Chronotype Is Independently Associated With Glycemic Control in Type 2 Diabetes

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OBJECTIVE—To examine whether chronotype and daily caloric distribution are associated with glycemic control in patients with type 2 diabetes independently of sleep disturbances.

RESEARCH DESIGN AND METHODS—Patients with type 2 diabetes had a structured interview and completed questionnaires to collect information on diabetes history and habitual sleep duration, quality, and timing. Shift workers were excluded. A recently validated construct derived from mid-sleep time on weekends was used as an indicator of chronotype. One-day food recall was used to compute the temporal distribution of caloric intake. Hierarchical linear regression analyses controlling for demographic and sleep variables were computed to determine whether chronotype was associated with HbA1c values and whether this association was mediated by a greater proportion of caloric intake at dinner.

RESULTS—We analyzed 194 completed questionnaires. Multiple regression analyses adjusting for age, sex, race, BMI, insulin use, depressed mood, diabetes complications, and perceived sleep debt found that chronotype was significantly associated with glycemic control (P = 0.001). This association was partially mediated by a greater percentage of total daily calories consumed at dinner.

CONCLUSIONS—Later chronotype and larger dinner were associated with poorer glycemic control in patients with type 2 diabetes independently of sleep disturbances. These results suggest that chronotype may be predictive of disease outcomes and lend further support to the role of the circadian system in metabolic regulation.

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The circadian system, controlled by the master circadian clock located in the suprachiasmatic nuclei of the hypothalamus, plays a major role in regulating daily rhythms of sleep/wake and various metabolic outputs, such as feeding behavior, peripheral tissue metabolism, and hormone secretions (1–3). Despite having this genetically regulated master circadian clock, humans living in modern industrialized societies with 24-h access to light often engage in behaviors that are inappropriately timed relative to their endogenous circadian rhythms. This mismatch in timing is termed “circadian misalignment” and has been associated with a number of negative health outcomes. Night shift work is an example of severe circadian misalignment, as workers are awake, active, and eating during their circadian night and trying to sleep and fast during their circadian day. Epidemiologic studies reveal that shift work is associated with health problems including peptic ulcer disease, coronary heart disease, and metabolic syndrome, as well as certain types of cancers (4). In controlled laboratory studies, experimentally induced circadian misalignment in healthy human volunteers resulted in impaired glucose tolerance (5,6). In animal experiments, mice fed a high-fat diet during their inactive period gained significantly more weight than mice fed during their active phase, despite consuming the equivalent amount of calories (7). Taken together, these data suggest that severe circadian misalignment involving eating and sleeping at an abnormal circadian time leads to impaired energy metabolism.

Many individuals in modern society experience a form of mild circadian misalignment, especially during the work or school week as they follow social rhythms imposed by professional obligation, school schedules, family, and other commitments (8). The degree of misalignment is dependent on the individual’s “chronotype” (8). Chronotype is a construct that captures an individual’s preference for being a “morning” or “evening” person. Late chronotype is typically associated with a greater degree of misalignment between social rhythms and the circadian clock (8). This misalignment phenomenon has been termed “social jetlag,” as it resembles the condition experienced after traveling across time zones (8) and can be observed by comparing the difference in sleep timing between work/school days and free days. In a large population study, larger amounts of social jetlag were recently reported to be associated with higher BMI in overweight individuals (9). In addition, a recent study found that patients with type 2 diabetes had significantly later bedtimes and wake times than participants without diabetes, suggesting that chronotype may play a role in glucose metabolism (10).

In addition to chronic circadian misalignment, late chronotypes or “evening types” tend to minimize or skip breakfast (11,12). Therefore, the daily distribution of food intake may be mismatched with circadian-controlled metabolic rhythms. It is well recognized that glucose tolerance is worse in the evening (13), suggesting that eating late may result in adverse metabolic consequences. Indeed, a study of healthy volunteers reported that the amount of calories consumed after 8:00 p.m. predicted a higher BMI after controlling for sleep timing and duration (14),
suggesting that the timing of food intake across the waking day is of metabolic relevance. To date, little is known about chronotonic variations in patients with type 2 diabetes and the potential associations with glycemic control. There is abundant evidence that sleep disturbances such as short sleep duration and poor sleep quality are linked to the risk of diabetes and obesity, as well as glycemic control in subjects with type 2 diabetes (15,16), but little is known about the association between chronotype and metabolism independently of these sleep characteristics. The aim of this study was to examine whether chronotype was independently associated with glycemic control in patients with type 2 diabetes. We hypothesized that late chronotype would be associated with worse glycemic control independently of sleep disturbances. Because the distribution of food intake across the day is associated with chronotype, we also examined whether daily caloric distribution contributed to glycemic control. We hypothesized that a greater percentage of daily calories consumed at dinner would be associated with worse glycemic control.

Research Design and Methods—Adults with type 2 diabetes who were being followed in endocrinology or primary care clinics at Rush University Medical Center were invited to participate. Exclusion criteria included pregnancy, inability to understand English or give informed consent, or any neurological or physical impairment that required the participants to depend on others for feeding. Nursing home residents, institutionalized patients, and patients receiving alternate routes of nutrition such as tube feeding or parenteral nutrition were also excluded. All participants gave written informed consent. The protocol was approved by the institutional review board at Rush University Medical Center, Chicago, Illinois.

Assessments
After informed consent was obtained, self-reported age and race were recorded. Weight was measured. Height, current medications, and most recent HbA1c values were extracted from patient medical records. Research personnel interviewed participants about their diabetes history and management using the University of Chicago Diabetes/Quality of Life Survey (17). Depressive symptoms were assessed using the Center for Epidemiologic Studies-Depression (CES-D) Scale (18). Employment status was collected and categorized into employed (working full-time or part-time), retired, or unemployed.

Participants were also asked to complete a 24-h dietary recall to determine the content and time of their meals over the previous day. Specific details (e.g., portion sizes, brand names, etc.) were clarified by the interviewer. Calorie consumption for each meal was calculated using an online dietary database (www.livestrong.com). Participants categorized each entry as breakfast, lunch, dinner, or snack. Breakfast and dinner meals were defined as entries including at least one food item (drink-only entries, such as coffee only, were not defined as a meal). Percent of daily calories consumed at breakfast and dinner were computed and used as indicators of daily caloric distribution. Late evening snack was defined as any caloric intake between last meal of the day and sleep onset. Participants were grouped into those who consumed a late evening snack and those who did not.

Subjective sleep and circadian measures
The Pittsburgh Sleep Quality Index (PSQI) (19) was used to assess sleep quality over the previous month (with scores >5 indicating poor sleep quality). Participants were asked to report usual bedtime, wake-up time, sleep-onset latency, and actual sleep duration on weekdays and weekends over the previous month. Participants were also asked whether they had a diagnosis of obstructive sleep apnea (OSA), and those without a previous diagnosis completed the Berlin questionnaire to assess the risk of OSA, which categorizes respondents as high or low risk of having OSA (18). Participants who had a diagnosis of OSA or were at high risk for OSA were identified together as a group with presence or high risk of OSA (OSA/risk).

The following circadian and sleep parameters were calculated. Mid-sleep time was calculated as the midpoint between sleep onset (bedtime plus sleep latency) and wake time. The primary outcome measure of mid-sleep time on free days (MSF), a metric of chronotype, was derived from mid-sleep time on weekend nights with further correction for calculated sleep debt as previously described (20,21). Specifically, the MSF equals the mid-sleep time on weekend nights subtracting 0.5 times the sleep debt, which is calculated as the difference between sleep duration (duration from sleep onset time until wake time) on weekends minus the weekly average sleep duration. This metric was first proposed by Roenneberg and colleagues with the assumption being that sleep timing on days when unconstrained by the social clock would more accurately reflect the underlying phase of the circadian system (22). Social jetlag, a behavioral indicator of circadian misalignment, was calculated based on the absolute difference between mid-sleep time on weekdays and weekends (9).

Sleep duration was computed using a weighted average of self-reported actual sleep duration between weekdays and weekends [(reported weekday actual sleep duration × 5 + reported weekend actual sleep duration × 2)/7]. In addition, because the perception of not getting enough sleep on weekdays has been shown to be better correlated with HbA1c than the reported sleep duration itself (15), perceived sleep debt was calculated using the difference between participants’ preferred weekday sleep duration (i.e., how many hours they would choose to sleep if their job, family, or other responsibilities did not limit the number of hours they slept) and their self-reported actual weekday sleep duration. Perceived sleep debt is a subjective variable that is likely to combine insufficient sleep duration and poor sleep quality.

Statistical analysis
All study data were checked for normality and presence of potential violations of statistical assumptions. HbA1c values were not normally distributed; therefore, the natural logarithm transformation of HbA1c was used in the analyses. HbA1c values were expressed as median (interquartile range). Diabetes duration was expressed as median (interquartile range) as well as categorized into ≤5, 6–10, 11–20, and >20 years. Diabetes complications were categorized as none or one or more. In order to account for a nonnormal distribution in social jetlag, this variable was categorized dichotomously as >30 min or ≤30 min.

For determination of the factors associated with glycemic control, Pearson correlations were used to explore the associations between the natural logarithm of HbA1c and continuous demographic, sleep, circadian, and dietary variables, while unpaired independent-samples
t tests were used to analyze differences in
the natural logarithm of HbA1c, for dichoto-
mous categorical variables. ANOVA was
used to compare differences in the natural
logarithm of HbA1c, among demographic
groups (according to diabetes duration
and employment status).

For characterization of the participants
according to chronotype, ANOVA was
used to analyze the relationship between
continuous demographic, metabolic, sleep,
and dietary variables among quartiles of
MSF. Tukey post hoc analyses were per-
formed. When the variables were not
normally distributed (diabetes duration,
HbA1c, and social jetlag), Kruskal-Wallis
tests were performed, while Mann Whittney
U tests were used for post-hoc analyses. \(\chi^2\)
tests were used to analyze differences in
categorical variables among quartiles of
MSF.

For determination of whether chron-
otype was independently associated with
glycemic control, a hierarchical mul-
tiple regression was performed to assess
the association between MSF and HbA1c,
controlling for demographic and sleep
variables. Demographic variables (age, sex
[males reference], race [nonwhite ref-
ference], BMI, diabetes complications, in-
sulin use, and CES-D) were entered in the
first step. The sleep variable significantly
associated with HbA1c in the bivariate ana-
lyses (perceived sleep debt) was en-
tered in the second step. In the final step,
chronotype as assessed by MSF was entered.
Collinearity analysis demonstr-
ated no collinearity among the vari-
ables.

For determination of whether daily
caloric distribution mediated the associa-
tion between chronotype and glycemic
control, four statistical analyses were
completed according to the Baron and
Kenny test for mediation (23). The first
step was a multiple regression analysis
to assess the association between MSF
and HbA1c, controlling for demographic
variables (age, sex [males reference], race
[nonwhite reference], BMI, diabetes com-
lications, insulin use, and CES-D) in steps
2 and 3, while controlling for demo-
graphics, the regression analyses were
performed to assess the association be-
tween MSF and percentage of daily calo-
ries consumed at dinner and between
percentage of daily calories consumed at
dinner and HbA1c, respectively. In the fi-
nal step, while controlling for demo-
graphics, both MSF and percentage of
daily calories consumed at dinner were
entered in multiple regression analysis
to assess their associations with HbA1c.
All analyses were performed using SPSS
Statistics, version 19.0 (Chicago, IL).

RESULTS—A total of 194 participants
(ages 18–85) completed the question-
naires. Baseline demographic characteris-
tics, as well as sleep, circadian, and dietary
parameters are shown in Table 1.

On average, the participants were
obese and had a median diabetes duration
of 11 years with a median HbA1c of 7.5% (58
mmol/mol). Slightly more than half
(55.7%) were using insulin, and 71.1% had
at least one diabetes complication.

Circadian parameters revealed that aver-
age MSF was 3:29 AM and 31.4% had
social jetlag of >30 min. Sleep quality
was generally poor as reflected by the ma-
jority of participants (59.7%) having a
PSQI score of >5. OSA/risk was present in
61.3% of the participants.

Regarding dietary parameters, 172
participants had breakfast entries, 180
had dinner entries, and 88 consumed a
late evening snack. Participants con-
sumed more of their daily calories at the
dinner meal (37%) than at the breakfast
meal (24%).

Association between HbA1c and
demographics and circadian, sleep,
and dietary parameters
Pearson correlations between glycemic
control and demographics and circadian,
sleep, and dietary parameters are shown
in Table 2. Higher HbA1c levels were sig-
ificantly correlated with younger age and
more depressive symptoms. There
were no differences in HbA1c levels be-
 tween the sexes. Participants of nonwhite
race had significantly higher HbA1c com-
pared with those of white race (7.7% [6.8–9.1] vs. 7.0% [6.4–8.1]; 61 mmol/
mol [57–76] vs. 53 mmol/mol [46–65],
P = 0.04). There were no differences in HbA1c levels among employment status
groups or when data were analyzed ac-
cording to categories of diabetes duration.
As expected, participants using insulin
had higher HbA1c compared with nonins-
sulin users (8.1% [7.3–9.4] vs. 6.8% [6.1–7.7]; 65 mmol/mol [56–79] vs. 51
mmol/mol [43–61], P < 0.001). Participants
with at least one diabetes complica-
tion had higher HbA1c than those without
complications (7.7% [6.8–9.1] vs. 7.1% [6.3–8.3]; 61 mmol/mol [51–76] vs. 54
mmol/mol [45–67], P = 0.04).

Higher HbA1c levels were significantly
correlated with later MSF. HbA1c levels in
subjects with social jetlag >30 min tended
to be higher than in those with social jetlag
≤30 min, though this result was only a
trend (7.7% [6.9–9.5] vs. 7.4% [6.6–8.5];
61 mmol/mol [52–80] vs. 57 mmol/mol
[49–69], P = 0.08).

Analyses of sleep parameters revealed
that higher HbA1c levels were correlated
with higher perceived sleep debt but not
with self-reported sleep duration or PSQI
scores. HbA1c levels were similar in par-
ticipants with or without OSA/risk (7.6% [6.8–8.9] vs. 7.4% [6.6–9.1]; 60 mmol/
mol [51–74] vs. 57 mmol/mol [49–76],
P = 0.75).

Analyses of caloric distribution
showed that percentage of daily calories
consumed at dinner, but not breakfast,
positively correlated with HbA1c levels.
There was no correlation between timing
of breakfast or dinner and glycemic con-
trast. There were no differences in HbA1c
levels between participants who con-
sumed late evening snacks and who did
not.

The hierarchical multiple regression
to assess the association between MSF
and HbA1c controlling for relevant demo-
graphic and sleep variables is presented
in Table 3. Demographic variables explained
20% of the variance in HbA1c. Of the mea-
sured sleep variables, only perceived sleep
debt was significantly correlated with gly-
cemic control in bivariate analysis; this
was added in the second step. Inclusion
of this variable did not improve the ex-
planatory power of the model
(\(\Delta R^2=0.00002, P = 0.95\)). Chronotype as
assessed by MSF was added in the final
model and was significantly associated
with HbA1c (unstandardized coefficient,
B = 0.025, P = 0.001). Each hour delay
in MSF was associated with an increase
in HbA1c of 2.5% of its original value.
Further, this model explained an additional
4.3% of the variance in HbA1c
(\(\Delta R^2=0.043, P = 0.001, \text{total adjusted}
R^2=0.24\)), which indicated that chron-
type contributed significantly to the
model's explanation of the variance of
HbA1c above and beyond demographic
and sleep variables.

Distribution of calories as a mediator between chronotype
and HbA1c
A series of regression models was used to
test for mediation, as previously de-
scribed. In the first regression model,
MSF was significantly associated with
HbA1c (B = 0.025, P = 0.001), and in the
second regression MSF was significantly
associated with percentage of daily
calories consumed at dinner.
Table 1—Descriptive demographic, circadian, sleep, and dietary data (n = 194 unless otherwise noted)

<table>
<thead>
<tr>
<th>Demographic data</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58.4 ± 13.0</td>
</tr>
<tr>
<td>Female</td>
<td>135 (69.6)</td>
</tr>
<tr>
<td>White</td>
<td>55 (28.4)</td>
</tr>
<tr>
<td>Employment</td>
<td></td>
</tr>
<tr>
<td>Working</td>
<td>55 (28.3)</td>
</tr>
<tr>
<td>Retired</td>
<td>78 (40.2)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>58 (30.0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>35.6 ± 8.3</td>
</tr>
<tr>
<td>DM duration (years)a</td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td>58 (29.9)</td>
</tr>
<tr>
<td>6–10</td>
<td>37 (19.1)</td>
</tr>
<tr>
<td>11–20</td>
<td>55 (28.4)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>43 (22.2)</td>
</tr>
<tr>
<td>HbA1C (%)</td>
<td>7.5 (6.7–8.9)</td>
</tr>
<tr>
<td>HbA1C (mmol/mol)</td>
<td>58 (50–74)</td>
</tr>
<tr>
<td>Insulin use</td>
<td>108 (55.7)</td>
</tr>
<tr>
<td>Diabetes complications ≥1</td>
<td>138 (71.1)</td>
</tr>
<tr>
<td>CES-D score</td>
<td>13.5 ± 9.0</td>
</tr>
<tr>
<td>Sleep parameters</td>
<td></td>
</tr>
<tr>
<td>Sleep duration (h)</td>
<td>6.64 ± 1.68</td>
</tr>
<tr>
<td>Perceived sleep debt (h)</td>
<td>1.60 ± 1.85</td>
</tr>
<tr>
<td>PSQI score</td>
<td>6.80 ± 4.13</td>
</tr>
<tr>
<td>PSQI score &gt;5</td>
<td>116 (59.7)</td>
</tr>
<tr>
<td>OSA risk</td>
<td>119 (61.3)</td>
</tr>
<tr>
<td>Dietary parameters</td>
<td></td>
</tr>
<tr>
<td>Total daily calories</td>
<td>1,470 ± 556</td>
</tr>
<tr>
<td>Breakfast calories (% of daily total)</td>
<td>24 ± 15</td>
</tr>
<tr>
<td>Dinner calories (% of daily total)</td>
<td>37 ± 20</td>
</tr>
<tr>
<td>Breakfast time, A.M.</td>
<td>8.35 ± 1.37</td>
</tr>
<tr>
<td>Dinnertime, A.M.</td>
<td>18.47 ± 1.26</td>
</tr>
<tr>
<td>Late evening snack</td>
<td>88 (45.3)</td>
</tr>
</tbody>
</table>

Data are means ± SD, median (interquartile range), or n (%). DM, diabetes. a n = 193. b Time is presented in 24-h clock time. c n = 172. d n = 180.

calories consumed at dinner (B = 0.024, P = 0.006). In the third model, percentage of daily calories consumed at dinner significantly predicted HbA1C (B = 0.0018, P = 0.005). Given that the first three steps were significant, the final and fourth step to examine mediation was completed, in which MSF and percentage of daily calories consumed at dinner were entered in one step and regressed on HbA1C along with covariates. Both MSF (B = 0.021, P = 0.005) and percentage of daily calories consumed at dinner (B = 0.0013, P = 0.02) were significantly associated with HbA1C, indicating that percentage of daily calories consumed at dinner only minimally partially mediated the relationship between chronotype and HbA1C, such that both remained independently associated.

Subjects’ characteristics in relation to chronotype
Since little is known about chronotypic characteristics in patients with type 2 diabetes, we explored the relationship among quartiles of MSF (Table 4). Participants with later chronotype tended to be younger, had a higher BMI, and had more depressive symptoms. There were no differences in sex or race distribution or employment status between groups.

Participants with later chronotype had significantly higher HbA1C levels, and more were using insulin, while there were no differences in diabetes duration or percentage of participants with diabetes complications between groups.

The difference in MSF between 1st quartile of MSF and 4th quartile MSF was ~4.3 h. Participants with later chronotype had significantly later bedtime and wake-up time and more social jetlag than those with earlier chronotype. Interestingly, there were no differences between groups in their sleep duration or PSQI score. However, perceived sleep debt, a subjective measure that likely combines insufficient sleep duration and poor sleep quality, was higher in participants with later chronotype.

While there were no differences in total daily caloric intake between groups, participants with later chronotype ate more of their daily calories at dinner and consumed breakfast and dinner at a significantly later time than those with earlier chronotype.

CONCLUSIONS—The current study demonstrates for the first time that chronotype is associated with glycemic control in patients with type 2 diabetes, independently of perceived sleep debt, a subjective measure of insufficient sleep duration and poor sleep quality. Each hour delay in MSF was associated with a modestly but significantly higher HbA1C of 2.5% of its original value after adjusting for age, sex, race, BMI, depressive symptoms, diabetes complications, insulin use, and sleep variables. For example, given similar demographic characteristics, an HbA1C level of 8% (64 mmol/mol) is expected to increase to 8.8% (73 mmol/mol) if MSF is 4 h later, which was the difference between the earliest and latest chronotype quartiles in this study. In addition, late chronotypes consumed a greater percentage of their daily caloric intake at dinner compared with early chronotypes, but the percentage of daily calories consumed at dinner only minimally mediated the association between chronotype and glycemic control, as the association with chronotype was only slightly reduced after adjustment for daily caloric distribution at dinner. Late chronotypes were associated with later bedtimes and wake-up times and a greater
degree of social jetlag than early chronotypes; however, social jetlag itself was not found to be significantly associated with HbA1c.

In addition, subjects with late chronotypes were found to be significantly younger and reported more depressive symptoms. These findings in our participants with type 2 diabetes are consistent with those in larger population-based studies (20,24). Interestingly, participants in the upper (latest) quartile of chronotype ate breakfast only ~2 h later and dinner only 1 h later than participants with an early chronotype despite having MSF that was 4 h later. This may reflect the need to conform to a typical social schedule, especially at dinner, which is generally considered a family meal. The meal timing itself, however, was not found to be associated with glycemic control.

Neurohormonal and metabolic dysregulations due to experimentally induced circadian disruptions have been demonstrated in laboratory studies of healthy volunteers. Severe circadian misalignment, involving sleep-wake and meal schedules ~12 h out of phase from their habitual times, resulted in increased postprandial glucose and insulin levels and elevated mean arterial pressure levels, as well as decreased leptin concentrations and a reversed daily cortisol rhythm (5). Another experimental study in healthy volunteers found that a combination of sleep restriction and circadian disruptions for 3 weeks resulted in impaired glucose tolerance with a 32% reduction in insulin response to a standardized meal (6). These laboratory findings suggest that chronic severe circadian misalignment, such as is found in night and rotating shift workers, may lead to increased cardiometabolic risks. Our study of patients with type 2 diabetes contributes to the emerging body of evidence in support of a link between circadian alignment and metabolic function and suggests that the adverse impact of late chronotypes may be clinically significant for those with impaired glucose metabolism as in diabetes. Patients in the current study were not shift workers; however, having a later chronotype, which placed them at greater risk of chronic mild circadian misalignment, was found to be associated with worse glycemic control.

Previous genetic data suggested the role of circadian genes in metabolic control. In animal experiments, Clock mutant mice were shown to shift their feeding and activity into their normally inactive phase and, as a result, developed obesity and metabolic syndrome (hyperlipidemia, hepatic steatosis, hyperglycemia, and hypoinsulinemia) (25). Interestingly, the findings in our participants with later chronotype mimicked those in Clock mutant mice as they shifted their activities and food intake into normally inactive time (i.e., later in the evening), indicated by later bedtime and larger percentage of daily calories consumed at dinner. In addition, participants with later chronotype were more likely to require insulin treatment despite a tendency of being younger and having had diabetes for about the same duration as those with earlier chronotype. While multiple factors can contribute to the need for insulin treatment, and our study did not assess β-cell function, it is possible that those with late chronotypes were more hypoinsulinemic, similar to the Clock mutant mice. Late chronotype subjects also tended to have a higher BMI. Genetic studies in humans have linked the circadian genotypes to metabolic phenotypes. Certain genotypes of Clock and Brain & Muscle Armt-like protein-1 (BMAL1) were associated with evening preference, resistance to weight loss, metabolic syndrome, and susceptibility to type 2 diabetes (26–28). In addition, rare MTNR1B variants, a gene encoding melatonin receptor 1B, have been linked to increased type 2 diabetes risk (29).

The current study revealed that eating more at dinner contributed to poorer

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**Table 2—Pearson correlation (r) between demographics and circadian, sleep, and dietary parameters and natural log of HbA1c (n = 194 unless otherwise noted)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>-0.25</td>
<td>&lt;0.001</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>0.09</td>
<td>0.19</td>
</tr>
<tr>
<td>CES-D score</td>
<td>0.20</td>
<td>0.005</td>
</tr>
<tr>
<td>Circadian parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronotype (MSF)</td>
<td>0.34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sleep parameters</td>
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<tr>
<td>Sleep duration (h)</td>
<td>-0.01</td>
<td>0.90</td>
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<tr>
<td>Perceived sleep debt (h)</td>
<td>0.15</td>
<td>0.04</td>
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<tr>
<td>PSQI score</td>
<td>0.09</td>
<td>0.22</td>
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<td>Dietary parameters</td>
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<tr>
<td>Breakfast calories (%)</td>
<td>-0.11</td>
<td>0.13</td>
</tr>
<tr>
<td>Dinner calories (%)</td>
<td>0.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Breakfast time</td>
<td>0.13</td>
<td>0.13</td>
</tr>
<tr>
<td>Dinnertime</td>
<td>0.11</td>
<td>0.14</td>
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**Table 3—Hierarchical regression analysis with natural log of HbA1c as the outcome (N = 194)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>P</td>
<td>B</td>
</tr>
<tr>
<td>Age</td>
<td>-0.004</td>
<td>0.001</td>
<td>-0.004</td>
</tr>
<tr>
<td>Sex (reference: male)</td>
<td>0.020</td>
<td>0.504</td>
<td>0.020</td>
</tr>
<tr>
<td>Race (reference: nonwhite)</td>
<td>-0.020</td>
<td>0.510</td>
<td>-0.020</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.001</td>
<td>0.716</td>
<td>-0.001</td>
</tr>
<tr>
<td>DM complications</td>
<td>0.037</td>
<td>0.226</td>
<td>0.037</td>
</tr>
<tr>
<td>Insulin use</td>
<td>0.142</td>
<td>&lt;0.001</td>
<td>0.142</td>
</tr>
<tr>
<td>CES-D</td>
<td>0.001</td>
<td>0.641</td>
<td>0.001</td>
</tr>
<tr>
<td>Perceived sleep debt</td>
<td>0.0005</td>
<td>0.950</td>
<td>0.0002</td>
</tr>
<tr>
<td>Adjusted R²</td>
<td>0.20</td>
<td>0.20</td>
<td>0.24</td>
</tr>
<tr>
<td>ρAdj</td>
<td>0.0002</td>
<td>0.950</td>
<td>0.043</td>
</tr>
</tbody>
</table>

B, unstandardized coefficient; DM, diabetes.
Chronotype and glycemic control

Table 4—Demographics and circadian, sleep, and dietary parameter comparisons by chronotype quartiles

|                          | MSF 1st quartile (n = 51) | MSF 2nd quartile (n = 46) | MSF 3rd quartile (n = 49) | MSF 4th quartile (n = 48) | P<
|--------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---
| Age (years)              | 60.5 ± 11.7               | 61.2 ± 11.2               | 56.1 ± 14.7               | 55.7 ± 13.5               | 0.07
| Female                   | 38 (74.5)                 | 29 (63.0)                 | 31 (63.2)                 | 37 (77.1)                 | 0.29
| White                    | 11 (21.5)                 | 19 (41.3)                 | 11 (22.4)                 | 11 (22.9)                 | 0.12
| Employment               |                           |                           |                           |                           | 0.67
| Working                  | 14 (27.5)                 | 17 (37.8)                 | 14 (28.6)                 | 10 (21.7)                 | 0.67
| Retired                  | 22 (43.1)                 | 18 (40.0)                 | 18 (36.7)                 | 20 (43.5)                 | 0.01
| Unemployed               | 15 (29.4)                 | 10 (22.2)                 | 17 (34.7)                 | 16 (34.8)                 | 0.01
| BMI (kg/m²)              | 34.8 ± 7.6                | 33.1 ± 7.0                | 37.4 ± 9.8                | 37.1 ± 7.9                | 0.03
| DM duration (years)      | 8.0 (2.0–20.0)            | 9.5 (4.9–19.2)            | 15.0 (5.0–22.8)           | 14.0 (8.0–18.0)           | 0.22
| ≤5                       | 20 (39.2)                 | 15 (32.6)                 | 13 (27.1)                 | 10 (20.8)                 | 0.40
| 6–10                     | 10 (19.6)                 | 9 (19.6)                  | 8 (16.7)                  | 10 (20.8)                 | 0.40
| 11–20                    | 10 (19.6)                 | 12 (26.1)                 | 13 (27.1)                 | 20 (41.7)                 | 0.40
| >20                      | 11 (21.5)                 | 10 (21.7)                 | 14 (29.1)                 | 8 (16.7)                  | 0.40
| HbA1c (%)                | 7.0 (6.4–7.7)             | 7.6 (6.4–8.8)             | 7.5 (6.3–8.8)             | 8.3 (7.2–9.4)             | 0.01
| HbA1c (mmol/mol)         | 53 (46–61)                | 60 (46–73)                | 58 (45–73)                | 67 (55–79)                | 0.01
| Insulin use              | 21 (41.2)                 | 22 (47.8)                 | 32 (65.3)                 | 33 (68.8)                 | 0.01
| Diabetes complications ≥1| 35 (68.6)                 | 31 (67.3)                 | 36 (73.4)                 | 36 (75.0)                 | 0.81
| CES-D score              | 11.3 ± 8.2                | 11.7 ± 9.1                | 16.3 ± 10.3               | 14.7 ± 7.6                | 0.02
| Circadian parameters     |                           |                           |                           |                           | 0.72
| Chronotype (MSF)         | 1:30 ± 0.46               | 2:48 ± 0.20               | 3:54 ± 0.17               | 5:50 ± 1:30               | <0.05
| Bedtime weekday, P.M.    | 21:22 ± 1:22              | 22:27 ± 0:42              | 23:09 ± 1:07              | 0:16 ± 1:54               | <0.05
| Bedtime weekend, P.M.    | 21:18 ± 1:09              | 22:40 ± 0:46              | 23:31 ± 1:00              | 1:13 ± 1:42               | <0.05
| Wake time weekday, A.M.  | 5:13 ± 1:13               | 6:20 ± 1:07               | 7:19 ± 1:11               | 8:46 ± 2:04               | <0.05
| Wake time weekend, A.M.  | 5:35 ± 1:21               | 6:44 ± 1:09               | 7:49 ± 1:15               | 9:53 ± 1:42               | <0.05
| Social jetlag (min)      | 0.0 (0.0–37.5)            | 0.0 (0.0–30.0)            | 0.0 (0.0–48.8)            | 8.8 (0.0–105)             | 0.03
| Social jetlag >30 min    | 13 (25.5)                 | 10 (21.7)                 | 16 (32.6)                 | 22 (45.8)                 | 0.06
| Sleep parameters         |                           |                           |                           |                           | 0.72
| Sleep duration (h)       | 6.43 ± 1.39               | 6.67 ± 1.37               | 6.68 ± 1.74               | 6.82 ± 2.14               | 0.04
| Perceived sleep debt (h) | 1.49 ± 1.77               | 1.11 ± 1.22               | 1.50 ± 1.63               | 2.20 ± 2.46               | 0.04
| PSQI score               | 6.3 ± 3.9                 | 6.1 ± 3.9                 | 7.6 ± 4.6                 | 7.2 ± 4.0                 | 0.24
| OSA/risk                 | 29 (56.9)                 | 28 (60.8)                 | 30 (61.2)                 | 32 (66.7)                 | 0.80
| Dietary parameters       |                           |                           |                           |                           | 0.99
| Total daily calories     | 1,481 ± 640               | 1,475 ± 477               | 1,472 ± 559               | 1,462 ± 565               | 0.95
| Breakfast calories (% of daily total) | 23 ± 15 | 24 ± 12 | 24 ± 15 | 23 ± 16 | 0.95
| Dinner calories (% of daily total) | 32 ± 20 | 35 ± 17 | 37 ± 19 | 43 ± 23 | 0.04
| Breakfast time, A.M.     | 7:47 ± 1:39               | 8:10 ± 1:17               | 8:43 ± 1:50              | 9:48 ± 1:22               | <0.001
| Dinnertime, P.M.         | 18:25 ± 1:13              | 18:34 ± 1:29              | 18:50 ± 1:24              | 19:19 ± 1:3               | 0.02
| Late evening snack       | 22 (43.1)                 | 19 (41.3)                 | 22 (44.8)                 | 25 (52.1)                 | 0.73

Data are means ± SD, median (interquartile range), or n (%) unless otherwise indicated. DM, diabetes. *P values are from ANOVA from comparisons for continuous variables and χ² for categorical variables unless otherwise indicated. †Kruskal-Wallis test. ‡Post hoc analyses: P < 0.05 compared with 1st, 2nd, and 3rd quartiles. §Post hoc analyses: P < 0.05 compared with 1st quartile. ¶Post hoc analyses: P < 0.05 compared with 2nd quartile. ‖Post hoc analyses: P < 0.05 among all quartiles except between 2nd and 3rd quartiles. **Post hoc analyses: P < 0.05 among all quartiles.

glycemic control. In humans, glucose tolerance has been shown to decrease from morning to evening from a combination of reduced glucose utilization, decreased insulin sensitivity, and inappropriately low insulin secretion (13). This could explain the independent effect of eating a large dinner on glycemic control.

The current study cannot address the direction of causality of the association between circadian regulation and metabolic function. It is possible that hyperglycemia influences the circadian system, as patients with diabetes exhibit dampened amplitude of rhythms of glucose tolerance and insulin secretion (30). Dietary factors, such as high-fat diet in mice, can modify behavioral circadian rhythms (2,31). Therefore, it is likely that the relationship between circadian disruptions and metabolic derangements is bidirectional (3).

Our study has limitations. We did not have objective measures of sleep or circadian parameters or of OSA severity, all of which could impact glycemic control (32,33). In addition, menopausal status, which could be associated with changes in sleep patterns and HbA1c, was not available. Future studies should obtain objective measures of sleep duration and quality as well as of circadian function. The most important question of whether shifting the circadian system earlier may improve glycemic control remains to be addressed. Simple behavioral modifications, such as going to bed and waking up earlier, keeping a regular sleep/wake
schedule, and modifying daily caloric distribution, may lead to improved glycemic control.

In summary, we demonstrated that later chronotype and larger percentage of daily calories consumed at dinner were both associated with worse glycemic control in patients with type 2 diabetes independently of sleep measures. The results support a role of circadian regulation in glycemic control in patients with type 2 diabetes.

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S.R. conceptualized the study, analyzed data, wrote the manuscript, contributed to discussion, and reviewed and edited the manuscript. M.H.M. and S.J.C. analyzed data, contributed to discussion, and reviewed and edited the manuscript. K.R. performed data analysis, wrote the manuscript, and edited the manuscript. E.V.C. contributed to discussion and reviewed and edited the manuscript. S.R. is the guarantor of this work and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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References