yrs, BMI<25kg/m^2, type2/type1 diabetes 69/3). Patients with depression, dementia, liver cirrhosis, renal failure, blindness, and shift work were excluded. Activity profiles were analyzed using nonparametric variables, including dichotomy indices, interdaily stability(IS), intradaily variability(IV), relative circadian amplitude(RA), nocturnal awakening (fNA(22:00-1:00), lNA(1:00-4:00)), and morning activities(MoA). To cluster diabetic clinical characteristics and determine the clusters predicting circadian rhythms disruption, principal factor analysis (PFA) was applied.
Results: BMI was positively correlated with IV and lNA(P=.006 and .004), and negatively correlated with IS and RA(P=.007 and =.008), while diabetic duration was associated with IS(P=.01). Patients with progressive diabetic retinopathy had significantly lower RA, compared to those without retinopathy (p=.02). Patients with symptomatic neuropathy had significantly lower IS, higher fNA, and lower MoA (P=.02, .03, and .02, respectively).The levels of urinary albumin excretion were positively correlated with IV and lNA(P=.005 and =.004), and negatively correlated with IS and RA(P=.004 and =.003). The significance remained after adjusting for BMI. Next, PFA identified two factors that explained 24 and 14 % of the variance in the variance in the dataset of diabetic clinical characteristics, respectively. These factors were interpreted as 1) a "duration" factor (DF) with positive loadings of diabetic duration, triopathic parameters, and the history of cardiovascular diseases, and 2) a "metabolic" factor (MF) with positive loadings of BMI, HbA_{1c}, TG, and HDL. Multivariate analysis with a model including DF and MF showed that both factors were independent predictors of IV (p=.04, and .04), and of IS(p=.02, and .006).
Conclusion: Diabetic complications, angiopathy and neuropathy, were associated with disruption of circadian rest- active rhythm. The current results indicate a key common regulator of circadian rhythms and neurovascular function. In addition, metabolic factors and duration factors were independently associated with disruption of circadian rest-activity rhythms. It can be speculated that lifestyles with irregular circadian rhythmicity will cause difficulty metabolic control including weight and daily blood sugar control, and thus hasten the development of these complications, resulting in a vicious cycle. Taken together, chronobiological approach, especially, circadian rhythms entrainment should be considered as a possible therapy for diabetes.

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Robust circadian clocks are ticking in beta and non-beta cells of human pancreatic islets

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Background and aims: Due to the emerging evidence of the pancreas clock impact on the islet function and on type 2 diabetes development as shown in rodents, we aimed to tackle the circadian clockwork in human islets. The oscillator properties were assessed in the intact islets, and as well as in β-cells.
Materials and methods: We established a system for long term bioluminescence recording in cultured human islets, employing lentivector gene delivery. β-cells were stably labeled by rat insulin2 promoter (RIP) fluorescent construct. Single islet/ cell oscillation profiles were measured by combined bioluminescence - fluorescence time lapse microscopy.
Results: Human islets exhibited robust self-sustained circadian oscillations of *Bmal1-luciferase* expression at the both populations and single islet levels, with the oscillation period of 23.6 and 23.9 hours respectively. Moreover, endogenous *Bmal1* transcript expression was circadian in synchronized islets over 48 hours, and antiphasic to *Reverba, Per2* and *Dbp* transcript circadian profiles. Importantly, single β- and non-β cells revealed oscillatory profiles well synchronized with each other.
Conclusion: We provide for the first time a compelling evidence for a robust cell autonomous clock ticking in human islets. Moreover, β-cells possess their own clocks oscillating in synchrony with non-β-cells in primary human islet cell culture.
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An isocaloric high fat diet modulates daily expression profiles of clock genes, LPS response and fat metabolism genes in human monocytes

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Background and aims: The circadian clock coordinates various behavioural and physiological processes including feeding, energy metabolism and inflammation response. In turn, metabolic processes feed back onto the circadian clock as shown in recent human and animal studies. However, there is little to no information about the effect of nutrition on circadian mechanisms in humans. To address this, we provided the analysis of daily expression profiles of clock genes, LPS response and fat metabolism genes in human blood monocytes before and after the high-fat diet intervention.
Materials and methods: Daily gene expression profiles were determined by real-time PCR in 30 non obese healthy individuals in terms of NUtriGenomics Analysis in Twins (NUGAT) study. Gene expression was measured at three time points (in the morning, in the middle of the day and afternoon) during three investigation days. The blood sampling was carried out before the beginning of the high-fat isocaloric diet (HFD, 45 % kcal from fat) and after one and six weeks of intervention.
Results: We demonstrated that clock genes (*PER1, PER2, PER3, BMAL1, REV-ERBα, DBP* and *TEF*) as well as genes contributing to LPS response *(CD14, IKBα, CD180, ERK1, IL1β, IL10, TNFα, CCL3)* and fat metabolism *(FASN, CPT1a)* exhibited significant daily variation in human monocytes. The HFD induced the increase of the expression of the *Period* genes *PER1, PER2* and *PER3* and *TEF* after one and six weeks of intervention (p<0.05) and alterations of synchronisation state within clock gene system. Moreover, the HFD effected the expression of LPS response genes *CD14, IKBα* and *IL8* and fat metabolism genes *ACOX3* and *IDH3A*. Furthermore, the expression levels of *Period* genes and *TEF* significantly correlated with blood cholesterol levels and with the *ACOX3* and *IDH3A* expression in monocytes.
Conclusion: Our results suggest that the consumption of an isocaloric HFD can influence the circadian clock as well as circadian expression of genes contributing to LPS response and fat metabolism in humans already after the short time intervention. This emphasizes the role of nutrition-clock interaction in the regulation of human metabolism and inflammation response.
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