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THE CLOCK DIET: A PRACTICAL NUTRITIONAL GUIDE TO MANAGE OBESITY THROUGH CHRONONUTRITION

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Prof. Elena Oliaro,

Editor-in-Chief of MINERVA MEDICA

February 11th, 2021

Dear Prof. Elena Oliaro,

On behalf of all the authors, I would like to kindly acknowledge the Editorial Board Member for the constructive comments on the manuscript. The modified text has been highlighted in green in the revised version of the manuscript. I respectfully trust that the changes we have made to the text could have contributed to ensure clarity to our findings and to have answered the pertinent and appropriate comments, as kindly requested.

Thank you very much and our best regards.

Sincerely yours,

Dr. Luigi Barrea,

Dipartimento di Medicina Clinica e Chirurgia, Unit of Endocrinology, Federico II University Medical School of Naples, Via Sergio Pansini 5, 80131 Naples, Italy.

Mail Address: c/o Dipartimento di Medicina Clinica e Chirurgia, *Endocrinology Unit*, Via S. Pansini, 5 - 80131 Naples, Italy. Tel. +39 081 7463779 FAX +39 081 7463668.

 # Editorial Board Member comments

Dear authors, an editorial board member has reviewed your work that has been found interesting. Some minor changes are requestes. Best regards In this review the authors discuss A PRACTICAL NUTRITIONAL GUIDE TO MANAGE OBESITY THROUGH CHRONONUTRITION. The authors discuss extensivley chronobiology and chrononutrition and their role in obesity.

We are very grateful to the Editorial Board Member for his/her appreciation of our findings and his/her most positive report. We are hopeful that the constructive suggestions and the proposed corrections will improve our exposition in the updated manuscript. All the corrections in the revised manuscript are made in green for the Reviewer's convenience.

There are too much references. The authors should reduce as required in the minerva Format the references to 100.

Author's response: We agreed with your suggestion and reduced the number of references.

Furthermore:

-I suggest to associate to the reference 140 the following reference that discuss also the potential role of microbiota in this context

- **Mediterranean diet and probiotics supplementation to treat non-alcoholic fatty liver disease. Abenavoli L, Scarpellini E, Pellicano R, Fagoonee S, Larussa T, Luzza F. Minerva Med. 2020 Dec;111(6):526-528.**

Author's response: We thank the reviewer for the suggestion. We have associate the suggested reference.

-I suggest to replace the reference 238 with Roles of polyphenols as dietary epigenetic modulators. Hyun, Tae Kyung

MINERVA BIOTECNOLOGICA Volume: 31 Issue: 2 Pages: 74-75 Published: JUN 2019

Author's response: We thank the reviewer for the interesting suggestion. As requested, we have replaced the specific reference.

The references in the References list do not mention the volume number and the pages. Please, correct the references in the References list.

Remember to cite articles from journals in this way:

-Liu H, Li J, Du L, Yang M, Yang D, Li J, et al. Short-term effects of core stability training on the balance and ambulation function of individuals with chronic spinal cord injury: a pilot randomized controlled trial. Minerva Med 2019;110:216-23.

Author's response: We have modified all references as suggested.

THE CLOCK DIET: A PRACTICAL NUTRITIONAL GUIDE TO MANAGE OBESITY THROUGH CHRONONUTRITION

Luigi BARREA [1,2,§,*], Evelyn FRIAS-TORAL [3,4,§], Sara APRANO [1,2,§], Bianca CASTELLUCCI [1,2], Gabriella PUGLIESE [1,2], Giovanni VITALE [5,6], Davide GENTILINI [7,8], Annamaria COLAO [1,2,9], Silvia SAVASTANO [1,2], Giovanna MUSCOGIURI [1,2].

[1] Dipartimento di Medicina Clinica e Chirurgia, *Unit of Endocrinology*, Federico II University Medical School of Naples, Via Sergio Pansini 5, 80131 Naples, Italy;

[2] Centro Italiano per la cura e il Benessere del paziente con Obesità (C.I.B.O), Department of Clinical Medicine and Surgery, *Endocrinology Unit*, University Medical School of Naples, Via Sergio Pansini 5, 80131 Naples, Italy;

[3] Research Committee, SOLCA Guayaquil, Av. Pedro Menendez Gilbert, Guayaquil 090505, Ecuador;

[4] Clinical Research Associate Professor for Palliative Care Residency from Universidad Católica Santiago de Guayaquil, Av. Pdte. Carlos Julio Arosemena Tola, Guayaquil 090615, Ecuador;

[5] Istituto Auxologico Italiano IRCCS, Laboratory of Geriatric and Oncologic Neuroendocrinology Research, Cusano Milanino, MI, Italy;

[6] Department of Medical Biotechnologies and Translational Medicine, University of Milan, Milan, Italy

[7] Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy;

[8] Istituto Auxologico Italiano IRCCS, Bioinformatics and Statistical Genomics Unit, Cusano Milanino, Milano, Italy;

[9] Cattedra Unesco "Educazione alla salute e allo sviluppo sostenibile", University Federico II, Naples, Italy.

[§] **Luigi Barrea, Evelyn Frias-Toral and Sara Aprano** have equal contribution and should be considered as co-first authors.

***The e-mail address, and telephone number of the corresponding author:**

Dr. Luigi Barrea; Dipartimento di Medicina Clinica e Chirurgia, *Unit of Endocrinology*, Federico II University Medical School of Naples, Via Sergio Pansini 5, 80131 Naples, Italy.

E-mail: luigi.barrea@unina.it; Tel. +39 081 746 3779 Fax +39 081 746 3668

Running title: OBESITY AND CHRONONUTRITION

Abstract

Chronobiology studies the biological rhythms or circadian cycles of living organisms and their adaptation to external changes. Biological rhythms can affect hormone production cycles such as sleep/wake, and nutrition/fasting, but these factors can also alter the circadian rhythm (CR). In recent years, numerous studies have highlighted how feeding times and frequency can influence biological rhythms. Additionally, individuals' chronotype, working shifts, and food intake can make a deep impact on people's tendency to develop obesity and metabolic diseases. In this context, a single food and a specific combination of these, can also affect the CR and fasting cycle and consequently body weight and *viceversa*. The purpose of the review is to propose practical nutritional recommendations to help in resynchronizing the circadian rhythm as a tool in weight control.

Keywords: circadian clock, Chrononutrition, obesity, endocrine factors, food timing, macronutrients, diet, Nutritionist

TEXT

Introduction

Chronobiology is a branch of biology that studies cyclical phenomena in living organisms and their adaptations to light and dark cycles, known as biological rhythms or circadian clock (CC) [1]. The synchronization of the endogenous CC allows the organism to adapt to environmental changes by modifying its behavioral and physiological functions [1]. The circadian system (CS) of mammalian is characterized by three components: the input, 24 hours oscillator, and the outputs. The most important circadian oscillator is a central pacemaker located in the suprachiasmatic nucleus (SCN) of the hypothalamus, driving circadian rhythmicity in other brain areas and peripheral tissues by sending them neural and humoral signals [1].

Most peripheral tissues and organs contain circadian oscillators. Usually, they are under the control of the SCN; however, under some circumstances (restricted feeding, jet-lag, and shift work), they can desynchronize from the SCN [1]. Most physiological and behavioral functions follow a circadian rhythm (CR), guided by central pacemakers and peripheral oscillators. Some of these over-rhythms (e.g., sleep/wake cycle and feeding time, physical exercise, core temperature) in turn, through feedback they can influence the function of SCN and peripheral oscillators [1]. It has been estimated that 7% to 13% of a cell's transcriptome is under circadian control, including genes encoding for modulators of transcription, signal transduction, protein turnover, and metabolism. The CC, through the fluctuations of the genes controlled by it, influences cellular/organ function in a time-of-day-dependent manner, through endocrine factors [1]. Both synthesis and abundance of various endocrine factors, and the target organs sensitive to these signals, are subject to rigorous time controls. The production of some endocrine factors whose levels change during the day, such as cortisol, growth hormone (GH), prolactin (PRL), thyroid hormone, and gonadal steroids are regulated by hypothalamic-pituitary axes [1]. Moreover, nutrient-sensitive hormones, insulin, and adipokines vary their circulating levels in a time-of-day-dependent pattern, in response to the environment and behaviors, such as feeding/fasting and light/dark cycle [2]. Feeding time is considered one of the most important external synchronizers. It has been observed that the timing of meals has important effects on metabolic and physiological parameters, highlighting that in the choice of food, it is important to consider both the nutritional value and the timing [2]. Fasting and feeding cycles appear to function as timing signals for peripheral clocks, bypassing the synchronization signals emitted by the brain's main clock [1].

Numerous studies suggest that mealtimes can influence physiological processes, including sleep/wake cycle, hormone levels, obesity, and metabolic syndrome [1].

Considering that the timed of food intake can affect obesity, and that some foods can affect the secretion of some hormones, which also follow circadian oscillations, we can hypothesize that the intake of food and macronutrients at certain times of the day, can contribute by on the one hand to restore the circadian oscillations of the watch genes, and on other to regulate body weight by preventing obesity and other metabolic alterations. Therefore, the purpose of the review is to propose nutritional recommendations useful in resynchronizing the circadian rhythm as tool in weight management.

Chronobiology and Chrononutrition

Chronobiology is a field of biology that evaluates the effects of time, biological rhythmical phenomena, and their adaptive fitness to solar- and lunar-related periodic phenomena [1]. In detail, the cell biological clock is composed of proteins that generate circadian oscillations through positive and negative transcriptional/translational feedback loops. The cellular oscillators positive are CLOCK (circadian locomotor output cycles kaput), BMAL1 (brain- and muscle- ANRT-like protein) that heterodimers and, through binding to E-box elements, drive the transcription of several genes: Cryptochrome (*Cry1, Cry2*), Period Circadian Protein (*Per1, Per2, Per3*), reverse erythroblastosis virus-α (*Rev-Erbα*), retinoic acid receptor-related orphan receptor-α (*Ror-α*) and multiple clinical commissioning groups (CCGs). After dimerization, PERs and CRYs are transported out of the nucleus and inhibit CLOCK–BMAL1-mediated transcription. When PER and CRY are degraded, CLOCK-BMAL1 is no longer repressed and binds E-box [3]. The CLOCK protein has a significant activity as a histone acetyltransferase facilitating gene transcription [3]. This activity is counteracted by Sirtuin-1, a histone deacetylase [3] that is related to energy metabolism and aging [3]. Recent evidence shows that clock genes also act as sensors of the cellular metabolic status through changes in the redox state [3]. This dependence of the molecular clock on energy uptake could explain why alterations in metabolic cues, such as restricted feeding or conflicting synchronizers, are able to modulate the activity of the timing CS. Those genes that are regulated by the CC, yet do not directly influence the activity of core clock components, are termed clock controlled/output genes.

Moreover, the term chrononutrition is used to describe the connection of food and the CS. It implies two features:

1) The CS has the capacity to impact the functions of food metabolism, such as digestion and absorption of food, and energy metabolism. If these aspects are considered when choosing the timing, amount, and composition of food intake or food, it will improve human health including body weight [3];

2) As the effect of light stimulation, time-restricted food or nutrient stimulation can have a positive effect on CS [3]. Feeding behavior is a principal factor that plays a vital role in the organism's nutritional status. An inherent timing mechanism predominantly dictates eating schedules, but also are affected by other factors such as food availability, hunger, and satiety, and also by social habits and convenience. Nowadays, it is widely accepted that these parameters are critical and that their alteration is associated with morbidity and mortality. Many papers affirm that feeding time has a dramatic effect on health and can be employed to prevent obesity

and various other metabolic pathologies [4]. That is why 'chrononutrition' refers to food administration in coordination with the body's daily rhythms. This concept reflects the basic idea that, in addition to the amount and content of food, the time of ingestion is also critical for the well-being of organism [1]. The clock genes in the gut that are rhythmically expressed control digestion and absorption in mammals. Hoogerwerf WA et al. stated that the phases of the rhythms in clock gene expression are different amid the cranio-caudal axes of the gut, thus proposing that the upper part of the gut entrains faster than the lower part of the intestine by changing the speeds of nutrient absorption. These authors, through a study on nocturnal mice with a scheduled feeding program in the daytime, found a phase shift in the rhythm of clock gene expression in the gastrointestinal tract, thus demonstrating that nutrient timing can deeply affect gut CS [5]. Moreover, the same authors described that colonic movements are more frequent during the day than at night [5] and indicated that rodents have a day/night rhythm in colonic movements, which is controlled by clock genes and neuronal nitric oxide synthase (nNOS) activity [5]. Since 1976, it was well documented that stool weight, colonic contractile response to acetylcholine, and intra-colonic pressure had a clear CR. Interestingly, these were altered in Per1 and Per2 double-knockout mice or in nNOS-knockout mice. The intestinal digestive enzyme sucrose also displays a CR activity, and it reaches a peak just before feeding time [6]. Gastrointestinal symptoms such as diarrhea or constipation were reported among shift workers and time-zone travelers; these conditions are connected with disruptions in CR [5,6]. All of these findings proved that the digestive system experiences circadian adjustments in both rodents and humans.

Many important transporters are under CR and any disturbance in these causes an abnormal absorption. Some studies investigated the effect of circadian changes in the intestinal absorption of peptides, glucose, lipids, and drugs by different transporters. It has been described that in the intestines of rodents the absorption of water and glucose is increased during night [6]. Several studies found that sodium/glucose cotransporter (SGLUT)-1, glucose transporter 2 (GLUT)-2, and GLUT-5 have circadian oscillations in their expression and they are regulated by clock genes through E-box activity [7]. Additionally, SGLUT1 is determined by PER1 activity independent of the E-box [7]. The SGLUT1 and H^+/peptide cotransporter 1 (PEPT1) were synchronized through scheduled feeding experiments. These evidences support the idea that these transporters are directly affected by feeding conditions [7]. In addition, it has also been reported that in clock mutant mice, peptide transportation was reduced, while lipid absorption was increased. Contrariwise, nocturnin-knockout mice showed a reduction in lipid absorption due to less chylomicron transit [8]. Furthermore, the expression of the

sodium pump (Atpa1a), channel (γEnac), transporters (Dra, Ae1, and Nhe3), and the Na^+/H^+ exchanger regulatory factor (Nherf1) in rat colonic mucosa showed circadian changes, suggesting that also NaCl absorption in the colon was under CR [8]. All these findings evidenced that the circadian clock controls many crucial transporters, thus a circadian disruption will cause an abnormal absorption.

The vast majority of studies have focused on the effect of scheduled meals on metabolic pathologies such as obesity and diabetes. However, all these findings lead to speculate that the 'optimal' feeding schedule might harbor important medical benefits not restricted to metabolic syndrome [2].

The influence on obesity

The prevalence of overweight and obesity has recently increased, contributing to the increment of different diseases, including type 2 diabetes mellitus [9–11], thyroid dysfunction and nonalcoholic fatty liver disease [12,13], breast cancer [14,15], elevated serum uric acid levels [16], hypovitaminosis D [17,18], inflammatory skin diseases [19], polycystic ovary syndrome [20–22], and others [23–25]. Accumulating results point to the chronic-inflammation in visceral adipose tissue, which, in turn, promotes low-grade systemic inflammation as a primary cause contributing to the development of obesity-related diseases [11,26,27]. In addition to bariatric surgery [28] and the pharmacological approach [29,30], physical activity and diet are the primary therapeutic approaches to reduce body weight and reduce the risk of developing obesity-related diseases [31–37].

A very well-organized structure originates human CR and their synchronization with the environment, previously described, the mammalian circadian timing [38]. An important aspect of the CS is its capacity to be modified by internal or external cues. In addition to light exposure, as a typical external signal, there are other untrainable factors such as temperature, exercise, drugs, humidity, social cues, sound, and food [38]. These external or environmental cues able to entrain or synchronize an organism's biological rhythms are also known by the name "Zeitgeber". The CC needs to keep a harmonious relationship among organ clocks and the environmental time since we find CR in the fasting/feeding cycle, sleep/wake cycle, immune response, hormone secretion, glycolysis, and many other processes in the human body. Different evidences emphasize the importance of CR and chronobiology in nutrition and how these deeply affect the physiological status. It is fundamental to understand the association between time-of-day of energy intake with metabolic disease, specifically obesity [1,3]. For this reason, when caloric restriction accompanies feeding time, behavioral and physiological circadian rhythms and gene expression in the SCN are shifted and/or entrained to meal time.

This temporal restriction generates activity before food availability, and this phenomenon is also known as food anticipatory activity (FAA). Tahara et al. reported that FAA appears approximately 2-3 hours before feeding time. In mice, they associated the FAA with foraging for food [4]. The presence of FAA suggested the hypothesis that animals have a food-entrainable oscillator (FEO). According to Storch et al., there are differences in the FAA in mice without genetic components of the CC; however, those mice maintained the capacity to show the FAA [39]. For these reasons, it can be speculated that the genetic control of FEO is different from other CS, in addition it has also been reported that FAA persisted in SCN-injured rats, suggesting that FEO is located in tissues outside of the SCN. Some papers are proposing that the FEO may be connected to the dorsomedial hypothalamic nucleus. but other reports focused on the possible activity of extra-hypothalamic brain regions in FAA [40]. To determine the localization of the FEO, more studies should be done since it can lie outside of the brain or depend upon the interaction among multiple tissues. Moreover, the reward and motivational value of food can also be a potent synchronizer for the SCN clock [41]. Therefore, these reports point out that energy metabolism and motivational properties of food can affect the CS of the SCN. Food-related cues may entrain clock genes of the SCN with an immediate effect, or be mediated indirectly by another neural or peripheral site [41]. In addition, there may also be multiple oscillator sites that could play a pivotal role as a FEO, responsible for anticipating meal [42]. Other studies, in animals, concluded that under normal conditions of *ad libitum* food, light is the typical Zeitgeber that synchronizes the SCN, and via neuronal and endocrine pathways synchronizes peripheral clocks leading to the control of the behavioral activity and feeding time. Light also maintains a dominant synchronizer of the SCN in a second scenario, where there is a temporal food restriction, and peripheral clocks are synchronized to feeding time. Furthermore, when there is temporal and energy food restriction, the SCN, and peripheral clocks are synchronized to the feeding time. Therefore, it is evident that the strong interaction between feeding time and quantity of food intake [43]. Evidence reported that genetic disruption of the CC had been associated with metabolic pathologies in rats. The CC conducts transcriptional programs for specific metabolic pathways. That is the case with CRY-1 that abolishes hepatic gluconeogenesis during fasting by the adjustment of cAMP/CREB signaling, the rhythmic repression of the glucocorticoid receptor gene, and the elimination of nuclear Forkhead box protein O1 (FOXO1) that, finally, decontrols gluconeogenesis [44]. PER-2 is another clock inhibitor; it commands lipid metabolism through direct control of peroxisome proliferator-activated receptor gamma (PPARγ) and mitochondrial rate-limiting enzymes [44]. Disturbance of CLOCK and BMAL1 has also been linked to hyperinsulinemia, obesity, and type

2 diabetes [44,45]. The circadian post-transcriptional regulator Nocturnin also manages lipid and cholesterol metabolism [8]. Dyar et al. published an atlas of circadian metabolic profiles across eight tissues showing temporal cohesion among tissues, and how a high fat (HF) diet affected each tissue in different ways [46]. Additionally, food intake and the oscillation of hormones such as insulin, glucagon, peptide YY, glucagon-like peptide 1 (GLP-1), corticosterone, leptin, and ghrelin adjust CC [46]. Despite all these valuable and clarifying publications about CC and its effect on metabolism, there are more aspects that require further research. It is clear that the feed timing should be aligned with the CR, considering that a disturbance between them will cause a metabolic dysfunction [47]. In addition, Agouti-related protein (AgRP) neurons, representing a specific hypothalamic nutrient and/or energy sensor, face daily rhythms as an answer to leptin [47]. Eckel-Mahan et al. proposed that the nutritive environment itself affects feeding behavior and causes drastic alterations in circadian gene expression in diet-induced obesity (DIO) model [48]. A study showed that one of these DIO-related effects is the occurrence of newly rhythmic oscillations of the lipogenic transcription factor sterol regulatory element-binding protein (SREBP), which regulates fatty acid synthesis and oxidation, and of the PPARα, a major regulator of fatty acid oxidation. This might be a result of CR that is aroused at the boosters of genes that are generally not rhythmic [4]. It also demonstrated that a PPARα agonist (WY-14,643) is more efficacious in diminishing lipids when administered at the circadian peak of PPARα expression. These findings are useful evidence to promote chrono-pharmacological interventions for the treatment of metabolic disorders because of the modulation of metabolism by the improvement of CR. Another essential element to consider when analyzing obesity causes is the loss of glucocorticoid circadian oscillations. In mice, it was evident that adipocyte differentiation does not proceed under regular circadian hormonal cycles. Instead, the changes were shown when the period of the pulse shortens or if the hormonal signal is flat or continuously elevated [48]. Alterations can develop this abnormal situation in feeding time or sleep cycles, long-term glucocorticoid hormone treatment, chronic stress, or metabolic syndrome [48]. These conditions were associated with an increase in the mass of subcutaneous and visceral fat pads in mice [48].

Finally, it is substantial to mention the connection between CC and autophagy. Autophagy is a process that recycles components of the cytoplasm in cells for tissue remodeling and eliminates non-functional organelles. Autophagy is rhythmically activated in a clock-dependent manner; it reduces cytoplasmic contents in lysosomes and degrades the repressor CRY-1, able to suppress hepatic gluconeogenesis. Another study to examine the role of autophagy in the regulation of the liver clock and glucose metabolism revealed that the

degradation of CRY1 by autophagic pathways allows glucose production [49]. Impressively, obesity intensifies the autophagic degradation of CRY1, ergo-higher glucose production, and higher blood glucose levels.

All of these processes show the complexity of the CC and interactions between central and peripheral mechanisms. Therefore, it is clear that CS plays an overarching role in regulating human physiology [49]. Disruption of CR is associated with different disorders including metabolic syndrome and obesity [46].

Association between chrononutrition and obesity: Studies in Humans

Eating behaviors are influenced by intrinsic timing mechanisms but also food availability, hunger, and satiety, as well as social habits [2]. CS can affect metabolism and *viceversa*. Many hormones such as insulin, glucagon, cortisol, GH, have circadian oscillations, regulated by the clock genes [2]. The activity of some metabolic enzymes, transport systems involved in the metabolism of cholesterol, glucose, and lipid receptors, are also regulated by the CS, for which an interruption of the circadian cycle (chrono destruction), can induce obesity, type 2 diabetes, dyslipidemias and hypertension [50]. Furthermore, even a diet rich in fat seems to have an impact on fasting / satiety cycles. This is due to the fact that dietary fat can affect the gene expression of watch gene [48]. In humans, the timing of food intake could be involved in the variability in the response to slimming treatment, as some observational studies on humans have observed the association of obesity and energy supply in different hours of day [38]. Lunchtime is predictive of weight loss regardless of calorie intake [52]. This has been confirmed by a randomized crossover study, which reported that eating lunch late is associated with decreased resting energy expenditure, fasting carbohydrate oxidation, reduced glucose tolerance, diminished thermal effect of food, and reduced daily cortisol variability [52]. In a prospective randomized controlled trial, Lucassen et al. reported that subjects having an evening chronotype exhibited an increase in body mass index, compared to subjects with a morning chronotype, and this was due to an unhealthy eating pattern, especially characterized by late dinner [53]. Food timing also has a role in predicting the trend of weight loss. Indeed, in a study involving a group of 270 patients undergoing bariatric surgery that were followed up for 6 years, subjects who lost less weight had lunch later (after 15:00 h) than patients having an earlier lunch [54]. In a recent randomized parallel-arm study, two groups of overweight or obesity women with metabolic syndrome were randomized to two isocaloric weight loss plans (~1400 kcal) for 12 weeks. A group breakfast, called BF, was given a food plan with an abundant hearty breakfast (~700kcal), a medium-sized lunch (~500kcal), and a small dinner (~200kcal). Instead, in another group dinner, called D, this meal plan has been reversed, so it has been given a small breakfast and a high-calorie dinner. After 12 weeks, it was observed: the more significant weight loss, the more considerable improvement in metabolic markers (glucose, insulin, HoMA-IR, triglycerides) and in satiety in group BF, compared to group D [2].

Obesity is now considered an increasing pandemic, and many researchers have associated it with exposure to light at night (LAN) and shift work [55]. The circadian clock adjusts humans for anticipated situations (food availability, and sleep). Alteration of this system produces circadian and metabolic disruptions. Coomans

et al. reported that four days of constant light (12-hours light-light) LL cycle, increased food intake (+26%), decreased energy expenditure (-13%), and consequently, body weight gain in mice [56]. As constant light debilitates rhythms of the central clock, altered feeding behavior, sleep/wake cycles, energy homeostasis, and thermogenesis might appear. Moreover, a variation of light conditions or feeding time influences metabolism, body temperature, and body weight within a few days. These immediate events are probably because of misalignment between internal clocks similar to jet lag. Chronic jet lag, including shift work, has a direct and high risk for metabolic disorders. Results from Cooman's study showed that LL produced a drastic depression in SCN amplitude, which stabilized within 3 days up to 44%. This reducing effect produced a complete desynchronization of CR in energy metabolism and hepatic and peripheral insulin sensitivity. These findings are similar to those in aging and neurodegenerative diseases [56]. In a typical scenario with regular 12-hours LD (light/dark) cycles, this input pathway maintains individual SCN neurons synchronized with each other and the environment with a majority of neurons that are active during the day and silent during the night. LL exposure originated desynchronization among neurons of the SCN, which restrains CR at the tissue level [54]. Another significant influence of LL is the disruption of corticosterone rhythm that diminishes corticosterone peak levels, so, it is directly linked to the restraint of the SCN, neuronal activity [54]. Other effects of reduced SCN rhythmicity are a disturbance in energy homeostasis, decreased energy expenditure, impaired oxidative response to food intake (metabolic inflexibility), debilitated insulin sensitivity, and finally, obesity [57]. Moreover, it has been known for several decades that a disturbance of CR by LL causes deregulation of glucoregulatory genes in the liver. The combination of all these outcomes but to LL leads to obesity and type 2 diabetes mellitus. Fonken et al. described a causal relationship between nighttime light exposure and obesity [58]. They found that mice housed in either bright LL or dim (DM) LAN have significantly increased body mass and reduced glucose tolerance compared with mice in a standard LD cycle, regardless of equivalent caloric intake and total daily activity output. Additionally, the timing of food consumption by DM and LL mice differs from that in LD mice [58]. In this study, it was evident that nocturnal rodents eat substantially more food at night than during the day. Less body mass gain was associated with restricting food consumption to the active phase in DM mice. Thus, it was well documented that LAN caused an important disturbance in the timing of food intake and other metabolic signals, and as a result, weight increased [58].

Among the best-studied examples of endocrine factors that fluctuate over the day are those whose production is governed by the hypothalamic-pituitary axes (**Table 1**), such as cortisol, GH, PRL, thyroid

hormone, and gonadal steroids [59]. Other factors, such as nutrient-sensitive hormones (insulin and adipokines), vary their circulating levels in part in response to the environment/behaviors, such as LD and feeding/fasting cycles, that typically occur in time-of-day-dependent pattern [60].

A combination of influences potentially mediates daily rhythms in the abundance of many endocrine factors. A classic view has often been that fluctuations in nutrients, hemodynamic stresses, body temperature, metabolism, sympathetic and autonomic tone, as well as various autocrine/paracrine factors are mediated by behavioral changes across the sleep/wake and feeding/fasting cycle [60]. In addition, there are extrinsic factors, as many human and animal studies, revealed, that give a significant contribution of an intrinsic timekeeping mechanism towards these oscillations. Gamble KL et al. demonstrated the contribution of sleep to oscillations to several endocrine factors in humans, by enforcing a state of arousal during the night, followed by sleep during the subsequent day. These studies demonstrated that some (e.g., cortisol, TSH), but not all (e.g., GH, PRL), oscillations in endocrine factors occur independently of sleep/wake cycle [60]. This raised the possibility that fluctuations in distinct endocrine factors for the day may be driven, at least in part, by an endogenous mechanism (i.e., independent of behavioral rhythms). Therefore did Carmona et al., when they reported that plasminogen activator inhibitor-1 (PAI-1) has a circadian rhythm in their plasmatic levels and their gene expressions are regulated by circadian system elements too [61].

Turek et al. evidenced that the CLOCK transcription factor is a critical component of the molecular CC within pacemaker neurons of the hypothalamic SCN. Clock mutant mice in this study were hyperphagic and obese and developed hyperleptinemia, hyperlipidemia, and hyperglycemia [44]. These results suggest that the CC gene network plays an essential role in mammalian energy balance [44]. In the study by Akira et al. was evident that HF-fed mice consumed a higher percentage of daily food intake during the rest (light) period. It was remarkable how the change in feeding rhythm in HF-fed mice took place well before the onset of substantial weight gain. This diet attenuates the amplitude of Clock Gene Expression Transcripts of the core CC genes (Clock, Bmal1 and Per2) in the mediobasal hypothalamus, fat, and liver. The 24 hours profiles of leptin, glucose, insulin, FFA (free fat acid), and corticosterone were altered in animals on the HF-diet. In particular, the changes included: 1) increased levels of leptin and glucose during both the light and dark periods; 2) increased insulin and FFA levels during the dark period; 3) decreased amplitude of the corticosterone rhythm. It is noteworthy to mention that each marker displayed changes not only in absolute expression but also in the temporal pattern of expression [56].

Finally, very recently the Mediterranean diet is a healthy nutritional pattern that has been reported to be associated with several metabolic diseases including prediabetes [62], non-alcoholic fatty liver disease [63], inflammatory skin diseases [64,65], and bone health [66]. Mediterranean diet is also considered as a tool to manage obesity in menopause [67,68], improve the immune system [69], affect vitamin D levels in adults [70], endocrine axes [71]. Of interest, Mediterranean diet has also been reported to be associated with better health and quality of sleep [72]. Very recently, in a cross-sectional study including 172 middle-aged adults enrolled in a campaign to prevent obesity called the OPERA (obesity, programs of nutrition, education, research and assessment of the best treatment) Prevention Project [73], we have investigated the association of chronotype categories with adherence to the Mediterranean diet [74] . We have reported that an evening chronotype was associated with a low adherence to the Mediterranean diet and that the chronotype score was negatively and positively associated with BMI and adherence to the Mediterranean diet, respectively. Concluding that in the management of obesity should be taken into account the assessment of chronotype [74].

Meal Composition and Chrononutrition

It has been highlighted that the intake of macronutrients at certain times of the day can influence the states of hunger and satiety, and consequently, body weight. These effects have a significant influence on the circadian oscillations of hormones, involved in their metabolism [43].

Proteins

In particular, the proteins consumed at breakfast (compared to lunch or dinner) lead to a greater initial and prolonged sensation of fullness and increased satiety [43]. It has been observed that high-protein diets, lead to greater reductions in total energy intake, body weight, and fat mass while preserving lean body mass compared to a normal protein diet [75]. The satiating effect of proteins has also been demonstrated by a study involving 13 adolescents with a body mass index ranging between normal and overweight (body mass index-percentile: 50-94° percentile) without metabolic disease and who frequently skipped breakfast (i.e., the absence of food/ calorie drinks before 11:00 am) < 5 *per* week. On separate days, the subjects randomly consumed three different kinds of breakfasts as normal-protein (PN) breakfast, a breakfast rich in protein (PR), and skipped breakfast (BS). After 5 hours, the subjects were provided with an ad libitum buffet lunch, and a food register was completed, which documented all the food/drinks consumed in the remaining 24 hours. The BS breakfast resulted in a higher and more prolonged appetite throughout the trial period compared to PN and PR, while the addition of breakfast with PN and PR led to a 4h reduction in postprandial appetite, compared to BS. As a result, the subsequent ad libitum intake assessed through the 24hours PR and PN food registrations also showed a lower introduction of kcal compared to BS [75]. A possible explanation of the satiating properties of protein at breakfast could involve energy-sensitive gastrointestinal hormones and macronutrients that regulate digestive behavior. Numerous studies reported that the satiating properties of a protein are probably due to the decrease in orexigenic hormones, such as ghrelin and the increase in anorexigenic hormones [76]. Jakubowicz et al. conducted a study in which it was observed that a diet with a breakfast rich in carbohydrates and proteins, reduced the sense of hunger and desire, reduced circulating ghrelin levels, thus avoiding weight recovery and obtaining a better adherence to diet [76]. It has also been shown by consuming protein in the morning, and in the evening, it improves postprandial blood glucose levels. This can be useful for subjects who have an evening chronotype. Therefore, as reported very recently by Davis R et al., eating in the evening *vs* compared to day time is associated with relative hyperglycemia contributing to an increased risk of developing type 2 diabetes

mellitus [77]. Therefore, the evening meal choice can adversely influence of postprandial glycaemia and related insulinemia. In this context, perturbations in glycaemia levels at nighttime are reduced with meals high in protein compared to meals high in carbohydrate [77]. Of interest, the authors concluded that if eating late in the evening it is advisable to eat a meal rich in protein and reduce the carbohydrate content in the meal, this leads to a more favorable postprandial metabolic response [77]. Most clinical studies on the satiating effect of protein, agree on the use of both animal and plant protein, such as whey, and vegetables like soy. For example, a randomized, single-blind study has analyzed that given 20 g of casein, whey, pea protein, egg albumin, as a preload of a meal, significantly increased satiety more than other protein sources [75].

Whey has a high content of essential and branched chain amino acids. It contains bioactive components such as glycomacropeptide (GMP), lactoferrin, and lactoperoxidase. GMP and αlac have a highly satiating effect due to their high content of essential amino acids like leucine, lysine, and tryptophan (TRP) [75]. In particular, TRP is both the precursor of serotonin, which acts as an anorexigenic signal, and precursor of melatonin, which regulates the sleep/wake cycle. Studies have shown that increasing the intake of TRP-rich foods for breakfast combined with daytime light exposure, increases melatonin concentrations, resulting in improved sleep [78].

Of interest, Wada et al., investigated whether a combination of TRP-rich breakfast with protein- and vitamin B6 - rich foods, and light with low color-temperature at night (exposure to incandescent light), could enhance melatonin secretion and encourage earlier sleep time [78]. Ninety-four participants were divided into 3 groups: no intervention; the group with protein-rich and vitamin B6-rich foods and sunlight exposure after breakfast; and last group, the same contents as the previous group and incandescent light exposure at night. The combined intervention on breakfast, morning sunlight, and evening-lighting it was more efficient to keep higher melatonin secretion at night associated to higher quality of sleep [78].

Similar, Fukushige H et al., investigated melatonin secretion and sleep quality after the changed TRP-consumption at breakfast combined with daytime light exposure. They concluded that melatonin secretion was promoted by a tryptophan-rich breakfast and bright light exposure during daytime [78].

However, TRP supplementation must be combined with other foods, rich in vitamin B6 and omega-3, which influence the functioning of the enzymes involved in the anabolic pathway of melatonin [79]. TRP-rich foods, vitamin B12 are meat, poultry, fish, eggs, and milk [80]. While melatonin has been found in many sources of plant origin such as nuts, fruit, seeds, cereals, oils, coffee, wine, and beer [79]. Particularly among fruit cherries,

strawberries, and kiwis have the highest concentrations, while among vegetables, peppers, tomatoes, and mushrooms [79], and finally for cereals, wheat, oats, and barley have respectively 14.9 ng/g, 7.7ng/g and 6.0 ng/g of melatonin [79].

Evidence reported that intake of melatonin rich foods may gain health impact by increasing circulating melatonin [79].

Moreover, recently Oseguera-Castro et al., evaluated the effects of dietary fiber intake (21 days/45 g portion) on the modulation of circadian rhythm in young adults. Cookies made with 3 different types of fibers were consumed: 1) isolated fiber from spent coffee grounds, 2) a combination of spent coffee grounds and fructooligosaccharides, and 3) fiber-free cookies [81]. The cookies with fibers isolated and with fructooligosaccharides decreased the evening chronotypes ($p<0.05$) improving the quality and length of sleep, enhancing the chronodisruption associated with colonic short chain fatty acid (SCFA) production [81]. Beyond the proper maintenance of gastrointestinal and metabolic functions, evidence reported the role of SCFA in the regulation of food intake and energy expenditure by increasing the host capacity to harvest excess energy from diet [82]. In addition, SCFA can regulate both metabolic and inflammatory pathways, thereby maintaining body energy homeostasis [82].

Carbohydrates

As for carbohydrates, epidemiological studies show that consuming them at the beginning of the day has protective benefits against the development of diabetes and metabolic syndrome [83]. A study showed that carbohydrate intake in the morning can have a long-term protective effect against the development of metabolic syndrome [83]. In this study, data were collected on 1488 patients in 10 years (from 43 to 53 years), replacing 5% of fat with 5% of carbohydrates in breakfast. After 10 years, they were less likely to develop metabolic syndrome, decreased circulating triglycerides, and lower visceral fat [83]. Excessive carbohydrate consumption in the evening leads to an increase in blood sugar following morning. Some studies have assessed whether the glycemic index (GI) of meals, taken at different times of the day, affects insulin levels and postprandial glucose response. A randomized crossover study on healthy subjects, showed that a high GI meal consumed in the evening induces a greater glucose and insulin response compared to morning [84]. The variation in glucose sensitivity, between morning and evening, is due to the circadian variation of insulin, which peaks in the daytime and then decreases its sensitivity in the evening [60]. In humans, glucose metabolism has a circadian

rhythm with a diurnal variation of glucose tolerance that typically peaks during daylight hours. This glucose rhythm is associated with food-intake, the peak of glucose tolerance is associated with food consumption (daylight hours), and it is reduced with fasting in the night-dark hours [85]. Of interest, hormones such as insulin and cortisol involved in glucose metabolism, exhibit circadian oscillation [2]. Thus, sensitivity and insulin secretion are closely regulated by the chronobiological rhythms, with strong effects on glucose metabolism. Factors such as chrononutrition (e.g. meal timing and nutrients), and effects of diet on circadian rhythmicity can contribute to circadian perturbance and they are associated with metabolic disorders, including type 2 diabetes [86].

A HF diet can have important effects on both obesity and chronobiology because the intake of saturated and unsaturated fats affects the circadian cycle differently. However, there could also be the possibility of developing metabolic syndrome, obesity, and insulin resistance [87].

It has also been reported that the amount of carbohydrates consumed at breakfast modulates the responses of glucose, insulin, and FFA in subsequent meal by regulating the CC, the metabolism of glucose and insulin [88]. Individuals who eat a high amount of carbohydrates in the first part of the day have a lower intake of fat and alcohol than those who take less carbohydrates, and are less likely to develop type 2 diabetes [89]. This can be explained by the fact that CR also regulates the physiological processes that influence glucose. During the night, insulin secretion is 50% higher, counterbalanced, however, by an increase in insulin clearance, which therefore translates into a lower sensitivity to insulin at night and consequently a decrease in glucose tolerance [89]. In light of the diurnal changes in carbohydrate metabolism, it is explained why eating a standard meal in the evening produces greater responses of glucose and insulin than the same meal eaten for breakfast [90]. This also explains why evening carbohydrate consumption is often associated with weight gain, obesity, and type 2 diabetes [89].

Maki et al., in a randomized, crossover study included two 4-week dietary interventions, with participants who incorporated into their habitual diets breakfast meals containing either 2 eggs/day for 6 days/week (Egg condition or high protein breakfast (HPB)), and non-egg, higher-CHO-based foods (Non-Egg condition). In their report, they found that compared with the baseline diet, consumption of 12 eggs/week for 4 weeks at breakfast was associated with less reduction in LDL-C, more lowering of systolic blood pressure, and did not adversely affect insulin sensitivity and other aspects of CHO homeostasis, than observed with non-egg-based, energy-matched, control foods higher in CHO [91]. Interestingly, both groups had modest effects on

the cardiometabolic risk profile in adults at risk for type 2 diabetes. Additionally, HPB was directly related to increased daily energy intake from non-study foods but was not associated with increased body weight.

Fatty Acids

Few *in vitro* studies have shown that monounsaturated fatty acids (MUFA) and polyunsaturated fatty acid (PUFA) could lead to epigenetic changes [92]. In particular, the intake of MUFA and PUFA can influence the methylation levels of the cytosine of the CpG islands in the CLOCK promoter, regulating the gene expression of the CC, inhibiting it based on the CLOCK polymorphism. The high intake of MUFA and olive oil are negatively associated with the methylation levels of CpG by CLOCK, while PUFA is positively associated. Therefore, CLOCK CpG methylation levels, together with other genes, could be used as markers for weight loss [92]. Moreover, studies have shown that some CLOCK polymorphisms respond differently when subjected to diet with different types of fat, showing better sensitivity with a MUFA intake of > 13%. While an increase in visceral fat is found with high intakes of saturated fatty acids (SFA) [92]. Likewise, some CLOCK polymorphisms show a more easily alterable CR. An example is CLOCK 3111T/C single nucleotide polymorphism (SNP) (rs1801260). Studies have shown that C carriers display a less altered CR than the corresponding homozygous TT [92].

In a study carried out in Spain, between 2006 and 2011, a self-assessment questionnaire Morningness-Eveningness (MEQ), was administered to patients who underwent bariatric surgery. The study showed that the evening chronotype was associated with greater obesity in severe subjects with obesity and a lower loss of weight after bariatric surgery. Furthermore, circadian preferences interact with CLOCK3111T/C for obesity [93]. Among the genes that could be used as markers for weight, loss is PERILIPIN1 (PLIN1). Triglycerides are stored in adipocytes in the form of lipid droplets. The process of formation of the single layer of these lipid droplets involving different proteins, including the perilipin gene [94]. There are several isoforms of this protein, but the isoform PLIN1 is another example of a circadian gene [94]. PLIN1 is involved in fat metabolism in adipocytes and consequently involved in energy homeostasis and adiposity [94]. PLIN1 also participates in catecholamine stimulated lipolysis through interaction with hormone-sensitive lipase [94]. PLIN1 shows a marked circadian variation in adipose tissue [95]. In this respect, in the ONTIME study, with 1287 overweight and obese patients, who had undergone the genotypization of the PLIN1 SNPs, they evaluated the association between PLIN1 and weight loss. They found that eating late (after 15:00) is related to a lower weight loss

among the carriers of the AA genotype in the PLIN1 114995A/T, compared to those who had lunch (early 15:00).

Genetics and Chronotype

These data further highlight the concept that beyond the time of the day when we take meals, it is also essential to examine which macronutrients we consume in order to improve appetite control, food intake, and consequently, weight control. However, beyond a personal decision regarding the time of the day in which we consume a meal, there is a genetic background that can make us more prone to consume meals at a specific time of the day more than another. Genetically, more than 100 SNP have been reported for obesity. Most of the genes are involved in the modulation of the circadian circuits, as well as in metabolic functions [96]. Evidence to support that food intake times have a genetic component and, therefore, heritable, comes from a study on both monozygotic (MZ) and dizygotic (DZ) twins, with overweight/ obesity, who live separately and away from the family environment. The MZ twins showed higher intra-couple correlations than the DZ twins for breakfast and lunchtime (but not for dinner time) and for waking, bed, and chronotype time [52]. This shows that heredity estimates are higher for meals at the start of the day (breakfast) than later (lunch and dinner) and other specific morning behaviors, such as waking times. On the contrary, the environmental component is mostly determining dinner times and other evening behaviors, such as bedtime. This evidence suggests that the intervention of a nutritionist could be more useful targeting unhealthy lifestyle habits later in the day because being mostly influenced by the environment, it could be modified by the individual [52]. The combination of CR and genetic components could, therefore provide circadian tailored recommendations for each person subjected to weight loss plan [93].

Nutritional Recommendations

In light of the results of the reported studies, we provide practical advices for drawing up a food program based on weight, body mass index and with the help of MEQ, to determine if the patient has an evening or morning chronotype. According to the results of the studies proposed in this article, the timing of nutrients and the macronutrient composition of meals have a crucial role in chronobiology. Consequently, the regularity of meals, nutrient composition, meal frequency, affected obesity, insulin resistance, and metabolic syndrome.

Several studies show that having breakfast can prevent metabolic syndrome and obesity as well as help restore a physiological circadian cycle compared to higher calorie intake in the evening, instead could favor the development of metabolic syndrome [97].

As for the content of macronutrients in meals, proteins have a satiating effect prolonged over time [74]. A high-protein breakfast has shown to increase energy expenditure and fat oxidation in healthy young adults, increase the production of anorexigenic hormones and decrease the production of orexigenic hormones such as ghrelin [75]. Many studies have shown that eating fiber and carbohydrates for breakfast could have a protective effect against the metabolic syndrome, reduction of energy intake from fats during the day, with a reduced prevalence of abdominal obesity [83]. Additionally, by combining fiber and carbohydrates with proteins, they can give a greater sense of satiety in the long term [76].

It has also been documented that the fat consumed can influence the genes involved in the CR through epigenetic modifications. Among the other most popular foods, capable of influencing the circadian cycle, there is caffeine, the most used psychoactive compound in the world, present in many foods and drinks. Caffeine has been shown to be able to influence the phase of gene expression of the CC of peripheral tissue in mice and its use is able to alter the CR after jetlag [98].

High consumption of sodium chloride can also affect the circadian cycle. High consumption of salt for two weeks makes progress alter the circadian cycle in the kidneys, liver, and lung [99]. Besides, the increase in salt also causes an increase in blood sugar because of the Na/K, SGLT co-transporters, and the salt increases the gene expression of GLUT2 and SGLT.

Even a high consumption of starch causes an increase in glucose and circulating insulin, which involves alteration in the liver clock in mice [100].

Alcohol appears to disrupt molecular, endocrine, and behavioral CR in humans and other animals [101].

Another group of compounds capable of influencing CR is polyphenols, including those of tea [102]. It has been shown that these polyphenols improve the metabolic syndrome through mechanisms related to the CC, restoring the genes of the nucleus, alleviating the attenuated diurnal variation, and controlling the clock of genes induced by constant darkness, reversing intolerance to glucose and insulin. This shows that there is an oscillator dependent on tea polyphenol [103].

Therefore, based on the evidence so far produced and analyzed on the modulation of hormonal response and clock genes, it is possible to formulate some practical nutritional recommendations:

- Do not skip breakfast;
- Prefer a balanced breakfast and lunch, composed of carbohydrates, fiber, proteins and the right amount of fat;
- Take an adequate protein intake, especially preferring whey proteins;
- Take most of the daily carbohydrates intake in the first half of the day;
- Reduce calorie intake and especially carbohydrates intake in the evening;
- Eat foods rich in tryptophan as meat, poultry, fish and milk;
- Take foods containing melatonin as fruit (cherries, strawberries and kiwis), vegetables (peppers, tomatoes and mushrooms), nuts, seeds, cereals, oils, coffee, wine and beer;
- Limit fat consumption by preferring PUFA-rich foods such as fish, seeds, and olive and seed oil;
- Consume foods rich in polyphenols such as tea, grapes, red fruits and dark chocolate;
- Avoid coffee, alcohol and HF foods intake.

In addition, **Figure 1** summarize these simple nutritional advices in order to resynchronize the biological rhythms and improve body weight management.

Conclusions

CRs are not only influenced by sleep/wakefulness, but are also controlled by the cycle of satiety/hunger. These cycles can be controlled or regulated, according to the different situations, with an appropriate food plan with specific macronutrients, prescribed at different times of the day. Also, giving importance to the regularity of meals, going to regulate, those cases of alteration of the physiological rhythms that can lead to metabolic disorders. On a typical food day, we recommend having a breakfast because skipping breakfast increases cortisol and loss of muscle mass. Between seven and eight in the morning, cortisol reaches its peak, to prepare the body for typical stress associated with awakening and consequent demand energy, promoting protein catabolism and increasing liver gluconeogenesis. The ideal would be to eat breakfast with complex carbohydrates, fiber, proteins, and a small amount of fat. In the middle of the day that is between 12 and 13, there is an increase in adiponectin produced by adipose tissue, known insulin sensitizer, whose peak is reached in the afternoon. Therefore, it is recommended to consume carbohydrates in the first part of the day, together with proteins that stimulate the release of anorexigenic hormones, inducing a greater sense of satiety, slowing down gastric emptying. Dinner, between 19 and 22, must be the lightest meal of the day. In the evening, there is an increase in the GH, which favors the formation of muscle mass. In the dark, the release of melatonin also increases. Therefore, the ideal would be to consume a protein-based meal that favors the increase of muscle mass and on the one hand, to promote the production of melatonin through intake of the amino acid tryptophan, to promote sleep. In the evening, simple sugars should be avoided, as carbohydrate tolerance decreases in the latter part of the day, due to reduced insulin secretion. Finally, specific foods such as coffee, alcohol, high-fat foods can alter the circadian cycle and sleep/wake rhythms, and therefore these foods should be avoided.

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Abbreviations.

CR (circadian rhythm); CC (circadian clock); CS (circadian system); SNC (suprachiasmatic nucleus); CLOCK (circadian locomotor output cycles kaput); BMAL1 (brain and muscle ANRT-like protein); CRY (cryptochromes); PER (period circadian regulator); REV-ERBα (reverse erythroblastosis virusα); RORα (retinoic acid receptor-releated orphan receptorα); CCGs (clinical commissioning groups); GH (growth hormone); PRL (prolactin); FAA (food anticipatory activity); FEO (food-entrainable oscillator); FOX01 (forkhead box protein01); PPARγ (peroxisome proliferator-activated receptor γ); HF (high fat); GLP-1 (glucagon-like peptide1); AgRP (agouti-related protein); DIO (diet-induced obesity); SREBP (sterol regulatory element-binding protein); nNOS (neuronal nitric oxide

synthase); SGLUT1 (sodium/glucose cotransporter1); GLUT2 (glucose transporter2); PEPT1 (H^+/peptide cotransporter1); LAN (light at light); LL (12-hours light-light); LD (light-dark); DM (dim); FFA (free fat acid); PN (normal protein); PR (rich protein); BS (skipped breakfast); GI (glycemic index); MUFA (monounsaturated fatty acids); PUFA (polyunsaturated fatty acids); SFA (saturated fat acids); SNP (single nucleotide polymorphism); MEQ (questionnaire morningness-eveningness); PLIN1 (perilipina1); GMP (glycomacropeptide); TRP (tryptophan); SCFA (short chain fatty acids); DHA (docosahexaenoic acid); EPA (eiocsapentanoic acid).

Figure.

Title to figure 1: Optimization of meals and macronutrients in relation to hormonal circadian oscillations.

Legend to figure 1: A balanced breakfast and lunch, composed of carbohydrates, fiber, proteins and the right amount of fat helps to lower the peak of cortisol in the morning, regulate post-prandial blood glucose for greater insulin sensitivity, and increase the sense of satiety during day. In the evening, the lightest meal of the day, it is preferable to limit the consumption of sugars for less insulin secretion, and to prefer a protein-based meal, in conjunction with the increase in GH and proteins containing the tryptophan amino acid or melatonin to promote sleep.

Table.

Title to Table 1: Circadian rhythms for Endocrine factors

Legend to figure 1: Source: Adapted from Gamble KL et al. Circadian clock control of endocrine factors. Nat Rev Endocrinol [60].

Hormone	Time of Peak	Functions
Growth Hormone (GH)	Secreted by pulses, increases amplitude at night	Insulin antagonist (decrease glucose utilization, increase lipolysis)
Vasopressin (AVP)	Middle of night	Important element of the neurocircuit from SCN AVP to paraventricular nucleus (PVN) oxytocin (Oxt), which relays light exposure to inhibit feeding behavior
Melatonin	Middle of night	Relay information regarding the environmental light-dark cycle, very sensitive to variations in day length that will trigger endocrine changes. Vasoconstrictor, vasodilator, anticonvulsant, antioxidant
Leptin	01h00	Appetite-regulating hormone
Thyroid stimulating hormone	01h00-02h00	Modulation of thyroid hormone release and growth of the thyroid gland
Prolactin	02h00 (amplitude larger in females)	Multiple roles in reproduction, lactation, and homeostatic roles in the organism
Triiodothyronine	02h30-03h30	Fundamental to maintain normal circulating levels of the thyroid hormones, T_4 and T_3
Ghrelin	02h00-04h30 (fed state) 13h00 (fasted state)	Appetite-regulating hormone
Cortisol	07h00-08h00	Body preparation for stresses associated with waking
Adiponectin	12h00-14h00	Insulin sensitizer. Promotes insulin action
Insulin	17h00	Stimulate glucose utilization and protein synthesis by peripheral tissues. Nutrient

		storage during awake/fed state, and subsequent mobilization during the sleep/fasted period

THE CLOCK DIET: A PRACTICAL NUTRITIONAL GUIDE TO MANAGE OBESITY THROUGH CHRONONUTRITION

Luigi BARREA [1,2,§,*], Evelyn FRIAS-TORAL [3,4,§], Sara APRANO [2,5,§], Bianca CASTELLUCCI [2,5], Gabriella PUGLIESE [2,5], Dolores RODRIGUEZ-VEINTIMILLA [6], Giovanni VITALE [7,8], Davide GENTILINI [9,10], Annamaria COLAO [2,5,11], Silvia SAVASTANO [2,5], Giovanna MUSCOGIURI [2,5,11].

[1] Dipartimento di Scienze Umanistiche, Università Telematica Pegaso, Via Porzio, Centro Direzionale, isola F2, 80143 Napoli, Italy; luigi.barrea@unipegaso.it

[2] Centro Italiano per la cura e il Benessere del paziente con Obesità (C.I.B.O), Department of Clinical Medicine and Surgery, *Endocrinology Unit*, University Medical School of Naples, Via Sergio Pansini 5, 80131 Naples, Italy;

[3] Research Committee, SOLCA Guayaquil, Av. Pedro Menendez Gilbert, Guayaquil 090505, Ecuador;

[4] Clinical Research Associate Professor for Palliative Care Residency from Universidad Católica Santiago de Guayaquil, Av. Pdte. Carlos Julio Arosemena Tola, Guayaquil 090615, Ecuador;

[5] Dipartimento di Medicina Clinica e Chirurgia, *Unit of Endocrinology*, Federico II University Medical School of Naples, Via Sergio Pansini 5, 80131 Naples, Italy;

[6] Clinical Nutrition and Dietetics Service, SOLCA Guayaquil, Ecuador. E-mail: dra.rodriguezv@yahoo.com. ORCID ID: 0000-0001-030-0461

[7] Istituto Auxologico Italiano IRCCS, Laboratory of Geriatric and Oncologic Neuroendocrinology Research, Cusano Milanino, MI, Italy;

[8] Department of Medical Biotechnologies and Translational Medicine, University of Milan, Milan, Italy

[9] Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy;

[10] Istituto Auxologico Italiano IRCCS, Bioinformatics and Statistical Genomics Unit, Cusano Milanino, Milano, Italy;

[11] Cattedra Unesco "Educazione alla salute e allo sviluppo sostenibile", University Federico II, Naples, Italy.

[§] **Luigi Barrea, Evelyn Frias-Toral and Sara Aprano** have equal contribution and should be considered as co-first authors.

***The e-mail address, and telephone number of the corresponding author:**

Prof. Luigi Barrea; Dipartimento di Scienze Umanistiche, Università Telematica Pegaso, Via Porzio, Centro Direzionale, isola F2, 80143 Napoli, Italy;.

E-mail: luigi.barrea@unipegaso.it; Tel. +39 081 746 3779 Fax +39 081 746 3668

Running title: OBESITY AND CHRONONUTRITION

Abstract

Chronobiology studies the biological rhythms or circadian cycles of living organisms and their adaptation to external changes. Biological rhythms can affect hormone production cycles such as sleep/wake, and nutrition/fasting, but these factors can also alter the circadian rhythm (CR). In recent years, numerous studies have highlighted how feeding times and frequency can influence biological rhythms. Additionally, individuals' chronotype, working shifts, and food intake can make a deep impact on people's tendency to develop obesity and metabolic diseases. In this context, a single food and a specific combination of these, can also affect the CR and fasting cycle and consequently body weight and *viceversa*. The purpose of the review is to propose practical nutritional recommendations to help in resynchronizing the circadian rhythm as a tool in weight control.

Keywords: circadian clock, Chrononutrition, obesity, endocrine factors, food timing, macronutrients, diet, Nutritionist

TEXT

Introduction

Chronobiology is a branch of biology that studies cyclical phenomena in living organisms and their adaptations to light and dark cycles, known as biological rhythms or circadian clock (CC) [1]. The synchronization of the endogenous CC allows the organism to adapt to environmental changes by modifying its behavioral and physiological functions [1]. The circadian system (CS) of mammalian is characterized by three components: the input, 24 hours oscillator, and the outputs. The most important circadian oscillator is a central pacemaker located in the suprachiasmatic nucleus (SCN) of the hypothalamus, driving circadian rhythmicity in other brain areas and peripheral tissues by sending them neural and humoral signals [1].

Most peripheral tissues and organs contain circadian oscillators. Usually, they are under the control of the SCN; however, under some circumstances (restricted feeding, jet-lag, and shift work), they can desynchronize from the SCN [1]. Most physiological and behavioral functions follow a circadian rhythm (CR), guided by central pacemakers and peripheral oscillators. Some of these over-rhythms (e.g., sleep/wake cycle and feeding time, physical exercise, core temperature) in turn, through feedback they can influence the function of SCN and peripheral oscillators [1]. It has been estimated that 7% to 13% of a cell's transcriptome is under circadian control, including genes encoding for modulators of transcription, signal transduction, protein turnover, and metabolism. The CC, through the fluctuations of the genes controlled by it, influences cellular/organ function in a time-of-day-dependent manner, through endocrine factors [1]. Both synthesis and abundance of various endocrine factors, and the target organs sensitive to these signals, are subject to rigorous time controls. The production of some endocrine factors whose levels change during the day, such as cortisol, growth hormone (GH), prolactin (PRL), thyroid hormone, and gonadal steroids are regulated by hypothalamic-pituitary axes [1]. Moreover, nutrient-sensitive hormones, insulin, and adipokines vary their circulating levels in a time-of-day-dependent pattern, in response to the environment and behaviors, such as feeding/fasting and light/dark cycle [2]. Feeding time is considered one of the most important external synchronizers. It has been observed that the timing of meals has important effects on metabolic and physiological parameters, highlighting that in the choice of food, it is important to consider both the nutritional value and the timing [2]. Fasting and feeding cycles appear to function as timing signals for peripheral clocks, bypassing the synchronization signals emitted by the brain's main clock [1].

Numerous studies suggest that mealtimes can influence physiological processes, including sleep/wake cycle, hormone levels, obesity, and metabolic syndrome [1].

Considering that the timed of food intake can affect obesity, and that some foods can affect the secretion of some hormones, which also follow circadian oscillations, we can hypothesize that the intake of food and macronutrients at certain times of the day, can contribute by on the one hand to restore the circadian oscillations of the watch genes, and on other to regulate body weight by preventing obesity and other metabolic alterations. Therefore, the purpose of the review is to propose nutritional recommendations useful in resynchronizing the circadian rhythm as tool in weight management.

Chronobiology and Chrononutrition

Chronobiology is a field of biology that evaluates the effects of time, biological rhythmical phenomena, and their adaptive fitness to solar- and lunar-related periodic phenomena [1]. In detail, the cell biological clock is composed of proteins that generate circadian oscillations through positive and negative transcriptional/translational feedback loops. The cellular oscillators positive are CLOCK (circadian locomotor output cycles kaput), BMAL1 (brain- and muscle- ANRT-like protein) that heterodimers and, through binding to E-box elements, drive the transcription of several genes: Cryptochrome (*Cry1, Cry2*), Period Circadian Protein (*Per1, Per2, Per3*), reverse erythroblastosis virus-α (*Rev-Erbα*), retinoic acid receptor-related orphan receptor-α (*Ror-α*) and multiple clinical commissioning groups (CCGs). After dimerization, PERs and CRYs are transported out of the nucleus and inhibit CLOCK–BMAL1-mediated transcription. When PER and CRY are degraded, CLOCK-BMAL1 is no longer repressed and binds E-box [3]. The CLOCK protein has a significant activity as a histone acetyltransferase facilitating gene transcription [3]. This activity is counteracted by Sirtuin-1, a histone deacetylase [3] that is related to energy metabolism and aging [3]. Recent evidence shows that clock genes also act as sensors of the cellular metabolic status through changes in the redox state [3]. This dependence of the molecular clock on energy uptake could explain why alterations in metabolic cues, such as restricted feeding or conflicting synchronizers, are able to modulate the activity of the timing CS. Those genes that are regulated by the CC, yet do not directly influence the activity of core clock components, are termed clock controlled/output genes.

Moreover, the term chrononutrition is used to describe the connection of food and the CS. It implies two features:

1) The CS has the capacity to impact the functions of food metabolism, such as digestion and absorption of food, and energy metabolism. If these aspects are considered when choosing the timing, amount, and composition of food intake or food, it will improve human health including body weight [3];

2) As the effect of light stimulation, time-restricted food or nutrient stimulation can have a positive effect on CS [3]. Feeding behavior is a principal factor that plays a vital role in the organism's nutritional status. An inherent timing mechanism predominantly dictates eating schedules, but also are affected by other factors such as food availability, hunger, and satiety, and also by social habits and convenience. Nowadays, it is widely accepted that these parameters are critical and that their alteration is associated with morbidity and mortality. Many papers affirm that feeding time has a dramatic effect on health and can be employed to prevent obesity

and various other metabolic pathologies [4]. That is why 'chrononutrition' refers to food administration in coordination with the body's daily rhythms. This concept reflects the basic idea that, in addition to the amount and content of food, the time of ingestion is also critical for the well-being of organism [1]. The clock genes in the gut that are rhythmically expressed control digestion and absorption in mammals. Hoogerwerf WA et al. stated that the phases of the rhythms in clock gene expression are different amid the cranio-caudal axes of the gut, thus proposing that the upper part of the gut entrains faster than the lower part of the intestine by changing the speeds of nutrient absorption. These authors, through a study on nocturnal mice with a scheduled feeding program in the daytime, found a phase shift in the rhythm of clock gene expression in the gastrointestinal tract, thus demonstrating that nutrient timing can deeply affect gut CS [5]. Moreover, the same authors described that colonic movements are more frequent during the day than at night [5] and indicated that rodents have a day/night rhythm in colonic movements, which is controlled by clock genes and neuronal nitric oxide synthase (nNOS) activity [5]. Since 1976, it was well documented that stool weight, colonic contractile response to acetylcholine, and intra-colonic pressure had a clear CR. Interestingly, these were altered in Per1 and Per2 double-knockout mice or in nNOS-knockout mice. The intestinal digestive enzyme sucrose also displays a CR activity, and it reaches a peak just before feeding time [6]. Gastrointestinal symptoms such as diarrhea or constipation were reported among shift workers and time-zone travelers; these conditions are connected with disruptions in CR [5,6]. All of these findings proved that the digestive system experiences circadian adjustments in both rodents and humans.

Many important transporters are under CR and any disturbance in these causes an abnormal absorption. Some studies investigated the effect of circadian changes in the intestinal absorption of peptides, glucose, lipids, and drugs by different transporters. It has been described that in the intestines of rodents the absorption of water and glucose is increased during night [6]. Several studies found that sodium/glucose cotransporter (SGLUT)-1, glucose transporter 2 (GLUT)-2, and GLUT-5 have circadian oscillations in their expression and they are regulated by clock genes through E-box activity [7]. Additionally, SGLUT1 is determined by PER1 activity independent of the E-box [7]. The SGLUT1 and H^+/peptide cotransporter 1 (PEPT1) were synchronized through scheduled feeding experiments. These evidences support the idea that these transporters are directly affected by feeding conditions [7]. In addition, it has also been reported that in clock mutant mice, peptide transportation was reduced, while lipid absorption was increased. Contrariwise, nocturnin-knockout mice showed a reduction in lipid absorption due to less chylomicron transit [8]. Furthermore, the expression of the

sodium pump (Atpa1a), channel (γEnac), transporters (Dra, Ae1, and Nhe3), and the Na^+/H^+ exchanger regulatory factor (Nherf1) in rat colonic mucosa showed circadian changes, suggesting that also NaCl absorption in the colon was under CR [8]. All these findings evidenced that the circadian clock controls many crucial transporters, thus a circadian disruption will cause an abnormal absorption.

The vast majority of studies have focused on the effect of scheduled meals on metabolic pathologies such as obesity and diabetes. However, all these findings lead to speculate that the 'optimal' feeding schedule might harbor important medical benefits not restricted to metabolic syndrome [2].

The influence on obesity

The prevalence of overweight and obesity has recently increased, contributing to the increment of different diseases, including type 2 diabetes mellitus [9–11], thyroid dysfunction and nonalcoholic fatty liver disease [12,13], breast cancer [14,15], elevated serum uric acid levels [16], hypovitaminosis D [17,18], inflammatory skin diseases [19], polycystic ovary syndrome [20–22], and others [23–25]. Accumulating results point to the chronic-inflammation in visceral adipose tissue, which, in turn, promotes low-grade systemic inflammation as a primary cause contributing to the development of obesity-related diseases [11,26,27]. In addition to bariatric surgery [28] and the pharmacological approach [29,30], physical activity and diet are the primary therapeutic approaches to reduce body weight and reduce the risk of developing obesity-related diseases [31–37].

A very well-organized structure originates human CR and their synchronization with the environment, previously described, the mammalian circadian timing [38]. An important aspect of the CS is its capacity to be modified by internal or external cues. In addition to light exposure, as a typical external signal, there are other untrainable factors such as temperature, exercise, drugs, humidity, social cues, sound, and food [38]. These external or environmental cues able to entrain or synchronize an organism's biological rhythms are also known by the name "Zeitgeber". The CC needs to keep a harmonious relationship among organ clocks and the environmental time since we find CR in the fasting/feeding cycle, sleep/wake cycle, immune response, hormone secretion, glycolysis, and many other processes in the human body. Different evidences emphasize the importance of CR and chronobiology in nutrition and how these deeply affect the physiological status. It is fundamental to understand the association between time-of-day of energy intake with metabolic disease, specifically obesity [1,3]. For this reason, when caloric restriction accompanies feeding time, behavioral and physiological circadian rhythms and gene expression in the SCN are shifted and/or entrained to meal time.

This temporal restriction generates activity before food availability, and this phenomenon is also known as food anticipatory activity (FAA). Tahara et al. reported that FAA appears approximately 2-3 hours before feeding time. In mice, they associated the FAA with foraging for food [4]. The presence of FAA suggested the hypothesis that animals have a food-entrainable oscillator (FEO). According to Storch et al., there are differences in the FAA in mice without genetic components of the CC; however, those mice maintained the capacity to show the FAA [39]. For these reasons, it can be speculated that the genetic control of FEO is different from other CS, in addition it has also been reported that FAA persisted in SCN-injured rats, suggesting that FEO is located in tissues outside of the SCN. Some papers are proposing that the FEO may be connected to the dorsomedial hypothalamic nucleus. but other reports focused on the possible activity of extra-hypothalamic brain regions in FAA [40]. To determine the localization of the FEO, more studies should be done since it can lie outside of the brain or depend upon the interaction among multiple tissues. Moreover, the reward and motivational value of food can also be a potent synchronizer for the SCN clock [41]. Therefore, these reports point out that energy metabolism and motivational properties of food can affect the CS of the SCN. Food-related cues may entrain clock genes of the SCN with an immediate effect, or be mediated indirectly by another neural or peripheral site [41]. In addition, there may also be multiple oscillator sites that could play a pivotal role as a FEO, responsible for anticipating meal [42]. Other studies, in animals, concluded that under normal conditions of *ad libitum* food, light is the typical Zeitgeber that synchronizes the SCN, and via neuronal and endocrine pathways synchronizes peripheral clocks leading to the control of the behavioral activity and feeding time. Light also maintains a dominant synchronizer of the SCN in a second scenario, where there is a temporal food restriction, and peripheral clocks are synchronized to feeding time. Furthermore, when there is temporal and energy food restriction, the SCN, and peripheral clocks are synchronized to the feeding time. Therefore, it is evident that the strong interaction between feeding time and quantity of food intake [43]. Evidence reported that genetic disruption of the CC had been associated with metabolic pathologies in rats. The CC conducts transcriptional programs for specific metabolic pathways. That is the case with CRY-1 that abolishes hepatic gluconeogenesis during fasting by the adjustment of cAMP/CREB signaling, the rhythmic repression of the glucocorticoid receptor gene, and the elimination of nuclear Forkhead box protein O1 (FOXO1) that, finally, decontrols gluconeogenesis [44]. PER-2 is another clock inhibitor; it commands lipid metabolism through direct control of peroxisome proliferator-activated receptor gamma (PPARγ) and mitochondrial rate-limiting enzymes [44]. Disturbance of CLOCK and BMAL1 has also been linked to hyperinsulinemia, obesity, and type

2 diabetes [44,45]. The circadian post-transcriptional regulator Nocturnin also manages lipid and cholesterol metabolism [8]. Dyar et al. published an atlas of circadian metabolic profiles across eight tissues showing temporal cohesion among tissues, and how a high fat (HF) diet affected each tissue in different ways [46]. Additionally, food intake and the oscillation of hormones such as insulin, glucagon, peptide YY, glucagon-like peptide 1 (GLP-1), corticosterone, leptin, and ghrelin adjust CC [46]. Despite all these valuable and clarifying publications about CC and its effect on metabolism, there are more aspects that require further research. It is clear that the feed timing should be aligned with the CR, considering that a disturbance between them will cause a metabolic dysfunction [47]. In addition, Agouti-related protein (AgRP) neurons, representing a specific hypothalamic nutrient and/or energy sensor, face daily rhythms as an answer to leptin [47]. Eckel-Mahan et al. proposed that the nutritive environment itself affects feeding behavior and causes drastic alterations in circadian gene expression in diet-induced obesity (DIO) model [48]. A study showed that one of these DIO-related effects is the occurrence of newly rhythmic oscillations of the lipogenic transcription factor sterol regulatory element-binding protein (SREBP), which regulates fatty acid synthesis and oxidation, and of the PPARα, a major regulator of fatty acid oxidation. This might be a result of CR that is aroused at the boosters of genes that are generally not rhythmic [4]. It also demonstrated that a PPARα agonist (WY-14,643) is more efficacious in diminishing lipids when administered at the circadian peak of PPARα expression. These findings are useful evidence to promote chrono-pharmacological interventions for the treatment of metabolic disorders because of the modulation of metabolism by the improvement of CR. Another essential element to consider when analyzing obesity causes is the loss of glucocorticoid circadian oscillations. In mice, it was evident that adipocyte differentiation does not proceed under regular circadian hormonal cycles. Instead, the changes were shown when the period of the pulse shortens or if the hormonal signal is flat or continuously elevated [48]. Alterations can develop this abnormal situation in feeding time or sleep cycles, long-term glucocorticoid hormone treatment, chronic stress, or metabolic syndrome [48]. These conditions were associated with an increase in the mass of subcutaneous and visceral fat pads in mice [48].

Finally, it is substantial to mention the connection between CC and autophagy. Autophagy is a process that recycles components of the cytoplasm in cells for tissue remodeling and eliminates non-functional organelles. Autophagy is rhythmically activated in a clock-dependent manner; it reduces cytoplasmic contents in lysosomes and degrades the repressor CRY-1, able to suppress hepatic gluconeogenesis. Another study to examine the role of autophagy in the regulation of the liver clock and glucose metabolism revealed that the

degradation of CRY1 by autophagic pathways allows glucose production [49]. Impressively, obesity intensifies the autophagic degradation of CRY1, ergo-higher glucose production, and higher blood glucose levels.

All of these processes show the complexity of the CC and interactions between central and peripheral mechanisms. Therefore, it is clear that CS plays an overarching role in regulating human physiology [49]. Disruption of CR is associated with different disorders including metabolic syndrome and obesity [46].

Association between chrononutrition and obesity: Studies in Humans

Eating behaviors are influenced by intrinsic timing mechanisms but also food availability, hunger, and satiety, as well as social habits [2]. CS can affect metabolism and *viceversa*. Many hormones such as insulin, glucagon, cortisol, GH, have circadian oscillations, regulated by the clock genes [2]. The activity of some metabolic enzymes, transport systems involved in the metabolism of cholesterol, glucose, and lipid receptors, are also regulated by the CS, for which an interruption of the circadian cycle (chrono destruction), can induce obesity, type 2 diabetes, dyslipidemias and hypertension [50]. Furthermore, even a diet rich in fat seems to have an impact on fasting / satiety cycles. This is due to the fact that dietary fat can affect the gene expression of watch gene [48]. In humans, the timing of food intake could be involved in the variability in the response to slimming treatment, as some observational studies on humans have observed the association of obesity and energy supply in different hours of day [38]. Lunchtime is predictive of weight loss regardless of calorie intake [52]. This has been confirmed by a randomized crossover study, which reported that eating lunch late is associated with decreased resting energy expenditure, fasting carbohydrate oxidation, reduced glucose tolerance, diminished thermal effect of food, and reduced daily cortisol variability [52]. In a prospective randomized controlled trial, Lucassen et al. reported that subjects having an evening chronotype exhibited an increase in body mass index, compared to subjects with a morning chronotype, and this was due to an unhealthy eating pattern, especially characterized by late dinner [53]. Food timing also has a role in predicting the trend of weight loss. Indeed, in a study involving a group of 270 patients undergoing bariatric surgery that were followed up for 6 years, subjects who lost less weight had lunch later (after 15:00 h) than patients having an earlier lunch [54]. In a recent randomized parallel-arm study, two groups of overweight or obesity women with metabolic syndrome were randomized to two isocaloric weight loss plans (~1400 kcal) for 12 weeks. A group breakfast, called BF, was given a food plan with an abundant hearty breakfast (~700kcal), a medium-sized lunch (~500kcal), and a small dinner (~200kcal). Instead, in another group dinner, called D, this meal plan has been reversed, so it has been given a small breakfast and a high-calorie dinner. After 12 weeks, it was observed: the more significant weight loss, the more considerable improvement in metabolic markers (glucose, insulin, HoMA-IR, triglycerides) and in satiety in group BF, compared to group D [2].

Obesity is now considered an increasing pandemic, and many researchers have associated it with exposure to light at night (LAN) and shift work [55]. The circadian clock adjusts humans for anticipated situations (food availability, and sleep). Alteration of this system produces circadian and metabolic disruptions. Coomans

et al. reported that four days of constant light (12-hours light-light) LL cycle, increased food intake (+26%), decreased energy expenditure (-13%), and consequently, body weight gain in mice [56]. As constant light debilitates rhythms of the central clock, altered feeding behavior, sleep/wake cycles, energy homeostasis, and thermogenesis might appear. Moreover, a variation of light conditions or feeding time influences metabolism, body temperature, and body weight within a few days. These immediate events are probably because of misalignment between internal clocks similar to jet lag. Chronic jet lag, including shift work, has a direct and high risk for metabolic disorders. Results from Cooman's study showed that LL produced a drastic depression in SCN amplitude, which stabilized within 3 days up to 44%. This reducing effect produced a complete desynchronization of CR in energy metabolism and hepatic and peripheral insulin sensitivity. These findings are similar to those in aging and neurodegenerative diseases [56]. In a typical scenario with regular 12-hours LD (light/dark) cycles, this input pathway maintains individual SCN neurons synchronized with each other and the environment with a majority of neurons that are active during the day and silent during the night. LL exposure originated desynchronization among neurons of the SCN, which restrains CR at the tissue level [54]. Another significant influence of LL is the disruption of corticosterone rhythm that diminishes corticosterone peak levels, so, it is directly linked to the restraint of the SCN, neuronal activity [54]. Other effects of reduced SCN rhythmicity are a disturbance in energy homeostasis, decreased energy expenditure, impaired oxidative response to food intake (metabolic inflexibility), debilitated insulin sensitivity, and finally, obesity [57]. Moreover, it has been known for several decades that a disturbance of CR by LL causes deregulation of glucoregulatory genes in the liver. The combination of all these outcomes but to LL leads to obesity and type 2 diabetes mellitus. Fonken et al. described a causal relationship between nighttime light exposure and obesity [58]. They found that mice housed in either bright LL or dim (DM) LAN have significantly increased body mass and reduced glucose tolerance compared with mice in a standard LD cycle, regardless of equivalent caloric intake and total daily activity output. Additionally, the timing of food consumption by DM and LL mice differs from that in LD mice [58]. In this study, it was evident that nocturnal rodents eat substantially more food at night than during the day. Less body mass gain was associated with restricting food consumption to the active phase in DM mice. Thus, it was well documented that LAN caused an important disturbance in the timing of food intake and other metabolic signals, and as a result, weight increased [58].

Among the best-studied examples of endocrine factors that fluctuate over the day are those whose production is governed by the hypothalamic-pituitary axes (**Table 1**), such as cortisol, GH, PRL, thyroid

hormone, and gonadal steroids [59]. Other factors, such as nutrient-sensitive hormones (insulin and adipokines), vary their circulating levels in part in response to the environment/behaviors, such as LD and feeding/fasting cycles, that typically occur in time-of-day-dependent pattern [60].

A combination of influences potentially mediates daily rhythms in the abundance of many endocrine factors. A classic view has often been that fluctuations in nutrients, hemodynamic stresses, body temperature, metabolism, sympathetic and autonomic tone, as well as various autocrine/paracrine factors are mediated by behavioral changes across the sleep/wake and feeding/fasting cycle [60]. In addition, there are extrinsic factors, as many human and animal studies, revealed, that give a significant contribution of an intrinsic timekeeping mechanism towards these oscillations. Gamble KL et al. demonstrated the contribution of sleep to oscillations to several endocrine factors in humans, by enforcing a state of arousal during the night, followed by sleep during the subsequent day. These studies demonstrated that some (e.g., cortisol, TSH), but not all (e.g., GH, PRL), oscillations in endocrine factors occur independently of sleep/wake cycle [60]. This raised the possibility that fluctuations in distinct endocrine factors for the day may be driven, at least in part, by an endogenous mechanism (i.e., independent of behavioral rhythms). Therefore did Carmona et al., when they reported that plasminogen activator inhibitor-1 (PAI-1) has a circadian rhythm in their plasmatic levels and their gene expressions are regulated by circadian system elements too [61].

Turek et al. evidenced that the CLOCK transcription factor is a critical component of the molecular CC within pacemaker neurons of the hypothalamic SCN. Clock mutant mice in this study were hyperphagic and obese and developed hyperleptinemia, hyperlipidemia, and hyperglycemia [44]. These results suggest that the CC gene network plays an essential role in mammalian energy balance [44]. In the study by Akira et al. was evident that HF-fed mice consumed a higher percentage of daily food intake during the rest (light) period. It was remarkable how the change in feeding rhythm in HF-fed mice took place well before the onset of substantial weight gain. This diet attenuates the amplitude of Clock Gene Expression Transcripts of the core CC genes (Clock, Bmal1 and Per2) in the mediobasal hypothalamus, fat, and liver. The 24 hours profiles of leptin, glucose, insulin, FFA (free fat acid), and corticosterone were altered in animals on the HF-diet. In particular, the changes included: 1) increased levels of leptin and glucose during both the light and dark periods; 2) increased insulin and FFA levels during the dark period; 3) decreased amplitude of the corticosterone rhythm. It is noteworthy to mention that each marker displayed changes not only in absolute expression but also in the temporal pattern of expression [56].

Finally, very recently the Mediterranean diet is a healthy nutritional pattern that has been reported to be associated with several metabolic diseases including prediabetes [62], non-alcoholic fatty liver disease [63], inflammatory skin diseases [64,65], and bone health [66]. Mediterranean diet is also considered as a tool to manage obesity in menopause [67,68], improve the immune system [69], affect vitamin D levels in adults [70], endocrine axes [71]. Of interest, Mediterranean diet has also been reported to be associated with better health and quality of sleep [72]. Very recently, in a cross-sectional study including 172 middle-aged adults enrolled in a campaign to prevent obesity called the OPERA (obesity, programs of nutrition, education, research and assessment of the best treatment) Prevention Project [73], we have investigated the association of chronotype categories with adherence to the Mediterranean diet [74] . We have reported that an evening chronotype was associated with a low adherence to the Mediterranean diet and that the chronotype score was negatively and positively associated with BMI and adherence to the Mediterranean diet, respectively. Concluding that in the management of obesity should be taken into account the assessment of chronotype [74].

Meal Composition and Chrononutrition

It has been highlighted that the intake of macronutrients at certain times of the day can influence the states of hunger and satiety, and consequently, body weight. These effects have a significant influence on the circadian oscillations of hormones, involved in their metabolism [43].

Proteins

In particular, the proteins consumed at breakfast (compared to lunch or dinner) lead to a greater initial and prolonged sensation of fullness and increased satiety [43]. It has been observed that high-protein diets, lead to greater reductions in total energy intake, body weight, and fat mass while preserving lean body mass compared to a normal protein diet [75]. The satiating effect of proteins has also been demonstrated by a study involving 13 adolescents with a body mass index ranging between normal and overweight (body mass index-percentile: 50-94° percentile) without metabolic disease and who frequently skipped breakfast (i.e., the absence of food/ calorie drinks before 11:00 am) < 5 *per* week. On separate days, the subjects randomly consumed three different kinds of breakfasts as normal-protein (PN) breakfast, a breakfast rich in protein (PR), and skipped breakfast (BS). After 5 hours, the subjects were provided with an ad libitum buffet lunch, and a food register was completed, which documented all the food/drinks consumed in the remaining 24 hours. The BS breakfast resulted in a higher and more prolonged appetite throughout the trial period compared to PN and PR, while the addition of breakfast with PN and PR led to a 4h reduction in postprandial appetite, compared to BS. As a result, the subsequent ad libitum intake assessed through the 24hours PR and PN food registrations also showed a lower introduction of kcal compared to BS [75]. A possible explanation of the satiating properties of protein at breakfast could involve energy-sensitive gastrointestinal hormones and macronutrients that regulate digestive behavior. Numerous studies reported that the satiating properties of a protein are probably due to the decrease in orexigenic hormones, such as ghrelin and the increase in anorexigenic hormones [76]. Jakubowicz et al. conducted a study in which it was observed that a diet with a breakfast rich in carbohydrates and proteins, reduced the sense of hunger and desire, reduced circulating ghrelin levels, thus avoiding weight recovery and obtaining a better adherence to diet [76]. It has also been shown by consuming protein in the morning, and in the evening, it improves postprandial blood glucose levels. This can be useful for subjects who have an evening chronotype. Therefore, as reported very recently by Davis R et al., eating in the evening *vs* compared to day time is associated with relative hyperglycemia contributing to an increased risk of developing type 2 diabetes

mellitus [77]. Therefore, the evening meal choice can adversely influence of postprandial glycaemia and related insulinemia. In this context, perturbations in glycaemia levels at nighttime are reduced with meals high in protein compared to meals high in carbohydrate [77]. Of interest, the authors concluded that if eating late in the evening it is advisable to eat a meal rich in protein and reduce the carbohydrate content in the meal, this leads to a more favorable postprandial metabolic response [77]. Most clinical studies on the satiating effect of protein, agree on the use of both animal and plant protein, such as whey, and vegetables like soy. For example, a randomized, single-blind study has analyzed that given 20 g of casein, whey, pea protein, egg albumin, as a preload of a meal, significantly increased satiety more than other protein sources [75].

Whey has a high content of essential and branched chain amino acids. It contains bioactive components such as glycomacropeptide (GMP), lactoferrin, and lactoperoxidase. GMP and αlac have a highly satiating effect due to their high content of essential amino acids like leucine, lysine, and tryptophan (TRP) [75]. In particular, TRP is both the precursor of serotonin, which acts as an anorexigenic signal, and precursor of melatonin, which regulates the sleep/wake cycle. Studies have shown that increasing the intake of TRP-rich foods for breakfast combined with daytime light exposure, increases melatonin concentrations, resulting in improved sleep [78].

Of interest, Wada et al., investigated whether a combination of TRP-rich breakfast with protein- and vitamin B6 - rich foods, and light with low color-temperature at night (exposure to incandescent light), could enhance melatonin secretion and encourage earlier sleep time [78]. Ninety-four participants were divided into 3 groups: no intervention; the group with protein-rich and vitamin B6-rich foods and sunlight exposure after breakfast; and last group, the same contents as the previous group and incandescent light exposure at night. The combined intervention on breakfast, morning sunlight, and evening-lighting it was more efficient to keep higher melatonin secretion at night associated to higher quality of sleep [78].

Similar, Fukushige H et al., investigated melatonin secretion and sleep quality after the changed TRP-consumption at breakfast combined with daytime light exposure. They concluded that melatonin secretion was promoted by a tryptophan-rich breakfast and bright light exposure during daytime [78].

However, TRP supplementation must be combined with other foods, rich in vitamin B6 and omega-3, which influence the functioning of the enzymes involved in the anabolic pathway of melatonin [79]. TRP-rich foods, vitamin B12 are meat, poultry, fish, eggs, and milk [80]. While melatonin has been found in many sources of plant origin such as nuts, fruit, seeds, cereals, oils, coffee, wine, and beer [79]. Particularly among fruit cherries,

strawberries, and kiwis have the highest concentrations, while among vegetables, peppers, tomatoes, and mushrooms [79], and finally for cereals, wheat, oats, and barley have respectively 14.9 ng/g, 7.7ng/g and 6.0 ng/g of melatonin [79].

Evidence reported that intake of melatonin rich foods may gain health impact by increasing circulating melatonin [79].

Moreover, recently Oseguera-Castro et al., evaluated the effects of dietary fiber intake (21 days/45 g portion) on the modulation of circadian rhythm in young adults. Cookies made with 3 different types of fibers were consumed: 1) isolated fiber from spent coffee grounds, 2) a combination of spent coffee grounds and fructooligosaccharides, and 3) fiber-free cookies [81]. The cookies with fibers isolated and with fructooligosaccharides decreased the evening chronotypes (p<0.05) improving the quality and length of sleep, enhancing the chronodisruption associated with colonic short chain fatty acid (SCFA) production [81]. Beyond the proper maintenance of gastrointestinal and metabolic functions, evidence reported the role of SCFA in the regulation of food intake and energy expenditure by increasing the host capacity to harvest excess energy from diet [82]. In addition, SCFA can regulate both metabolic and inflammatory pathways, thereby maintaining body energy homeostasis [82].

Carbohydrates

As for carbohydrates, epidemiological studies show that consuming them at the beginning of the day has protective benefits against the development of diabetes and metabolic syndrome [83]. A study showed that carbohydrate intake in the morning can have a long-term protective effect against the development of metabolic syndrome [83]. In this study, data were collected on 1488 patients in 10 years (from 43 to 53 years), replacing 5% of fat with 5% of carbohydrates in breakfast. After 10 years, they were less likely to develop metabolic syndrome, decreased circulating triglycerides, and lower visceral fat [83]. Excessive carbohydrate consumption in the evening leads to an increase in blood sugar following morning. Some studies have assessed whether the glycemic index (GI) of meals, taken at different times of the day, affects insulin levels and postprandial glucose response. A randomized crossover study on healthy subjects, showed that a high GI meal consumed in the evening induces a greater glucose and insulin response compared to morning [84]. The variation in glucose sensitivity, between morning and evening, is due to the circadian variation of insulin, which peaks in the daytime and then decreases its sensitivity in the evening [60]. In humans, glucose metabolism has a circadian

rhythm with a diurnal variation of glucose tolerance that typically peaks during daylight hours. This glucose rhythm is associated with food-intake, the peak of glucose tolerance is associated with food consumption (daylight hours), and it is reduced with fasting in the night-dark hours [85]. Of interest, hormones such as insulin and cortisol involved in glucose metabolism, exhibit circadian oscillation [2]. Thus, sensitivity and insulin secretion are closely regulated by the chronobiological rhythms, with strong effects on glucose metabolism. Factors such as chrononutrition (e.g. meal timing and nutrients), and effects of diet on circadian rhythmicity can contribute to circadian perturbance and they are associated with metabolic disorders, including type 2 diabetes [86].

A HF diet can have important effects on both obesity and chronobiology because the intake of saturated and unsaturated fats affects the circadian cycle differently. However, there could also be the possibility of developing metabolic syndrome, obesity, and insulin resistance [87].

It has also been reported that the amount of carbohydrates consumed at breakfast modulates the responses of glucose, insulin, and FFA in subsequent meal by regulating the CC, the metabolism of glucose and insulin [88]. Individuals who eat a high amount of carbohydrates in the first part of the day have a lower intake of fat and alcohol than those who take less carbohydrates, and are less likely to develop type 2 diabetes [89]. This can be explained by the fact that CR also regulates the physiological processes that influence glucose. During the night, insulin secretion is 50% higher, counterbalanced, however, by an increase in insulin clearance, which therefore translates into a lower sensitivity to insulin at night and consequently a decrease in glucose tolerance [89]. In light of the diurnal changes in carbohydrate metabolism, it is explained why eating a standard meal in the evening produces greater responses of glucose and insulin than the same meal eaten for breakfast [90]. This also explains why evening carbohydrate consumption is often associated with weight gain, obesity, and type 2 diabetes [89].

Maki et al., in a randomized, crossover study included two 4-week dietary interventions, with participants who incorporated into their habitual diets breakfast meals containing either 2 eggs/day for 6 days/week (Egg condition or high protein breakfast (HPB)), and non-egg, higher-CHO-based foods (Non-Egg condition). In their report, they found that compared with the baseline diet, consumption of 12 eggs/week for 4 weeks at breakfast was associated with less reduction in LDL-C, more lowering of systolic blood pressure, and did not adversely affect insulin sensitivity and other aspects of CHO homeostasis, than observed with non-egg-based, energy-matched, control foods higher in CHO [91]. Interestingly, both groups had modest effects on

the cardiometabolic risk profile in adults at risk for type 2 diabetes. Additionally, HPB was directly related to increased daily energy intake from non-study foods but was not associated with increased body weight.

Fatty Acids

Few *in vitro* studies have shown that monounsaturated fatty acids (MUFA) and polyunsaturated fatty acid (PUFA) could lead to epigenetic changes [92]. In particular, the intake of MUFA and PUFA can influence the methylation levels of the cytosine of the CpG islands in the CLOCK promoter, regulating the gene expression of the CC, inhibiting it based on the CLOCK polymorphism. The high intake of MUFA and olive oil are negatively associated with the methylation levels of CpG by CLOCK, while PUFA is positively associated. Therefore, CLOCK CpG methylation levels, together with other genes, could be used as markers for weight loss [92]. Moreover, studies have shown that some CLOCK polymorphisms respond differently when subjected to diet with different types of fat, showing better sensitivity with a MUFA intake of > 13%. While an increase in visceral fat is found with high intakes of saturated fatty acids (SFA) [92]. Likewise, some CLOCK polymorphisms show a more easily alterable CR. An example is CLOCK 3111T/C single nucleotide polymorphism (SNP) (rs1801260). Studies have shown that C carriers display a less altered CR than the corresponding homozygous TT [92].

In a study carried out in Spain, between 2006 and 2011, a self-assessment questionnaire Morningness-Eveningness (MEQ), was administered to patients who underwent bariatric surgery. The study showed that the evening chronotype was associated with greater obesity in severe subjects with obesity and a lower loss of weight after bariatric surgery. Furthermore, circadian preferences interact with CLOCK3111T/C for obesity [93]. Among the genes that could be used as markers for weight, loss is PERILIPIN1 (PLIN1). Triglycerides are stored in adipocytes in the form of lipid droplets. The process of formation of the single layer of these lipid droplets involving different proteins, including the perilipin gene [94]. There are several isoforms of this protein, but the isoform PLIN1 is another example of a circadian gene [94]. PLIN1 is involved in fat metabolism in adipocytes and consequently involved in energy homeostasis and adiposity [94]. PLIN1 also participates in catecholamine stimulated lipolysis through interaction with hormone-sensitive lipase [94]. PLIN1 shows a marked circadian variation in adipose tissue [95]. In this respect, in the ONTIME study, with 1287 overweight and obese patients, who had undergone the genotypization of the PLIN1 SNPs, they evaluated the association between PLIN1 and weight loss. They found that eating late (after 15:00) is related to a lower weight loss

among the carriers of the AA genotype in the PLIN1 114995A/T, compared to those who had lunch (early 15:00).

Genetics and Chronotype

These data further highlight the concept that beyond the time of the day when we take meals, it is also essential to examine which macronutrients we consume in order to improve appetite control, food intake, and consequently, weight control. However, beyond a personal decision regarding the time of the day in which we consume a meal, there is a genetic background that can make us more prone to consume meals at a specific time of the day more than another. Genetically, more than 100 SNP have been reported for obesity. Most of the genes are involved in the modulation of the circadian circuits, as well as in metabolic functions [96]. Evidence to support that food intake times have a genetic component and, therefore, heritable, comes from a study on both monozygotic (MZ) and dizygotic (DZ) twins, with overweight/ obesity, who live separately and away from the family environment. The MZ twins showed higher intra-couple correlations than the DZ twins for breakfast and lunchtime (but not for dinner time) and for waking, bed, and chronotype time [52]. This shows that heredity estimates are higher for meals at the start of the day (breakfast) than later (lunch and dinner) and other specific morning behaviors, such as waking times. On the contrary, the environmental component is mostly determining dinner times and other evening behaviors, such as bedtime. This evidence suggests that the intervention of a nutritionist could be more useful targeting unhealthy lifestyle habits later in the day because being mostly influenced by the environment, it could be modified by the individual [52]. The combination of CR and genetic components could, therefore provide circadian tailored recommendations for each person subjected to weight loss plan [93].

Nutritional Recommendations

In light of the results of the reported studies, we provide practical advices for drawing up a food program based on weight, body mass index and with the help of MEQ, to determine if the patient has an evening or morning chronotype. According to the results of the studies proposed in this article, the timing of nutrients and the macronutrient composition of meals have a crucial role in chronobiology. Consequently, the regularity of meals, nutrient composition, meal frequency, affected obesity, insulin resistance, and metabolic syndrome.

Several studies show that having breakfast can prevent metabolic syndrome and obesity as well as help restore a physiological circadian cycle compared to higher calorie intake in the evening, instead could favor the development of metabolic syndrome [97].

As for the content of macronutrients in meals, proteins have a satiating effect prolonged over time [74]. A high-protein breakfast has shown to increase energy expenditure and fat oxidation in healthy young adults, increase the production of anorexigenic hormones and decrease the production of orexigenic hormones such as ghrelin [75]. Many studies have shown that eating fiber and carbohydrates for breakfast could have a protective effect against the metabolic syndrome, reduction of energy intake from fats during the day, with a reduced prevalence of abdominal obesity [83]. Additionally, by combining fiber and carbohydrates with proteins, they can give a greater sense of satiety in the long term [76].

It has also been documented that the fat consumed can influence the genes involved in the CR through epigenetic modifications. Among the other most popular foods, capable of influencing the circadian cycle, there is caffeine, the most used psychoactive compound in the world, present in many foods and drinks. Caffeine has been shown to be able to influence the phase of gene expression of the CC of peripheral tissue in mice and its use is able to alter the CR after jetlag [98].

High consumption of sodium chloride can also affect the circadian cycle. High consumption of salt for two weeks makes progress alter the circadian cycle in the kidneys, liver, and lung [99]. Besides, the increase in salt also causes an increase in blood sugar because of the Na/K, SGLT co-transporters, and the salt increases the gene expression of GLUT2 and SGLT.

Even a high consumption of starch causes an increase in glucose and circulating insulin, which involves alteration in the liver clock in mice [100].

Alcohol appears to disrupt molecular, endocrine, and behavioral CR in humans and other animals [101].

Another group of compounds capable of influencing CR is polyphenols, including those of tea [102]. It has been shown that these polyphenols improve the metabolic syndrome through mechanisms related to the CC, restoring the genes of the nucleus, alleviating the attenuated diurnal variation, and controlling the clock of genes induced by constant darkness, reversing intolerance to glucose and insulin. This shows that there is an oscillator dependent on tea polyphenol [103].

Therefore, based on the evidence so far produced and analyzed on the modulation of hormonal response and clock genes, it is possible to formulate some practical nutritional recommendations:

- Do not skip breakfast;
- Prefer a balanced breakfast and lunch, composed of carbohydrates, fiber, proteins and the right amount of fat;
- Take an adequate protein intake, especially preferring whey proteins;
- Take most of the daily carbohydrates intake in the first half of the day;
- Reduce calorie intake and especially carbohydrates intake in the evening;
- Eat foods rich in tryptophan as meat, poultry, fish and milk;
- Take foods containing melatonin as fruit (cherries, strawberries and kiwis), vegetables (peppers, tomatoes and mushrooms), nuts, seeds, cereals, oils, coffee, wine and beer;
- Limit fat consumption by preferring PUFA-rich foods such as fish, seeds, and olive and seed oil;
- Consume foods rich in polyphenols such as tea, grapes, red fruits and dark chocolate;
- Avoid coffee, alcohol and HF foods intake.

In addition, **Figure 1** summarize these simple nutritional advices in order to resynchronize the biological rhythms and improve body weight management.

Conclusions

CRs are not only influenced by sleep/wakefulness, but are also controlled by the cycle of satiety/hunger. These cycles can be controlled or regulated, according to the different situations, with an appropriate food plan with specific macronutrients, prescribed at different times of the day. Also, giving importance to the regularity of meals, going to regulate, those cases of alteration of the physiological rhythms that can lead to metabolic disorders. On a typical food day, we recommend having a breakfast because skipping breakfast increases cortisol and loss of muscle mass. Between seven and eight in the morning, cortisol reaches its peak, to prepare the body for typical stress associated with awakening and consequent demand energy, promoting protein catabolism and increasing liver gluconeogenesis. The ideal would be to eat breakfast with complex carbohydrates, fiber, proteins, and a small amount of fat. In the middle of the day that is between 12 and 13, there is an increase in adiponectin produced by adipose tissue, known insulin sensitizer, whose peak is reached in the afternoon. Therefore, it is recommended to consume carbohydrates in the first part of the day, together with proteins that stimulate the release of anorexigenic hormones, inducing a greater sense of satiety, slowing down gastric emptying. Dinner, between 19 and 22, must be the lightest meal of the day. In the evening, there is an increase in the GH, which favors the formation of muscle mass. In the dark, the release of melatonin also increases. Therefore, the ideal would be to consume a protein-based meal that favors the increase of muscle mass and on the one hand, to promote the production of melatonin through intake of the amino acid tryptophan, to promote sleep. In the evening, simple sugars should be avoided, as carbohydrate tolerance decreases in the latter part of the day, due to reduced insulin secretion. Finally, specific foods such as coffee, alcohol, high-fat foods can alter the circadian cycle and sleep/wake rhythms, and therefore these foods should be avoided.

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NOTES

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Abbreviations.

CR (circadian rhythm); CC (circadian clock); CS (circadian system); SNC (suprachiasmatic nucleus); CLOCK (circadian locomotor output cycles kaput); BMAL1 (brain and muscle ANRT-like protein); CRY (cryptochromes); PER (period circadian regulator); REV-ERBα (reverse erythroblastosis virusα); RORα (retinoic acid receptor-releated orphan receptorα); CCGs (clinical commissioning groups); GH (growth hormone); PRL (prolactin); FAA (food anticipatory activity); FEO (food-entrainable oscillator); FOX01 (forkhead box protein01); PPARγ (peroxisome proliferator-activated receptor γ); HF (high fat); GLP-1 (glucagon-like peptide1); AgRP (agouti-related protein); DIO (diet-induced obesity); SREBP (sterol regulatory element-binding protein); nNOS (neuronal nitric oxide

synthase); SGLUT1 (sodium/glucose cotransporter1); GLUT2 (glucose transporter2); PEPT1 (H^+/peptide cotransporter1); LAN (light at light); LL (12-hours light-light); LD (light-dark); DM (dim); FFA (free fat acid); PN (normal protein); PR (rich protein); BS (skipped breakfast); GI (glycemic index); MUFA (monounsaturated fatty acids); PUFA (polyunsaturated fatty acids); SFA (saturated fat acids); SNP (single nucleotide polymorphism); MEQ (questionnaire morningness-eveningness); PLIN1 (perilipina1); GMP (glycomacropeptide); TRP (tryptophan); SCFA (short chain fatty acids); DHA (docosahexaenoic acid); EPA (eiocsapentanoic acid).

Figure.

Title to figure 1: Optimization of meals and macronutrients in relation to hormonal circadian oscillations.

Legend to figure 1: A balanced breakfast and lunch, composed of carbohydrates, fiber, proteins and the right amount of fat helps to lower the peak of cortisol in the morning, regulate post-prandial blood glucose for greater insulin sensitivity, and increase the sense of satiety during day. In the evening, the lightest meal of the day, it is preferable to limit the consumption of sugars for less insulin secretion, and to prefer a protein-based meal, in conjunction with the increase in GH and proteins containing the tryptophan amino acid or melatonin to promote sleep.

Table.

Title to Table 1: Circadian rhythms for Endocrine factors

Legend to figure 1: Source: Adapted from Gamble KL et al. Circadian clock control of endocrine factors. Nat Rev Endocrinol [60].

Hormone	Time of Peak	Functions
Growth Hormone (GH)	Secreted by pulses, increases amplitude at night	Insulin antagonist (decrease glucose utilization, increase lipolysis)
Vasopressin (AVP)	Middle of night	Important element of the neurocircuit from SCN AVP to paraventricular nucleus (PVN) oxytocin (Oxt), which relays light exposure to inhibit feeding behavior
Melatonin	Middle of night	Relay information regarding the environmental light-dark cycle, very sensitive to variations in day length that will trigger endocrine changes. Vasoconstrictor, vasodilator, anticonvulsant, antioxidant
Leptin	01h00	Appetite-regulating hormone
Thyroid stimulating hormone	01h00-02h00	Modulation of thyroid hormone release and growth of the thyroid gland
Prolactin	02h00 (amplitude larger in females)	Multiple roles in reproduction, lactation, and homeostatic roles in the organism
Triiodothyronine	02h30-03h30	Fundamental to maintain normal circulating levels of the thyroid hormones, T_4 and T_3
Ghrelin	02h00-04h30 (fed state) 13h00 (fasted state)	Appetite-regulating hormone
Cortisol	07h00-08h00	Body preparation for stresses associated with waking
Adiponectin	12h00-14h00	Insulin sensitizer. Promotes insulin action
Insulin	17h00	Stimulate glucose utilization and protein synthesis by peripheral tissues. Nutrient

		storage during awake/fed state, and subsequent mobilization during the sleep/fasted period