

Original Article

Simultaneous coffee caffeine intake and sleep deprivation alter glucose homeostasis in Iranian men: a randomized crossover trial

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Background and Objectives: Sleep deprivation and coffee caffeine consumption have been shown to affect glucose homeostasis separately, but the combined effects of these two variables are unknown. **Methods and Study Design:** Forty-two healthy Iranian men, aged 20-40 years old, were assigned to three groups in a randomised crossover trial involving three treatments with two-week washout periods. Subjects were moderate coffee consumers (≤ 3 cups/day), and had a Pittsburgh Sleep Quality Index ≤ 5 . Each treatment involved three nights of deprived sleep (4 hrs. in bed) plus 3 \times 150 cc/cup of boiled water (BW treatment), decaffeinated coffee (DC treatment, without sugar, 99.9% caffeine-free), and caffeinated coffee (CC treatment, without sugar, 65 mg caffeine/cup). DC and CC treatments were blinded. At the end of each treatment, fasting serum glucose (using enzyme assays) and insulin (using electrochemiluminescence immunoassay) were measured and, again, two hours after an oral glucose tolerance test (OGTT). Insulin resistance was quantified with the homeostasis model. **Results:** Repeated measures ANOVA indicated no significant difference between the treatments in fasting serum glucose ($p=0.248$) or insulin resistance ($p=0.079$). However, ANOVA demonstrated differences between treatments in fasting serum insulin ($p=0.004$) and glucose, as well as insulin after OGTT ($p<0.001$). Pairwise comparisons test (within subjects) showed that the CC treatment yielded higher serum glucose and insulin after OGTT ($p<0.001$), higher fasting serum insulin ($p=0.001$), and increased insulin resistance ($p=0.039$) as compared to the DC treatment. **Conclusions:** Thus caffeinated coffee was more adverse for glucose homeostasis compared to decaffeinated coffee in individuals who were simultaneously sleep deprived.

Key Words: coffee caffeine, sleep deprivation, glucose homeostasis

INTRODUCTION

In today's fast-paced world, sleep is often considered an inefficient activity, and voluntary bedtime restrictions have turned into a distinctive feature of modern societies.¹ However, sleep deprivation and even less severe forms of sleeplessness can have adverse consequences such as insulin resistance and increased serum glucose and insulin. There is a higher risk of type 2 diabetes in healthy individuals who restrict sleep.²

At the same time, caffeine is an accepted pharmacological substance, widely used through coffee and tea consumption.³ People habitually consume it when they intend to sleep less.⁴ While studies have previously shown acute coffee caffeine consumption to negatively affect glucose metabolism in healthy subjects,⁵ evidence from more recent studies has demonstrated a decreased risk of type 2 diabetes mellitus, following regular consumption of caffeinated coffee and even decaffeinated coffee.^{6,7}

In this context, the lifestyle of Iranians has changed due to modernization, including a significant increase in

working hours. As a result, many Iranians have experienced a reduction in the number of hours of sleep they get at night.⁸ As the most common sleep disorders, sleep deprivation affects more than 31% of Iranians, leading to several clinical and mental outcomes.⁹ Meanwhile, Iran is transforming into a million-dollar market for coffee growers.¹⁰ In seeking new markets, coffee traders have finally succeeded in altering Iranians' tea-friendly preferences.¹¹ Since Iranians have reported drinking coffee in order to sleep less,¹² the simultaneous effects of sleep deprivation and caffeine consumption in coffee could

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have greater health implication. Despite the growing evidence that reduced sleep duration or increased consumption of caffeine in coffee appears to conversely affect glucose homeostasis, no study has yet to determine the simultaneous effects of both sleep deprivation and coffee caffeine intake.

In the present study, we defined glucose homeostasis as the process of maintaining blood glucose at a steady-state level of 70-99 mg/dL.¹³ Research has shown any defect in glucose homeostasis to be characterized by hyperglycaemia, impaired insulin action/or insulin secretion, impaired glucose tolerance and insulin resistance.¹⁴ Therefore, this study aimed to determine the effects of caffeine consumption in coffee coupled with sleep deprivation on selected metabolic biomarkers related to glucose homeostasis (serum glucose, insulin levels, and insulin resistance) among healthy Iranian adult men. We hypothesized that there would be no significant changes in the levels of metabolic biomarkers related to glucose homeostasis when sleep deprivation was simultaneously coupled with caffeine consumption in coffee.

METHODS

Subjects, study design, and sampling method

The study was conducted among healthy Iranian adult men, aged 20-40 years old, who were living in Tehran, the capital of Iran. Ethical approval was obtained from the Ethics Committee, the Tehran University of Medical Sciences, and all participants signed a written consent prior to participation in the study. To detect a significance difference ($p < 0.05$) with a statistical power of 0.86, we calculated a total sample size of 36 subjects in three groups of 12.¹⁵ Due to the nature of partial sleep deprivation (PSD) in which people show a lesser tendency toward nocturnal awakenings, we employed the consecutive sampling method. Therefore, by studying everybody available, a good representation of the overall population was recruited in a reasonable period of time.¹⁶

Subject selection and recruitment

We initially distributed a Persian version of the Pittsburgh Sleep Quality Index (P-PSQI) questionnaires¹⁷ among 722 men, aged 20 to 40 years old living in four geographical areas in the north, south, west and east of Tehran. Subjects with a PSQI ≤ 5 (good sleepers) were invited for further screening, including an interview and anthropometric measurements of weight, height, waist, and hip circumferences (WC & HC). We also calculated the waist-to-hip ratio (WHR) and BMI, defined as the body mass in kilograms divided by the square of the height in square meters. To predict body fat percentage (BF%) based on current BMI, where gender was considered equal to 1 for adult men, we employed the following age and sex prediction formula $BF\% = (1.20 \times BMI) + (0.23 \times \text{age}) - (10.80 \times \text{gender}) - 5.40$.^{18,19}

The inclusion criteria for the study were general healthiness with no family history of serious medical problem, such diabetes, lung or heart disease, arthritis, other rheumatic disease, cancer or other chronic condition. Subjects were habitual coffee drinkers, no more than 3 cups/day with moderate physical activity (irregular and ≤ 5 h/wk) and a BMI of 18-24.9 kg/m². Excluded from the study

were subjects who took medications or supplements, followed a prescribed diet, worked split shift, smoked, or travelled across time zones during the 4 weeks before the study.

Adaptation night

Subjects who met the study criteria stayed one night in the research unit to familiarize themselves with the study protocol. They were instructed to set their bedtime between 23:00 pm and 7:00 am and mealtimes at 8:00 am, 13:00 and 20:00 pm for the following two weeks. However, we permitted a deviation of ± 30 mins from the specified times was. We asked subjects to continue with their habitual dietary intake; they did not need to have any special changes in their food habits or to follow a particular diet in the following two weeks. However, we did provide a list of caffeine-containing foods they should avoid. We reminded subjects to avoid heavy physical activities, fasting, and taking supplements or medications over the following two weeks. We measured the baseline metabolic indicators the next morning after a one-night stay in the research unit in order to ensure that we had recruited subjects with normal biomarker blood levels to participate in the study.

Run-in period

Subjects were then allowed to return to their normal lives for a two-week run-in period for washout of caffeine and to ensure that they would be able to endure caffeine depletion.^{20,21} Meanwhile, they also had an opportunity to adapt to the study's protocol and the instructions received during adaptation night, such as fixed bedtimes and mealtimes. Subjects were required to complete three 24-hour dietary recalls/week (two for weekdays and one for weekend day). These recalls involved a call interview during the two-week run-in period. We used the Dorosti Food Processor (DFP) software, created by the National Research Institute of Nutrition and Food Science (Iran), to calculate the dietary intakes of energy from carbohydrate, fat, and protein.^{22,23} The results were combined to calculate a subject's mean reported Energy Intake (rEI) obtained through the six 24-hour food recalls during the two-week run-in period.

We calculated the total energy requirements using the Harris-Benedict equation. This equation has validity in normal weight adults^{24,25} at the group level,^{22,23} similar to the current study. Adding a physical activity level (PAL)²⁸ for each subject individually, we calculated the predicted Energy Requirement (pER) as follow: energy requirement (for men) = $[66.5 + (13.75 \times W) + (5 \times H) - (6.77 \times Y)] \times PAL$, where W was actual weight in kilograms, H was height in centimeters, and Y was age in years. We compared the rEI with pER for each subjects individually. Based on the McCrory equation,²⁹ we identified subjects whose mean reported energy intake was more or less than 30% of their predicted energy requirements as over-reporting or under-reporting subjects, respectively. Thus, only subjects with a rEI of a lower limit of 70% to an upper limit of 130% ($70\% \text{ pER} < \text{rEI} < 130\% \text{ pER}$) were recruited to participate in the study.

Randomized crossover controlled trial

Subjects were randomized to one of three groups. They consume a light meal before coming to the research unit. Each participated in a randomized crossover trial including three treatments in random order separated by two-week washout intervals. This two-week period was intended to washout caffeine from coffee intake and to minimize carry-over effects that might have arisen due to treatment sequence.^{20,21} Each treatment comprised three consecutive nights of deprived sleep with only 4 hours in bed and three 150 cc/cup of boiled water (BW treatment), decaffeinated coffee (DC treatment), or caffeinated coffee (CC treatment), which were given at 20:00 (one cup), 20:40 (one cup) and 21:20 (one cup).

The selected caffeinated/decaffeinated coffee brand had no added sugar, and was Nescafe - Original Instant Coffee, Black. While the decaffeinated coffee was 99.9% caffeine-free³⁰ each cup of 150 cc selected caffeinated coffee (2 gr coffee) contained 65 mg caffeine.³¹ Therefore, subjects received an amount of 195 mg caffeine^{32,33} regarded as safe as three cups of caffeinated coffee in the CC treatment. Subjects were not allowed to eat or drink, except for the water or study beverages in the treatment specified. They were blinded to decaffeinated and caffeinated coffee in the DC treatment and CC treatment, but naturally not to boiled water in the BW treatment. However, the primary researcher was blinded to all three treatments. When not engaged in task, subjects were permitted to study, participate in sitting games, or interact with each other and/or research team. Subjects were kept awake (with light activities) until bedtime at 2:45 am (Night 1), when the lights were turned off until the next morning at 07:00 am (Day 1). An experienced researcher continually monitored each group of subjects throughout the night.

For identical conditions, all subjects were required to stay in the research unit for the entire three days. The study was designed to keep subjects in a condition mirroring their typical lifestyle and physical activity levels. During the prolonged waking hours due to the sleep deprivation protocol, subjects spent time on personal activities and made use of facilities available in the research unit. They were able to study, play sitting games and watch unexciting movies. Controlled by researchers, subjects were not permitted to do any moderate to heavy physical activities or to nap during the day. We used a fixed PAL of 1.53²⁸ to calculate energy requirements. The energy intake of each subject was divided into five meals during the day, including breakfast (at 8:00 am), first snack (at 10:00 am), lunch (at 13:00 pm), second snack (at 16:00 pm), and diner at (19:00 pm). As described, the three cups of boiled water or one of the study beverages of caffeinated or decaffeinated coffee were consumed at 20:00, 20:40 and 21:20 pm in the treatment specified.

The same procedures were repeated for Nights 2 and 3 and Day 2. However, subjects were not given breakfast at 8:00 am on Day 3 for the purpose of metabolic assays. The assays were similar to the baseline assays carried out after the adaptation night. Each group received three treatments in random order with two-week washout intervals in between. We measured the metabolic biomarkers at the end of each treatment.

Assays

We measured fasting serum glucose and insulin (time 0) and glucose and insulin levels 2 hours after an OGTT (time 2) at baseline and end of each treatment. In the case of OGTT, subjects were given a ready-to-use test solution containing 75 g glucose dissolved in 300 mL water, immediately after fasting blood sampling. They were instructed to gently drink the test solution within 5 mins. The second blood sample was typically drawn 2 hours (120 mins) after drinking the ready-to-use test solution. To measure serum blood glucose, we employed enzyme assays³⁴ using commercial kits (Pars Azmoon, Tehran, Iran) with a sensitivity of 0.11 mmol/L or 2 mg/dL on auto analyzer Biolis. To measure the values of serum insulin, we used the electrochemiluminescence immunoassay (ECLIA)³⁵ and commercial Kits (Roche, Mannheim, Germany) with a lower detection limit of 0.2 μ IU/mL on Elecsys analyzer. To quantify insulin resistance, we used HOMA-IR (Homeostasis Model of Assessment - Insulin Resistance) and the US formula: fasting glucose (mg/dL) \times fasting insulin (μ U/mL) / 405.³⁶

Statistical analysis

We performed statistical analyses using SPSS for Mac version 21. The blood values of metabolic biomarkers at baseline and during different treatments of the study are presented as mean \pm SD. The baseline values were measured to evaluate health and, ensure that subjects had normal metabolic values.³⁷

The Kolmogorov-Smirnov test showed that the outcome variables were normally distributed. Thus, a one-way repeated measures analysis of variances (ANOVA) was conducted to evaluate the null hypothesis that there was no significant beverage effect on the levels of metabolic biomarkers studied when sleep deprivation was simultaneously coupled with boiled water, decaffeinated coffee or caffeinated coffee. The statistical differences within-subjects effects/between the treatments were reported at a significance level of 0.05. When $p < 0.05$, the statistical difference between three treatments was considered as significant. This indicated that the statistical data analysis (ANOVA) found significant evidence to reject the null hypothesis, suggesting that there were significant changes in the levels of metabolic biomarkers related to glucose homeostasis when sleep deprivation was simultaneously coupled with boiled water, decaffeinated coffee and caffeinated coffee.

However, as ANOVA does not identify where differences occur, when ANOVA indicated a statistically significant difference, we used the Least Significant Difference (LSD) in order to determine which specific means (pairwise treatments) differed in a statistically significant manner. In other words, the follow-up comparisons of the LSD test determined whether or not the differences between boiled water and decaffeinated coffee (the BW and the DC treatments), boiled water and caffeinated coffee (the BW and the CC treatments), and decaffeinated coffee and caffeinated coffee (the DC and the CC treatments) were statistically significant among subjects who were simultaneously sleep deprived.

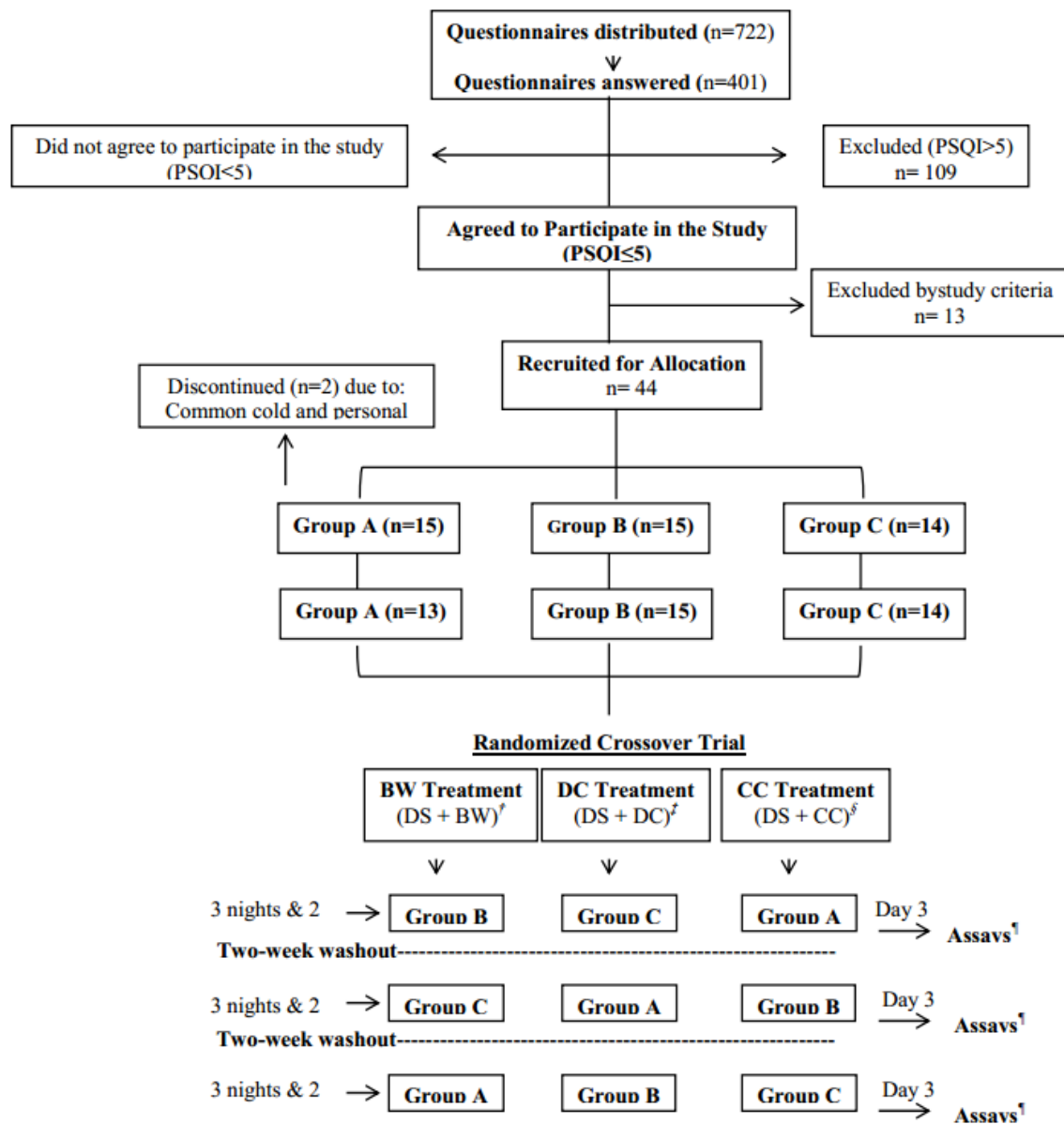


Figure 1. Flowchart of subjects' recruitment and randomized crossover trial determining the simultaneous effects of sleep deprivation and coffee caffeine consumption on biomarkers related to glucose homeostasis among healthy Iranian adult men.

[†]BW Treatment: deprived sleep (3 nights as 4 hrs. in bed) + 3 cups of 150 cc boiled water (DS + BW).

[‡]DC Treatment: deprived sleep (3 nights as 4 hrs. in bed) + 3 cups of 150 cc decaffeinated coffee - 99.99% caffeine-free (DS + DC).

[§]CC Treatment: deprived sleep (3 nights as 4 hrs. in bed) + 3 cups of 150 cc caffeinated coffee - 65 mg caffeine/cup (DS + CC).

[¶]Fasting serum glucose and insulin, and the levels of glucose and insulin 2 hours after an oral glucose tolerance test.

RESULTS

Recruitment and attrition rate

Figure 1 presents a flowchart of subjects' recruitment and the study design. As shown in Figure 1, of total of 722 sleep questionnaires distributed, only 57 subjects with a $PSQI \leq 5$ (good sleepers) agreed to participate in the study. Out of 57 subjects, six subjects were excluded from the study: one construction worker, one shift worker and four others because of a BMI of greater than 24.9 kg/m^2 . Seven subjects were also excluded because of misreporting of energy intake records during the run-in period; amongst them five subjects were identified as under-reporting and two as over-reporting records. Consequently, only 44 subjects remained, of which one withdrew because of personal reasons and one left the study due to common

cold. Therefore, a final number of 42 subjects completed the study's randomized crossover trial. Figure 1 displays how subjects were placed in the three groups of 13 (group A), 15 (group B), and 14 (group 3). When calculating sample size, this distribution was compatible with the total sample size of 36 subjects in three groups of 12.

Randomised crossover controlled trial

Table 1 shows the baseline characteristics of the 42 subjects who participated in the study. The table indicated that the mean PSQI of the subjects was 2.88 ± 1.84 , and they had an average sleep time of 3 hours and 51 mins during the trial. As shown in table 1, the mean age was 27.9 ± 4.45 and subject had a mean BMI of $22.8 \pm 1.41 \text{ kg/m}^2$. The mean serum glucose was $81.0 \pm 3.33 \text{ mg/dL}$ in

Table 1. Mean baseline physical and biochemical characteristics of the subjects (n=42)

Characteristics	Values (mean±SD)
Age (y)	27.9±4.45
Weight (kg)	73.0±7.02
Height (cm)	179±6.61
BMI (kg/m ²)	22.8±1.41
WC (cm)	88.3±3.24
HC (cm)	96.0±5.23
WHR	0.92±0.03
Body fat (%)	17.6±1.96
Average sleep time	3 h 51 mins
PSQI	2.88±1.84
Glucose (mg/dL)	
Time 0	81.0±3.33
Time 2	96.4±3.47
Insulin (μIU/mL)	
Time 0	6.93±0.79
Time 2	23.5±3.29
HOMA-IR	1.39±0.22

WC: waist circumference; HC: hip circumference; WHR: waist-hip ratio, BF: body fat; PSQI: the Pittsburgh Sleep Quality Index.

Time 0: fasting serum glucose/insulin.

Time 2: levels of glucose/insulin 2 hours after oral glucose tolerance test.

time 0 (fasting) and 96.4±3.47 mg/dL in time (2 hour after OGTT). The mean values for insulin time 0 and 2 were 6.93±0.79 μIU/mL and 23.5±3.29 μIU/mL, respectively, while the mean value for HOMA-IR was 1.39±0.22.

Table 2 shows the mean values of HOMA-IR and glucose and insulin in time 0 and time 2 during the study's three different treatments. Figure 2 presents the analysis of variances for the mean level of metabolic biomarkers related to glucose homeostasis by time in the study's different conditions.

Serum glucose

Table 2 shows that the lowest mean glucose time 0 was in the BW treatment when subjects were sleep deprived (4 hrs/night in bed during 3 consecutive nights) and received

3×150 cc/cup of boiled water. The highest mean glucose time 0 was found in the DC treatment, when the same subjects were given 3×150 cc/cup of decaffeinated coffee (No added sugar - 99.9% caffeine free). For glucose time 2, the lowest mean value was found in the DC treatment, while the highest occurred in the CC treatment, when subjects received 3×150 cc/cup of caffeinated coffee, no added sugar containing 65 mg caffeine/cup (Table 2). As shown in Table 2, glucose time 0 and glucose time 2 fluctuated following different study treatments.

A repeated measures ANOVA indicated no statistically significant beverage effect on mean glucose time 0, $F(2, 82)=1.42$, $p=0.248$ (Figure 2a). Thus, we found no significant evidence to reject the null hypothesis, suggesting that boiled water, decaffeinated coffee and caffeinated coffee does not significantly change fasting serum glucose when subjects were simultaneously requested to be sleep deprived. Although not required, post hoc tests of LSD found no statistical differences (Figure 2a, $p>0.05$) in the fasting serum glucose between the BW and DC treatments ($p=0.072$), BW and CC treatments ($p=0.488$), or DC and CC treatments ($p=0.371$).

A one-way repeated measures analysis of variances (ANOVA) determined that mean glucose time 2 differed significantly between the treatments $F(2,82)=110$, $p<0.001$ (Figure 2b). Follow-up comparisons using LSD tests (Figure 2b) revealed that the DC treatment caused a statistically significant decrease ($p<0.001$) in glucose time 2 as compared to the BW treatment (109±5.10 mg/dL vs 117±5.85 mg/dL, respectively). However, when subjects received the CC treatment, glucose time 2 increased to 128±6.83 mg/dL, which was statistically significantly different for both the BW and DC treatments ($p<0.001$).

Serum insulin

Table 2 shows that the lowest mean insulin time 0 was in the DC treatment and the highest occurred in the CC treatment. For insulin time 2, the lowest mean value occurred in the BW treatment, while the highest in the CC treatment (Table 2). As shown in table 2, while insulin time 0 fluctuated slightly, insulin time 2 has steady ele-

Table 2. Mean of metabolic biomarkers related to glucose homeostasis according to the study treatments (n=42)

Parameters	BW treatment [†]	DC treatment [‡]	CC treatment [§]
	DS+BW (Range)	DS+DC (Range)	DS+CC (Range)
Glucose (mg/dL)			
Time 0	90.9±4.88 (83.6-100)	92.8±5.13 (83.2-103)	91.7±5.49 (82.1-102)
Time 2	117±5.85 (107-127)	109±5.10 (99.3-119)	128±6.83 (116-140)
Insulin (μIU/mL)			
Time 0	8.25±1.39 (6.00-10.60)	7.74±1.38 (5.40-10.2)	8.66±1.09 (6.50-10.5)
Time 2	28.9±3.85 (20.7-36.6)	30.7±3.98 (22.7-38.5)	44.7±5.85 (33.5-56.9)
HOMA-IR	1.87±0.41 (1.24-2.62)	1.79±0.42 (1.11-2.59)	1.98±0.36 (1.32-2.65)

[†]BW Treatment (DS + BW): deprived sleep (3 nights as 4 hrs. in bed) + boiled water (3 cups of 150 cc).

[‡]DC Treatment (DS + DC): deprived sleep (3 nights as 4 hrs. in bed) + decaffeinated coffee (3 cups of 150 cc- 99.99% caffeine-free).

[§]CC Treatment (DS + CC): deprived sleep (3 nights as 4 hrs. in bed) and caffeinated coffee (3 cups of 150 cc- 65 mg caffeine/cup).

Time 0: fasting serum glucose/insulin.

Time 2: serum glucose/insulin two hours after OGTT.

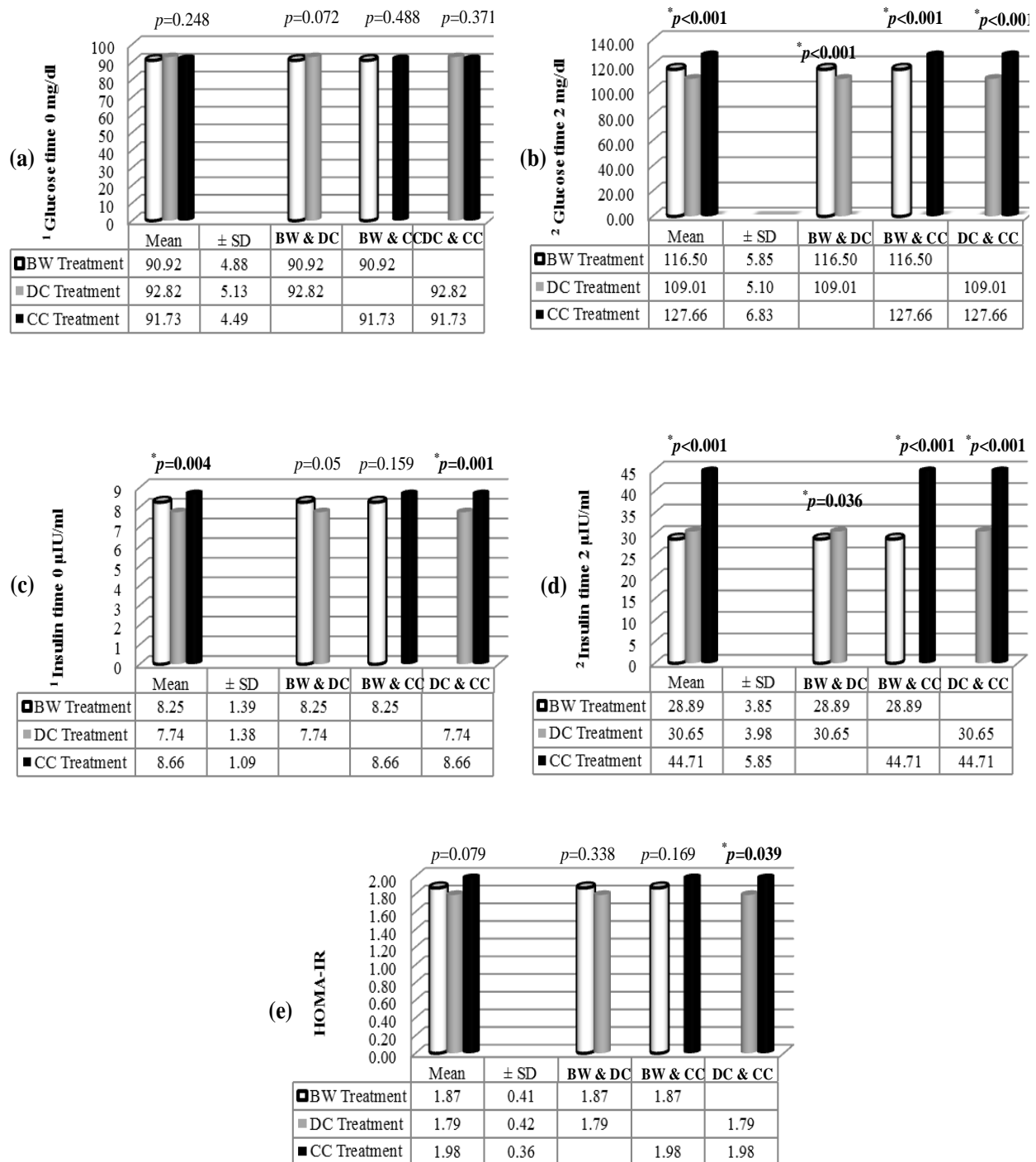


Figure 2. Analysis of variances for fasting serum glucose (a) and insulin (c), the levels of glucose (b) and insulin (d) two hours after OGTT as well as HOMA-IR (e) in a randomized crossover trial, determining the simultaneous effects of sleep deprivation and coffee caffeine consumption on biomarkers related to glucose homeostasis among healthy Iranian adult men (n=42).

BW Treatment: Deprived Sleep (3 nights as 4 hrs. in bed) + 3 cups of 150 cc Boiled Water (DS + BW)

DC Treatment: Deprived Sleep (3 nights as 4 hrs. in bed) + 3 cups of 150 cc Decaffeinated Coffee - 99.99% caffeine-free (DS + DC)

CC Treatment: Deprived Sleep (3 nights as 4 hrs. in bed) + 3 cups of 150 cc Caffeinated Coffee - 65 mg caffeine/cup (DS + CC)

¹Fasting serum glucose/insulin. ²Serum glucose/insulin two hours after OGTT.

*Significant.

vated from the BW treatment to the DC and then the CC treatments.

A repeated measures ANOVA revealed that mean insulin time 0 differed in a statistically significant manner between treatments $F(2,82)=5.90$, $p=0.004$ (Figure 2c). Post hoc tests of LSD (Figure 2c) indicated that the DC treatment resulted in a slight decrease in insulin time 0 as compared to the BW treatment (7.74 ± 1.38 $\mu\text{IU/mL}$ vs

8.25 ± 1.39 $\mu\text{IU/mL}$, respectively), which was not statistically significant ($p=0.05$). However, when subjects received the CC treatment, insulin time 0 increased to 8.66 ± 1.09 $\mu\text{IU/mL}$, which was statistically significant for the DC treatment ($p=0.001$) but not to the BW treatment ($p=0.159$).

A one-way repeated measures analysis of variances (ANOVA) showed that mean insulin time 2 differed sig-

nificantly between treatments $F(2,82)=143$, $p<0.001$ (Figure 2d). Post hoc tests of LSD (Figure 2d) revealed that when subjects were given the CC treatment, insulin time 2 increased to 44.8 ± 5.85 $\mu\text{IU/mL}$, a statistically significant difference ($p<0.001$) for both the BW treatment (28.9 ± 3.85 $\mu\text{IU/mL}$) and the DC treatment (30.7 ± 3.98 $\mu\text{IU/mL}$). Pairwise comparisons also indicated a statistically significant difference in insulin time 2 between the BW and DC treatments ($p=0.036$).

Insulin resistance using HOMA-IR model assessment

Table 2 shows that the highest HOMA-IR was in the CC treatment and the lowest in the DC treatment (Table 2). As shown in Table 2, the mean HOMA-IR fluctuated in a similar fashion to glucose time 2 and insulin time 0 during different study treatments.

A repeated measures ANOVA indicated no statistically significant beverage effect on mean HOMA-IR $F(2, 82)=2.62$, $p=0.079$ (Figure 2e). Although not required, we employed a follow-up comparisons test to identify any probable differences between the treatments (Figure 2e). The LSD test revealed that the DC treatment caused a slight decrease in HOMA-IR as compared to the BW treatment (1.79 ± 0.42 vs 1.87 ± 0.41 , respectively), which as expected, was not statistically significant ($p=0.338$). However, the HOMA-IR increased to 1.98 ± 0.36 in the CC treatment, which surprisingly differed significantly from the DC treatment ($p=0.39$), but, not from the BW treatment ($p=0.169$).

DISCUSSION

In this study, we found no significant changes in fasting serum glucose following coffee consumption (either caffeinated or decaffeinated) or boiled water among healthy Iranian adult men who were simultaneously requested to be sleep deprived for 3 consecutive nights with 4 hours in bed (Figure 2a). The study showed higher fasting serum insulin (Figure 2c) and increased level of glucose (Figure 2b) and insulin (Figure 2d) 2 hours after an OGTT following consumption of caffeinated coffee as compared to decaffeinated coffee or boiled water. The study revealed that decaffeinated coffee led to a decreased level of glucose (Figure 2b) but increased level of insulin (Figure 2c) 2 hours after an OGTT as compared to boiled water. Although no significant beverage effect on HOMA-IR was found, caffeinated coffee increased insulin resistance compared to decaffeinated coffee, when subjects were simultaneously sleep deprived (Figure 2e).

The study found that there were no significant changes in fasting serum glucose, consistent with the capability of healthy adults to effect glucose homeostasis.¹³ However, other evidence has indicated a negative effect of sleep deprivation on fasting serum glucose.² Moreover, there was a contrast between recently reported coffee caffeine intake studies and this one reporting higher fasting insulin levels with and increased serum glucose and insulin 2 hours after an OGTT among caffeinated coffee receivers as compared to decaffeinated coffee or boiled water. In a randomized crossover trial Gavrieli et al³⁸ (2013) showed that even 200 mL coffee caffeine may strongly delay the rise of insulin in response to a standard meal among normal-weight healthy men. Ohnaka et al³⁹ (2012) revealed

that 5 cups/day instant caffeinated coffee was associated with lower glucose levels 2 hours after an OGTT as compared to decaffeinated coffee, even during a long period of 16 weeks following a two-week run-in period for caffeine washout.

It remains difficult to explain these contradictory findings. The differences may be attributable to possible interaction/s between caffeine consumption from coffee and simultaneous sleep deprivation. In fact, the possible interaction/s between simultaneous consumption of coffee caffeine and sleep deprivation may contribute to fluctuating fasting serum glucose within a physiological range that may not be statistically significant. Another possible explanation is that, when moderate coffee drinkers were exposed to sleep deprivation for three consecutive nights (4 hours in bed/night), the possible effects of decaffeinated/caffeinated coffee (either positive or negative) on fasting blood glucose might become insignificant. Nevertheless, further studies are required to clarify the mechanism/s involved in the interaction between simultaneous sleep deprivation and coffee consumption.

In the case of coffee consumption on its own, without any other variable like sleep deprivation, researchers have suggested several probable mechanisms to elucidate on protective role of caffeinated/decaffeinated coffee against type 2 diabetes mellitus. Studies show caffeinated coffee to increase adiponectin^{7,40,41} and decaffeinated coffee to decrease fetuin-A levels⁷, the two proteins contributing to the observed association between habitual coffee consumption and a lower risk of type 2 diabetes mellitus. Some studies have examined the association between flavonoid substances and insulin resistance⁴² as well as markers of inflammation, such as IL-18,³⁹ which increase following coffee consumption. Researches have also shown magnesium and chlorogenic acid, a phenol compound of coffee, to stimulate glucose transport in skeletal muscle. This function is mediated by AMP-activated protein kinase⁴⁴ or trigonelline.⁴⁵

However, when it comes to simultaneous consumption of coffee consumption and sleep deprivation, the independent variable of sleep deprivation may play a critical role. The irregular nocturnal bedtime reported in shift workers appears to be a strong risk factor for increased inflammation and diabetes.⁴⁶ The inflammatory stress in elderly with sleep difficulties has reportedly improved with the intake of magnesium supplements.⁴⁷ However, caffeine from coffee appear to be conversely affected by the same mechanisms, indicating a negative role for sleep deprivation against positive impacts of coffee caffeine. Thus, further studies may need to observe various parameters (i.e. inflammatory stress or magnesium) when investigating mechanisms involved in the simultaneous effects of coffee caffeine consumption and sleep deprivation.

On the other hand, sleep deprivation on its own has been reported to increase fasting HOMA-IR, either immediately after eating breakfast⁴⁸ or following an iVGTT.⁴⁹ Such findings may suggest lower insulin sensitivity and higher insulin resistance. Approximating to the sleep status of the present study, these clinical studies involved a small number of subjects exposed to partial sleep conditions over consecutive nights. Furthermore, decreased insulin sensitivity has been found even in less-

severe short sleep circumstances more likely to occur in real life, when subjects spent up to 5.5 hours in bed over 14 nights.⁵⁰

However, the present study did not show any significant changes in HOMA-IR between the study treatments (Figure 2e). Nevertheless, this study's higher HOMA-IR following intake of caffeinated coffee as compared to decaffeinated coffee may indicate hidden potential for a negative impact of caffeinated coffee on insulin resistance among healthy subjects with normally shortened sleep duration. This finding may also elaborate on the possible role of caffeinated coffee in increasing the risk of diabetes mellitus among these individuals.

This study found higher fasting serum insulin only following caffeinated treatment as compared to decaffeinated (Figure 2c) but failed to show any significant changes in fasting serum glucose (Figure 2a). Therefore, the probable coffee caffeine-induced effect on insulin resistance in deprived sleep subjects appears to be associated with changes in insulin secretion, not glucose.

Nevertheless, it is difficult to attribute all of the changes to caffeine in coffee. The study showed decaffeinated coffee resulted in a rise in insulin for time 2 (Figure 2d) followed by a fall in glucose time 2 (Figure 2b) as compared to boiled water. This finding indicates that increased insulin secretion could result from the lack of caffeine in coffee; the simultaneous effects of sleep deprivation and coffee consumption may lead to a protective role against increased glucose level. This finding suggests the existence of possible mechanisms (s) and/or component (s) other than caffeine in coffee. Other interactions may affect the studied metabolic biomarkers, such as hormonal changes like leptin, ghrelin or possibly cortisol following coffee consumption and sleep deprivation,^{32,51-54} which stimulate insulin secretion.⁵⁵⁻⁵⁷ However, further studies are required to understand and to fully elucidate on the mechanisms or complexities involved. Additional research should also consider the extent to which such mechanisms may be affected when sleep deprivation is simultaneously coupled with coffee consumption.

The study has several strengths and some limitations. We used a continuous monitoring and control procedure and observed a strict list of criteria during subject recruitment. We also used the PSQI, one of the most reliable sleep questionnaires in terms of validity and reliability. The formulas we chose to use have been validated in many studies and took into account subject characteristics such as energy requirements, body fat percentage and misreported food records. Strict inclusion criteria reduced the probability of recruiting subjects who might be affected by possible confounders. In addition, to minimize drastic changes in daily routine, we provided similar activities to those practiced in their normal daily lives. In terms of unique features, while most coffee studies are designed to examine only the effects of caffeinated and decaffeinated coffee, the boiled water reference in the present study provided a control group unaffected by coffee/decaffeinated coffee.

However, the study was of a relatively small group of only young healthy adult men (to exclude potential sex- & age- specific considerations). Therefore, the findings cannot be generalized to women, other age groups or un-

healthy people. Only non-smokers with a moderate habitual coffee intake participated in the study; smokers or people with other coffee consumption habits may behave differently. Nevertheless, to the best of our knowledge, no other similar study has been conducted. The findings may encourage similar investigations.

Conclusion

When simultaneously coupled with sleep deprivation, caffeinated coffee increased serum glucose and insulin 2 hours after an OGTT. It also increased fasting serum insulin and insulin resistance, which represents a risk of diabetes mellitus compared with decaffeinated coffee. The apparent advantages of decaffeinated coffee on glucose homeostasis apply people with a sleep debt. The simultaneous effects of sleep deprivation and caffeine intake from coffee was not better than the reference boiled water intake in so far as glycaemic status was concerned. This finding implies a negative role for sleep deprivation against the positive impacts of caffeinated coffee consumption on improving glucose metabolism. Regardless of the potential ability of coffee caffeine to shorten sleep duration, such a finding also demonstrates the need to avoid caffeinated coffee consumption prior to normal bedtime, i.e. nocturnal sleep.

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Original Article

Simultaneous coffee caffeine intake and sleep deprivation alter glucose homeostasis in Iranian men: a randomized crossover trial

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咖啡中咖啡因的摄入和睡眠剥夺改变伊朗男性葡萄糖稳态：一项随机交叉试验

背景与目的：睡眠剥夺和咖啡中咖啡因的摄入对葡萄糖稳态的影响已分别被证明，但这两个变量的综合效果尚不知道。**方法与研究设计：**42 名年龄在 20-40 岁之间的伊朗男性在本随机交叉试验中被分配到 3 个试验组，试验组间有两周的洗脱期。研究对象为中度咖啡消费者 (≤ 3 杯/天)，并且匹兹堡睡眠质量指数 ≤ 5 。每种试验包括 3 晚上的睡眠剥夺 (在床上 4 小时)，加 3 杯开水 (BW 试验，每杯 150 毫升)、无咖啡因的咖啡 (DC 试验，不加糖，99.9% 无咖啡因) 或含咖啡因的咖啡 (CC 试验，不加糖，每杯含 65 毫克咖啡因)。DC 和 CC 处理采用盲法。每种试验结束后，测量空腹血糖 (采用酶法测定) 和胰岛素 (采用电化学发光免疫分析法测定)，口服葡萄糖耐量试验 (OGTT) 两个小时后再次测量血糖和胰岛素。胰岛素抵抗采用稳态模型量化。**结果：**重复测量方差分析表明各试验组间的空腹血糖 ($p=0.248$) 和胰岛素抵抗 ($p=0.079$) 没有显著差异。然而，方差分析表明各试验组间空腹血清胰岛素、血糖和 OGTT 后的胰岛素有差异。配对比较 (研究对象间) 表明：与 DC 试验组相比，CC 试验组 OGTT 后血糖和胰岛素较高 ($p<0.001$)，空腹血清胰岛素 ($p=0.001$) 和胰岛素抵抗 ($p=0.039$) 也增加。**结论：**对睡眠被剥夺的人，含咖啡因的咖啡比不含咖啡因的咖啡更不利于葡萄糖稳态。

关键词：含咖啡因的咖啡、睡眠剥夺、葡萄糖稳态