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Review Article

How Much of Coffee is Risk-Free for You? The Answer Lies in Your Genes

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Abstract

Coffee is the most popular social drink, owing to its refreshing aroma and tiredness-averting qualities. One cup of coffee contains approximately 96 mg of caffeine. Generally, healthy adults can tolerate up to 400 mg of caffeine in a day (which equates to 2-3 cups of coffee/tea). But in some people caffeine is retained in the blood for a longer time due to certain unfavorable genetic changes, leading to caffeine-associated health risks such as sleep deprivation, anxiety, hypertension, and palpitation. Precisely addressing the underlying genetic cause will aid in effectively managing caffeine-associated health risks through subjective quantification of caffeine and alternating the extra cup of coffee with another refreshing beverage [1,2].

Keywords: Caffeine; Gene; Allele; Single Nucleotide Polymorphism/SNP; CYP1A2 (Cytochrome Enzyme P-450 1A2); Fast/Rapid Metabolizers; Intermediate Metabolizers; Slow Metabolizers; Sleep Latency; Insomnia; ACE/Angiotensin Converting Enzyme

Caffeine and health – the hidden nutrigenetic link

The gene-nutrient interplay in caffeine metabolism is explained in the following sections.

Caffeine metabolism

How quickly do you metabolize caffeine?

Caffeine, the component responsible for giving us alertness or briskness on consuming coffee/tea is a non-nutrient. And hence our body has a mechanism of eliminating this component. An enzyme present in our liver, CYP1A2 (cytochrome enzyme P-450 1A2) takes up the responsibility of eliminating caffeine from our body. Based on the efficiency of this enzyme, caffeine gets eliminated at varying timelines (say 3 to 6 hours) in each of us. This inter-individual difference is caused by the CYP1A2 gene. Low CYP1A2 activity due to an unfavorable genetic change has been associated with higher caffeine toxicity. For instance, a single nucleotide polymorphism (163A>C) in CYP1A2 gene (rs762551) makes its 'C' allele carriers slow metabolizers, while the 'A' allele carriers of this SNP are fast metabolizers of caffeine. The 'C' allele carriers of this intron variant have a 62 to 70% lower CYP1A2 enzyme activity as indicated with a relatively low level of caffeine metabolites like 1,7-dimethylxanthine and 1,7-dimethyluric after a dose of caffeine. The same amount of caffeine will, therefore, tend to have more negative health effects on CYP1A2 slow metabolizers. It is always ideal to revise caffeine recommendations for such sub-groups as below 100 milligrams in a day which equates to 1 cup of coffee/ 2 cups of tea. Slow metabolizers can include antioxidant-rich beverages like green tea in their routine which are low in caffeine content. Nutrigenetic recommendations suggest

regular inclusion of cruciferous vegetables (like broccoli, cabbage, cauliflower, kale, radish and turnip) in the diet as they can increase the rate of caffeine metabolism. Consuming 500g of broccoli can increase caffeine elimination from your body by upto 1.2 times, thus minimizing the ill effects of slow caffeine metabolism. On the contrary, vegetables like carrot, celery, pasley and parsnip can slow down caffeine metabolism, hence do not consume these vegetables for at least an hour after caffeine intake [3].

How likely are you to over-consume caffeine?

Fast metabolizers of caffeine run a risk of caffeine overuse. As they quickly eliminate caffeine from their body, they tend to consume more hiking their dependency. There is a strong genetic link for caffeine overuse which is scientifically evidenced through multiple genes of caffeine metabolism. For instance, the 'T' allele carriers of rs2472297 and rs2470893 in CYP1A2 are susceptible for caffeine overuse due to its fast metabolism.

Caffeine and smoking

Is it ok to consume coffee while smoking?

Smoking amplifies caffeine metabolism. Tobacco in cigarette is a known CYP1A2-inducer. The induction of CYP1A2 is mediated by binding of polycyclic aromatic hydrocarbons of the tobacco smoke to the aryl hydrocarbon receptor (AHR) with consequent transcriptional activation of the CYP1A2 gene. The average change in the rate of CYP1A2 activity shows dose-dependence with cigarettes smoked per day, notably, it varies from 1.22-fold (1–5 cigarettes/day), 1.47-fold (6–10 cigarettes/day), 1.66-fold (11–20 cigarettes/day) to nearly 1.72-fold (>20 cigarettes/day). Smokers who are rapid metabolizers of caffeine tend to be high consumers of caffeinated foods and beverages. Cigarette smoke aggravates their tendency to over-consume caffeinated foods and beverages by up-regulating their caffeine elimination from their body. And this over-consumption can pose a risk for high blood pressure, increased heartbeat and palpitation for a short while after consumption. Hence analyzing genes that have a role in our body's response to cigarette smoke and caffeine elimination can aid in planning appropriate nutrigenetic recommendations. For instance, smokers who are fast metabolizers carrying 'AA' genotype of rs762551 in CYP1A2 gene, metabolize caffeine at 1.6 times the rate of the other genotypes (AC/intermediate metabolizers and CC/slow metabolizers). It is ideal for them to choose decaffeinated foods and beverages during smoking. Inclusion of vegetables like carrot, celery, pasley and parsnip at least an hour before smoking, can bring down their tendency for caffeine overuse [4-6].

Caffeine and sleep deprivation

Is caffeine stealing away your night sleep?

Sleep is the best and easiest meditation and we all love it. Its importance in health is so pronounced that we should act promptly even if we miss a bit of it. Sleep inadequacy can have its root cause in caffeine metabolism. Caffeine can impact the onset of sleep and reduce the sleep quality. Caffeine-interrupted sleep can lead to sleep deprivation the following day, which will show up as fatigue and problems with learning, memory and problem-solving. Caffeine being a brain-stimulant, we use it after waking up in the morning or to remain alert during the day. Caffeine makes us feel alert by blocking certain sleep-inducing chemicals in the brain. Adenosine is a sleep-inducing chemical that our brain produces and keeps accumulating during our waking hours. The more it builds up, the sleepier we become towards the end of the day. Adenosine build-up relates with our circadian rhythm or sleep-wake cycle, wherein the darkness of night and adenosine build-up induce sleep. Adenosine makes your body aware that it is time to go to sleep, and hence if your adenosine levels are low because of caffeine, you would find it difficult to fall asleep. Caffeine interferes with the process of adenosine build-up wherein we remain alert and vigilant during the supposedly sleepy hours of night (insomnia).

The Adenosine receptors encoded by the ADORA2A gene mediate caffeine effects on sleep cycle by regulating the adenosine levels of brain. Unfavorable changes in this gene can impact sleep (sleep latency and quality) and hence caffeine intake should be managed accordingly. A single nucleotide polymorphism in the ADORA2A gene, namely rs5751876 (1976 C→T) makes its 'CC' genotypes more susceptible for caffeine-induced insomnia compared to the 'TT' genotypes. The favorable genetic expression (1976T at rs5751876) reduces the probability of caffeine-induced sleep disturbances and hence avoidance of caffeine-containing foods and beverages nearly 6 hours prior to sleep is sufficient. While individuals who are predisposed to caffeine-induced sleep disturbances due to unfavorable genetic changes (1976C at rs5751876) are recommended to avoid the consumption of caffeine-containing foods and beverages for at least 8 hours prior to their sleep [7-9].

Caffeine and anxiety

Have you experienced anxiety after a cup of coffee?

Caffeine's popularity worldwide can be attributed to its ability to promote wakefulness, enhance mood and cognition. At optimal levels, it renders alertness and enhances cognitive performance. But at higher levels, it can cause anxiety and its symptoms like nervousness, rapid breathing, trembling, jitteriness, high blood pressure and palpitation. Caffeine can diminish the levels of a chemical called adenosine in the brain. Caffeine blocks adenosine receptors, causing increases in components like dopamine, noradrenalin, and glutamate. These can potentially increase blood pressure and heartbeat/ heart rate. Due to genetic changes in adenosine receptors (ADORA2A), some people are more prone to experience the negative responses of caffeine. For example, a genetic variation in ADORA2A gene, rs35320474, makes its 'T' allele carriers more prone to caffeine-induced anxiety and panic disorder compared to its 'C' allele carriers. Following are gene-specific recommendations to combat the ill effects of this unfavorable genetic change. Exercise for at least 30 minutes in a day (30 minutes at once or 2 to 3 segments of 10 - 15 minutes). This way you can enjoy a positive mood with feel-good components like endorphins and also alleviate anxiety. Essential fatty acids and functional foods such as resveratrol, berberine, curcumin and the flavonoid genistein, modulate AMPK dependent processes. Adenosine monophosphate-activated kinase/AMPK, is a serine/ threonine kinase that preserves intracellular homoeostasis, and it gets activated with higher levels of intracellular AMP (adenosine monophosphate). The AMPK improves mitochondrial metabolism and promotes neurogenesis in the hippocampus. This results in enhanced memory and learning, alongside a reduction in anxiety and depression. So adequately include foods like fresh grapes, peanut, peanut butter, pistachios, avacado, blueberries, chia seeds and flax seeds which are filled with anxiety-relieving nutrients (like resveratrol, B vitamins, copper, magnesium and essential fatty acids) [7,10,11].

Caffeine and blood pressure

Does coffee bother you with high blood pressure?

Coffee is one of the world's most beloved beverages. Its caffeine content may cause a short, but noticeable increase in your blood pressure, even if you are normotensive. And this effect is due to the temporary vasoconstriction induced by caffeine (say up to 3 hours after consumption). On an average, 200-300 mg caffeine, that is the amount equivalent to 2 to 3 cups can increase the upper (systolic) and lower (diastolic) numbers of your BP by around 8 mm Hg 6 mm Hg. To see if caffeine might be raising your blood pressure, check your blood pressure before drinking a cup of caffeinated beverage and again 30 to 120 minutes afterward. If your blood pressure increases by about 5 to 10 points, you may be sensitive to the blood pressure raising effects of caffeine. The blood pressure response to caffeine differs from person to person, probably due to genetic changes. For instance, the 'C' allele carriers of the CYP1A2 gene (gene variant rs762551) are considered slow metabolizers and tend to have an increased risk of caffeine-induced hypertension when they consume more than 100 mg of caffeine per day. If you plan to cut back on caffeine, do so gradually over several days to a week to avoid withdrawal headaches. Milk (skimmed or low fat varieties with fat content not exceeding 3%) has the potential to lower BP, as it has bioactive peptides and ACE-inhibitors to normalize blood flow. Hence add more milk to your caffeinated beverages. Vegetables like carrot, celery, pasley and parsnip can make caffeine stay in your body for longer, hence do not consume these vegetables for at least an hour after caffeine intake. Also, if you have high blood pressure, avoid caffeine right before activities that naturally increase your blood pressure, such as exercise, weightlifting or hard physical labor [12-14].

Caffeine and heart health

Do you have a risk for heart health abnormality on consuming caffeine?

Caffeine has a tendency to increase blood pressure and heart beat for a short while (say 1 to 3 hours) after consumption. Both these effects can negatively impact heart health if the consumption exceeds the recommended intake. Commonly relatable signs of such heart health disturbance are palpitation, shortness of breath and profuse sweating. The extent to which caffeine affects heart health varies from person to person. People who eliminate caffeine slowly have a chance of retaining it for a longer time in the body and this implies as higher probability for its negative effects. 'Slow' caffeine metabolizers, that is, carriers of 'CC' genotype at rs762551 in the CYP1A2 gene might have an increased risk for myocardial infarction if their caffeine intake is high (their recommendation is not more than 100 mg of caffeine per day).

Following is a probable mechanism for caffeine-induced heart health disturbances. Caffeine has a half-life of 5.7 hours, and its maximum concentrations are reached within an hour of consumption. With nearly 100% bioavailability, caffeine exerts varied effects on adenosine receptors, intracellular calcium trafficking and sympathetic activation. Caffeine blocks calcium reuptake into the sarcoplasmic reticulum resulting in a rise in cytosolic calcium concentration. An increase in intracellular calcium potentially increases sinus rate and induces atrial arrhythmia by enhancing automaticity of atrial pacemaker cells and after depolarization-induced triggered activity. 250 mg of caffeine equating to nearly 3 cups of coffee can acutely increase the levels of norepinephrine (by 75%) and epinephrine (by 207%) [15-19].

Caffeine and blood sugar

Is there a risk of blood sugar hike after consuming coffee?

Caffeine can interfere with glucose disposal from the blood following a meal. After a meal, ideally there is a rise in blood glucose until it is absorbed by our cells for energy and the surplus being stored for future use. Caffeine when consumed along with a meal, escalates the post-meal blood glucose rise. That's because caffeine can affect how your body responds to insulin, the hormone that allows blood sugar to enter your cells and get changed into energy. Therefore it is good to avoid caffeine intake along with a meal. People with blood sugar disturbances, especially those with pre-diabetes or diabetes should strictly follow this. In a research study conducted by Lane., *et al*. 2004, intake of 375 mg of caffeine prior to meal consumption, resulted in a 21% increase in postprandial glucose and a 48% increase in insulin AUC amongst individuals with type 2 diabetes.

Genes have a crucial role in caffeine-induced hyperglycemia, and it is supported by the following example. A genetic variation in the ADORA2A gene, rs5751876 (1976T > C), makes its 'CC' genotypes more vulnerable to elevated blood glucose levels after consuming caffeine along with carbohydrates. This effect was not seen in CT/TT genotypes. A possible mechanism for caffeine-induced postprandial glycemia is an increase in the epinephrine and norepinephrine levels due to the antagonization of adenosine receptors and their excitatory influence on the sympathetic nervous system. Adenosine, the product of adenosine 5-triphosphate (ATP) metabolism, inhibits the sympathetic nervous system, consequently constraining the release of norepinephrine and epinephrine. Epinephrine and norepinephrine halt glucose disposal and up-regulate glucose mobilization. Caffeine and its metabolites, such as methylxanthine and theophylline competitively bind with the adenosine receptor (ADORA2A) acting as its potent antagonists, thus paving way for postprandial hyperglycemia when consumed along with carbohydrates. Hence the nutrigenetic recommendation is to avoid consuming caffeinated foods and beverages along with your main meal as caffeine can increase blood sugar. Also make sure that 1 hour before- and after- a meal you refrain from caffeinated foods and beverages. Include cruciferous vegetables like broccoli, cabbage, cauliflower, kale, radish, turnip and garlic in your diet as they can lower blood sugar and favorably alter caffeine metabolism [20,21].

Caffeine and bone health

Are you so much addicted to caffeine that you are unknowingly compromising on bone health.

We all are aware that calcium is our bone-friendly mineral, and its lack can hence give us bone health issues. Caffeine can pull calcium away from our bones causing an increased calcium excretion. Every cup of coffee is linked with a 5 mg net loss of calcium from our body owing to a decreased intestinal calcium absorption and an increased excretion of the mineral. This in the long run can lead to low bone mineral density resulting in osteoporosis, osteopenia and other conditions that relate with unhealthy bones. People who consume more of caffeine-containing foods/ beverages are therefore at risk of caffeine-induced calcium loss from the bone. Genes like CYP1A2 take up the responsibility of eliminating caffeine from our body. Fast metabolizers carrying 'CC' genotype of rs11854147 in CYP1A2 gene, metabolize caffeine faster compared to the other genotypes (CT/intermediate metabolizers and TT/ slow metabolizers). Quicker the elimination, higher would be the tendency to consume more of caffeinated foods and beverages and a resultant low bone mineral density (BMD). Thus high consumers are at a risk for bone health issues. It is healthy to add more milk (choose skimmed or low fat varieties with fat content not exceeding 3%) to your caffeinated beverages as milk is a great source of calcium and other bone-healthy nutrients. Also remember to avoid the intake of caffeine for at least half-an-hour before and after your exercise. This is because exercise adds on to bone health, and this benefit can get affected by caffeine [22].

Caffeine and iron absorption

Is coffee having an effect on your iron absorption?

The caffeine, to some extent, and mainly the polyphenols present in coffee and tea interfere with our iron absorption. A cup of coffee when consumed along with a meal can reduce iron absorption by about 35%, while tea with a higher tannin content can reduce iron absorption by up to 62%. Coffee consumption may also have an effect on iron storage levels. The 'Framingham Heart Study' amongst the elderly revealed that five cups of coffee per week could be associated with a 6% lower level of ferritin, a protein that indicates iron storage levels. Caffeine's effects will last for several hours, depending on how quickly or slowly it is metabolized by the body. Hence in 'slow' caffeine metabolizers, that is, carriers of 'CC' genotype at rs762551 in the CYP1A2 gene, caffeine that is retained for an unusually longer time can drastically bring down iron absorption. Effects of caffeine on iron absorption rely on when you drink your coffee. Supporting research evidence indicated that a cup of drip coffee or instant coffee ingested along with a meal reduced iron absorption from 5.88% to 0.97%. Notably, when the strength of the instant coffee was doubled, iron absorption reduced to a further 0.53%. The same effect persisted when coffee was consumed an hour after the meal. Hence, it is healthy to avoid consuming caffeinated foods and beverages along with your main meal as iron absorption gets lowered. Also make sure that 1 hour before- and after- a meal you refrain from caffeinated foods and beverages. Vitamin C rich foods like guava, amla, orange, lemon, kiwi, strawberries, blackberries, blueberries and tomato improve iron absorption. Hence combine iron-rich foods with those rich in vitamin C, for example, dates along with blueberries [23-26].

Caffeine and appetite

Does coffee affect your appetite?

Asprosin is a hormone released in our body to stimulate appetite. Caffeine can reduce asprosin levels and consequently lower our appetite perception. This negative effect of caffeine is observed in some people who tend to over-consume caffeinated foods and beverages. Caffeine over-consumption is seen in individuals who rapidly eliminate caffeine from their body. Quicker the elimination, higher would be the tendency to consume more of caffeinated foods and beverages. And high consumers are at a risk for appetite suppression if caffeine is consumed shortly before a meal. Apart from this, their food quantity can also get affected if caffeine is consumed along with a meal. Considering the CYP1A2 gene as an example, its variation rs762551 revealed high coffee consumption amongst 'AA' genotypes who were rapid/fast metabolizers compared to slow metabolizers/CC genotypes ($P = 0.008$ after adjustment for age, sex, and BMI). The 'AA' genotype was associated with lower appetite perception, reduced energy and dietary fat intake and a relatively lower BMI along with decreased circulating asprosin levels. A supporting research evidence states coffee consumption 3 hours prior to a meal had minimal influence on food and macronutrient intake, while if caffeine is consumed just half-an-hour before a meal, it might acutely suppress the energy intake. Hence it is ideal to avoid the consumption of caffeinated foods and beverages for at least an hour prior to the main meal because caffeine can reduce the levels of asprosin. And also make sure not to consume caffeine along with your meal to enjoy your adequate meal quantity. Include vegetables like carrot, celery, parsley and parsnip as they can avert caffeine-induced appetite suppression [27,28].

Caffeine and sports performance

Caffeine favors endurance or sprint in you?

Fast metabolizers may quickly metabolize caffeine and achieve its benefits during high intensity, short duration exercises (sprinting/power). Whereas, slow caffeine metabolizers might have a beneficial effect from limited caffeine intake (say less than 100 mg) when competing in a longer duration event (>1 h) as the biologically active levels of caffeine stay for more time in the body. Therefore, individuals may require different levels of circulating caffeine to receive an equitable effect based on their genetics. Fast metabolizers of caffeine may perform well in sprinting/power athletic events in response to caffeine intake of not more than 400 mg in a day. The ergogenic effects of caffeine on aerobic exercises or endurance sports is significantly higher in 'AA' genotypes/ fast metabolizers of rs762551 in CYP1A2 gene compared to the other genotypes. While slow metabolizers might require caffeine restriction (not more than 100mg) to carry out athletic activities. The dose-dependent effect of caffeine on various CYP1A2 genotypes was researched in male athletes who were on 10-km cycling time-trial performance. Caffeine was ingested at doses such

as 0 mg, 2 mg (low dose) or 4 mg (moderate dose) per kg body mass. In 'AA' carriers, the cycling time improved by 6.8% at 4 mg/kg of caffeine dose. While amongst CC genotypes, the same dosage impaired performance by 13.7% [29,30].

Conclusion

Caffeine, though a non-nutrient, holds an inseparable role in our routine owing to its rich aroma, and tiredness-resistance. Still, overconsumption is not warranted as it can cause deleterious effects on health. Overconsumption is ascertained mainly through the rate of its metabolism, hence, genetic insights are much needed to define dosage and the susceptibility for overuse. Sudden caffeine withdrawal may trigger unpleasant health signals like headache, so it is necessary to opt for nutrigenetic recommendations to cope with the compromise in metabolism rate.

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