



Timing of food intake and obesity: A novel association[☆]



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HIGHLIGHTS

- Changes in meal timing influence obesity and success of weight loss therapy.
- Unusual feeding time can induce a disruption of the circadian system.
- Digestive enzymes express in a circadian manner and are synchronized by food.
- Feeding is the source of energy for adipose tissue. The time of feeding is decisive.
- Clock genes are important in meal timing by changes in circadian control of hunger.

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ABSTRACT

Recent studies link energy regulation to the circadian clock at the behavioral, physiological and molecular levels, emphasizing that the timing of food intake itself may have a significant role in obesity. In this regards, there is emerging literature in animals demonstrating a relationship between the timing of feeding and weight regulation. Unusual feeding time can produce a disruption of the circadian system which might produce unhealthy consequences in humans. In a longitudinal study, we recently showed that the timing of the main meal was predictive of weight loss during a 20-week dietary intervention and that this effect was independent from total 24-h caloric intake. The importance of caloric distribution across the day on weight loss therapy was supported by a recent 12-week experimental study showing that subjects assigned to high caloric intake during breakfast lost significantly more weight than those assigned to high caloric intake during the dinner.

Furthermore, one of the most influential discoveries relevant for this area of research in the last years is the presence of an active circadian clock in different organs related to food intake. This is the case for stomach, intestine, pancreas or liver. New data also suggest that there is a temporal component in the regulation of adipose tissue functions. Thus, a specific temporal order in the daily patterns of adipose tissue genes appears to be crucial for adipose tissue to exclusively either accumulate fat or to mobilize fat at the proper time. Taking into account that feeding is the source of energy for adipose tissue, the time of feeding, particularly for high-energy content meals, may be decisive, and changes in this timing could have metabolic consequences for the development of obesity and for weight loss.

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1. Introduction

1.1. Timed meals: Evidence of influence in obesity

The meal times (and number of meals consumed) differ greatly from culture to culture and through time. Indeed, timing of food intake is a modifiable behavior that may influence energy regulation and consequently the risk of obesity. Several studies performed in experimental animals have demonstrated that when the animals eat at the “wrong

time” they become obese, although they apparently eat and expend the same amount of energy. In this line, the study performed by the group of Professor Fred Turek in 2009 [1] demonstrated that mice fed with a high fat diet only during the “right” feeding time (i.e., during the dark) weigh significantly less than mice fed only during the time when feeding is normally reduced (i.e., during the light) [1]. Indeed, within two weeks of maintenance on the high-fat diet, the light-fed animals weighed significantly more than the dark-fed animals and remained significantly heavier over the next four weeks. Note that neither activity nor caloric intake differed significantly between the light fed group and the dark fed group [1]. These results are outstanding because they strongly suggest that the timing of food intake is relevant for obesity. Further studies performed in humans have shown similar results: for example, Wang et al. [2], demonstrated that while energy intake in the morning was not associated with obesity, those who consumed $\geq 33\%$ of daily energy intake in the evening were two-fold

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more likely to be obese than morning eaters [2]. Authors concluded that eating more of the day's total energy intake at midday is associated with a lower risk of being *overweight/obese*.

Lighter changes in meal timing, i.e., the distribution of caloric intake across the normal wake episode, appear to influence not only obesity, but also the success of *weight loss* therapy. Indeed, it has been shown in a 12-week experimental study that subjects assigned to high caloric intake during breakfast lost significantly more weight than those assigned to high caloric intake during the dinner [3]. The breakfast group showed greater weight loss and waist circumference reduction. Moreover, insulin resistance decreased to a greater extent in the breakfast group than in the dinner group during the weight loss treatment. Of note, in response to meal challenges, the overall daily ghrelin, and mean hunger scores were significantly lower, whereas mean satiety scores were significantly higher in the breakfast group than in the dinner group. Therefore authors concluded that “High-calorie breakfast with reduced intake at dinner was beneficial and might be a useful alternative for the management of obesity and metabolic syndrome”.

Other studies have shown similar results, for example our group of research have recently demonstrated that the timing of the main meal (lunch) in a Mediterranean population from Spain, was predictive of the weight loss during a 20-week dietary intervention conducted in 420 obese and overweight individuals. In addition, the effect was independent from the total 24-h caloric intake [4]. Another relevant result from this study was that insulin sensitivity, as estimated by HOMA, was lower in late eaters as compared to early eaters. However, the physiological explanation for this novel discovery is still unknown.

2. Reasons for this evidence

2.1. Energy intake and expenditure

It has been hypothesized that individuals who do not eat early in the day may tend to be hungry later on and they may consume a greater number of calories during the evening hours than individuals who eat consistently throughout the day, greater energy intake may result in greater fat storage and thus may be one of the factors leading to an increase in body weight, and this may be the case why in general population late eaters may be more obese. There are also reports indicating

that individuals who do not eat breakfast have a greater overall daily energy intake [5]. However, in the above mentioned studies, performed in subjects that are submitted to a weight loss program, with restricted caloric intake, this doesn't seem to be the case. Indeed, results indicate late eaters lose less weight than early eaters, in spite of eating the same amount of calories. Although underreporting may be implicated in these results [6], data suggest that other aspects may be influencing results some of them will be described along this review (Fig. 1).

2.2. Unusual feeding time may produce chronodisruption

One of the most important findings in the last years has been the existence of peripheral clocks. Since 2001 we know that apart from the central clock located in the suprachiasmatic nucleus (SCN), we also have different clocks in several parts of our body, such as the heart, the liver or the pancreas [7]. The existence of all these clocks working together and synchronized by the central clock, with many hormones and physiological variables changing during the day, make this circadian system rather complicated. Indeed, when the peripheral clocks are desynchronized from the central clock, we talk about chronodisruption (CD) [7]. This physiological alteration is related to different illnesses such as cancer, cardiovascular diseases, depression, obesity and metabolic syndrome.

Food is one external synchronizer of our peripheral clocks. The primary role of the circadian clock is to entrain the organism to the environmental cues; this allows the animal to predict food availability. Limiting food access to a particular time of the day has profound effects on the behavior and physiology of the animals. For example, today it is well known that *acute deprivation* induce food seeking behaviors, while *chronic deprivation* promote physiological changes to facilitate the acquisition of nutrient and energy from ingested foods, and to reduce energy expenditure [5], these adaptations implicate entrainments of circadian clocks in the brain and in peripheral organs by stimuli associated with food intake [5].

It has been clearly demonstrated that several physiological functions and variables are elevated before eating, they are able to anticipate food intake and are synchronized by restricted daily feeding schedules. Some examples are body temperature, serum hormones such as cortisol, blood amino acids and glucose or liver enzymes (Table 1). Indeed,

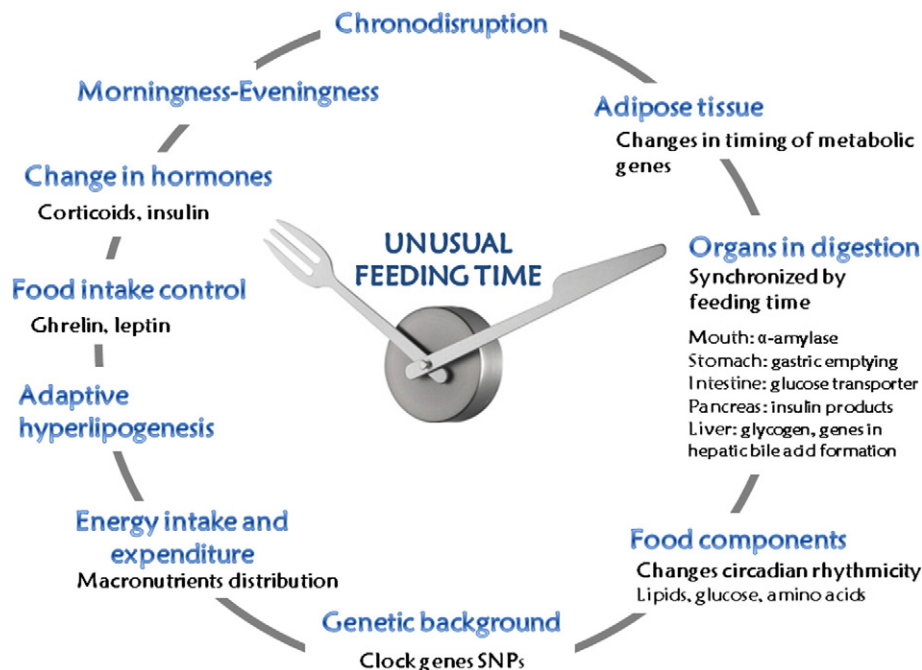


Fig. 1. Consequences of an unusual feeding time.

Table 1

Some daily biological rhythms which show at least some synchronization by restricted daily feeding schedules.

Adapted from Boulus and Terman (1979) [52].

Biological rhythms		Examples
Behavior	⇔	– Locomotor activity – Sleep stages
Temperature	⇔	– Body temperature
Blood hormones	⇔	– Corticosterone – Other hormones: blood amino acids, enzymes and glucose
Energy metabolism	⇔	– O ₂ consumption – CO ₂ emission
Liver	⇔	– Glycogen – Tyrosine transaminase
Intestine	⇔	– Intestinal enzymes

restriction of food intake to the wrong hours in experimental animals may affect all these physiological variables and modify the phase of circadian gene expression in peripheral cell types by up to 12 h, while leaving the phase of cyclic gene expression in the SCN unaffected [6]. In other words, changes in timing of food may lead to an uncoupling of peripheral oscillators from the central pacemaker [6]. Therefore unusual feeding time can induce a disruption of the circadian system which might produce unhealthy consequences in humans.

2.3. Timing of food intake and changes in hormones

Although the mechanisms linking meal timing and weight loss are unknown, hormones may be involved [1]. The rhythmic expression and activity of the metabolic pathways is mainly attributed to the robust and coordinated expression of clock genes in different organs and tissues. Changes in timing of food intake may alter this well-built coordination and as a consequence may also modify the circadian rhythmicity of many hormones involved in metabolism, such as insulin, glucagon, adiponectin, corticosterone, leptin, chemerin, lipocain and visfatin. In fact studies performed in laboratory conditions [8] have found that the times during which subjects were awake and eating during their biological night resulted in multiple metabolic changes including increased concentration of both glucose and insulin. In fact the postprandial responses of some of these healthy subjects during the biological night were equivalent to the responses of a prediabetic individual. In this same experiment, when eating during the biological night leptin plasma values were significantly decreased [8]. It has been proposed that changes in the levels of circulating satiety hormones, such as leptin or ghrelin, by circadian misalignment could influence energy intake and expenditure. Leptin is an anorexigenic hormone released from adipose tissue in proportion to lipid stores. This hormone acts inhibiting NPY/AgRP neurons and activating POMC/CART neurons, resulting in decreased food intake and increased energy expenditure. In humans, leptin plasma values display circadian rhythmicity, and this is also the case for *LEPTIN* adipose tissue gene expression [9]. In fact, leptin rhythms are the result of daily variations in food intake (leptin increases after feeding and decreases during fasting) and an endogenous clock [9]. However, if food is “timed” and restricted only

to the middle of the light period (wrong timing in mice) the rhythm of plasma leptin and the adipocyte clock are inverted [10–12].

2.3.1. Timing of food intake and organs involved in digestive processes

Organs and tissues related to food intake present a large number of genes that display oscillations in their expression and encode for important regulators of carbohydrates, lipids and proteins metabolism [13]. Examples of these organs are those involved in digestive processes as motility, digestion and absorption of nutrients, such as stomach, intestine and pancreas. Other examples include liver, implicated in post absorptive process, or adipose tissue, involved in energy storage or mobilization.

The digestive process begins in the mouth where food is chewed and mixed with saliva, which contains enzymes that begin the chemical process of digestion. An example of a circadian enzyme is the salivary α -amylase, which is involved in the chemistry degradation of polysaccharides (starch) to disaccharide such as maltose. A study has suggested that the salivary α -amylase levels may be associated with the individual chronotypes being lower in the morning-type than in the evening-type subjects [14]. Although digestion begins in the mouth, most of digestive processes are performed in the stomach and intestine with the help of the pancreas. It is now well known that a large number of digestive and intestinal enzymes are expressed in a circadian manner and are synchronized by food. In stomach the most important processes related to digestion are those connected to the mechanical digestion. In this sense, it has been demonstrated that the rate of gastric emptying changes during the day, and it shows lower rates after evening meals than after morning meals [15]. A similar situation occurs with the rhythms of migrating motor complexes associated with gastrointestinal motility [16,17], with lower nocturnal rates. All these processes reveal the existence of circadian rhythms in digestion and the impairment of the digestive process after evening meals. Eating late during the day or having a high caloric intake during dinner may be associated with an impaired digestion. Moreover, stomach is highly related to the control of food intake though ghrelin, one orexigenic hormone secreted by stomach and popularly known as the “hunger hormone”. Circulating levels of ghrelin increase before meals and decrease after food intake: it has been shown that this hormone may anticipate food intake [18]. Changes in timing of food intake may modify ghrelin 24 h rhythmicity,

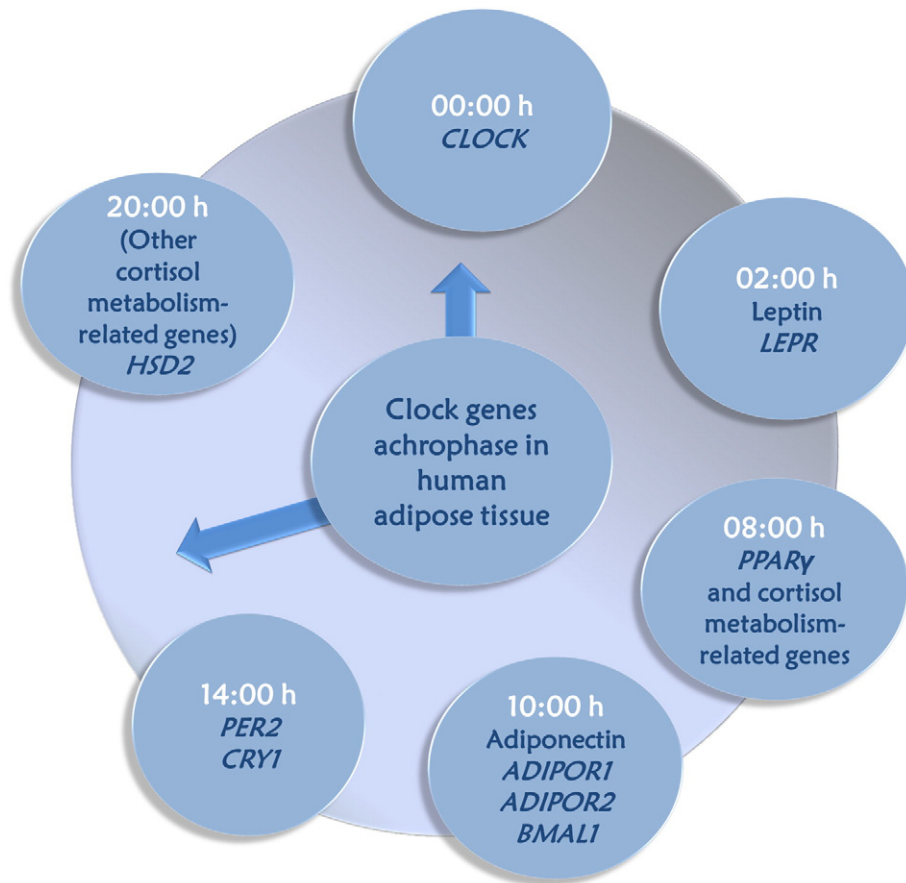


Fig. 2. Temporal order in human adipose tissue. Achrophase (time of maximum expression) of different relevant genes in adipose tissue. Adapted from Garaulet et al. (2011) [31].

and consequently may alter the physiological control of hunger, influencing total energy intake and as a result weight loss.

Absorptive processes in intestine may also be modulated rhythmically. An example is the absorption rhythm of glucose due to the action of several transporters (SGLT-1 in enterocytes and GLUT-2 in the basolateral membrane) which show circadian rhythms [19,20]. Several authors have revealed that in rats fed ad libitum, glucose absorption displays 24 h changes, being lower during the day and higher during the night. Some intestinal enzymes also show synchronization with the feeding rhythm, this is the case of intestinal disaccharidases, especially maltase and sucrase in rats. Their enzymatic activity increases around one hour before feeding and falls 3 h afterwards [21,22]. All these rhythmic patterns are independent of the light–dark cycle and are synchronized by feeding time [20,23], as occurs with the rhythmic ghrelin expression [18].

Not only gastric and intestinal secretions but also those from pancreas show rhythmic patterns. Thus the expression of islet-specific genes involved in glucose sensing (*glucose transporter 2* (*GLUT-2*), *glucokinase*), insulin production (*insulin*) and secretion (*migration inhibitory factor* (*MIF*), *somatostatin* and *syntaxin 1A*) are modulated in a circadian manner. Moreover several elements of the “cell-clock” are expressed at extremely high levels in human pancreatic islets compared to other tissues, suggesting a potentially important circadian regulation of these cells [24].

Liver is the most important organ implicated in the post absorptive phase of digestion. Most of the liver genes which encode enzymes or regulatory proteins involved in food processing, display rhythmic expression. A classical example is the circadian oscillation in glycogen metabolism. Several studies have showed how the glycogen storage

changes throughout the day coinciding with changes in the activity of the key enzymes in its storage, such as glycogen synthase, glycogen phosphorylase and glucose-6-phosphatase [25,26]. Other examples include cholesterol 7 α hydroxylase (limiting enzyme in the synthesis of bile acids); transcription factors governing fatty acid metabolism, such as PPAR and spot 14; metabolic enzymes involved in cholesterol metabolism; a number of cytochrome P450 enzymes involved in detoxification and elimination of food components (e.g., coumarin hydroxylase) and many more. Taking into account that the major function of circadian oscillators in the liver is the coordination of physiological needs during digestive process, changes in food timing may strongly alter the function of the liver. Ogawa et al. (1997) showed that the transcriptional regulation of some genes implicated in the hepatic bile acid formation of nocturnal rats (consume most of their food during the night) was severely altered when food was provided during morning [27]. Indeed, in nocturnal animals, feeding during day inverted the phase of circadian oscillators in hepatocytes. Others studies have also demonstrated that gene expression in the liver are entrained to the feeding schedule [28].

2.4. Timing in adipose tissue (AT)

In the last years, one of the most influential discoveries relevant for this area of research is the presence of an active circadian clock in adipose tissue (Fig. 2). In particular, our group has recently demonstrated that the circadian clockwork can oscillate accurately and independently of the SCN in AT explants [29,30]. Moreover, we have provided an overall view of the internal temporal order of circadian rhythms in human AT including genes implicated in metabolic processes such as energy

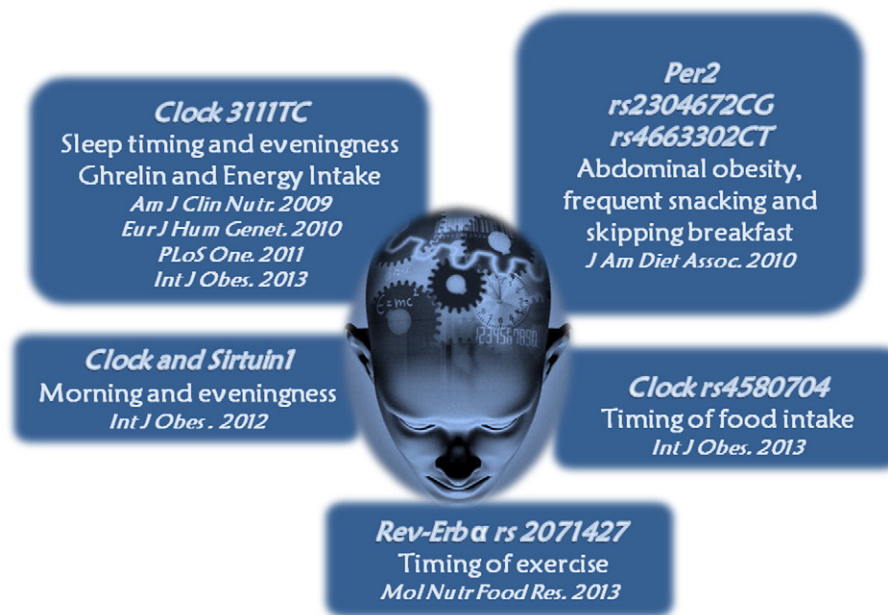


Fig. 3. Clock variants and obesity, through timing.
Adapted from Garaulet and Ordovás (2013) [53].

intake and expenditure, insulin resistance, adipocyte differentiation, dyslipidemia, and body fat distribution [31]. Thus, a specific temporal order in the daily patterns of these genes appears to be crucial for adipose tissue to exclusively either accumulate fat or to mobilize fat at the proper time, a phenomenon known as temporal compartmentalization [32]. Taking into account that feeding is the source of energy for adipose tissue, the time of feeding, particularly for high-energy content meals, may be decisive, and changes in this timing could have metabolic consequences for the development of obesity and perhaps for weight loss.

2.5. Timing of food intake and effect of food components

Although circadian system drives temporal changes in metabolic pathways related to food intake, the metabolic and nutritional status is also able to alter core molecular components of the circadian rhythms. In fact, several nutrients are capable of entraining or phase-shifting circadian rhythms. Interestingly, the synchronizing effect of foods may vary depending on a) the time of the meal: for example, the first meal following a long fasting period provides an important synchronizing signal to peripheral clocks in mice [33], while in humans it has been demonstrated alterations of internal circadian phase relationships after morning versus evening carbohydrate-rich meals [34] b) food volume [35] c) energy content d) type of macronutrient. For example glucose can phase-shift the clock in peripheral tissues. In vitro, rat fibroblasts treated with glucose produce a decrease of *Per1* and *Per2* expression and as a result, clock resetting. Moreover, in rats glucose is able to shift the phase of activity and this effect was not related to the higher energy content. Indeed, the same experiment performed with vegetable oils did not result in a phase shift [36]. Interestingly, the type of carbohydrate, and the rate of absorption is an important factor in the synchronizing effect [37]. Phase shifting of the liver clock is greater when the starch component of a mixed diet provides a large postprandial concentration [37], and it has been also suggested that mixed macronutrients are necessary for food entrainment in liver. Amino acids, may also influence circadian rhythmicity, indeed infusion of several amino acids in the jugular vein of rats resulted in a change of the acrophase of *Per2* in the SCN and the liver [38].

Studies performed in lipids have also revealed that a high-fat (HF) diet leads to disrupted circadian expression of metabolic factors and

obesity. However, timing can prevent obesity and rectify the harmful effects of a HF diet. Authors demonstrated that long-term (18 weeks) clock resetting by Restricted Feeding (RF) which limits the time and duration of food availability without calorie reduction and can attenuate the disruptive effects of diet-induced obesity [39]. Other examples are sodium, ethanol, and caffeine that may alter circadian rhythms of several physiological functions [39].

2.6. Timing of food intake and “adaptive hyperlipogenesis”

Several studies have shown that restricted daily feedings produce an increase in lipid formation, an effect called “adaptive hyperlipogenesis” [40] which accompanies changes in body composition. These changes have been attributed to specific alterations in different metabolic pathways, based on reports of altered levels of hormonal and enzymatic activity in rats adapted to daily feeding schedules. However, further studies should be performed, indeed some of these experiments are comparing hormones levels at the same timing point, and it could be the case that changes are due to differences in the rhythm phase so levels at the same points are not comparable, as is the case of insulin [41].

2.7. Timing of food intake and genetic background

Genetics is a factor to consider in the association between meal timing, obesity and weight loss (Fig. 3). The circadian system must continuously adapt to and synchronize our physiology with the environment, and genes are implicated in this adaptation. Genetic variance in clock genes may be important in meal timing, possibly in part by changes in the recently demonstrated circadian control of hunger and appetite. Indeed rs4580704 C/G variation in the *CLOCK* (intronic) on human chromosome 4, has been related to the time of lunch, and a higher frequency of minor allele carriers (G) was present among late eaters [4]. This genetic variation has been previously related to individual susceptibility to obesity, metabolic risk and energy intake; with minor allele carriers showing higher obesity and higher energy intake than major allele carriers C [42,43]. This was the first study to report the association of clock genetic variations with the timing of food intake. Earlier studies have identified allelic variants in leptin (*LEP*) and leptin receptor (*LEPR*) that significantly influenced the energy intake distribution across meals, but not the time of meals [44]. Other clock genes as

PERIOD 2 have been also relate to obesity through timing of food intake. Indeed minor allele carriers of *PER2* polymorphisms rs2304672C > G used to skip breakfast and to display extreme snacking more frequently than major carriers C, and they also had a greater probability of being obese and of dropping out a weight loss treatment [45].

2.8. Timing of food intake and morningness–eveningness

Decreased weight loss achieved in late eaters as compared to early eaters [4] may be related to the fact that late eaters were more evening types as determined by the morningness–eveningness questionnaire [46]. Previous studies indicate that evening types have higher propensity to put on weight and less ability to lose it. Indeed, a delayed phase of the circadian rhythmicity has been associated with metabolic alterations and obesity [47,48]. For example, C genetic variants in *CLOCK* 3111 T/C are more obese and lose less weight in a dietary and behavioral treatment for obesity than TT carriers and they are also more evening-type subjects as determined by the morning evening questionnaire [49]. These results were further confirmed with an additional study in which we measured wrist temperature during 24 h which showed that C carriers displayed a less robust circadian rhythm than TT and a delayed acrophase that characterizes ‘evening-type’ subjects [50]. Wrist temperature is one of the most practical measures used to diagnose circadian disorders in ambulatory conditions and it has been shown to be a good predictor of future weight loss. Indeed, in a study performed in 85 overweight and obese women who attended a weight loss program a low responders showed a more flattened temperature circadian rhythm a higher fragmentation of rhythms and an impaired wrist temperature [51].

3. Conclusion

Timing of food intake is related to obesity and to the success of weight-loss therapy. Unexpectedly, total energy intake, dietary composition and estimated energy expenditure were not explaining these results. Changes in the chronotype, genetic background and/or circadian system function may be implicated in this outcome. Novel therapeutic strategies should consider not only the caloric intake and macronutrient distribution but also the timing of food.

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