"Impact of melatonin, food timing and receptor gene variant on type 2 diabetes risk"

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EXCLUSION CRITERIA

-Age between 18 and 70 years.
-No diabetes.
-Without any relevant medication use such as:
Diabetes-related medications
Growth hormones
Anti-coagulants
Beta-blockers
Hypnotics
Melatonin use or other sleep-related medications.

MEASUREMENTS

1. Habitual dinner timing:
In order to evaluate food habits, initial dietary intake will be determined by a 24-hour dietary recall in both populations at the initial screening. A smartphone application that transmits a time-stamp and photograph of each snack/meal taken during the 7 days and nights prior to the tests was used. This was supplemented with a 7-day food record.

2. Light exposure:
Light exposure was measured during the start of the early and late evening OGTTs. For the late evening OGTT, light intensity will be kept dim (0-25 lux), and for the early evening OGTT, light intensity will be kept bright ((≥450 lux).

3. Other traits:
- BMI
- Waist and Hip (cm)
- Sex, age

4. Melatonin at time of OGTT early and late:
Plasma melatonin will be measured 4 times per subjects at T0 and T120 during both OGTTs (2-time points x 2 OGTT) at the same laboratory by radioimmunoassay (RIA) (IBL, Germany). The intra- and inter-assay precision was 6.7% and 10.4% respectively.

5. Behavioral characteristics:
Physical activity will be assessed by the International Physical Activity Questionnaire (IPAQ) which determines physical activity over the last 7 days. Habitual weekday and weekend sleep timing and duration will be estimated by questionnaire and supplemented by 7-days of smartphone application.

6. OGTTs
A 75g OGTT will be performed twice on 750 participants, once in the early and once in the late evening. After an 8 hour fast, blood samples will be collected to measure glucose and insulin at 0 (fasting) and 30, 60, 90 and 120 minutes will be measured. Glucose will be measured using the Gluco-quant hexokinase test, COBAS Integra 400 (Roche, Indianapolis, IN) with a sensitivity of 2mg/dL and an intra- and interassay precision of 1.0% and 1.7%. Insulin was measured using the ECLIA ELECSYS test, COBAS e-801 (Roche Diagnostics GmbH, Mannheim, Germany) with a sensitivity of 0.2 uIU/ml and an intra- and interassay precision of 0.8-1.5% and 3.2-3.7%.

2 measures or conditions:
- Early: 4 h before their habitual bedtime.
- Late: 1 h before their habitual bedtime (should come 1h before of the T0 and kept in the dim light condition). The samples will be just before the glucose T0 and at T30´, T60´, T 90´y T120´ minutes after the glucose.

7. Biochemical determinations

- Glucose and insulin in the 5 times (T0, T30´, T60´, T 90´y T120´)
- Melatonin in T0´ and T120´

8. Statistical analysis plan

Postprandial glucose and insulin responses were estimated during the 120 minutes using incremental area under-the-curve (AUC) and were calculated by the trapezoidal method. An ANOVA of repeated measurements (ANOVArm) was used to compare glucose and insulin responses between early and late eating conditions. If significant, paired t-tests were performed to examine statistical significance between each OGTT time point. Insulin sensitivity was evaluated using the insulin sensitivity index (ISI) calculated from the OGTT data as 10,000/ (fasting glucose × fasting insulin × mean OGTT glucose × mean OGTT insulin)$^{1/2}$. Beta-cell function was assessed as the corrected insulin response (CIR) during the OGTT (100 × insulin30/ [glucose30 × (glucose30 – 3.89)]). Finally, the disposition index (DI) was calculated as a measure of insulin secretion in relation to insulin sensitivity (DI= ISI×CIR). Paired t-tests were performed to compare metrices in the two conditions.