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Temperature as a Circadian Marker in Older Human Subjects: Relationship to Metabolic Syndrome and Diabetes

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Background: Circadian rhythms are characterized by approximate 24-hour oscillations in physiological and behavioral processes. Disruptions in these endogenous rhythms, most commonly associated with shift work and/or lifestyle, are recognized to be detrimental to health. Several studies have demonstrated a high correlation between disrupted circadian rhythms and metabolic disease. The aim of this study was to determine which metabolic parameters correlate with physiological measures of circadian temperature amplitude (TempAmp) and stability (TempStab).

Methods: Wrist skin temperature was measured in 34 subjects (ages 50 to 70, including lean, obese, and diabetic subjects) every 10 minutes for 7 consecutive days. Anthropometric measures and fasting blood draws were conducted to obtain data on metabolic parameters: body mass index, hemoglobin A1C, triglycerides, cholesterol, high-density lipoprotein, and low-density lipoprotein. A history of hypertension and current blood pressure was noted.

Results: Analysis of the data indicated a substantial reduction in TempAmp and TempStab in subjects with metabolic syndrome (three or more risk factors). To determine the impact of individual interdependent metabolic factors on temperature rhythms, stepwise multilinear regression analysis was conducted using metabolic syndrome measurements. Interestingly, only triglyceride level was consistently correlated by the analysis. Triglyceride level was shown to contribute to 33% of the variability in TempAmp and 23% of the variability in TempStab.

Conclusion: Our results demonstrate that elevated triglycerides are associated with diminished TempAmp and TempStab in human subjects, and triglycerides may serve as a primary metabolic predictor of circadian parameters.

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Freeform/Key Words: triglycerides, obesity, metabolic syndrome, circadian rhythm

Circadian rhythms, or the 24-hour oscillations in physiological and behavioral processes, are essential to health [1, 2]. These rhythms are generated by a molecular clock present in every cell of an organism and entrained to environmental cues [3–5]. In mammals, the master clock is located in the suprachiasmatic nucleus of the hypothalamus and serves to orchestrate synchronization among all other clocks in the body, referred to as peripheral clocks [6, 7]. Impaired or desynchronized rhythms among tissues have been shown to be connected to a

Abbreviations: BMI, body mass index; BP, blood pressure; HbA1C, hemoglobin A1C; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MetS, metabolic syndrome; TempAmp, temperature amplitude; TempStab, temperature stability; TG, triglycerides.

multitude of the diseases that plague us today, including cardiovascular disease, metabolic disease, cancer, and stroke [1, 8, 9]. Many studies have demonstrated a link between metabolic disease and circadian rhythms. Night shift workers have been shown to have increased risk of diabetes [10]. Misalignment of feeding and light cycles causes desynchronization of clocks and development of metabolic syndrome (MetS) in mice [11]. In addition, irregular activity rhythms, independent of total activity, are linked to elevated risk of dyslipidemia, hypertension, obesity, diabetes, and MetS in adults [12].

In a previous study, we demonstrated a substantial decrease in circadian amplitude and stability of temperature rhythms in young men with higher body fat or the presence of at least one factor of MetS [13]; however, body fat is only one of a variety metabolic characteristics. Although it is well established that metabolism and circadian rhythms are interdependent, it is still unclear whether certain metabolic aspects are more strongly associated with circadian rhythms [3, 14, 15]. To investigate this, we collected fasting laboratory values and anthropometric measurements and evaluated circadian rhythms by measuring wrist skin temperature, which has been validated as a good circadian assessment [16–19]. Because MetS becomes much more prevalent with age, we recruited participants between the ages of 50 and 70 years with a body mass index (BMI) of 27 to 40 kg/m². Using wrist skin temperature data from these individuals, we were able to compare circadian temperature amplitude (TempAmp) and stability (TempStab) to MetS associated factors such as BMI, blood pressure (BP), hemoglobin A1C (HbA1C), cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides (TG). Our findings demonstrate that TG is the most substantial factor associated with both TempAmp and TempStab and that as TG levels increase, a reduction in TempAmp and TempStab is observed.

1. Methods

A. Subjects

Participants were recruited on a volunteer basis through institutional review board–approved advertisements such as flyers, Web postings (University of Kentucky Clinical Research), and ResearchMatch. Thirty-four subjects of both sexes between the ages of 50 and 70 years and a BMI of 27 to 40 kg/m² were included in this study. Individuals with limited mobility, renal disease, severe heart failure, shift work, unpredictable social situations, obstructive sleep apnea, and uncontrolled mental health disorders were excluded. The women included in the study were postmenopausal or had previously undergone a hysterectomy. All subjects were euthyroid with a normal thyrotropin. Among the 34 subjects, 10 had diagnosed type 2 diabetes, of which five were being treated with insulin. MetS was defined as the presence of at least three metabolic risk factors [20]. These risk factors include TG \geq 150 mg/dL, fasting blood glucose \geq 100 mg/dL, BP \geq 130/85 mm Hg (elevated systolic or diastolic), or a history of hypertension and on treatment, HDL $<$ 40 in men or $<$ 50 in women, and waist circumference \geq 35 or 40 inches in women or men, respectively. Of the 34 subjects, 18 had a history of hypertension and were on medications; of the other 16 subjects without a history of hypertension, only two exhibited hypertension (systolic BP $>$ 140 mm Hg, diastolic BP $>$ 90 mm Hg) at the screening visit.

Preceding the initiation of the study, each individual signed an informed consent as approved by the University of Kentucky institutional review board.

B. Vital Signs and Blood Sampling

Participants were weighed using a calibrated scale, and standing height was determined by measurement with a wall-fixed stadiometer for calculation of BMI. Heart rate and BP were measured after participants had been seated a minimum of 5 minutes. Blood laboratory values were drawn after an overnight ($>$ 8 hours) fast, and samples were sent to Quest Diagnostics (Madison, NJ) for analysis of lipids, thyrotropin, and HbA1C.

C. Circadian Rhythm Assessment

Circadian analysis was done using noninvasive wrist skin temperature measurements as described by us previously [13]. Wrist skin temperature was monitored and recorded every 10 minutes with a sensitivity of 0.0625°C using the iButton device (Thermochron iButton; Embedded Data Systems, Lawrenceburg, KY). Participants were instructed to wear the iButton on the inside nondominant-hand wrist for 7 consecutive days. The iButton was secured to the wrist with strips of latex-free dressing tape (Hypafix; Smith & Nephew Inc, Memphis, TN) and a cotton sports wrist band provided to the participants. Subjects were instructed to limit the removal of the iButton (*i.e.*, bathing) to limit disruptions in recordings. Data were transferred from the iButton through an adapter (SK-IB-R-iButton Connectivity Kit; Embedded Data Systems). Recorded data from 7 days wearing the iButton were used to determine the circadian amplitude and stability using the software program JTK-Cycle [13, 21]. Amplitude is defined by the peak and midline values. Stability was defined as the variation in the oscillatory pattern of the individual's circadian data over the days of data collection.

D. Statistical Analysis

Subjects were categorized as either having MetS or no MetS; corresponding descriptive data are shown as mean \pm standard deviation for continuous variables and count (%) for categorical variables. Comparisons were made via the use of two-sample *t* tests and Fisher exact tests. Pearson correlations were used to quantify associations between continuous variables in bivariate analyses, whereas multiple linear regression was used when numerous variables were used as predictors of TempAmp and TempStab. For estimates from the regression models to correspond to adjusted Pearson correlations, variables were centered and standardized. All tests were two-sided, and statistical significance for all tests was set at $P \leq 0.05$. Analyses were conducted in GraphPad Prism (version 5, GraphPad Software, San Diego, CA), Statistical Package for Social Sciences (version 23, Armonk, NY), and SAS version 9.4 (SAS Institute, Cary, NC).

2. Results

Previous research has demonstrated diminished temperature rhythms in individuals with MetS [12, 13, 16, 22, 23]. We verified this relationship in our own study population by comparing TempAmp and TempStab between subjects with MetS (3+ risk factors) and those without MetS (0 to 2 risk factors). Individuals with MetS displayed a significantly lower TempAmp (MetS: 0.65 ± 0.12 vs no MetS: 0.98 ± 0.08 , $P = 0.03$) and TempStab (MetS: 79.96 ± 16.87 vs no MetS: 131.50 ± 13.23 , $P = 0.04$) (Fig. 1).

MetS involves a number of clinical features, some of which may have stronger relationships with circadian rhythms than others. We were interested in determining how specific metabolic factors tracked with TempAmp and TempStab (Table 1). Using data on BMI, age, sex, HbA1C, cholesterol, HDL, TG, LDL, and BP, we determined the correlation between each parameter and TempAmp or TempStab (Table 2). As seen in Fig. 2, univariate regression exhibited significant correlations for TG with TempAmp ($r = -0.58$, $P < 0.001$) and TempStab ($r = -0.48$, $P < 0.001$). Although TG, HbA1C, and HDL all showed univariate correlations with TempAmp and TempStab (Table 2), these metabolic factors, and others we examined, are not independent of each other. Therefore, to evaluate the adjusted associations between each metabolic variable and TempAmp and TempStab, we used multiple linear regression analyses (Table 2). Multivariate analysis revealed TG (TempAmp: $r = -0.58$, $P < 0.001$; TempStab: $r = -0.48$, $P < 0.001$) as the sole factor significantly correlated with TempAmp and TempStab. The relationship between TG and TempAmp can be seen in the representative temperature traces from two subjects in Fig. 3.

These data included all 34 subjects, but we also examined the relationship between TG and TempAmp and TempStab in the diabetic subjects alone (Table 3). Stepwise multilinear

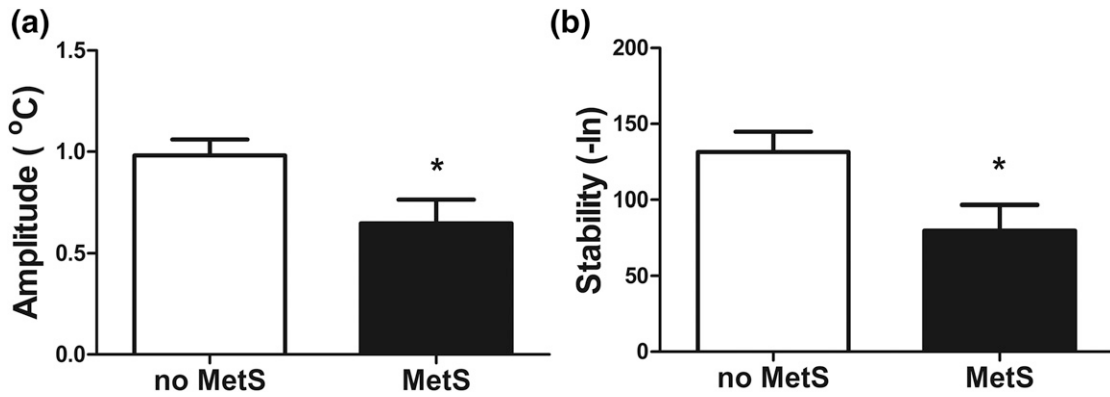


Figure 1. Temperature amplitude and stability data for MetS groups. (a) Circadian amplitude for individuals with MetS (more than three risk factors) ($n = 10$) or without MetS ($n = 24$) ($P = 0.023$). (b) Circadian stability for individuals with MetS ($n = 10$) or without MetS ($n = 24$) ($P = 0.049$).

regression analysis created two models for TempAmp, both of which include TG. The first model identifies TG as the only explanatory variable, contributing 68% to the variability of TempAmp ($r = -0.82$, $P = 0.001$). The second model uses both age ($r = 0.413$, $P < 0.05$) and TG ($r = -0.765$, $P < 0.01$) to explain the variability of TempAmp. The model for TempStab, however, includes TG only ($r = -0.75$, $P < 0.05$), with TG explaining 56% of the variability of TempStab. Therefore, even in the smaller subset of diabetic participants, TG is the most prominent factor affecting TempAmp and TempStab. Overall, these data suggest that TG has the greatest impact on circadian temperature rhythms and is the predominant MetS marker for disrupted circadian rhythms.

3. Discussion

A number of physiological processes in the human body oscillate over the course of a 24-hour day. One such process that is highly linked at both the cellular and systems level to circadian rhythms is metabolism [2, 3, 24, 25]. As previously mentioned, circadian rhythm disruption and MetS are highly associated [22, 23, 26], but MetS encompasses a variety of

Table 1. Baseline Features of Participants With and Without MetS

	No MetS (<3 Risk Factors)	MetS (3+ Risk Factors)	<i>P</i> Value
BMI	28.9 ± 4.3	34.2 ± 5.3	<i>0.01</i>
Systolic BP (mm Hg)	115.5 ± 12.2	128.6 ± 9.9	<i>0.01</i>
Diastolic BP (mm Hg)	68.7 ± 10.0	76.9 ± 6.6	<i>0.03</i>
Waist (inches)	38.8 ± 6.7	44.9 ± 5.5	<i>0.02</i>
HDL	69.4 ± 17.8	44.4 ± 16.6	<i><0.001</i>
Triglycerides (mg/dL)	89.9 ± 12.8	179.4 ± 50.3	<i><0.001</i>
Glucose (mg/dL)	90.3 ± 12.8	117.7 ± 32.9	<i><0.001</i>
HbA1C	5.6 ± 0.4	6.5 ± 1.2	<i><0.001</i>
Diagnosed hypertension (%)			0.01
Yes	9 (37.5)	9 (90)	
No	15 (62.5)	1 (10)	
Patients with diabetes (%)			0.16
Yes	3 (12.5)	4 (40.0)	
No	21 (87.5)	6 (60.0)	
Sex (%)			0.40
Male	5 (20.8)	4 (40.0)	
Female	19 (79.2)	6 (60.0)	

Data shown as mean ± standard deviation. *P* values of <0.05 are shown in italics.

Table 2. Correlation Coefficients Between Demographic and Clinical Features and TempAmp and TempStab

Variable	Amplitude		Stability	
	Pearson <i>r</i>	<i>P</i> Value	Pearson <i>r</i>	<i>P</i> Value
Univariate analysis				
BMI	-0.217	0.218	-0.097	0.583
Sex	0.142	0.424	0.234	0.183
Age	0.105	0.554	0.026	0.882
HbA1C	-0.450	<i>0.008</i>	-0.400	<i>0.009</i>
Cholesterol	0.126	0.478	0.083	0.642
HDL	0.454	<i>0.008</i>	0.305	0.080
TG	-0.577	<i>0.000</i>	-0.480	<i>0.004</i>
LDL	0.057	0.748	0.063	0.725
Systolic BP	0.100	0.574	-0.047	0.791
Diastolic BP	-0.163	0.356	-0.208	0.239
Diagnosed hypertension	0.223	0.206	0.221	0.209
Multivariate analysis				
BMI	0.071	0.672	0.166	0.353
Sex	-0.017	0.914	0.112	0.498
Age	0.220	0.136	0.120	0.456
HbA1C	-0.132	0.494	-0.155	0.455
Cholesterol	0.013	0.931	-0.012	0.939
HDL	0.147	0.441	0.000	0.999
TG	-0.577	<i>0.000</i>	-0.480	<i>0.004</i>
LDL	-0.036	0.809	-0.014	0.928
Systolic BP	0.285	0.057	0.095	0.563
Diastolic BP	0.017	0.914	-0.065	0.695
Diagnosed hypertension	-0.030	0.853	0.019	0.916

P values of <0.05 are shown in italics.

measurements; it is still unclear how strongly each factor relates to temperature rhythms. Therefore, the goal of this study was to begin to identify which variables serve as the strongest predictors of two parameters of circadian rhythms: TempAmp or TempStab.

Based on a previous publication in which fat mass was exposed as an explanatory variable for temperature stability in young men [18], we expected BMI to be included in the multilinear regression models for TempAmp and TempStab. Interestingly, BMI was not correlated in either model and rather TG was the primary predictor of TempAmp and TempStab. In fact,

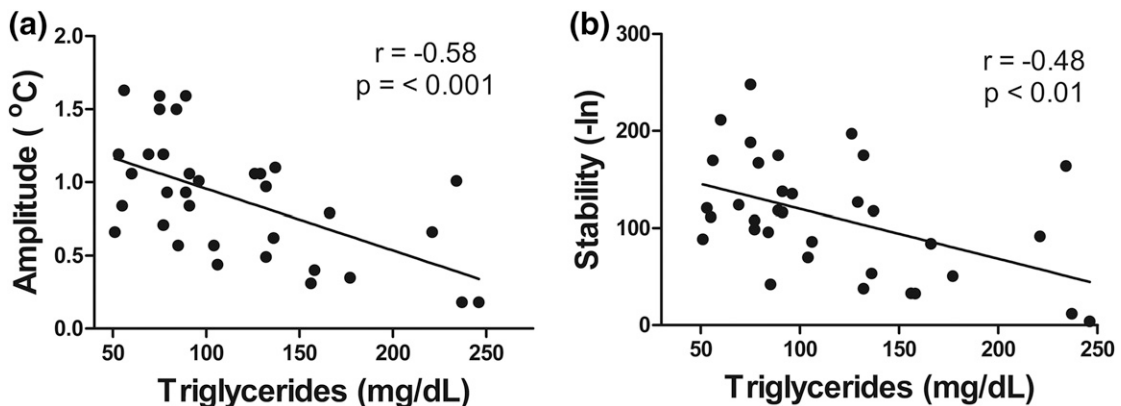


Figure 2. Correlation data. (a) Linear regression for triglycerides (mg/dL) and temperature amplitude ($r = -0.58$, $P < 0.001$). (b) Linear regression for triglycerides (mg/dL) and temperature stability ($r = -0.48$, $P < 0.01$). $N = 34$.

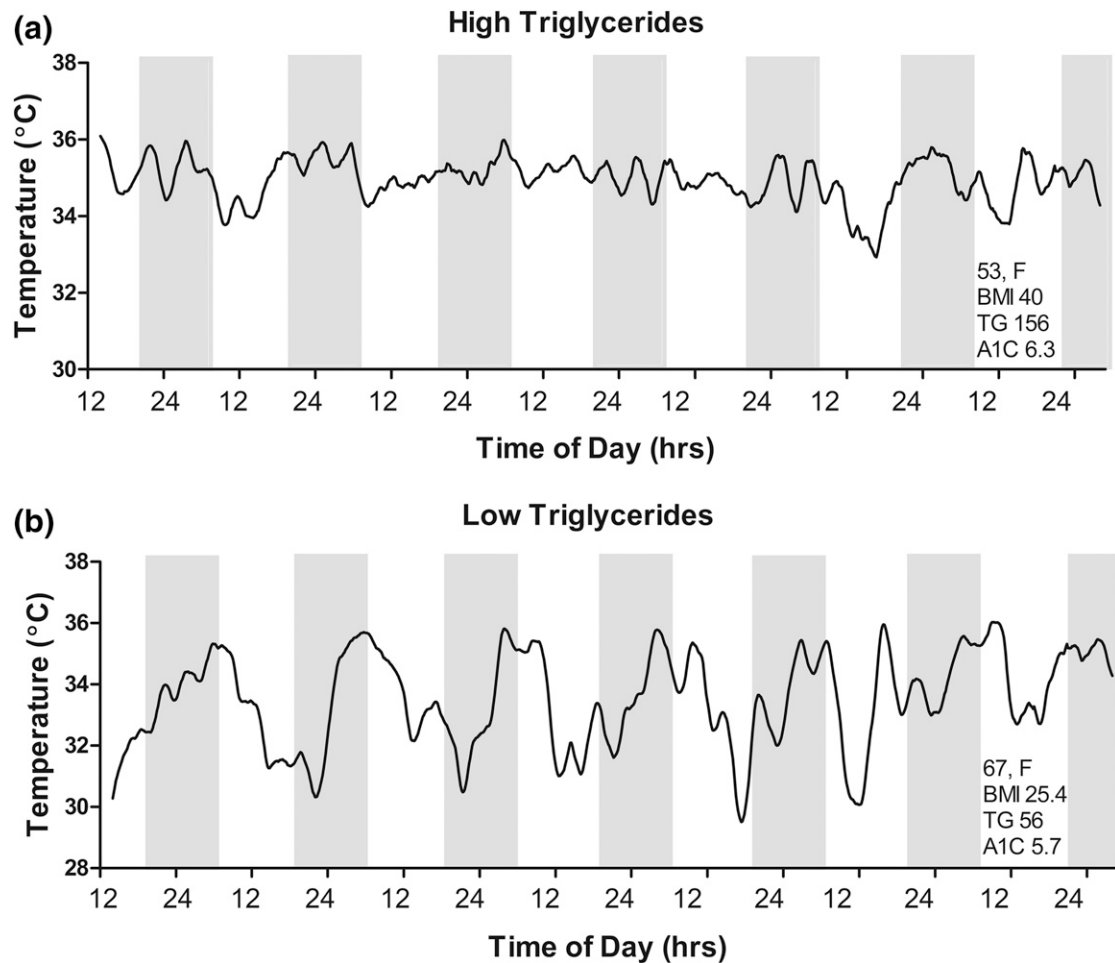


Figure 3. Representative 7-day traces for temperature amplitude in an individual with (a) low triglycerides and (b) high triglycerides. Shaded regions indicate typical dark hours, whereas nonshaded regions represent typical light hours. As seen by the traces, the amplitude of temperature oscillation over time of day is diminished with high levels of triglycerides.

TG was the only explanatory factor and accounted for 33% of the variability in TempAmp and 23% of the variability in TempStab. The predicting power of TG was further supported by our analysis of the patients with diabetes alone. TG was included in the models for both TempAmp and TempStab for patients with diabetes, and accounted for an even greater proportion of the TempAmp (68%) and TempStab (56%). The greater impact of TG as an explanatory variable in patients with diabetes could be due to the smaller group size ($n = 10$), but it is still compelling evidence for TG as the main metabolic component related to temperature rhythms.

Although regression analyses provide information on the variables' contribution to variance, they do not specify cause and effect. The data do not indicate why TG is correlated with temperature rhythms and or why it is the most important predicting factor. We know that TG levels are regulated in part by circadian rhythms [27–32]. As such, it could be that diminished circadian amplitude and stability in our participants led to high TG levels. This is feasible considering previous publications regarding animals and humans demonstrating the development of MetS following circadian clock disruption [2, 24, 33]. In contrast, it could be that abnormal metabolic parameters led to diminished circadian rhythms. Elevated TG may indicate increased insulin secretion [34–36]. A number of studies have demonstrated that hypertriglyceridemia is a consequence of increased hepatic triglyceride production in

Table 3. Correlations With TempAmp and TempStab in Patients With Diabetes

Variable	Diabetic					
	Amplitude		Stability			
	Pearson <i>r</i>	<i>P</i> Value	Pearson <i>r</i>	<i>P</i> Value		
Univariate analysis						
BMI	-0.607	0.062	-0.424	0.222		
Sex	0.165	0.648	0.274	0.443		
Age	0.521	0.122	0.503	0.138		
HbA1C	-0.630	0.051	-0.628	0.052		
Cholesterol	-0.038	0.918	-0.003	0.993		
HDL	0.563	0.090	0.510	0.132		
TG	-0.823	<i>0.003</i>	-0.750	<i>0.012</i>		
LDL	0.033	0.927	0.068	0.852		
Systolic BP	-0.311	0.381	-0.322	0.364		
Diastolic BP	-0.432	0.212	-0.349	0.322		
Diagnosed hypertension	0.623	0.054	0.416	0.232		
Multivariate analysis						
	Model 1		Model 2			
BMI	-0.286	0.230	-0.162	0.400	-0.096	0.743
Sex	-0.101	0.664	-0.056	0.751	0.045	0.868
Age	0.413	<i>0.029</i>	0.430	<i>0.029</i>	0.406	0.083
HbA1C	-0.168	0.559	-0.151	0.485	-0.245	0.461
Cholesterol	-0.287	0.185	-0.171	0.332	-0.228	0.383
HDL	-0.524	0.194	-0.152	0.688	-0.488	0.310
TG	-0.823	<i>0.003</i>	-0.765	<i>0.001</i>	-0.750	<i>0.012</i>
LDL	-0.270	0.227	-0.178	0.308	-0.204	0.448
Systolic BP	-0.013	0.958	0.089	0.626	-0.055	0.842
Diastolic BP	-0.215	0.337	-0.039	0.841	-0.148	0.580
Diagnosed hypertension	0.347	0.118	0.082	0.740	0.134	0.633

P values of <0.05 are shown in italics.

response to inflated postprandial insulin secretion [37, 38]. The liver is central to the regulation of lipid metabolism, and prior research has shown insulin can phase shift the expression of core clock gene *Per2* in the liver, which ultimately shifts the hepatic clock [39]. A phase shift of the hepatic clock could result in dyssynchrony between the master (suprachiasmatic nucleus) clock and peripheral tissues. Phase shifting or dyssynchrony may contribute to diminished circadian rhythm parameters [39]. Further research is needed to define the relationship between TG and circadian parameters.

Another surprising finding of this study was that TG had a greater association with temperature rhythms than did hypertension or BP. As seen in Fig. 2, systolic BP, diastolic BP, and diagnosed hypertension were all included in the multivariate regression analysis. None of these parameters was correlated in the model. Most of the subjects in this study were being treated for hypertension; hence, this study cannot precisely report the relationship between temperature rhythms and BP. In summary, our data show a substantial relationship between circadian rhythms and circulating TG levels in adults. Our analyses demonstrate TG as the most prevalent predictor of TempAmp and TempStab, which has not previously been shown. Disrupted circadian rhythms are related to a variety of diseases, including cardiovascular disease, obesity, strokes, and cancer [1, 8, 9]. Because of the relationship between TG and circadian parameters, this metabolic parameter may possibly be used to assess risk of circadian-related diseases. If TG levels not only predict circadian parameters, but affect them as well, TG may serve as a target to improve circadian rhythmicity. However, further investigation is required to both establish the causality between the investigated metabolic factors and circadian rhythms.

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