Review
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Endocrine Effects of Coffee Consumption

Kahvenin Endokrin Etkileri

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Abstract

Caffeine has been found to exert various biological effects including, antiangiogenic, antiproliferative, antimetastatic activity, increased fat oxidation and mobilization of glycogen in muscle, increased lipolysis, and reduction of body fat. The aim of this review is to analyze the endocrine effects of coffee consumption. A systematic literature search was conducted on PubMed and Web of Science databases seeking articles published until May 2019, dealing with coffee consumption and diabetes, osteoporosis, thyroid gland, adrenal, and gonads. The results of the most epidemiologic studies reported that coffee consumption has positive effects on combating type 2 diabetes risk, has no significant effects on bone mineral density levels but fracture risk was shown to be higher in the high coffee consumer group. Coffee intake has no significant effect on thyroid cancer, increases sex hormone binding globulin levels, has no effect on fertility but higher consumption was related to spontaneous abortion. Studies pertaining to coffee consumption and endocrine effects have contrary results. More randomized clinical studies with a long term follow up period are required.

Keywords: Coffee; diabetes mellitus; fertility; gonadal hormones; osteoporosis; thyroid diseases

Özet

Kafeinin; antiproliferatif, antianjiyogenik, antimetastatik etkileri, artmış yağ oksidasyonu, glikojenin kas içinde mobilizasyonu, artmış lipoliz gibi çeşitli biyolojik etkileri gösterilmiştir. Bu çalışmada amacımız, kahve tüketiminin endokrin sistem üzerine olan etkilerini incelemektir. Mayıs 2019'a kadar kahve tüketimi ve diyabet, osteoporoz, tiroid hastalıkları, adrenal ve gonad fonksiyonları hakkında yayımlanan makaleler PubMed ve Web of Science veri tabanlarında sistematik olarak tarandı. Epidemiyolojik çalışmalar, kahve tüketiminin Tip 2 diyabet riskini azaltmada olumlu etkisi olduğunu, kemik mineral yoğunluğu üzerinde anlamlı bir etkisinin olmadığını, ancak yüksek kahve tüketen grupta kırık riskinin daha yüksek olduğunu, tiroid kanseri üzerinde anlamlı etkisinin olmadığını, seks hormon bağlıyıcı globulin seviyelerini arttırdığı, doğurganlık üzerine etkisi olmadığını, ancak spontan abortus riskini artırdığını göstermiştir. Kahve tüketimi ve endokrin etkiler üzerine yapılan çalışmaların çelişkili sonuçları olup net etkilerini belirleyebilmek için uzun takip süreli klinik çalışmalar gereklidir.

Anahtar kelimeler: Kahve; diabetes mellitus; fertilite; gonadal hormonlar; osteoporoz; tiroid hastalıkları

Introduction

Coffee is one of the most popular beverages consumed worldwide, thereby enhancing its market demand (1).

Statistics reveal that the average consumption of coffee ranges from 2-4 cups per day in western societies. Western countries prefer to consume brewed coffee while instant coffee is popular among the North Europeans. Boiled coffee is frequently consumed by the inhabitants of the Balkan area, Ireland, North Africa, and Turkey.

Scientists have extracted numerous bioactive compounds, such as chlorogenic acids (CGA), polyphenols, diterpenes, caffeine, and caffeine metabolites (1,2) from this complex beverage.

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Owing to the presence of these bioactive components, there is an increased scientific interest in the potential health benefits of regular coffee consumption. Recent studies have reported that coffee exerts functional effects on human health. The effect of coffee intake on malignancy has already been reported in various studies. Presently, research is mostly focused on exploring the scientific aspect of the effect of coffee on type 2 diabetes, cardiovascular, and cerebrovascular diseases. All these medicinal effects of coffee are attributed to the presence of various bioactive compounds like caffeine, chlorogenic acid, and cafestol. Caffeine has been known to exhibit several biological effects, such as antiproliferative, antiangiogenic, antimetastatic activities, increased fat oxidation, and mobilization of glycogen in muscles, increased lipolysis, and decreased body fat (3).
Recent clinical and laboratory data implicate that endocrine tissues could also be the targets of coffee compounds. The present review aims to analyze the clinical trials that evaluated the consequences of coffee consumption on endocrine disorders.

Methods

A systematic literature search was conducted on PubMed and Web of Science databases seeking articles published until May 2019 using a combination of the following Medical Subject Headings terms and keywords: coffee 'AND' (diabetes 'OR' type 2 diabetes 'OR' thyroid 'OR' goiter 'OR' hypothyroid 'OR' hyperthyroid 'OR' thyroid cancer 'OR' infertility 'OR' osteoporosis 'OR' vitamin D 'OR' adrenal).
Constraints were used for advanced search: adults, human, clinical trial, and search fields: title/abstract. Additionally, we scrutinized references within identified papers as well as articles that had come to our attention through other means.

Coffee and Type 2 Diabetes

Q1: Does coffee consumption reduce type 2 diabetes risk?

Although the correlation of coffee with the pathogenesis of diabetes is still controversial, special attention has been given to estimate the possible beneficial effects of coffee on developing type 2 diabetes.

Epidemiological studies conducted among different populations throughout the world highlighted the positive effects of coffee in combating the risk of type 2 diabetes, in a dose-dependent manner. Studies suggested that 3-4 cups of coffee per day were capable of reducing the risk of development of T2DM (Type 2 Diabetes Mellitus) by approximately 25%, as compared to those consuming less than 2 cups per day. The relative risk of T2DM for the highest level of coffee intake (>6 cups/day) was estimated to be 0.71 (0.67-0.76) for caffeinated coffee and 0.79 (0.69-0.91) in case of decaffeinated coffee (1,4). In addition, increasing coffee consumption +1 cup/day incurred a decrease of 11% on T2DM risk in the following four years. On the other hand, reducing coffee consumption by more than 1 cup/day increased the risk of development of T2DM in four years by 17% (1,5). Both caffeinated and decaffeinated coffee, filtered and instant coffee were associated with reduced risk of T2DM (6-8). Studies also suggested that this inverse association was applicable to very high levels of coffee consumption. Dose-response analysis suggested that 12% (0.88 (0.86-0.90)) reduced risk of T2DM was attributed to the intake of every 2 cups/day of caffeinated coffee. On the other hand, intake of every 2 cups/day of decaffeinated coffee was associated with an 11% (0.89 (0.82-0.98)) reduced risk (9). A recent study from a low coffee consumer country, Iran also concluded a lower risk of diabetes or pre-diabetes among the coffee consumer group (10).
However, few epidemiologic studies failed to report any correlation between coffee consumption and type 2 diabetes risk (11).

Q 2: Is it the caffeine in coffee that causes diabetes?

Published reports opined that both caffeinated and decaffeinated coffee consumption lowered the risk of type 2 diabetes (7,10,12,13).
There are controversial studies about the effect of decaffeinated coffee on type 2 diabetes risk. A prospective cohort study reported a negative relationship between caffeinated coffee and type 2 diabetes risk. However, this study failed to establish any effect of decaffeinated coffee on the development of T2DM (14).

Q3: Does coffee consumption affect glycemic control?

There are a few studies reflecting the outcome of coffee consumption on glucose levels in type 2 diabetic patients. Studies suggested that exaggerated postprandial glucose and altered insulin responses owing to the presence of caffeine might lead to impaired glycemic control (15). This contradictory effect might result from the acute effect of coffee. However, habitual consumption might indulge in the positive effects of this beverage. Therefore, it is difficult to compare the studies investigating acute metabolic effects.

Q4: Are there any effects of coffee consumption on glucose metabolism and insulin sensitivity in healthy individuals?

Oral glucose tolerance test (OGTT) was conducted among euglycemic individuals where subjects were provided with a 75-gram glucose load and the blood glucose level was estimated, henceforth. Such cross-sectional studies among healthy populations revealed that second-hour glucose levels, following the glucose load, were lower in the coffee consumer group (16). Another study also reported second-hour glucose levels in a coffee consumer group to be lower among 1328 healthy individuals (17).

Randomized controlled studies in healthy individuals observed reduced insulin sensitivity attributed to acute caffeine load. However, the plasma glucose levels remained unaffected. Contrary to these findings, one study indicated a disruption in the second-hour glucose levels in healthy volunteers with a single dose of coffee (18).

Contradictory reports are available regarding the effect of coffee consumption on postprandial glucose levels. Some data indicated that tolerance to the adverse consequences of coffee on insulin sensitivity may occur as a long term effect.

In a randomized controlled clinical trial from Japan, overweight men were randomly classified into three groups: one group receiving five cups of caffeinated coffee, the second group consumed five cups of decaffeinated coffee, and the third group did not receive any coffee for 16 weeks. Second-hour glucose levels were found to be lower for the caffeinated group. When adjusted according to waist circumference, caffeinated and decaffeinated groups were associated with a modest reduction in glucose levels post 2-hour glucose load (19).

Randomized controlled trials were also conducted estimating the short-moderate term effects of coffee on glucose metabolism and insulin sensitivity. In a trial, the glucose and insulin levels were recorded during the second week of the regular coffee intake period and two weeks of abstinence period in 26 healthy volunteers. Fasting plasma glucose levels were similar but fasting insulin levels were higher after the coffee intake period (20).

Another study among euglycemic individuals compared the insulin sensitivity among 5 cups/day caffeinated, 5 cups/day decaffeinated, and no coffee consumers for a period of eight weeks. Though insulin sensitivity was reduced due to short term effects of coffee, positive effects on adipocyte and liver functions were witnessed (21).

Q5: What is the main mechanism of the beneficial effects of coffee?

The main mechanism behind the beneficial effects of coffee on glucose metabolism has not been elucidated so far. Some *in vivo* and *in vitro* studies have been conducted to screen the pharmacological activity of the biological compounds present in coffee. In a cross-over trial, 12 gram decaffeinated coffee, 1 gram chlorogenic acid, 500 mg trigonelline, and 1 gram mannitol used as placebo were compared. Chlorogenic acid and trigonelline ingestion were associated with significantly lower glucose and insulin concentrations, 15 min after an oral glucose load was given. However, OGTT insulin and glucose under the curve areas were not reduced when compared with the placebo. So it was claimed that the positive effects on glucose metabolism may be due to chlorogenic acid and trigonelline, present in coffee (22). Studies involving animal models postulated that the reduction of blood glucose concentration by chlorogenic acid was mediated by the activation of adenosine monophosphate-activated protein kinase (AMPK), affecting fat and glucose metabolism at the cellular level (1,23). Evaluation of the effect of chronic consumption of caf-

feine by animals was found to restore insulin sensitivity and revert age-induced insulin resistance in the rat. The effect on Glut 4 transporters present in the skeletal muscles and AMPK activity along with the anti-oxidant and anti-inflammatory effects of coffee were hypothesized to contribute to glucose metabolism (1).

The results of observational and clinical studies about the effects of coffee on glucose metabolism are contrary. Clinical trials mostly focus on the short term effects of coffee on glucose and insulin parameters, long term randomized controlled studies are essential to establish the preventive effect of coffee from type 2 diabetes.

Conclusion

The results of the most epidemiologic studies establish the dose-dependent beneficial effect of coffee consumption on reducing type 2 diabetes risk.

Although the number of patients was high and the follow-up period was long in epidemiological studies, the coffee drinking and dietary habits of the participants were evaluated with a validated self-reported questionnaire. However, lengthy follow up period of these cohort studies, often result in miss assessments. Differences in cup sizes and brewing types also need to be taken into consideration.

In randomized-controlled studies, there may be bias as most of the studies in the literature are not double-blinded.

Coffee consumption failed to portray significant beneficial effects on glucose control in diabetic patients.

Coffee and Osteoporosis

Q1: Does coffee consumption has an association with increased osteoporosis risk?

As coffee is one of the most consumed beverages, its outcomes on bone health were also studied extensively. In experimental studies, high doses of caffeine were shown to suppress osteogenesis (24) and increase osteoclastic formation (25). However, these unfavorable consequences on bone health were in contradiction with the results obtained from clinical and observational studies.

Q2: How coffee consumption affects BMD (Bone Mineral Density) levels?

Studies pertaining to the effect of coffee on BMD have contrary results. Studies reported positive, negative or neutral effects of coffee consumption on BMD, as shown in Table 1. Most of the studies measured BMD with QUS (quantitative ultrasound) or with DXA (Dual-energy x-ray absorptiometry) in premenopausal, postmenopausal women or male population.

Coffee consumption was negatively correlated with the prevalence of osteoporosis in postmenopausal and premenopausal women (26). Yu et al. evaluated the prevalence of osteoporosis among 992 Chinese men, aged between 30-90 years. Osteoporosis was recorded according to T scores and the prevalence of osteoporosis was found to be less frequent in Chinese men with moderate coffee intake (27). Yang et al. (2015) evaluated the association between osteoporosis and coffee consumption in postmenopausal women. Osteoporosis in 1,817 participants was investigated by calcaneus quantitative ultrasound and T scores were recorded (26). A study from the Korean premenopausal population of 1,761 participants failed to ascertain the significant correlation between BMD and coffee consumption (28). Choi et al. (2016) explored 4,066 postmenopausal women according to BMD levels measured by DXA and coffee consumption. The participants in the highest quartile for coffee consumption had 36% lower odds for osteoporosis (29). França et al. from Brazil, found adverse effects of coffee on BMD, in a study population of 156 postmenopausal women (30). A study from Turkey, in 2005, analyzed a study population of 200 postmenopausal women and found no association between BMD levels and coffee consumption (31). A recent study from the Taiwanese population examined the association between coffee consumption and T scores. The study revealed higher T scores in the coffee consumer group but half of the women in the study were premenopausal, so the evaluation of this study should be done carefully (32).

Q3: Does coffee consumption have an association with increased fracture risk?

Conflicting results of clinical studies are available in the literature regarding the ef-

Table 1. Coffee consumption and risk of osteoporosis.

Study	Country	Sample size	Sample type	Design	Osteoporosis diagnosis	Coffee dose	Result
Yu et al.,2016	China	992 men	30-90 years	Cross-sectional	BMD measured at calcaneus by quantitative US	Seldom or moderate	Prevalence of osteoporosis less frequent in Chinese men with moderate coffee intake
Yang et al., 2015	China	1.817 women	Postmenopausal	Cross-sectional	BMD meaured at calcaneus by quantitative US	Seldom, sometimes, always	Coffee consumption was negatively correlated with the prevalence of osteoporosis
Choi et al., 2016	Korea	4.006 women	Postmenopausal	Cross-sectional	L1-4 and femoral DXA	9 categories almost no- 3/day	Coffee consumption may have protective effects on bone
França et al., 2015	Brazil	156 women	Postmenopausal and osteoporotic	Cross-sectional	L1-4 and femoral DXA	3 day food diary	Caffeinated beverages exert a negative effect on BMD
Demirbag et al., 2005	Turkey	200 women	Postmenopausal	Cross-sectional	L1-4 and femoral DXA	Cups/day	No relation between coffee consumption and BMD
Chang et al., 2017	Taiwan	2.929 women	1.366 premenopausal, 1.593 postmenopausal	Cross-sectional	Quantitative US	Cup/day	Positive effect in premenopausal and neutral in postmenopausal
Choi et al., 2014	Korea	1.761 women	Postmenopausal	Cross-sectional	L1-4 and femoral DXA	<1/day, 1/day, 2/day, 3/day	No significant association between BMD and coffee consumption

fect of coffee consumption on the risk of fracture. There are large cohort studies that claim increased fracture risk in the high coffee consumer group (>4 cups/day). The studies pertaining to coffee consumption and fracture risk are enlisted in Table 2.

A cohort study in the United States (US) for a period of six years among middle-aged women consuming more than 4 cups of coffee per day was found to be associated with a three-fold increase in the risk of low impact trauma hip fractures (33). Another cohort study with 31,527 Swedish middle-aged women found a modestly increased fracture risk in the 4 cups/day or more coffee consumer group (34). Jokinen correlated the risk factors for cervical and trochanteric fractures with coffee consumption of over 5 cups per day and he found increased trochanteric fractures among the coffee consumers (35). A recent study from China also documented that the coffee intake of four or more cups was associated with increased fracture risk in both men and women (36).

Literature also contains few studies that negate the effect of coffee on fracture risk. Halstrom et al. (2012) explored the effects of coffee in a cohort of 61,433 women and high coffee consumption was associated with a small reduction in bone density. However, no significant association between high coffee intake and an increase in fracture risk was witnessed (37). Albrand et al. also failed to correlate caffeine consumption with fracture risk (38).

Most of the studies focus on the risk of fracture in postmenopausal women. Few studies also investigated the risk in men. Halstrom et al., in 2014, examined and found no increase in fracture risk in the coffee consumer group comprising of a cohort of 42, 978 middle-aged men (39). Another cohort study among the geriatric population failed to establish any association between hip fractures and caffeine intake (40).

Another interesting observation was obtained from a clinical study that scrutinized the risk of fracture in postmenopausal women based on the fracture site. Coffee consumption was found to have a positive association with a wrist fracture, whereas there was no significant association with hip or vertebral fracture (41).

A meta-analysis report documented no significant increase in fracture risk with coffee consumption; however, the relative risk increased from the highest to the lowest category of coffee intake, when compared with those who never drank coffee. The pooled RR of hip fracture was found to be 1.13 (95%CI: 0.86 to 1.48) for individuals with the highest level of coffee consumption (42).

Q4: What are the possible mechanisms of action of coffee on the bone?

As the studies in the literature have contradictory results, possible mechanisms for the negative effects of coffee were predicted to be due to increased urinary calcium excretion and decreased intestinal calcium absorption (41). The estrogenic effects, antioxidant activity or anti-inflammatory property of coffee might contribute to its positive effects on bone. Allred et al. demonstrated that trigonelline, a compound present in coffee, can function as an estrogen receptor agonist in estrogen receptor-positive breast cancer (29,43). Studies have also highlighted prominent antioxidant property of coffee as compared to grape juice, orange, raspberry (44). Chlorogenic acid, an ingredient in coffee, was shown to exhibit an inhibitory effect on osteoclastogenesis (29,45). The anti-inflammatory activity of coffee was attributed to nitric oxide synthase and COX–2 inhibition (46).

Earlier studies have mostly been based on food questionnaires such as the number of cups per day, while randomized controlled trials are lacking. Therefore, further studies are needed with detailed information on confounding factors, coffee types, and longer follow-up periods.

Conclusion

Cohort studies indicated increased fracture risk in high coffee consumer group >4 cups/day coffee consumption.

The results of the studies should be interpreted carefully as some of the studies employed QUS, which is not the gold standard for the assessment of BMD. Also, the coffee intake was assessed with a self-reported food questionnaire in most of the studies. Thus standardization of the cup sizes and brewing types was not considered in most of the studies.

Table 2. Coffee consumption and risk of fracture.

Study	Country	Sample size	Sample type	Design	Follow up time	Coffee dose	Result
Hernandez et al., 1991	USA	84.484 women	Middle aged women	Cohort	6 years	Cup/day	>4 cups/day increase osteoporotic fracture risk
Hallstrom et al., 2006	Sweeden	31.527 women	40-76 aged	Cohort	10.3 years	Never to 4 times or more	Daily intake of 330 mg of caffeine or more (>4 cups/day) is associated with modest increased risk of fracture
Jokinen et al., 2010	Finland	1.681 women	Age 70-73 years	Cohort	10 years	Cups/day	>5 cups/day coffee consumption is associated with trochanteric fractures
Halstrom et al. 2012	Sweeden	61.433 women	Middle aged and older	Cohort	19.4 years	Cups/day	Reduction in bone density but no increased fracture risk
Hansen et al.	USA	34.703 women	55-69 years, postmenopausal	Cohort	6.5 years	Cups/day	Modest association between coffee and fracture risk varying by site
Hallstrom et al., 2014	Sweeden	42.978 men	45-79 years men	Cohort	11.2 years	Cups/day	High coffee consumption was not associated with increased fracture risk
Albrand et al., 2003	France	1.039 women	31-89 years	Cohort	5.3±1.1 years	Cups/day	No association between caffeine consumption and fracture risk
Zhaoli et al.	China	27.959 men, 35.298 women	45-74 years	Cohort	5 years	Cups/day	>4 cups/day is associated with increased fracture risk

Randomized controlled studies are required.

Coffee Consumption and Adrenal Hormones

Limited resources are available regarding the effects of coffee consumption on adrenal hormone metabolism. A double-blind, randomized, cross-sectional study investigated the effect of caffeine ingestion on plasma renin activity and catecholamines. The results suggested that caffeine ameliorated the plasma renin activity by 57%, plasma norepinephrine by 75%, and plasma epinephrine by 207% (47). Caffeine's effect on the hypophysis adrenal axis was investigated previously. Caffeine was found to enhance the levels of ACTH (adrenocorticotropic hormone) and cortisol and remained for 3 h after caffeine ingestion. This suggested that caffeine led to a cortisol rise with the action of ACTH. The blockage of adenosine receptors and interference with cyclic adenosine monophosphate were the possible mechanisms behind this action of caffeine (48).

A placebo-controlled study explored the effects of caffeine on heart rate, blood pressure, and urinary excretion of catecholamines at work and home. The results portrayed increased levels of urinary epinephrine in the caffeine group. Blood pressure and heart rate were also elevated in this caffeine group (49).

A more recent study that investigated the acute effects of caffeine on appetite, inflammation, and energy intake, reported no effect on these parameters. However, this study reported high levels of cortisol in the morning in the caffeinated coffee group (50).

In another randomized, double-blind, placebo-controlled trial, caffeine was found to have an insignificant effect on DHEA-S, androstenedione levels. Contrary to the previous research, this study failed to display the ameliorating effect of caffeine on cortisol levels (51).

Conclusion

Though coffee consumption failed to show promising effects on steroid metabolism, it was associated with elevated urine catecholamine levels.

Coffee Consumption and Thyroid

Q1: Does coffee consumption affect thyroid function in healthy people?

Limited data indicated that coffee has no effect on thyroid function tests in healthy individuals.

In a prospective study from the Netherlands, 2 gr/day Arabica and Robusta oils were given to 11 healthy volunteers for three weeks and serum total and free thyroxine (T4), triiodothyronine (T3), and thyroid-stimulating hormone (TSH) remained unaffected in all the study subjects (52).

To date, no study was found in the literature that correlated the effect of coffee consumption on thyrotoxicosis, goiter or hypothyroidism.

Q2: Does coffee consumption affect levothyroxine treatment?

Clinical and experimental data indicated that coffee may negatively affect levothyroxine absorption in hypothyroid patients.

In a prospective study in 2008 from Italy, 8 hypothyroid patients and 9 volunteers were given LT4 with only water or coffee, and water one hour after coffee. Italian-style coffee physically interacted with LT4 and reduced the intestinal absorption of LT4 (53).

Q3: Is there a relation between coffee consumption and thyroid cancer?

Clinical and epidemiological data provided controversial results regarding the effect of coffee consumption and differentiated thyroid cancer.

A total of 24 studies about thyroid cancer and coffee were found, out of which a total of 10 studies were included after the exclusion of duplications (n=8) and 'not suitable' (n=14) articles.

As documented in Table 3, no association between coffee consumption and thyroid cancer could be extracted from the population-based cohort studies (54-56) and meta-analyses of cohort and case-control studies (57,58).

While a few case-control studies reported contradictory results. Two case-control studies detected coffee consumption reduced the risk of thyroid cancer (59,60) and two studies [a case-control (61), a cohort study

Table 3. Studies without any significant relationship between coffee consumption and thyroid cancer.

Study type	Date and country	Number of subjects	Follow up time	Results
European Prospective Cohort[56]	European muticentric 2018	476.108	14 years	No association was observed between coffee consumption and the risk of total differentiated TC, papillary tumor and follicular tumor in either sex
A prospective Cohort study[54]	USA 2015	97.334	10 years	No association with caffeinated and decaffeinated coffee intake with thyroid cancer
Population-based Cohort[55]	Japan 2011	100.507	14.2 years	No association between coffee consumption and thyroid cancer risk in both for men and women
Meta-analyses[58]	USA 2003	2.725 thyroid cancer cases, 4.776 controls	-	No association between coffee consumption and thyroid cancer
Meta-analyses[57]	Korea 2017	1.039 thyroid cancer, 220.816 controls	-	No association between coffee consumption and thyroid cancer

(62)] showed drinking only caffeinated coffee had a preventive effect on thyroid cancer. In all these studies coffee intake was assessed by a food-frequency questionnaire. The mechanism behind this effect was postulated to be increasing intracellular adenosine monophosphate levels. The antioxidant nature of this adenosine monophosphate yielded an inhibitory effect on tumor growth.

Only two studies have explored the effect of caffeinated or decaffeinated coffee consumption on thyroid cancer (TC) separately. The first one was a case-control study from German and detected that drinking decaffeinated coffee was associated with an increased risk of TC, whereas drinking caffeinated coffee had a preventive effect on thyroid cancer (57,61). The second one was a prospective cohort study from the USA with 167,720 non-white and white participants with 15.3 years follow-up period. This study also observed an inverse association of coffee consumption with thyroid cancer and TC was prevalent among participants who consumed caffeinated coffee, but not in those who consumed decaffeinated coffee. The associations with TC were mostly manifested in whites and it was a dose-dependent relationship (62).

A meta-analysis of 7 seven studies (2 prospective cohorts, 5 case-control studies) also failed to detect any significant association of coffee consumption with TC (57).

Similar findings were observed in another pooled meta-analysis of 14 case-control studies where no consistent association between coffee intake and thyroid cancer could be derived (58).

Conclusion

- Results from most of the cohort studies and meta-analyses reported that coffee consumption does not affect the progression of thyroid cancer.
- Only two studies discriminated between caffeinated and decaffeinated coffee and detected that caffeinated coffee had a preventive effect on thyroid cancer (57).

Coffee Consumption and Gonads

We retrieved 159 studies from a literature search in PubMed and Web of Science. After removing duplicates (n=18) and not suitable (n=109), a total of 32 studies were considered to identify the relationship of coffee consumption with the fertility-fecundability.

Q 1: Does coffee consumption affect female fertility?

Controversial results were reported. Numerous studies recognized a nonsignificant association between coffee or total caffeine consumption and female fertility, as represented in Table 4.

Several studies showed coffee or total caffeine consumption led to reduced fertility (63-72). Most of this effect was found to be dose-dependent (63,64,66-68,70-72). Hakim et al. (72) evaluated coffee consumption with a dietary diary, whereas, other studies used a questionnaire. Higher fecundability was reported with moderate caffeine (400-700 mg/day) intake. On the other hand, heavy caffeine intake (>700 mg/day) was inversely proportional to fecundability (73).

Q 2: Does coffee consumption affect male fertility?

A literature survey portrayed a limited number of studies with men. All of these studies documented coffee consumption by interviews. Coffee intake was positively correlated with SHBG (sex hormone-binding globulin) levels in men (74,75). Cross-sectional studies showed caffeine intake was associated with reduced semen volume (76), sperm concentration, total sperm count, and higher (%14) testosterone levels (75,77). A pregnancy follow-up cohort showed higher maternal coffee consumption at the time of pregnancy was associated with diminished semen volume and testosterone levels (77). Inversely, current male caffeine intake was associated with increased (%14) testosterone levels, but with normal semen quality (77).

Two cross-sectional studies found no association between male coffee consumption and semen quality (78,79). Contrary to this, Adelusi et al. (80), Marshburn et al. (81), and Sobreiro et al. (82) found a positive association between coffee consumption and sperm motility. Nonetheless, Parazzini et al. (83) reported coffee intake increased the propensity of poor semen quality.

Few prospective studies also reported that male caffeine consumption was associated with reduced fecundability (70,73). Coffee intake might indulge in DNA breaks and aneuploidy (84). Curtis et al. (65), Wesselink et al. (85) also found a slight decrease in fecundability with coffee consumption. Male caffeine intake had no significant influence on fertilization, pregnancy or live birth delivery (86,87).

Q3: Does coffee consumption affect gonadal hormone metabolism?

Coffee consumption positively affected SHBG concentrations in women (88,89). Numerous studies indicated conflicting results between free estradiol level and coffee/caffeine intake. Significant associations between caffeine consumption and sex hormone levels in women were detected in some studies (88). Higher caffeine intake (≥200 mg/d), which was evaluated by dietary recalls, was inversely associated with free estradiol concentrations among white women and positively associated among Asian women (90). Other studies estimated higher estrogen levels (88,91) and total testosterone (75) resulting from coffee consumption. Kotsopoulos et al. (89) determined the inverse correlation between increased caffeine intake and luteal free E2 levels. Reduced duration of the menstrual cycle was observed in subjects with a daily caffeine consumption >300 mg (92). On the other hand, androgen or estrogen concentrations remain unaffected as a result of caffeinated beverage consumption (74,93).

Choi et al. (87) determined that higher caffeine intake inversely affected peak E2 in women, undergoing infertility treatment. Elevated or insufficient E2 concentrations can inhibit ovulation. However, altered E2 levels associated with moderate coffee intake failed to modulate ovulatory function (90). Besides, the caffeine levels in serum and follicular fluid were correlated (94). Caffeine levels were inversely related to the number of eggs. However, the association was not established between the success rate of pregnancy and caffeine consumption (94).

Q4: Does coffee consumption affect menopause time?

A cross-sectional study from Norway with 2123 women found that coffee consumption, as estimated by a questionnaire, remained unassociated with early menopause (95). Kinney et al. (96), Cramer et al. (97), and Nilsson et al. (98) also indicated no association between caffeine and age of menopause.

Table 4. Studies without any significant relationship between coffee consumption and female fertility.

Study type	Date and country	Number of subjects	Follow up time	Results
A prospective Cohort study[63]	USA 2016	2.135 pregnancy planners, 662 male	12 m	Total caffeine intake among males, but not females, was non-monotonically associated with fecundability
A prospective population based Cohort study[64]	Denmark 2018	7.574 women	20 yrs	No association between coffee or total caffeine consumption and the risk of primary infertilty in women
A prospective Cohort study[65]	Denmark 2012	3.628 pregnancy planners	12 m	No monotonic trend of coffee consumption on fecundability
A prospective Cohort study[66]	USA 2011	470 pregnancy planners	12 m	No effect of caffeine on fecundability
A prospective Cohort study[67]	USA 1998	187 pregnancy planners	12 m	No effect of caffeine on fecundability
A prospective Cohort study[68]	USA 2009	18.555 women	8 years	No association between intake of coffee or decaffeinated coffee and risk of ovulatory infertility
Cross sectional[69]	Denmark 1991	10.886 pregnant women	-	No association with only low dose coffee intake, smokers and more than 8 cups of coffee consumers showed increased infertility risk
Meta-analysis[70]	Denmark 2017	5 fecundability, 27 spontaneous abortus, 3 medically assisted reproduction study	-	No effect of caffeine or coffee on fecundability, but dose-dependent increased risk of abort

Contrary to this, another cross-sectional study found that a higher intake of coffee was inversely associated with later menopause after controlling for age, total energy, parity, menarche age, and relative weight (99).

A case-control study with postmenopausal women found a positive association between SHBG and caffeinated coffee. However, no relation was observed with caffeinated coffee and sex hormones (93). Similar results were also reported in a cross-sectional study with 2377 women (100).

Nonselective blocking of adenosine receptors by caffeine, chlorogenic acid, and other phytochemicals, resulted in enhanced intracellular concentration of cyclic AMP. As a result of improving liver function by blocking liver adenosine receptors, serum SHBG concentrations may increase.

Caffeine and other bioactive substances in coffee are known to possess a high affinity for the estrogen receptor (101). Besides, both caffeine and estradiol are metabolized by the hepatic enzyme CYP1A2, thus a common metabolism pathway may be responsible for the effect of caffeine on estradiol levels (101).

Q5: What are the effects of coffee consumption on pregnancy?

Caffeine can traverse the placental barrier and therefore, the fetus gets exposed to the same level as that of the mother. This results in an increased level of catecholamines and cyclic adenosine monophosphate that can impact placental blood flow. As a consequence, high dose coffee consumption (≥300 mg/d) is associated with an increased number of spontaneous abortions (94,101,102).

Studies have shown that those who consumed more than 300 mg/day caffeine were associated with fetal growth restriction compared to those consuming below 100 mg/day (103).

The European Food Safety Authority (EFSA, 2015) and the WHO recommend a daily caffeine intake below 200 mg and 300 mg, respectively.

Conclusion

- Relation of coffee consumption with increased SHBG levels, testosterone levels, estradiol level results were conflicting.
- Fecundability studies were also contradictory. However, higher consumption was related to spontaneous abortus.

Summary

Coffee consumption may exert positive effects on reducing type 2 diabetes risk, may have negative effects on the bone with increased risk of fracture over 4 cups/day of coffee consumption, may enhance abortion risk, and have no effect on thyroid cancer development. There are limited data about the effects of coffee consumption on thyroid and adrenal hormones.

Long term randomized controlled studies are essential to elucidate any possible biological interactions of coffee on the endocrine system.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Dilek Gogas Yavuz; Design: Dilek Gogas Yavuz; Control/Supervision: Dilek Gogas Yavuz; Data Collection and/or Processing: Dilek Gogas Yavuz, Ceyda Dinçer, Tuğçe Apaydın; Analysis and/or Interpretation: Dilek Gogas Yavuz, Ceyda Dinçer, Tuğçe Apaydın; Literature Review: Dilek Gogas Yavuz, Ceyda Dinçer, Tuğçe Apaydın; Writing the Article: Ceyda Dinçer, Tuğçe Apaydın; Critical Review: Ceyda Dinçer, Tuğçe Apaydın.

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