Original Article

Insufficient sleep disrupts glucose metabolism during pregnancy by inhibiting *PGC-1α*

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Background: Gestational diabetes mellitus (GDM) impacted about 17 million pregnancies globally and predisposes both the mother and her offspring to metabolic disorders. Insufficient sleep has been shown to be associated with GDM. This study aimed to explore the molecular link between sleep and GDM.

Methods: The sleep of pregnant mice was disturbed with motion a rod and the mice received either dimethyl sulfoxide (DMSO) or ZLN005. Insulin resistance was assessed by intraperitoneal glucose tolerance test (GTT). Adenosine triphosphate (ATP), reactive oxygen species (ROS), and cytokines were measured with respective commercial kits. Gene expression was analyzed with quantitative polymerase chain reaction (qPCR), western blot, and/or immunohistochemistry (IHC).

Results: Sleep disturbance increased blood glucose level and insulin resistance, increased ROS and inflammatory cytokines, and reduced ATP level in pregnant mice. The expression levels of *PGC-1α* and downstream metabolic genes and antioxidant genes in pregnant mouse muscle were inhibited by sleep disturbance. ZLN005 promoted expression of *PGC-1α* and its target genes, increased muscle ATP level, decreased muscle ROS, and reduced blood glucose level and insulin resistance in sleep disturbed pregnant mice, indicating that *PGC-1α* played a critical role in sleep insufficiency caused GDM and might be a target for intervention.

Conclusions: PGC-1 was a key player in the sleep disorder GDM and might be a target for treatment.

Keywords: Gestational diabetes mellitus (GDM); sleep disturbance; *PGC-1α*; insulin resistance; ZLN005

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Introduction

Gestational diabetes mellitus (GDM) is typically first diagnosed during weeks 24–28 of pregnancy, which affects approximately 17 million pregnancies worldwide each year (1,2). Due to the maternal need for higher caloric intake and elevated insulin resistance, glycemic control during pregnancy can be challenging. Maternal hyperglycemia accelerates intrauterine growth and increases the risk of macrosomia or the fetus being born large for gestational age (3), which may increase the risk of preeclampsia, neonatal hypoglycemia, shoulder dystocia, late stillbirth, or the need for caesarean section or neonatal intensive care (4-6). Moreover, maternal hyperglycemia can cause abnormal carbohydrate metabolism beyond the second generation (7-9). It has been shown that GDM modifies neurodevelopmental processes resulting in learning disability, attention deficit, and motor impairment in

children (10-12) and rodents (13-15).

Sleep disturbance is implicated in numerous health problems including diabetes, cerebrovascular disease, cardiovascular disease, malignant neoplasm, accidents, septicemia, and hypertension (16). Shortened and fragmented sleeping patterns may cause metabolic disturbances resulting in an increased risk of weight gain and skeletal muscle degradation. The metabolic damage may stimulate systemic inflammation, insulin resistance, and suppress muscle protein synthesis, which may disrupt energy balance and skeletal muscle metabolism (17). Poor sleep quality during early pregnancy significantly increases the risk of GDM, especially in women aged 30 years and above (18,19). Abnormally long or short sleep duration increases random blood glucose levels in pregnant women and a duration sleep greater than 10 hours per night significantly increases the risk for GDM (20). Furthermore, gestational sleep deprivation is associated with higher offspring body mass index (BMI), diastolic blood pressure, and waist circumference, and increases the risk for overweight or obesity (21).

Peroxisome proliferator-activated receptor gamma co-activator 1 alpha (PPARGC1A or short form *PGC-1α*), the master regulator of mitochondrial biogenesis and energy production, is important in controlling many cellular pathways, including metabolism, energy homeostasis, insulin sensitivity, oxidative state, and inflammation (22-26). The messenger RNA (mRNA) levels of *PGC-1α* mRNA on the fetal side of the placenta from GDM mothers were found to be significantly lower compared to the control group, whereas the methylation level of the *PGC-1α* gene and blood glucose level were comparatively higher in the GDM group (27). Emerging evidence indicates that sleep loss inhibits *PGC-1α* expression, reduces mitochondrial function, and subsequently increases insulin resistance (28). However, the mechanism of how sleep disturbance induces gestational diabetes is not yet clear. This study is aimed to yield evidence that *PGC-1α* serves as the connection between sleep loss and GDM. We present the following article in accordance with the ARRIVE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5551/rc).

Highlight box

Key findings

- This study reports increased blood glucose and insulin resistance, downregulation of energy metabolism and antioxidant genes, and metabolic disruption were all signs of sleep disturbance-induced GDM. In sleep-deprived pregnant mice, activating *PGC-1α* with ZLN005 enhanced expression of *PGC-1α* and its target genes, raised muscle ATP levels, lowered muscle ROS, and decreased blood glucose levels and insulin resistance.

What is known and what is new?

- Risk of sleep disorder increases gestational diabetes, hypertension, *PGC-1α* is important in controlling many cellular pathways, including metabolism, energy homeostasis, insulin sensitivity, oxidative state, and inflammation.
- The mechanism of how sleep disturbance induces gestational diabetes is not yet clear.

What is the implication, and what should change now?

- This study is aimed to yield evidence that PGC-1α serves as the connection between sleep loss and GDM.

Methods

Gestational sleep disturbance mouse model

Adult B57bl/6 mice (7 weeks of age) were purchased from Cavens Laboratory Animals (Changzhou, China) and acclimated for a week before mating. Every male mouse was housed with 3 female mice in each cage. Mice were housed at 22–24 ℃ with 50% humidity, a 12-hour light/dark cycle, and free access to water and standard chow (000521; Zeyakejiao, Shanghai, China). To initiate pregnancy, every male mouse was housed in a cage with 3 female mice in the evening and the copulatory plug was checked the next morning. Mated female mice were randomly divided into a control group (5 mice) and a sleep disturbance group (15 mice) and the mice in both groups were allowed to eat freely.

Sleep disturbance was performed in rodent sleep deprivation machine (KW-BD; KEW Basis Biotechnologies, Nanjing, China) from 8:00 am to 6:00 pm daily with the disturbing rod set at 1 rpm. Body weight and water consumption were recorded daily. Fasting blood glucose level and intraperitoneal glucose tolerance were measured after 5 days of sleep disturbance. The mice with higher blood glucose level and glucose intolerance were randomly divided into 2 groups to receive either 50 μL of 0.5% dimethyl sulfoxide (DMSO) or ZLN005 (15 mg/kg in 50 μL of 0.5% DMSO) (S7447, Selleck Chemicals, Houston, TX, USA) daily via gavage for 7 days. The speed of sleep deprivation machine was reduced to 0.1 rpm during this period of time. At the end of the treatment regime, blood was collected via retro-orbital bleeding before mice were euthanized and the

Table 1 Sequences of primers used in the study

Primer	Sequence
Pgc1α(Mouse)-F	CAGGAACAGCAGCAGAGACAAAT
Pgc1α(Mouse)-R	TGGGGTCAGAGGAAGAGATAAAG
Errα(Mouse)-F	CGGCGGACGGCAGAAGTACAAAC
Errα(Mouse)-R	CCACCAGCAGATGCGACACCAGA
Sirt1(Mouse)-F	TCAGATAAGGAAGGAAAACTAC
Sirt1(Mouse)-R	GATTAAAAATGTCTCCACGAAC
Glut4(Mouse)-F	CTTCCTTCTATTTGCCGTCCTCC
Glut4(Mouse)-R	ACTGGGTTTCACCTCCTGCTCTA
Sod2(Mouse)-F	AGCGTGACTTTGGGTCTTTTGAG
Sod2(Mouse)-R	GGAATAAGGCCTGTTGTTCCTTG
Ucp2(Mouse)-F	CATTGTCAACTGTGCTGAGCTG
Ucp2(Mouse)-R	AGAAGTGAAGTGGCAAGGGAGG
Gpx1(Mouse)-F	GAGAAGTGCGAAGTGAATGGTGAGA
Gpx1(Mouse)-R	CAAAGTTCCAGGCAATGTCGTTGCG
Tfam(Mouse)-F	CAAAGTTCCAGGCAATGTCGTTGCG
Tfam(Mouse) -R	TTTTTCTGCTTCTGGTAGCTCCCTC
mt-Nd1(Mouse)-F	ACATTGTTGGTCCATACGGCATTTT
mt-Nd1(Mouse)-R	TATTGGTAGGGGAACTCATAGACTT
mt-Cox1(Mouse)-F	GAGTGTCATCTATTTTAGGTGC
mt-Cox1(Mouse)-R	AAAGTTGTGTTTAGGTTGCGGT
mt-Atp6(Mouse)-F	CACACACCAAAAGGACGAACAT
mt-Atp6(Mouse)-R	AATTACGGCTCCAGCTCATAGT
Gapdh(Mouse)-F	CCTTCCGTGTTCCTACCCCCAATGTG
Gapdh(Mouse)-R	TCGCAGGAGACAACCTGGTCCTCAGT
COX IV(Mouse)-F	CTATGTGTATGGCCCCATCCCTC
COX IV(Mouse)-R	CACTTCTTCCACTCATTCTTGTC

gastrocnemius and soleus muscles were harvested.

Experiments were performed under a project license (No. 2020KY235) granted by Institutional Animal Care and Use Committee (IACUC) of Nanjing Medical University, in compliance with national guidelines for the care and use of animals.

Intraperitoneal glucose tolerance test

The intraperitoneal glucose tolerance test (IGTT) was performed essentially following a previously published procedure (29). Briefly, mice were fasted for 12 hours and given 2 g/kg (of body weight) glucose (400 mg/mL) solution via intraperitoneal injection. Blood glucose levels at 0, 15, 30, 60, and 120 minutes after glucose injection were measured with a glucometer (One Touch Ultra2, LifeScan, Shanghai, China).

Enzyme-linked immunosorbent assay

Serum *PGC-1α* (JL49160, Jianglai Bio, Shanghai, China), interleukin (IL)-1β (JYM0531Mo, ColorfulGene, Wuhan, China), TNF-*α* (JYM0218Mo, ColorfulGene), IL-6 (JYM0012Mo; ColorfulGene), and insulin (SEKM0141, SolarBio, Beijing, China) levels were assessed with an enzyme-linked immunosorbent assay (ELISA) commercial kit according to the manufacturer's protocols.

Real-time polymerase chain reaction (RT-PCR)

Total RNA was extracted with Trizol (Invitrogen, Shanghai, China) and then 0.5 μg was reverse transcribed using RevertAid First Strand cDNA Synthesis Kit (K1622, Thermo Fisher Scientific, Shanghai, China). The relative mRNA levels of the studied gene were analyzed by RT-PCR using DyNAmo Flash SYBR Green qPCR Kit (F415XL, Thermo Fisher Scientific) on an ABI 7500 (Thermo Fisher Scientific). The sequences of primers used in this study are listed in *Table 1*. The relative gene expression level was calculated by $2^{-\Delta\Delta Ct}$ method with glyceraldehyde 3-phosphate dehydrogenase (GAPDH) as the internal control.

Measurement of adenosine triphosphate (ATP) level

The ATP levels of muscle tissues were measured with an ATP content assay kit (BC0300, SolarBio) according to manufacturer's instructions and normalized to protein content.

Histopathological staining

The histopathological changes of mouse muscle tissue were

examined by Oil red O (G1261, SolarBio) and hematoxylin and eosin (HE; ab245880, Abcam, Cambridge, MA) staining following the manufacturer's procedures.

Immunohistochemical staining

Slides of mouse gastrocnemius and soleus muscle tissues were deparaffinized by immersing in xylene for 30 minutes, followed by another round in xylene for 10 minutes, and then rehydrated in ethanol alcohol gradient (100% to 50%) to phosphate-buffered saline (PBS). After performing antigen retrieval, quenching endogenous peroxidase activity, and blocking with 5% bovine serum albumin (BSA), slides were incubated with primary antibodies at 4 ℃ overnight. Antibodies used were anti-GLUT4 (bs-0384R, Bioss, Woburn, MA, USA), *PGC-1α* (66369-1-AP, Proteintech, Wuhan, China), TFAM (22586-1-AP, Proteintech), and UCP2 (11081-1-AP, Proteintech). The slides were washed and incubated with appropriate horseradish peroxidase (HRP)-conjugated secondary antibody (PV-9001 or PV-9002, ZSGB Bio, Beijing, China) at room temperature for 30 minutes, washed 3 times, incubated with DAB Chromogenic Solution (ZLI-9017, ZSGB Bio) and counterstained with hematoxylin (170103, Shanghai Zhanyun Chemicals, Shanghai, China).

Reactive oxygen species (ROS) assessment

ROS levels in mouse muscle tissues were assessed using a Green Fluorescence Test Kit for Oxidative Stress ROS in Living Tissues (GMS10016.3, GENMED Scientifics, Shanghai, China) following the protocol provided by the manufacturer.

Western blot

Mouse muscle tissues were ground in liquid nitrogen and lysed in radioimmunprecipitation assay (RIPA) buffer (Beyotime, Shanghai, China) with 1 mM phenylmethylsulfonyl fluoride (PMSF; P7626, Sigma, St. Louis, MO, USA). Then, 25 μg total protein was resolved in 8% polyacrylamide gel and transferred onto polyvinylidene fluoride membranes (HATF00010, Millipore, Shanghai, China). The membranes were blocked with 5% BSA for 2 hours at room temperature (A9647, Biosharp, Hefei, China), incubated with specified primary antibodies at 4 ℃ overnight, washed, and incubated with HRP-conjugated secondary antibodies at room temperature for 1 hour before visualization with enhanced chemiluminescence (ECL) working solution (ECL-0011, Beijing Dingguo Changsheng Biotech, Beijing, China).

Statistical analysis

Statistical analysis was performed with GraphPad 12 (GraphPad Software, San Diego, CA, USA). Data were expressed as mean ± SD. The differences among groups were analyzed using one-way analysis of variance (ANOVA) or *t*-test. A P value less than 0.05 was considered statistically significant.

Results

Sleep disturbance promoted GDM

To examine the effects of sleep disturbance on gestational health, newly mated female mice were subjected to motion-induced sleep disturbance. Although sleep disturbance did not have any effect on their body weight (*Figure 1A*), it induced a significant increase of fasting blood glucose level (*Figure 1B*) and insulin resistance (*Figure 1C*).

The levels of PGC-1α and its downstream targets were affected by sleep disturbance

As *PGC-1α* is a master regulator of metabolism and plays a critical role in insulin resistance (29), we next tested the hypothesis that sleep disturbance causes the perturbation of *PGC-1α*-regulated metabolic and antioxidant pathways which leads to gestational diabetes. *PGC-1α* expression was significantly down regulated by sleep disturbance in mouse gastrocnemius (*Figure 2A*,*2B*) and soleus (*Figure 2C*,*2D*) muscles. Sleep disturbance induced the inhibition of a wide range of *PGC-1α* target genes including *Erra*, *SOD2*, *UCP2*, *GPx1*, *Tfam*, and others in mouse muscle tissue (*Figure 2A-2E*). Treating sleep disturbed mice with *PGC-1α* transcriptional activator ZLN005 substantially increased both mRNA (*Figure 2A*,*2C*) and protein (*Figure 2B*,*2D*,*2E*) levels of *PGC-1α* and its target genes in mouse muscle tissues.

PGC-1α activation attenuated sleep disturbance-induced oxidative stress and inflammation

Sleep disturbance caused elevation of ROS level in the

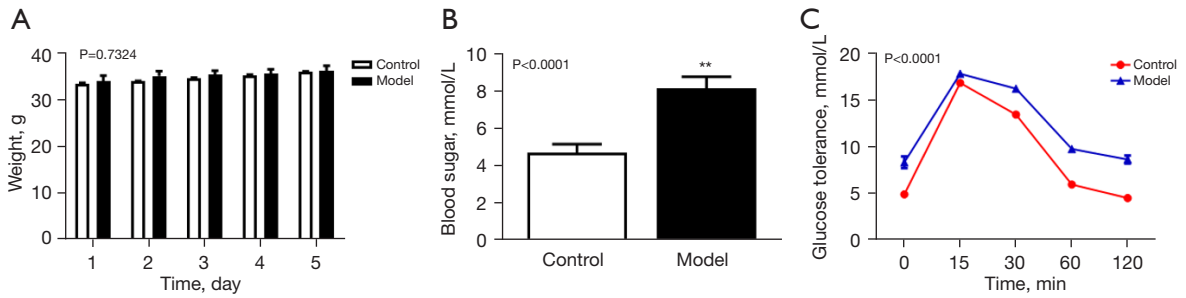

Figure 1 Sleep disturbance-induced GDM. (A) Female mice with copulatory plug were fed with a fat-enhanced diet combined with or without motion-induced sleep disturbance. Body weight was monitored daily. Fasting blood glucose (B) and intraperitoneal glucose tolerance (C) were checked after 5 days of sleep disturbance. **P<0.01 compared to control. GDM, gestational diabetes mellitus.

gastrocnemius and soleus muscles of pregnant mice (*Figure 3A*). Meanwhile, serum levels of inflammatory cytokines IL-1β, IL-6, and TNF-α were significantly increased in sleep disturbed mice (*Figure 3B*). Treating sleep disturbed pregnant mice with ZLN005 markedly reduced ROS level (*Figure 3A*) and inflammation (*Figure 3B*).

PGC-1α mediated the effects of sleep disturbance on tissue ATP levels

We next assessed whether sleep disturbance impacted muscle tissue ATP contents and if and *PGC-1α* played a role in this process. Sleep disturbance caused a significant decrease of the ATP level of the gastrocnemius and soleus muscles of pregnant mice (*Figure 4*). ZLN005 treatment substantially relieved sleep disturbance-induced reduction of ATP contents in the muscle tissues of pregnant mice (*Figure 4*).

Sleep disturbance-induced metabolic abnormality was reversed by PGC-1α activation

Sleep disturbance significantly increased the blood glucose (*Figure 5A*), serum insulin (*Figure 5B*), and glucose resistance (*Figure 5C*) levels of pregnant mice. ZLN005 treatment lowered blood glucose levels by about 30% (*Figure 5A*) and serum insulin level by around 20% (*Figure 5B*) compared to those of sleep disturbed pregnant mice receiving DMSO. Moreover, the blood glucose level receded much faster from the peak in IGTT in ZLN005 treated mice than sleep disturbed pregnant mice without ZLN005 (*Figure 5C*).

ZLN005 reduced lipid accumulation in muscle tissue of sleep disturbed pregnant mice

Sleep disturbance did not obviously change the histology of the gastrocnemius and soleus muscles of pregnant mice (*Figure 6A*). However, Oil red O staining showed that sleep disturbance significantly increased lipid droplets in the muscles of pregnant mice and this increase was partially inhibited by ZLN005 treatment (*Figure 6B*).

Discussion

Sleep disturbance of gestational mice induced a significant increase of blood glucose level and insulin resistance, accompanied by an increase of inflammatory cytokines, elevation of oxidative stress, and reduction of ATP production in muscle tissues, downregulation of *PGC-1α*, and a range of *PGC-1α*-regulated genes. Treating sleep disturbed pregnant mice with the *PGC-1α* transcriptional activator ZLN005 relieved the inhibition of expression of *PGC-1α* and its target genes in mouse muscle affected by sleep disturbance, which inhibited ROS production and inflammation and increased ATP level. These changes eventually led to improvement of gestational glucose metabolism.

Sleep disturbance resulted in higher blood glucose levels and higher insulin resistance in pregnant mice, which was consistent with the trends in pregnant women (30). Poor sleep quality and extreme sleep duration increased the risk of GDM (31). Objective assessment found that short sleep duration and a later sleep midpoint significantly increased the risk of GDM (32). Similarly, short or long sleep

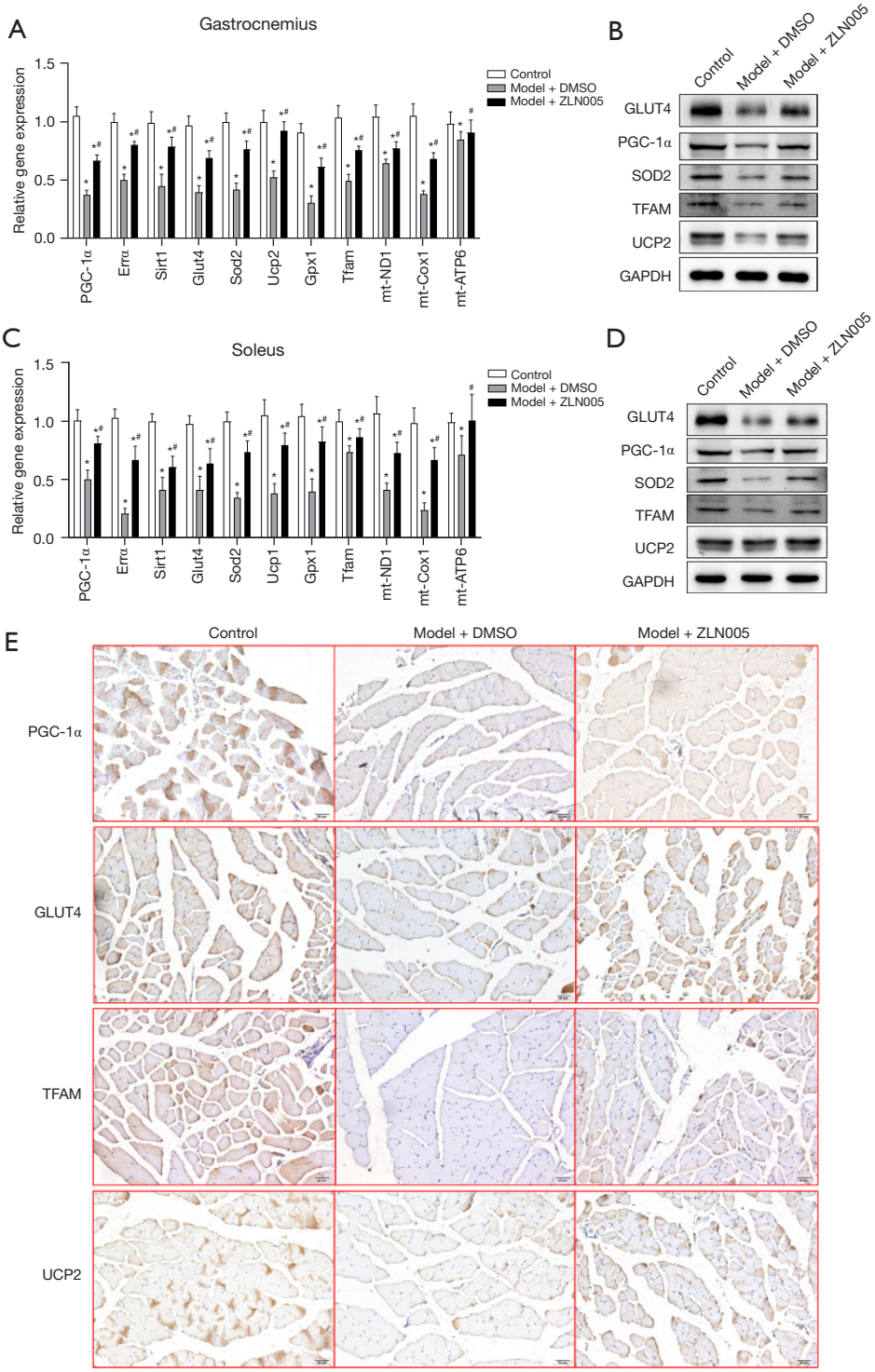

Figure 2 Sleep disturbance downregulated metabolism and antioxidant genes through PGC-1α. Pregnant female mice with high blood glucose level and insulin resistance were given either 50 μL of 0.5% DMSO or ZLN005 (15 mg/kg in 50 μL of 0.5% DMSO) daily for 7 days. The mRNA (A,C) and protein (B,D) levels of PGC-1α and its target genes in gastrocnemius (A,B) and soleus (C,D) were assessed by qRT-PCR and western blot respectively. (E) PGC-1α, GLUT4, TFAM, and UCP2 protein levels of gastrocnemius were examined by IHC staining. *P<0.05 compared to control; #P<0.05 compared to Model + DMSO. DMSO, dimethyl sulfoxide; mRNA, messenger RNA; qRT-PCR, quantitative real-time polymerase chain reaction; IHC, immunohistochemical.

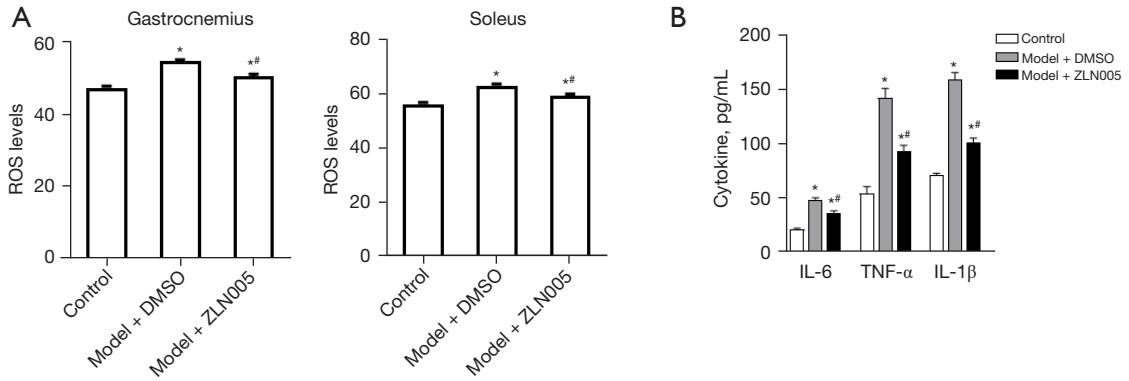

Figure 3 Sleep disturbance induced oxidative stress and inflammation in pregnant mice. (A) ROS level of gastrocnemius and soleus was analyzed using Green Fluorescence Test Kit for Oxidative Stress ROS in living tissues. (B) Serum IL-1β, IL-6, and TNF-α levels were measured by ELISA. *P<0.05 compared to control; #P<0.05 compared to Model + DMSO. ROS, reactive oxygen species; ELISA, enzyme-linked immunosorbent assay; DMSO, dimethyl sulfoxide.

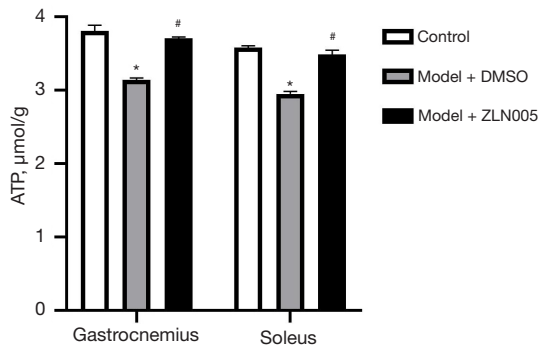

Figure 4 Sleep disturbance disrupted energy metabolism of pregnant mice. The ATP levels of mouse muscle tissues were measured using ATP content assay kit. *P<0.05 compared to control; #P<0.05 compared to Model + DMSO. ATP, adenosine triphosphate; DMSO, dimethyl sulfoxide.

duration incrementally increased the risk of type 2 diabetes (33,34). Sleep duration, slow wave sleep suppression, and rapid eye movement sleep were shown to be associated with insulin resistance in children and adolescents (35). Taken together, sleep duration and sleep quality were associated with the risk of GDM and type 2 diabetes in general population.

Dysregulation of mitochondrial function and downregulation of glucose transporter (GLUT4) are main factors of insulin resistance (36) and *PGC-1α* has been identified as a master regulator of metabolism (22). Studies have shown that the expression level of *PGC-1α* in energy-consuming tissues of diabetic cases is significantly reduced (22,36). Similarly, *PGC-1α* expression in the skeletal muscle tissues of pregnant mice was inhibited by sleep disturbance, which led to downregulation of genes involved in energy metabolism and antioxidization, and increase of blood glucose level and insulin resistance. These adverse effects of sleep disturbance in pregnant mice were suppressed by *PGC-1α* activator ZLN005 (37), confirming the roles of *PGC-1α* in mediating metabolism disruption caused by sleep disturbance.

Conclusions

In summary, sleep disturbance-induced GDM was evidenced by increased blood glucose and insulin resistance, downregulation of energy metabolism and antioxidant genes, and perturbation of metabolism. Activating *PGC-1α* with ZLN005 in sleep disturbed pregnant mice promoted expression of *PGC-1α* and its target genes, increased muscle ATP level, decreased muscle ROS, and reduced blood glucose level and insulin resistance. These data indicated that *PGC-1α* played a critical role in sleep insufficiency caused GDM and might be a target for intervention.

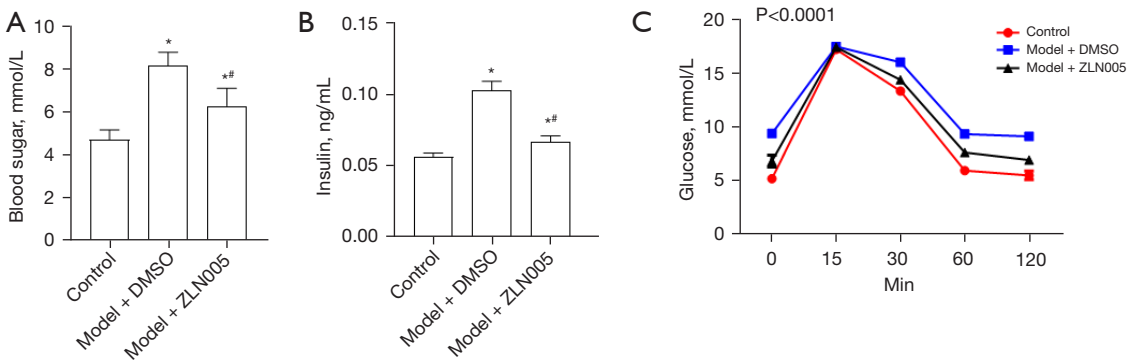

Figure 5 PGC-1α ameliorated sleep disturbance caused insulin resistance. Pregnant mice with higher blood glucose level and glucose intolerance were randomly divided into two groups to receive either 50 μL of 0.5% DMSO or ZLN005 (15 mg/kg in 50 μL of 0.5% DMSO) daily for 7 days. Fasting blood glucose (A), serum insulin (B) and intraperitoneal glucose tolerance (C) were checked after 7 days of treatment. *P<0.05 compared to control; #P<0.05 compared to Model + DMSO. DMSO, dimethyl sulfoxide.

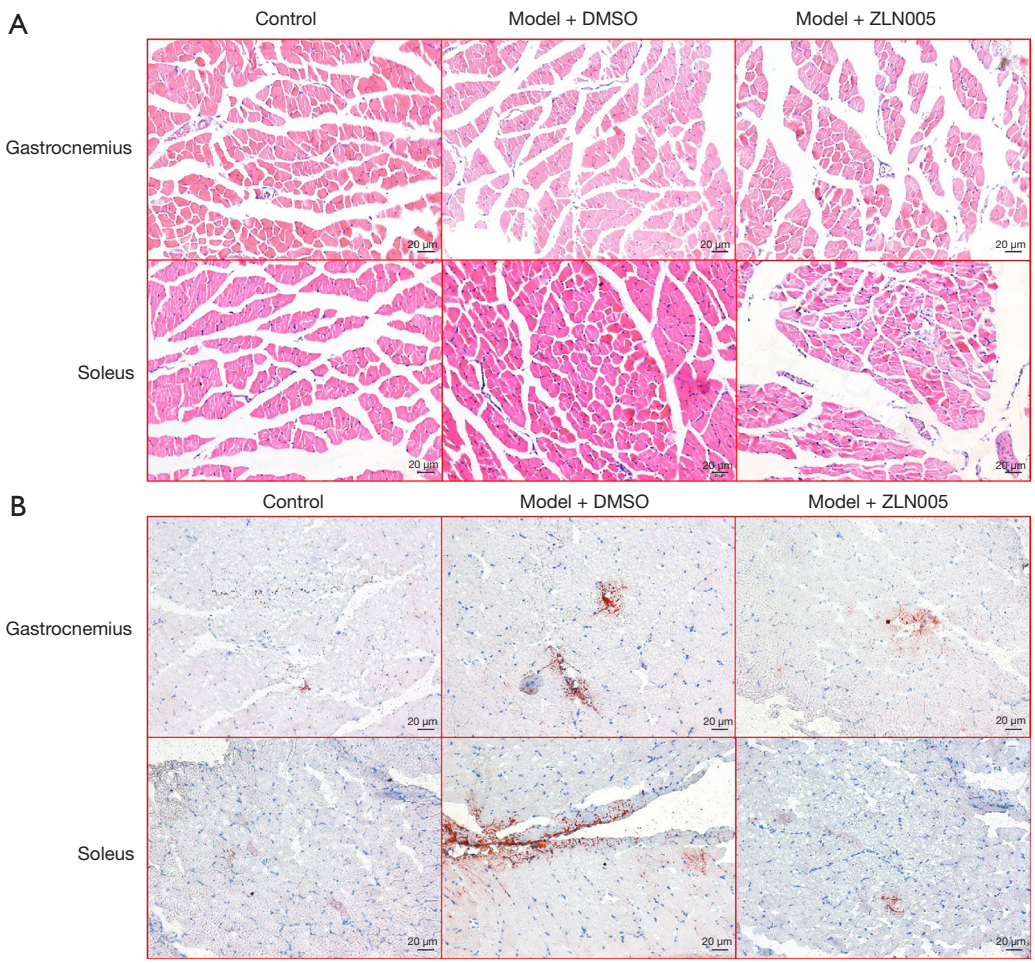

Figure 6 Sleep disturbance caused lipid accumulation in pregnant mouse muscles was inhibited by PGC-1α activation. (A) The histology of mouse muscles was evaluated by HE staining. (B) Muscle lipid accumulation was assessed by Oil red O staining. HE, hematoxylin and eosin; DMSO, dimethyl sulfoxide.

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Footnote

Reporting Checklist: The authors have completed the ARRIVE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5551/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5551/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5551/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Experiments were performed under a project license (No. 2020KY235) granted by Institutional Animal Care and Use Committee (IACUC) of Nanjing Medical University, in compliance with national guidelines for the care and use of animals.

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