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# Food, Biological Clocks and Health: the Deadly Triangle?

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## Abstract

Very recent research has unravelled a most important component of human metabolic homeostasis: the existence and the crucial role of biological clocks.. Modern lifestyle has introduced a new paradigm, i.e. the collision between ancestral clock settings and their close interactions with changing alimentary and eating habits. Despite the very beginning of this potential revolutionary medical field, direct consequences of clock desynchronizations become already evident and leave little doubt that major practical consequences in nutrition and medical care will soon emerge for preventing further aggravation of the obesity and cardiometabolic syndrome burden. Food composition and eating time schedules are among the most likely to be first candidates to take into close consideration. This part aims at summarizing this new, exploding area of medical research, making the physicians familiar with practical aspects which might soon be of upmost importance for social health care within few years.

**Keywords:** Circadian; Clock; Nutrition; Metabolism; Lifestyle

## Introduction

Recent literature continuously reveals that most, if not all, of physiological and biochemical parameters exhibit circadian variations. In the cardiometabolic area, for example, glucose, insulin, cortisol, adipokines and many other substances involved in metabolic regulation exhibit circadian rhythmicity. In particular glucose tolerance is reduced in late evening hours and triglycerides are higher during night [1]. Furthermore the physiological rhythmicity of glucose tolerance is disturbed in 1st degree relatives of T2DM [2]. When similar meals are compared, insulin sensitivity is higher after breakfast than after lunch [3]. Meals influence each other, which has led to the notion of "2nd meal effect", for example how dinner influences metabolic handling of the breakfast and how breakfast influences lunch digestion. The concept is mainly based on the potential advantage of a "preinsulinization" induced by food intake favouring the handling of the next meal. Thus it was shown that eating a protein-rich snack (soya yogurt) two hours before a late breakfast reduced the postprandial glycaemic excursion by about 40% [4]. Another study, based on the same principle, investigated the effect of bedtime carbohydrate supplementation to type 1 diabetic patients: although post breakfast glucose tolerance was improved due to an insulin-induced reduction in FFA, no long-term effects could be observed on glycated haemoglobin and insulin sensitivity [5].

## Metabolic Effects of Nutrients

### Carbohydrates versus fat versus proteins: basics

Generally speaking, carbohydrates induce insulin secretory responses which are clearly higher than with fat or proteins [3, 6, 7]. While fat increases circulating FFA levels, carbohydrates rather augment triglycerides. Proteins induce low insulin response but protein-rich dinners increase fasting glycaemia and glucagon [8], while carbohydrate or fat content of dinner does not modify the glyacemic index of next morning breakfast [9].

### Influence of time

Eating breakfast decreases, while eating at night increases daily food intake. This effect seems macronutrient specific:

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carbohydrates eaten in the morning reduce daily carbohydrate intake, while correspondingly fat reduces daily fat intake [10]. In contrast skipping breakfast leads to obesity [11] and food presentation at incorrect circadian time results in insulin resistance [2]. Late dinner favours obesity in childhood [12] and, conversely, it is known that obese subjects eat later in the evening [13]. This has recently led to the concept of "obesity being a chronobiological disease" [14]. Changing feeding time indeed modifies the hormone secretion (insulin, glucagon, ghrelin, leptin, melatonin, corticosteroids) [15]. Comparing the effects of time-varied intake of a same meal showed that a high fat meal taken at 4, 8 or 12 am increased cortisol levels, while no effect occurred with the same meal eaten in afternoon or evening [16]. Interestingly, in rodents a recent publication showed that metabolic flexibility was conserved if high fat was consumed at the beginning of the active (locomotor) period; in contrast a high carbohydrate diet led to insulin resistance, impaired glucose tolerance, hypertriglyceridemia and increased body weight [17]. These few data clearly reveal that a meal is not metabolically handled the same way according to the time of the day.

## Influence of food type/composition

### *Fat: from theory to practice*

In general a combination rich in fat and carbohydrates is more prone to induce insulin resistance and impaired glucose tolerance than high fat alone, independently of caloric intake. On the other hand high carbohydrates alone lead to high insulin but no glucose intolerance [18]. These data highlight the crucial role played by food composition in glucose tolerance. However the amount of fat is only one determinant. It is accepted currently that fat is harmless as long as the meal fat content is below 30% [19]. In another study no negative effect was seen until 40% of fat [20]. In fact the harmfulness of fat in the diet is strongly dependent on the type of fat: some fatty acids are harmful, some are neutral and some highly beneficial. Therefore there is a lively debate about the deleterious role of fat (also versus carbohydrates) in nutrition research and particularly about the relation between fat intake and insulin resistance.

High content of monounsaturated fatty acids improves insulin sensitivity, provided the total amount of fat is below 38% [20]. Indeed monounsaturated fatty acids (olive oil) generate much less inflammatory factors than short chain fatty acids (coconut oil) or polyunsaturated fatty acids ( sun flower oil) [21]. High fat leads to adiposity if fat is saturated [22]. Insulin sensitivity is partly determined by membrane phospholipid composition [23]; it is expected that n-3 and n-6 fatty acids are beneficial, while short chain fatty acids are harmful: a diet rich in short chain fatty acids induces reductions in skeletal muscle glucose uptake by an augmentation of intramyocellular lipids [24]. However membrane fatty acid composition is also determined by the local transformation of fatty acids via elongases and desaturases. Reducing Δ5-desaturase and elongase leads to insulin resistance and obesity [22]. Mice deficient in the elongase-encoding gene Elovl6, which transforms palmitate into stearate, become obese and develop non-alcoholic hepatic steatosis on a high-fat diet [25]. Insulin resistance correlates with a reduction in Δ5-desaturase but also with an increase in Δ6 and Δ9 desaturase [26, 27]. To make things more complex, the efficiency of these enzymes depends on the presence or absence of other fatty acids [28]. Finally another important factor is the presence of trans-fatty acids: in rats a diet containing 10% trans-fatty acids increases hepatic and visceral (but not skeletal muscle) fat and reduces glucose uptake [24]. Trans fatty acids reduce the activity of desaturases [22]. Their harmfulness is illustrated by an increase in coronary heart diseases and metabolic syndrome when their proportion is as low as 2% [29].

These data, largely based on "predictive biochemistry", are however not corroborated by long-term human investigations: while short-term studies with monounsaturated appear positive, long term data are not and, when adjusted for body mass index, there was no correlation between fat intake and insulin resistance [22]. While there is little or no effect of n-3 fatty acids in healthy individuals [30, 31], a positive effect seems also absent in diabetic patients [32]. Moreover very recently, and in contrast to expectations, a meta-analysis showed that 12 of 15 clinical studies failed to demonstrate a relation between fat quality and insulin resistance [33].

### *Carbohydrates*

Acutely a high carbohydrate meal leads to postprandial hyperglycaemia, hyperinsulinemia and hypertriglyceridemia [20]. Chronic hyperglycaemia induces hypertriglyceridemia, and increases cytokines, insulin resistance and diabetes. In general meals with a high glycaemic index result in higher plasma glucose levels than low glycaemic index meals [34].

Here again food composition is an important determinant: for example it is well known that fructose (or sucrose) is more harmful than glucose [35]. On the other hand if fibre-rich, low glycaemic index foods are eaten, the metabolic abnormalities are much more limited [20]. Recent investigations also showed that evening meals rich in non-digestible carbohydrates, such as cooked barley kernels, increase insulin sensitivity and decrease postprandial glycaemia after next morning breakfast [36], as compared with white bread [37]. The beneficial effect of barley has been attributed to propionic acid generated by the colonic fermentation. In dedicated experiments proprionate indeed reduced fasting hyperglycaemia [38]. It is now assumed that short chain fatty acids (propionate, butyrate, acetate) have beneficial effects notably by a reduction of cytokines [36]. It seems advisable

to use non-digestible carbohydrates for the treatment of type 2 diabetes [39].

## Food and Rhythms

As seen above, there is a mutual interaction between circadian rhythms and metabolism. Whereas the suprachiasmatic nucleus reacts to light/darkness, peripheral clocks are also under direct influence of metabolism via multiple pathways (for recent overview, see [40]). Both are connected, as illustrated for example by the physiology of melatonin which is involved in both domains while melatonin is a key "Zeitgeber" for the hypothalamus, its absence leads to nocturnal increase of gluconeogenesis and hepatic glucose production [41]. The functional relationship between the control and the peripheral clocks, however, can be easily disturbed since, while the first is hardly flexible the others are. Modern life style (see part A) leads to confrontation between both systems and consequently to disturbances. Time of food intake is important: rodents eat during darkness (i.e. their active locomotor period) and when light is kept on their time of food intake is shifted, it leads to glucose intolerance and increased body weight [42]. If mice are fed during the day (i.e. their resting period), they gain weight [43]. In a paper just appeared it is shown that disrupting circadian clocks by putting mice in 20 h-light/dark cycles (in contrast to their normal 24 h circadian period) has negative consequences not only on metabolism but also on cerebral functions and behaviour [44]. In humans glucose tolerance decreases physiologically during the evening hours [45], suggesting that late eating is potentially harmful.

Conversely food influences rhythms. This has been mainly investigated about lipids. High fat diet modifies periods of locomotor activity in rodents [46], which is corroborated by alterations in circadian clock gene expression [47]. One proposed mechanism is fat modifying synchronization to light [48] but other studies failed to demonstrate an influence of fat on the central clock [49]. It was also shown that high fat disrupts the circadian expression of adiponectin, a very important regulator of glucose homeostasis and insulin sensitivity. The circadian rhythmicity of adiponectin is also altered by high insulin in humans [50]. On the other hand no difference in the rhythmic gene expression in human adipose tissue was found between lean, obese or diabetic subjects [51]. In rodents, short chain fatty acids modify the circadian eating pattern: a butter diet shifts eating from dark to light periods, leading to weight gain [52]. In humans it was shown that a high fat dinner was not followed by readjustment of fat intake after breakfast in prepubertal obese girls [53]. In diabetics, nocturnal FFAs are 50% higher than in healthy individuals [54].

Very recently animal studies suggested that, as is the case for metabolic syndrome components and obesity, disturbances in circadian gene expression and rhythms may originate from perinatal malnutrition [55, 56]. Finally the importance of circadian rhythms is also pointed out by a new discovery showing that expression of angiopoietin-like2 in epididymal fat improves diabetes in C57BL/6J mice [57].

## Conclusion

The reciprocal influence of biological rhythms and metabolism has been the subject of a real burden of publications in the last 3-4 years. Currently our knowledge is currently still limited and largely based on animal studies. Clearly a number of human studies should now be implemented to define what the real connection is and what are the medical consequences of both factors. As is seen with the lipid food studies, predictions from theoretical biochemistry do not necessarily prove correct in long-term human investigations. The clearcut relation between cardiometabolic complications in shift workers or studies in more short-term time frames such as jet lag or sleep disturbances leave little doubt that a lot is still to be unravelled. It is also suggested that disease states such as metabolic syndrome do not necessarily simply rely on excessive food intake and/or poor physical activity. It is comprehensible that eating at wrong times (late evening) confronts modern life style with ancestral physiology and gene regulation. However such studies might also show that "chronobiological nutrition" will reveal an important new domain of research for social health. Indeed not only quantity of food but also quality (composition) and time of ingestion ("eat what, when") could well appear to be cardinal determinants of correct metabolic homeostasis.

While every meal has its own characteristics in both its composition and its handling by target organs, the variations in normal physiology over 24 h seem to indicate that dinner should be more particularly scrutinized. Indeed dinner preceeds the long period of physical inactivity due to nocturnal sleep. Considering the evening reduction occurring physiologically in glucose tolerance, the overnight profiles of insulin secretion and lipid metabolism, it seems clear that dinner composition and time of ingestion are key factors which must be taken into consideration. For example one might propose that evening meals, in addition to be limited in quantity, should avoid sugars with high glycaemic index as well as saturated fatty acids and ideally include non-digestible carbohydrates. This simple type of consideration should be checked in dedicated clinical protocols in order to provide clearcut answers to better identify what should be eaten when. These informations will then deliver safe advices for general medical practice, especially in young populations who are still able to integrate and efficiently apply these notions in their lifestyle. Thereby they may be able to fight against the increasing risk of cardiometabolic disorders linked to modern ways of life.

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