12 mg (French press and Turkish coffee), while a cup of filtered coffee contains only 0.2–0.6 mg of diterpenes. However, in vitro studies using small concentrations of cafestol (10^{-10} to 10^{-6} M) have shown a dual action: a significant increase in insulin secretion (insulinoma cells) and also in the glucose uptake (skeletal muscle cells), suggesting that cafestol may contribute, even in the low concentrations present in filtered coffee, to the preventive effects on T2DM in coffee drinkers [36].

Animal and in vitro studies indicate that cafestol and kahweol can operate by modulating multiple enzymes involved in the detoxification process of carcinogens responsible for hepatocellular carcinoma [37]. Different mechanisms appear to be involved in this chemoprotective effect: an induction of conjugating enzymes (e.g., glutathione S-transferases, glucuronosyl S-transferases), an increased expression of proteins involved in cellular antioxidant defense (e.g., gamma-glutamylcysteine synthetase and heme oxygenase-1) and an inhibition of the expression and/or activity of cytochromes P450 involved in carcinogen activation (e.g., CYP2C11, CYP3A2) [38–40].

Chlorogenic acids (CGAs)

Chlorogenic acids are the most common bioactive compounds in plant foods such as coffee, apple, tea and berries, as well as in beverages, such as wine [41]. Coffee is the major source of CGAs in the American diet. CGAs refer to a family of isomers with no chloride in the formula. CGAs are esters formed by the binding of quinic acid and *trans*-cinnamic acids (mainly caffeic, ferulic and p-coumaric acids). 5-Caffeoylquinic acid (5 CQA) also known as chlorogenic acid is the most abundant CGA in coffee [20, 42]. CGAs are partly absorbed in the small intestine [43] and partly in the large intestine after being metabolized by bacteria [44]. According to a study in rats, metabolites from coffee appear in the blood in two phases: 30 min to 2 h and then 8–12 h after coffee administration. This indicates that coffee bioactive compounds are initially absorbed in the stomach and small intestine (first phase) and further fermented by the gut microbiota and absorbed/excreted in the colon during the second phase [45–47]. It has been reported that around 90 % of the CGA from coffee would be available to reach gastrointestinal (GI) mucosa and suffer hydrolysis by esterases, conjugation or absorption in the free form. One-third of the CGAs is absorbed intestinally, and the remainder will be metabolized by colonic microflora into glucuronides and sulfates derivatives from caffeic acid and subsequently absorbed and distributed to the tissues (enterohepatic cycle) [48]. A more detailed description of CGAs' fate in the human body can be found in Farah and Duarte [18].

Melanoidins

Coffee brew contains many polyphenols and phenolic compounds, well known for their antioxidant properties [49–51]. During the roasting process, antioxidants such as chlorogenic acids are partly decomposed or incorporated into melanoidins. The latter represents a heterogeneous group of polymers with a variable range of molecular weight. They have been proposed to impart antioxidant activity through an ability to chelate metal ions [52]. Recent studies [53] of the antiradical activity of roasted coffee arabica showed

that the highest antiradical activity was associated with a low molecular weight fraction (<3 kD) of the coffee brew, suggesting a predominant role of phenolics non-bound to melanoidins. Lastly, it is important to mention the main by-product of coffee brewing, known as spent coffee, which is also a rich source of phenolic acids. Coffee companies produce annually >2 billion tons of spent grounds, most of which is disposed without recycling [54–56]. Several applications have been proposed for coffee by-products as a source of bioactive compounds such as antioxidant (food preservative), antitumor and antiallergic action [20].

Coffee consumption, gut microbiota, metabolomics profile versus obesity

Current research suggests that altered gut microbiota profile is associated with obesity and T2DM [45, 57]. Humans, rats and mice gut microbiota are made up of two main phylotypes—*Bacterioidetes (B)* and *Firmicutes (F)*. There is some consistency within reports that obesity and high-fat feeding are associated with an abundance of *Firmicutes* as opposed to *Bacteroidetes,* when compared to lean individuals [45]. In vitro studies [58] using equivalent amount of CGA (80.8 mg) showed a significant increase in the growth of Bifidobacterium (B type), Clostridium coccoides–Eubacterium rectale group. Similar results were observed in a study in diet-induced obese rats under chronic use of coffee [45]. They showed that the gut microbiota change had positive impact on the serum metabolome resulting in: (a) decreased body weight, adiposity, liver triglycerides and energy intake; (b) increase in the metabolites indicative of carbohydrate and fatty acid metabolism. Coffee reduced some, but not all the detrimental effects of high-fat diet since they found coffee consumption to be associated with insulin resistance. The authors discussed that this resistance could be due to an antagonist effect of caffeine and suggest that future studies should examine the effect of caffeine and other coffee bioactive compounds independently.

Coffee and type 2 diabetes: possible mechanisms of preventive effect

There is a body of evidence through in vitro/ex vivo models, in vivo experiments and in clinical trials of a positive modulation of human health attributed to phenolic compounds or CGAs and caffeine [59]. Figure 6 summarizes the majority of mechanisms that explain the beneficial effects of regular coffee consumption associated with reduced risk of developing type 2 diabetes mellitus. White squares represent in vivo studies and black squares in vitro studies. The studies mentioned here were based on the administration of caffeinated, decaffeinated or simply coffee with no distinction between the two. Some of them involved administration of specific amounts of caffeine and/or chlorogenic acid. Therefore, the conclusions are in reference to effects of the two main components of coffee: chlorogenic acids and caffeine.

In this section, a summary of the latest data on those experiments is discussed. It is focused on the effects of GCAs on glucose and lipid metabolism, since the possible mechanisms to explain the preventive effect of coffee on the development of obesity and T2DM are related to both pathways. It is of note that some of the mechanisms proposed for coffee effects on diabetes are shared with actual drugs currently used to treat T2DM and disorders of the lipid metabolism. Examples of those drugs are inside the parenthesis aside of the corresponding mechanism in Fig. 6.

CGAs and glucose metabolism

Several mechanisms have been proposed for the effects of CGAs on the metabolism of glucose. As depicted in Fig. 6, we can divide those studies into the three different tissue groups: GI (absorption of glucose); skeletal muscle, liver and adipose tissue (main sites of glucose storage); and pancreas (hormonal regulation of glucose metabolism).

The effects of CGAs on glucose absorption are evidenced by: (1) inhibition of α-amylase, enzyme responsible for the breakdown of starch present in the saliva and pancreatic juice inhibiting sugar absorption from the dietary starch [60, 61]; (2) preventing the action of alpha-1, 4-glucosidase, enzyme responsible for the degradation of glycogen (glucose storage form) present on the brush border cells of the small intestine [62, 63]; (3) modulation of gastrointestinal peptides such as gastric inhibitory polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) (incretin hormones with opposing effects on glucose absorption), shifting glucose absorption to a more distal region in the GI tract [62, 64]; (4) stimulation of the translocation of glucose transporter 4 (GLUT4), increasing glucose uptake by the peripheral tissues [62, 65]; (5) glucose-6-phosphatase (Glu-6-Pase) inhibition, enzyme responsible for hydrolyzing the phosphate from glucose-6-phosphate releasing free glucose into the systemic circulation. In consequence, there will be a reduction in the levels of glucose in the blood [62, 66, 67]; (6) upregulation of TCA and urea cycles, promoting a metabolic shift and causing increased ATP turnover [68]; and (7) mitigation of insulin resistance by decreasing plasma glucose levels and increasing tyrosine phosphorylation of insulin receptor substrate-1 (IRS-1) [66].

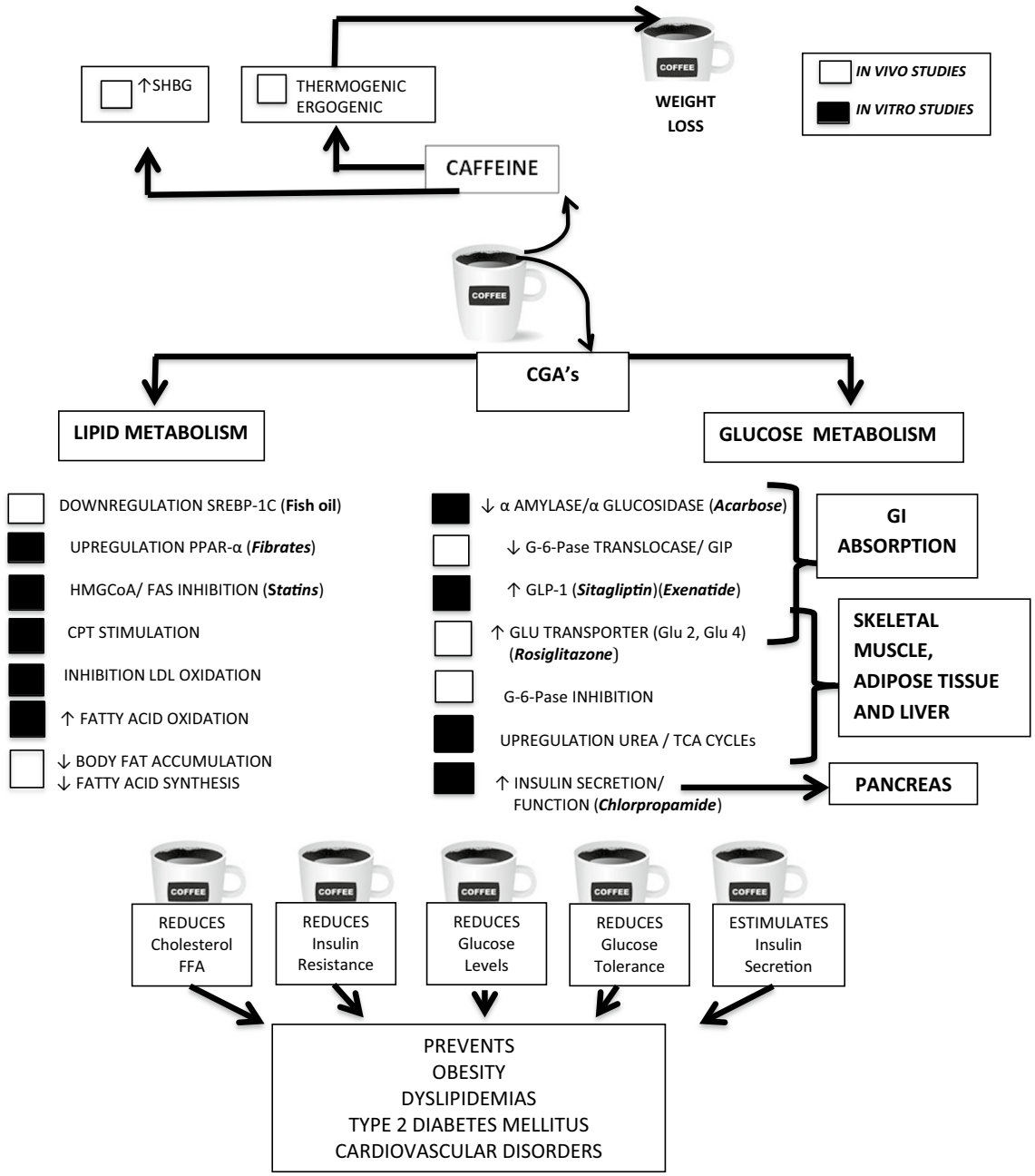

Fig. 6 Summary of all the major mechanisms of two coffee constituents: caffeine and chlorogenic acids in the prevention of type-2 diabetes. White square represents mechanism suggested through in vivo studies, black square represent mechanism suggested by in vitro studies

CGAs and Lipid Metabolism

The effects of the CGAs in the lipid metabolism are also depicted in Fig. 6. The first mechanism involves the downregulation of sterol regulatory element-binding protein (SREBP)-1C. The mRNA levels of this protein in the mouse liver were significantly lower in coffee (poly) phenols (CPP) or CPP-fed mice than in high-fat control mice. These findings indicate that CPP enhance energy metabolism and reduce lipogenesis by downregulating SREBP-1c and related molecules, which leads to the suppression of body fat accumulation [69, 70]. SREBP-1c is the main genetic switch controlling lipogenesis. Omega-3 fatty acids (fish oil) elicit hypotriglyceridemic effects in part by coordinately suppressing hepatic lipogenesis through reducing levels of SREBP-1c in the liver [71, 72]. This is another example of CGAs preventive effect on type 2 diabetes that share the same mechanism with the current

therapy in the treatment of obesity, type 2 diabetes and metabolic disorder.

The next two mechanisms depicted in Fig. 6 are well known by their application in the treatment of dyslipidemias. Fibrates' mechanism of action is primarily as a ligand for the nuclear transcription receptor peroxisome proliferator-activated receptor alpha (PPAR-α) [73]. This receptor when activated acts as a lipid sensor and regulates lipid metabolism. The liver is its major target tissue, and its key genes are enzymes involved in the β-oxidation of fatty acid [74]. CGA's and caffeic acid stimulated the expression of PPAR-α in high-fat diet-induced obese mice, showing antiobesity property by improving lipid metabolism [74]. The same paper from Ae-Sim Cho et al. looked at the activities of hepatic lipid-regulating enzymes, such as 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-Co-A reductase) and fatty acid synthase (FAS). They found an inhibitory effect of those enzymes in the group of mice fed with caffeic acid and chlorogenic acid. They concluded that CGA and caffeic acid were inhibitors of fatty acid and cholesterol synthesis as well as stimulants of fatty acid oxidation in the liver, the same mechanism of action of statins.

Carnitine palmitoyltransferase (CPT) is a rate-limiting enzyme that catalyzes the transport of fatty acids to the mitochondria for β-oxidation. A study in mice fed with green bean coffee extract showed that neochlorogenic acid or 5-O-caffeoylquinic acid (5-CQA) and feruloylquinic acid mixture, members of the CGAs family present in the coffee extract, can enhance hepatic CPT activity [75]. This positive effect of coffee to increase lipid beta-oxidation is in addition to the effect of coffee on another protein, PPAR-α, which is also upregulated by CGAs and acts as a transcriptional factor upregulating the expression of CPT [76].

A study that included 16 subjects exhibiting pre-obesity levels (BMI between 25 and 30), euthyroid, non-diabetic, non-hypertensive and not receiving steroids between ages of 22–46 was targeting the effects of high CGA green coffee extract (350 mg CGA 3xday) on body fat accumulation and weight loss [61]. They found that out of 16 initially classified as overweight, six finished the study in the normal BMI category and 10 out of 16 showed at least 10 % weight loss. They concluded that, compared with the currently approved treatment for weight loss, such as sibutramine, orlistat and rimonabant, CGA green coffee bean extract has effects superior of the prescription drugs.

An animal study in mice aimed to investigate the effect of CGAs and caffeine present in green coffee extract on fat accumulation and body weight [75]. The results showed that after 14 days consuming green coffee bean extract (10 % caffeine and 26 % of CGA) caused a suppressive effect on weight gain and visceral fat accumulation in mice.

As a result from the previous mechanisms of CGAs on the lipid metabolism, there will be an increase in fatty acid oxidation due to an upregulation of PPAR-α and a reduction in synthesis of fatty acid, due to inhibition of HMG-Co-A reductase and FAS enzymes in the liver as displayed in Fig. 6.

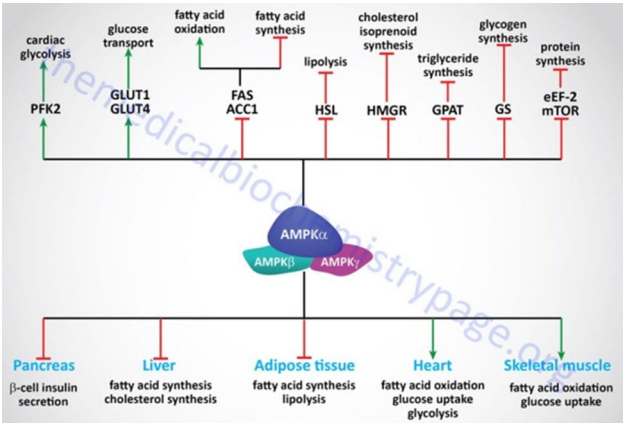

Fig. 7 AMPK and its modulation of carbohydrate, lipid and protein metabolism and as a key player in the development of obesity and type-2 diabetes. Green arrow represent stimulation and red line represent inhibition. Reproduced with permission of the medical biochemistry page, LLC

There are, though, a couple of theories that try to embrace the majority of the effects seen with coffee, the adenosine monophosphate kinase (AMPK) activation theory and the sex-hormone-binding globulin (SHBG) theory.

AMPK theory

AMPK is a heterotrimeric enzyme, composed of one active subunit alpha and two regulatory subunits beta and gamma. The change in the ratio AMP/ATP triggers its activation that consists in phosphorylation of residue Trh172 of the α-subunit rescuing the energy balance. As a result of AMPK activation, the cellular metabolism switches from anabolic to catabolic processes [77]. This kinase is a main point for metabolic control in all eukaryotes with vital functions in several organs and tissues (Fig. 7) [77–83]. Considering AMPK's pivotal role in the control of carbohydrate, lipid and protein homeostasis, it is considered a key player in various diseases such as obesity, type 2 diabetes, dyslipidemias, just to mention a few [77, 84–87].

SHBG theory

Sex-hormone-binding globulin (SHBG) has been associated with type 2 diabetes, metabolic syndrome and hormone-dependent cancers. Goto et col. [88] studied the correlation of levels of SHBG and the use of estrogen with

body mass index and lifestyle factors such as physical activity, smoking, alcohol consumption coffee intake and dietary factors in a population of 13,547 postmenopausal women who were enrolled in the Women's Health Initiative Study between 1993 and 1998 in 40 centers in the USA. A self-administered food frequency questionnaire was applied to estimate average daily dietary intake over the previous 3-month period. The lifestyle factors included, beside others mentioned above are: the intake of coffee, decaffeinated coffee and tea. The results showed that higher regular coffee intake (≥2 cups per day compared with no cups of coffee per day), but not decaffeinated coffee or tea, was associated with higher SHBG concentration. The same positive relationship with SHBG levels was found for physical activity and negative relationship with BMI. Previous studies on SHBG effects [89] had shown that increased BMI, waist circumference and hip circumference were associated with increased levels of estrone, estradiol and free estradiol and negatively associated with SHBG. They concluded that there is a consistent and significant ($p \leq 0.05$) association between adiposity and elevated concentrations of estrogens and androgens, as well as between increased physical activity and decreased concentration of these hormones. These indications suggest that these hormones can be modified by lifestyle changes.

The suggested molecular mechanism for the positive relationship between caffeinated coffee and SHBG levels could be based on the fact that SHBG is primarily synthesized and metabolized in the liver, where coffee is known to present components such as caffeine, cafestol and kahweol that alter enzyme activity and expression in the liver [90]. Also the fact that a recent study [91] concluded that caffeinated coffee and caffeine intakes, but not with decaffeinated coffee, were positively associated with SHBG levels. Nevertheless, this theory needs further experimental investigation.

Other coffee constituents and effects on glucose metabolism

Coffee is also rich in trigonelline, a pyridine alkaloid derived from the methylation of nicotinic acid or niacin. Trigonelline represents 1 % of the dry weight of roasted coffee beans [92–94] and 50–100 mg of a cup of coffee [95, 96]. The administration of trigonelline to a rat model of diabetes mellitus resulted in reduced glucose levels in a tolerance glucose test [97], and similar results from other animal studies showed that trigonelline exerts a hypoglycemic effect [95, 98]. In addition, it was also reported beneficial effects in rats displaying peripheral neuropathy [99]. It was found in animal studies, which could be added to the overall effect of coffee. Trigonelline regulates key enzymes of glucose and lipid metabolism, such as glucokinase, glucose-6-phosphatase, fatty acid synthase and carnitine palmitoyltransferase in diabetics rats [94, 100], which could explain the effects of trigonelline on diabetes. In addition, niacin, its parent molecule, is indicated in the treatment of dyslipidemias due to its inhibition of VLDL secretion and consequent decreased production of LDL and triglycerides [73].

Among the minerals present in coffee, magnesium contributes with 7 mg/cup of the American coffee, according to the nutritional tables of the US Department of Agriculture [95]. Magnesium displayed in many studies a positive effect on glucose metabolism by increasing insulin sensitivity [94, 95, 101]. Magnesium acts as a cofactor of various enzymes involved in the metabolism of glucose [62, 102], possibly playing a role in glucose homeostasis and in the prevention of T2DM [62, 103, 104].

Other possible mechanisms

One of the first effects of coffee to be noticed and maybe the only one explored by pharmaceutical industry is the antioxidant property of the chlorogenic acids and other cinnamates present in the coffee, making coffee the main source of those antioxidants in American diet [105]. The antioxidative property could also contribute to the overall effect of coffee in the prevention of diabetes, considering that oxidative stress plays a role in the development of insulin resistance and T2DM [67, 106, 107]. There are other studies that interpret this effect of coffee as an indirect rather direct effect on our own endogenous antioxidant defenses through an increase in glutathione and GST activity [94].

The white adipose tissue, as opposed to the brown one, is involved in energy homeostasis and energy control. It plays a key role by secreting various biomolecules called adipokines or adipocytokines [108]. Adiponectin is the most abundant peptide secreted by the adipocytes, and its actions are mediated by two main receptors: AdipoR1, involved in the stimulation of AMPK in the muscle, and AdipoR2, involved with PPAR-γ in the liver. Those two receptors mediate an increased fatty acid oxidation in the liver and glucose uptake by the muscle [109, 110]. Serum adiponectin levels are inversely related to body fat mass and to the degree of insulin resistance, and therefore, it is accepted that adiponectin ameliorates sensitivity to insulin and glucose tolerance [109, 111]. Chlorogenic acid and caffeic acid supplemented diet on high-fat diet-induced obese mice lowered plasma triglycerides and total cholesterol and chlorogenic acids supplementation significantly increased the plasma adiponectin levels [74]. A review article on the mechanisms of adiponectin as a target for metabolic

syndrome, diabetes and coronary diseases concluded that considering that the levels of adiponectin are consistently inversely related to these ailments, the search for pharmacologic agents that could improve its plasma levels should be target of intense research [109].

Coffee and type 2 diabetes: epidemiological evidence of preventive effect

Innumerous reports from epidemiological studies have been published claiming that regular coffee intake, caffeinated or decaffeinated, averaging 3–4 cups a day, reduces significantly the risk of developing T2DM [67, 91, 112–119]. There are some reports, though, that their findings are not conclusive or fail to show a significant correlation [120]. A review article on epidemiological studies of the association between habitual coffee consumption and diabetes risk, healthy glucose metabolism or both, concluded that only three of the 20 studies did not find a protective effect and none found a deleterious effect [121]. They also found that the majority of the studies suggest that long-term consumption of coffee and decaffeinated coffee can reduce the risk of diabetes. This implies that there are some evidences that one or more non-caffeine constituents in coffee or both may be better suited for enhancing glucose tolerance and insulin sensitivity than in caffeinated coffee.

A more recent review on the role of coffee in modulating diabetes risk [95] researched the number of publications between 1950 and 2010 in Medline tagging the words of coffee and diabetes and showed that the first paper was published in 1970s [122] and the first epidemiological report on inverse association between coffee consumption and risk of T2DM came only in 2002 [112]. Since then, the author says the number of studies has increased exponentially and by the time it was published they found 437 articles (PubMed, February 17, 2012). The same search today yield 651 articles (PubMed, February 5, 2016).

Discussion

The estimated contents of the bioactive compounds of coffee in the majority of the studies are based on the average amount value cited in the literature. Nevertheless, a review article from Crozier et al. [123] claims that there is a great variation in batch-to-batch coffee bean composition, probably due to the usual blending of two different species of coffee, *arabica* and *robusta* beans, and the roasting, grinding and coffee making/barista processes. Very few studies predetermine the amount of CGAs and/or caffeine in the coffee administered or consumed during the study. Additionally, the use of 'one cup' as a measure of the volume of coffee cannot be considered as a reproducible measure, since the size of the cup varied among studies and among coffee drinkers within the study populations [94]. Zanotti et al. [41] discuss that most of the in vitro studies currently published presents data obtained from exposure to coffee constituents in their natural form occurring in the plant food. It constitutes a significant bias since they do not consider the fast modification of those chemicals by human and microbial enzymes into metabolites after ingestion. Overall, it exempts the derivatives and metabolites of coffee bioactive compounds to be at least partially responsible for the observed beneficial/toxic effects [41, 43, 124, 125]. It can get even more complicated, if we consider that the lack of commercial availability of different isoforms of CQAs (3- and 4-CQA) and quinolactones or quinides (3- and 4-CQL), which are predominant in the coffee brew, as well as standards for sulfated and glucuronidated forms of the CGAs and derivatives are also unavailable. ([18, 105, 123]. Therefore, all these factors are certainly weaknesses of most of the current studies on coffee consumption. However, at the same time they also explain why there is so limited literature available on the disposition of those plant-derived compounds in the human body, healthy or diseased. Consequently, it was not yet possible to determine the therapeutic concentrations of those bioactive compounds or in which amount they should be present in coffee to promote health benefits. They concluded that future in vitro studies should target the cellular activity of their principal metabolites through bioavailability studies. In a most recent review [94], Crozier et al. conclude that a large part of the conflict in the epidemiological studies is because research has not specifically focused, during the design stage, on the beverages, so that the level of detail collected in the surveys is inadequate to quantify and characterize long-term consumption.

Conclusion

The pathophysiological mechanisms involved in obesity and development of type 2 diabetes are very complex and overlay with metabolism of three major nutrients: carbohydrates, lipids and proteins. The two first ones being more closely interrelated considering that carbohydrates is our number one source of energy and lipids the way we storage energy in our body. A multitude of mechanisms is proposed to account for the beneficial effects of coffee consumption on the development of obesity and T2DM. Some theories, such as the theory of the activation of AMPK, in which AMPK works as a switch between anabolism (ATP expenditure) and catabolism (ATP production), sound very comprehensive.

In conclusion, coffee has a complex chemical composition that fluctuates according a range of factors (type of beans, blend, roasting, grounding, brewing). After ingestion, coffee constituents go through biotransformations that occur during their disposition in the human body (absorption, metabolization and enterohepatic cycling), which there is little information about the possible effects of the metabolites. Studies investigating the bioavailability, metabolism and bioactivity of the different compounds present/produced in the coffee are urgently needed. As of today, there is mounting evidence of the reduced risk of developing type 2 diabetes by regular coffee drinkers of 3–4 cups a day. The effects are likely due to the presence of chlorogenic acids and caffeine, the two constituents of coffee in higher concentration after the roasting process.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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