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Habitual Shortened Sleep and Insulin Resistance: an Independent Relationship in Obese Individuals

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Abstract

Objective—Short sleep duration has been reported to be associated with obesity, type 2 diabetes, and pre-diabetes. Since excess weight, glucose abnormalities, and insulin resistance tend to cluster, the individual role insulin resistance may have in habitual shortened sleep is unclear. The study purpose was to assess whether habitual sleep curtailment is independently related to insulin resistance in obese individuals.

Materials/Methods—Non-diabetic, overweight/obese individuals from the community were stratified as insulin-resistant (n=35) or insulin-sensitive (n=21) based on steady-state plasma glucose concentrations (SSPG) during the insulin suppression test. Seventy-five gram oral glucose tolerance tests were performed. Participants were asked, “On average, how many hours of sleep do you get per night?” Shortened sleep duration was defined as less than 7 hours of sleep per night.

Results—SSPG concentrations differed 2.5-fold ($P<0.001$) between insulin-resistant and insulin-sensitive individuals. Impaired fasting glucose and glucose intolerance were prevalent in both groups (>40%); however, body mass index, waist circumference, mean fasting or 2-hr post-glucose glucose concentrations were not significantly different. Insulin-resistant individuals reported (mean $\pm$ SD) fewer hours of sleep than did insulin-sensitive individuals (6.53 ± 1.1 vs 7.24 ± 0.9 hours, $P<0.05$). Shortened sleep duration was more prevalent among insulin-resistant as compared with insulin-sensitive individuals (60% vs 24%, $P<0.05$).

Conclusions—Non-diabetic, insulin-resistant individuals averaged fewer hours of sleep and were more likely to report shortened sleep duration as compared with similarly obese insulin-sensitive individuals. There appears to be an independent association between habitual shortened sleep and insulin resistance among obese, dysglycemic adults without diabetes.

Keywords

sleep duration; insulin resistance; obesity; glucose intolerance

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Author contributions

A.L. contributed to the design and conduct of the study, data collection and analysis, and manuscript writing. C.K. and G.R. contributed to the study design and manuscript writing.

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1. Introduction

Type 2 diabetes (T2DM) is estimated to affect more than 20 million Americans, and is associated with considerable morbidity and mortality. Given projections that prevalence of T2DM may double by 2050 [1], present efforts at risk modification are paramount. The potential association of short sleep with T2DM has come to recent attention [2]. The trend over the past decades has seen Americans receiving fewer hours of sleep than they did previously [3,4]. Observational studies have suggested that short sleep duration may be linked to obesity [5], prediabetes [2,6], and insulin resistance [7,8]. Given that excess weight, glucose abnormalities, and insulin resistance tend to cluster together, it is not clear whether habitual shortened sleep is associated with insulin resistance, independent of adiposity or dysglycemia. To test this hypothesis, we compared self-reported sleep duration in individuals within a similar BMI range, divided into insulin-resistant and insulin-sensitive subgroups by a direct measurement of insulin-mediated glucose uptake. Oral glucose tolerance tests were also performed to evaluate further glucose metabolism.

2. Methods

Volunteers (n=104) from the San Francisco Bay area were recruited consecutively in response to advertisements for our research studies on insulin resistance. Study protocols were approved by the Stanford Administrative Panels for the Protection of Human Subjects. All participants gave informed consent. Inclusion criteria included apparently healthy individuals without known diabetes, liver, kidney, or heart disease. They were selected to be moderately overweight to obese (body mass index [BMI] 27.0 – 34.9 kg/m²). Individuals with known obstructive sleep apnea (OSA) or depression (self-reported depression and/or taking medications for treatment of depression) were excluded, leaving an experimental cohort of 78 individuals. Waist circumference was measured midway between the iliac crest and rib cage at end-expiration. Fasting lipid/lipoprotein concentrations were measured by conventional methods. A 75-gram glucola drink was administered after a 12-hour overnight fast. Glucose measurements were obtained before and 2 hours after glucola ingestion. Impaired fasting glucose and impaired glucose tolerance were defined as plasma glucose 100 mg/dL and 140 mg/dL, respectively.

Insulin-mediated glucose uptake was quantified by the modified [9] insulin suppression test [10], which is highly correlated ($r > 0.9$) with the euglycemic clamp [10]. After an overnight fast, individuals were infused with octreotide (0.27 µg/m²/min), insulin (32 mU/m²/min), and glucose (267 mg/m²/min) over 180 minutes. Plasma glucose and insulin concentrations were measured every 10 minutes during the final 30 minutes and averaged to obtain steady-state plasma glucose (SSPG) and insulin concentrations. Because steady-state plasma insulin concentrations are similar for all individuals, SSPG provides a direct measure of the ability of insulin to mediate disposal of the infused glucose load. Thus, the higher the SSPG, the more insulin-resistant the individual. Cut-points to identify insulin-resistant and insulin-sensitive individuals were defined as SSPG 180 mg/dL and 120 mg/dL, respectively, based on prospective studies demonstrating that clinical syndromes associated with insulin resistance occur in those classified as insulin-resistant and not in the insulin-sensitive subgroup [11], as well as a prior study of the distribution of SSPG concentrations in a reference population [12]. Applying these cut-points to the 78 participants evaluated, 56 were classified as being either insulin-resistant (n=35) or insulin-sensitive (n=21). The remaining participants were determined to be intermediate, and not further studied.

Participants were asked by written questionnaire, “On average, how many hours of sleep do you get per night?” Responses were allowed to be reported in half-hour increments. Shortened sleep duration was defined as fewer than 7 hours of sleep per night.

Data analyses were performed using SPSS 20.0 (Chicago, IL). Between-group comparisons were made using *t*-tests for continuous variables. Categorical variables were compared using chi-square or Fisher's exact tests. Triglyceride, HDL-cholesterol, and LDL-cholesterol concentrations were log transformed to improve normality. Linear and logistic regression analyses were conducted to adjust for BMI. Statistical significance was defined as $P < 0.05$.

3. Results

Characteristics of the 56 participants are shown in Table 1. By selection, insulin-mediated glucose uptake differed substantially between the insulin-resistant and insulin-sensitive subgroups (2.5-fold, $P < 0.001$). Insulin-resistant individuals had somewhat higher values for BMI ($P = 0.07$). Dysglycemia was prevalent in both groups (>40% had impaired fasting glucose and/or glucose tolerance). However the 2 groups did not differ in prevalence of impaired fasting glucose or glucose intolerance, mean fasting glucose, or 2-hr glucose concentrations. Insulin-resistant individuals exhibited higher triglyceride and lower HDL-cholesterol concentrations, and somewhat higher systolic blood pressure ($P = 0.06$).

Sleep characteristics of insulin-resistant and insulin-sensitive individuals are shown in Table 2. Insulin-resistant individuals reported significantly less sleep than did insulin-sensitive persons (6.53 ± 1.1 vs 7.24 ± 0.9 hours, $P < 0.05$), and were more likely to report shortened sleep duration (60% vs 24%, $P < 0.05$). Since BMI tended to be greater in the insulin-resistant group, these differences were adjusted for BMI, and differences in sleep characteristics remained statistically significant.

4. Discussion

Previous studies have described an association between shorter sleep and excess adiposity [5], and various degrees of glucose intolerance [2,6]. The present study extends these findings by comparing sleep duration in two groups that differed dramatically in insulin sensitivity; our results demonstrate that reported sleep duration was shortened among insulin-resistant individuals, after adjustment for BMI. Furthermore, although prevalence of impaired fasting glucose and glucose intolerance was increased in both insulin-resistant and insulin-sensitive individuals, there was no significant difference between the two groups in these glucose measurements.

Prior investigations of the association between insulin resistance and shorter sleep duration have yielded somewhat mixed results. Two studies performed in young, lean adults [7,8], using the Homeostasis Model of Insulin Resistance (HOMA-IR) to assess insulin resistance, described an association between shortened sleep and insulin resistance. In contrast, short sleep duration was not correlated with HOMA-IR in Caucasian and African-American adults spanning a broad BMI range [13].

Although there are several possible reasons for the discrepant findings of the association between insulin resistance and shorter sleep duration, the most obvious one is the use of HOMA-IR as the measure of insulin action. While HOMA-IR may be useful in population-based studies, it accounts for no more than ~1/3 of the variability in insulin action in non-diabetic adults [14]. To the best of our knowledge, the present study is unique in that it is the first to separate the experimental populations into insulin-resistant and insulin-sensitive subgroups, and demonstrate using a direct method to quantify insulin action an independent association of insulin resistance with habitual sleep curtailment. It is noteworthy that the relationship between shortened sleep and insulin resistance was apparent, even within an obese population with a high prevalence of glucose abnormalities.

These findings can be interpreted to suggest that a state of chronic sleep deprivation confers a deleterious effect on glucose metabolism. This formulation is supported by a number of small studies showing that experimental sleep deprivation or restriction in healthy, non-obese adults led to modest declines in glucose tolerance or insulin sensitivity [15–18]. These observations are consistent with our results; however, they involve small numbers of subjects and were non-obese. Furthermore, it is not clear that experimentally-induced acute sleep deprivation accurately represents the impact of chronic sleep deprivation.

Although our findings can be interpreted to mean that shortened sleep duration decreases insulin sensitivity, it could also be argued that insulin resistance may create an environment conducive to shorter sleep. While evidence in this direction is limited, one prospective study lends support to this hypothesis [19]. HOMA-IR was found to be associated with increased odds of incident observed apnea, suggesting that insulin resistance might precede OSA, a condition characterized by repetitive sleep disruption and chronic sleep deprivation. Postulations for this relationship have included insulin-mediated inflammatory activity or diminished upper airway muscle tone [20].

A main strength of our study was the use of rigorous methods to characterize individuals metabolically. A main limitation of the study was reliance on self-reporting rather than an objective measure to determine sleep duration. However, over- or under-reporting was likely to be random and unlikely to bias results. While individuals with known diagnoses of OSA were excluded, it is possible participants could have had occult or undiagnosed OSA which may impact sleep duration responses. Lack of information from individuals with intermediate values of SSPG concentration also precludes our ability to define a general relationship between insulin action and sleep duration. Finally, this study was observational in nature and causal relationships speculative.

In summary, our results suggest that habitual shortened sleep is independently associated with insulin resistance in obese, dysglycemic individuals without diabetes. The interaction between sleep duration and risk for T2DM may have important implications for the role of sleep behavior modification to reduce cardio-metabolic disease.

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Abbreviations

HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
OSA	obstructive sleep apnea
SSPG	steady-state plasma glucose
T2DM	type 2 diabetes

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Table 1

Characteristics of insulin-sensitive and insulin-resistant individuals

Variable	Insulin-sensitive Individuals	Insulin-resistant Individuals	P
n	21	35	
Steady-state plasma glucose (mg/dL)	91 ± 21	220 ± 26	<0.001
Number of Men/Women	8/13	15/20	0.79
Race (White/Asian/Hispanic or Latino/Black or African-American/Mixed)	18W/2A/1H	18W/9A/5H/2B/1M	0.13
Age (years)	55 ± 9	56 ± 9	0.76
BMI (kg/m ²)	30.5 ± 2.5	31.6 ± 2.1	0.07
Waist circumference (cm)	102 ± 10	106 ± 8	0.12
Fasting glucose (mg/dL)	100 ± 7	102 ± 8	0.34
% Impaired fasting glucose	47.6	54.3	0.78
Glucose 2-hr post 75g glucola (mg/dL)	126 ± 33	142 ± 34	0.10
% Impaired glucose tolerance	42.9	48.6	0.79
Systolic blood pressure (mm Hg)	122 ± 12	129 ± 15	0.06
Diastolic blood pressure (mm Hg)	73 ± 8	77 ± 9	0.16
Total cholesterol (mg/dL)	187 ± 38	194 ± 37	0.50
LDL-cholesterol (mg/dL)	115 ± 33	113 ± 31	0.84
HDL-cholesterol (mg/dL)	56 ± 11	49 ± 14	0.04
Triglycerides (mg/dL)	83 ± 41	158 ± 74	<0.001

Data are means ± SD unless otherwise specified.

BMI, Body Mass Index; HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein.

Table 2

Comparison of self-reported sleep duration in insulin-sensitive and insulin-resistant individuals

Variable	Insulin-sensitive Individuals	Insulin-resistant Individuals	<i>P</i>	<i>P^a</i>
n	21	35		
Average sleep per night (hours) ^b	7.24 ± 0.9	6.53 ± 1.1	0.018	0.04
Number reporting fewer than 7 hours of sleep per night (%)	5 (23.8)	21 (60)	0.013	0.016

Data are number (percentage) of subjects or mean ± SD.

^aAdjusted for BMI.^bReported as fraction of hour.