

# Mind your clocks! The role of the biological clock in human metabolic health

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## Valorization

### Background

Through the last century, changes in social- and economic status together with technological advance such as artificial light and fridges have enabled humans to disengage from their primordial day-night rhythm. Obviously, this comes not without risks. Since 1980 the obesity prevalence has more than doubled in over 70 countries [7], while the number of T2D diagnoses almost quadrupled [8]. This development entails increased risks for obesity related comorbidities, ultimately resulting in shortened burden free lifetime and overall life expectancy [7, 9]. Further, epidemiological studies indicate that the recent lifestyle changes contribute to a disruption of day-night rhythm, which has been associated with negative consequences for metabolic health [3, 6, 10, 11]. With this in mind, it is important to realize that about 15-20% of the working population is involved in shift work or regularly travels across several time zones [12]. However, disengaging from our natural day-night rhythm is not limited to occupational environment, but rather has become an indispensable part of our society. In fact, in Central Europe over 70% of a surveyed population suffers from social jetlag [2] – a condition at which one suffers from a jetlag imposed by social aspects, such as working in shift, partying through the night or sleeping in on weekends. Similar to travelling time-zones, social jetlag occurs by a misalignment of the behavioral cycle (food, sleep, activity) with the internal biological clock. To date, it is not fully understood how disturbances of the biological clock promote the risk to develop obesity and T2D.

### Target groups and clinical relevance

The manifestation of obesity and type 2 diabetes is mainly caused by behavioral and environmental factors, such as low level of physical activity and energy dense diets. It has been shown that potent and cost-effective treatment strategies can be increasing physical activity and reducing calorie intake to improve skeletal muscle mitochondrial function, peripheral insulin sensitivity and overall metabolic health. Yet, such interventions are difficult to implement and maintain in a population that has been living the opposite lifestyle for years. In the light of the central aspect of social jetlag, it appears to be even more difficult to expect sufficient compliance. The difficulties are versatile e.g. rapidly

changing schedules can impede implementing new habits, food consumption at arbitrary times can alter social interaction and choice for food, tiredness can impact willingness and capability to comply with food and exercise regimes. Nevertheless, epidemiological studies demonstrate compelling evidence for an association of shift work [3], late meal timing [4], late chronotype [5] and social jetlag [6] with increased risk for obesity and T2D, thus demanding effective treatment strategies.

Additionally, as reported in this thesis, we included healthy young participants enduring a 12-hour circadian misalignment. In contrast to the target population, these participants were guided to maintain a normal lifestyle with respect to diet, activity and sleep, also during misalignment. Yet, without altering food intake, physical activity or sleep duration, circadian misalignment in healthy young participants led to acute decreased insulin sensitivity and adverse energy metabolism. It should be noted, that dietary choices and physical activity in individuals in real life may alter vastly due to aspects of free choice and also environmental availability (e.g. healthy food prepared freshly at 3 AM) [13-15]. Thereby, the potential metabolic health threat for the population suffering regularly from jetlag may likely be even larger than demonstrated in our healthy volunteers.

### **Innovation**

In this thesis, we used a two-strategy approach employing in vitro and in vivo studies to investigate the link between biological clock disruption and deranged energy metabolism. We first targeted to prove that human skeletal muscle cells indeed employ a molecular clockwork and to further examine whether such clockwork might be altered by metabolic state. To this end, we raised a unique cell bank of primary skeletal muscle cells of human donors ranging in metabolic health. This cell bank we used to compare intrinsic (genetic and possibly epigenetic) aspects of the skeletal muscle molecular clock and metabolism isolated from donor (patho)physiology. In this thesis, as indicated by the in vitro model studies, rhythmic expression of metabolic regulators of the molecular clock are dampened in well-synchronized cells of type 2 diabetes patients. Thus, we identified two regulatory intersections that could serve as promising targets in novel drug prevention and treatment strategies. Further, the general concept of this model may also be used for fine-tuning treatment timing to improve drug efficacy of novel and existing drugs.

Furthermore, with the state of the art Metabolic Research Unit Maastricht, we were capable of providing authentic ‘normal – but standardized – living conditions’ to examine biological rhythms in human energy metabolism. Most comparable human studies so far were using complex behavioral intervention routines with limited translation to normal living conditions. With the human studies performed in this thesis, detailed characterization of skeletal muscle and whole body metabolism under ‘normal day’ conditions were achieved. Especially, showing that acute 12-hour circadian misalignment itself can lead to substantial metabolic adverse events, such as decreased peripheral insulin sensitivity and altered mitochondrial function in healthy young lean volunteers is an alarming result. It is tempting to speculate, that individuals with severe overweight or type 2 diabetes may suffer from greater health implications upon circadian misalignment, due to manifested reduced metabolic flexibility.

### **Societal relevance**

Over the last decades, awareness about circadian rhythm has been raising interest in both academia and industry. Current technological advances have made it fairly easy to monitor behavioral and physiological aspects of our everyday lives. Mobile phones and wearables nowadays can measure by default e.g. light exposure, heart rate, physical activity levels, and can be used to actively assist in implementing lifestyle changes. Although, these applications and devices do not always reach the standards necessary to be useful in assisting to implement a healthy lifestyle, but a trend towards improved usability and functionality is undeniable. However, the current hype that increased the availability of these ‘technological advances’ to the general population must be noticed with care, as the predictive value for individuals with regard to their health advantages can be limited.

Furthermore, the findings from this thesis underscore the idea that treatment strategies for metabolic diseases such as type 2 diabetes may benefit from implementing chronotherapeutic approaches. This could be realized on different levels, such as modifying artificial light and ambient temperature in housing and nursing environment, but also timed administration of drugs that were fine-tuned to the time of highest efficacy. Additionally, given the technological advances, personalized day-night rhythm coaching, considering

aspects of social and work life, healthy diet and physical activity level may be implemented to strengthen current prevention and treatment strategies.

### **Conclusion**

This thesis has shed light on the subjected link between disturbances of the molecular clock and human metabolic health. A vast majority of the world's population is at risk for a disturbed biological clock and therefore is at risk to suffer from metabolic derangement. Hence, profound understanding by which the disruption of the biological clock leads to metabolic disease is needed to provide effective treatment strategies. Here, we identified two molecular intersections between the molecular clock and metabolism that are altered in type 2 diabetes. Further, we were able to demonstrate that maximal circadian misalignment leads to serious metabolic derangements in young healthy men. This alarming result is important, as the vast majority of individuals regularly exposed to social jetlag is of lower metabolic health, and hence may be at even greater risk to develop adverse metabolic conditions.

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