

Biological rhythms, chronodisruption, and chrono-enhancement: the role of physical activity as synchronizer in correcting steroids circadian rhythm in metabolic dysfunctions and cancer

Physical activity synchronizes the circadian rhythms in health and diseases

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Abstract

Rhythms can be observed at all levels of the biologic integration in humans. The observation that a biological or physiological variable shows a circadian rhythm can be explained by several multifactorial systems including external (exogenous), internal (endogenous), and psychobiological (lifestyle) mechanisms. Our body clock can be synchronized with the environment by external factors, called “synchronizers”, i.e. the light-dark cycle, but it is also negatively influenced by some pathological conditions or factors, called “chronodisruptors”, i.e. aging or low physical activity. The desynchronization of a 24-h rhythm in a chronic manner has been recently defined “chronodisruption” or “circadian disruption”. A very large number of hormonal variables, such as adrenal and gonadal stress steroids, are governed by circadian rhythmicity. Such hormones, in normal conditions, show a peak in the first part of the day while their typical diurnal fluctuations are totally out of sync in subjects affected by cancer or metabolic diseases, such as obesity, diabetes, and metabolic syndrome. In general, it has been observed a flatter slope with altered peaks in cortisol and testosterone circadian rhythms in pathological individuals. Physical activity, specifically chronic exercise, seems to play a key role as synchronizer for the whole circadian system in such pathologies even if specific data on steroids circadian pattern are still sparse and contradictory. Recently, it has been proposed that low-intensity chronic physical activity could be an effective intervention to decrease morning cortisol levels in pathological subjects. The standardization of all confounding factors is needed to reach more clear evidence-based results.

Keywords: circadian Rhythm; synchronizer; physical activity; inflammation; cancer.

Introduction - The importance of physical activity for health and homeostasis maintenance

The main global risks for mortality in the world, regardless of the geographic location and the income group of belonging (high, middle, and low) are: high blood pressure (12.8% of deaths globally), tobacco use (8.7%), high blood glucose (5.8%), physical inactivity (5.5%), and overweight and obesity (4.8%). These risks are responsible for chronic diseases such as heart disease, diabetes and cancers (2009). According to the WHO report of 2009 (2009), physical activity (PA) is associated with a reduced risk of cardiovascular disease, some cancers (e.g., colorectal (Brenner et al., 2017; Eaglehouse et al., 2017), prostate, lung, breast, ovarian, endometrial (Brenner et al., 2017), oesophageal (Castro et al., 2017)), and type 2 diabetes (T2DM). It can also improve musculoskeletal health, control body weight and reduce symptoms of depression. PA occurs across different domains, including work, transport, domestic duties and during leisure. In high-income countries, most activity occurs during leisure time, while in low-income countries most activity occurs during work, chores or transport. Physical inactivity is estimated to cause around 21–25% of breast and colon cancer burden, 27% of T2DM and about 30% of ischaemic heart disease burden (2009). Moreover, physical inactivity directly contributes to the severity of the other mentioned risk factors since it is a determinant for blood pressure (Masala et al., 2017), blood glucose levels (Rosenberg et al., 2005; Zhang et al., 2017), overweight and obesity (Zhang et al., 2017) and the triad of obesity, high caloric intake, and physical inactivity constitutes the second leading cause of cancer in the USA and Europe (Lauby-Secretan et al., 2016). A recent meta-analysis, including 81 perspective studies and randomized trials, investigated the association between T2DM, in terms of relative risk (RR): the results provide strong evidence about an inverse association between PA and T2DM, which may be partly mediated by the reduced adiposity. All subtypes of PA appeared to be beneficial with an optimal length of 5-to-7h per week. Interestingly, T2DM risk reduction was found to be greater at low activity level than high activity levels (Aune et al., 2015).

Positive effects of PA also on immune system, and bone, muscle, and energy metabolisms

through a complex close endocrine interconnection (Lombardi et al., 2016). For example, it is well known that PA is a key stimulus for bone metabolism, hence, reducing fracture risk (which is an independent factor risk for mortality, but also by activating a bone-mediated regulation of the energy metabolism on pancreatic β -cells, skeletal muscle cells, and adipose deposits (Lombardi et al., 2016; Lombardi et al., 2017; Sansoni et al., 2017). At this purpose, we recently published an overview of systematic reviews and meta-analyses in which we support the notion about the positive effects of high-impact and combined (endurance and high impact) exercises on bone health in females along the different life stages (Xu et al., 2016). PA is, thus, a potent modulator of the homeostatic processes underlying the correct integration of the signals coming from all tissues and organs. A practical example is given by interleukin (IL)-6. Considered, for a long time, as a pro-inflammatory mediator (Assier et al., 2010) it has been recently revised a bivalent effector, with either pro- or anti-inflammatory effects depending on the production site (liver or skeletal muscle) and the kinetic of release (constantly high or pulsatile) (Lombardi et al., 2016; Pedersen, 2011; Pedersen et al., 2008).

The impact of exercise on whole-body homeostasis is well described by the changes in circulating factors responsible for energy handling. Adipocytes secrete more than 600 factors (adipokines) that have autocrine/paracrine/endocrine functions (Lehr et al., 2012). Parallel, more than 300 molecules have been identified to be secreted by the skeletal muscle (myokines), some of which shared with the adipose tissue (Hartwig et al., 2014; Pedersen et al., 2003). The great majority of these adipose- and skeletal muscle-derived factors are modified by exercise (Norheim et al., 2011).

As described below, several pathological conditions are associated with a deregulation of the circadian rhythm of hormones and cytokines (Laermans et al., 2016). The establishment of a circadian rhythm represents an evolutionary-acquired tool useful in making an organism adaptable to environmental changes and to conservatively respond to day/night, feed/starvation, warm/cold (Reppert et al., 2002). The coupling between the intrinsic molecular clock and the metabolic

process and, hence, between circadian rhythms and metabolic diseases, has been defined by several studies (Cao et al., 2017; Huang et al., 2011; Laermans et al., 2016). The synthesis and the release of hormones and endocrine factors involved in metabolism are under control of the circadian clock; disorders in this rhythm influence physiological parameters such as blood pressure, as well as endocrine secretion, cell cycle, DNA repair etc. (Gamble et al., 2014). Based on this knowledge, chronotherapies (e.g., environmental and behavioural stimuli triggering the circadian rhythm) has been applied for treatment of several diseases, including cancer, with the aim to optimize the therapy plans (Innominato et al., 2010). In this context, PA represents a formidable stimulus for the re-synchronization of the endocrine system and for recovering the homeostasis.

Therefore, aims of this review article are to: 1) describe what “synchronizers” are and their key role to counteract chronodisruption (CD); 2) to give an overview about the CD occurring in metabolic pathologies and cancer; 2) to describe the current literature on the role of PA in synchronizing altered steroids circadian rhythms, specifically cortisol (C) and testosterone (T).

Chronobiology, biological rhythms, and synchronizers

Chronobiology (the word derives from three Greek terms: “kronos” for time, “bios” for life, and “logos” for study) is the science that objectively quantifies and investigates mechanisms of biologic time structure. Rhythms show different frequencies and they can be observed at all levels of biologic integration: ecosystem, population, group, individual, organ-system, organ, tissue, cell and subcellular structure (Halberg et al., 1977). A rhythm is hence defined as a periodic component of time series with specific quantifiable characteristics: 1) Acrophase (\emptyset): a measure of timing and it indicates the time interval within which the highest values of a biological variable are expected; 2) Amplitude (A): a measure of one half the extent of rhythmic variation in a cycle; 3) MESOR, acronym of Midline Estimating Statistic of Rhythm (M): is the rhythm-determined mean. (Deprins et al., 1977; Koukkari et al., 2006) Time structure characterizes any biologic entity exhibiting one or more of the following frequencies: 1) Ultradian: period < 20h. It relates to rhythms with a frequency higher than circadian; 2) Circadian: period between 20h and 28h. It relates to biologic variations of about 24h cycle length; 3) Infradian: period > 28h. It relates to rhythms with a frequency lower than circadian. Infradian rhythms include circaseptan, circadiseptan, circavigintan, circatrigintan, and circannual rhythms. (Halberg et al., 1977)

The observation that a variable shows a circadian rhythm can be explained by several multifactorial systems at the same time, including external (exogenous), internal (endogenous), and psychobiological (lifestyle) mechanisms (Reilly et al., 2009). Specifically, endogenous factors refers to a complex cooperation of neural, hormonal and cellular systems that interact with each other. The master circadian clock, commonly called also “body clock”, resides within the suprachiasmatic nuclei (SCN) of the anterior hypothalamus (Moore et al., 1972), nonetheless it is now recognized that also autonomous circadian clocks are present in nearly all tissues (Yoo et al., 2004). These peripheral clocks regulate several functions of their residing tissues and they contribute to the homeostasis of living organisms (Ko et al., 2006; Takahashi et al., 2008). Therefore, the real role of the SCN is the synchronization of these peripheral clocks by multiple

neuroendocrine pathways, complex cycles of transcription, translation, protein–protein interaction, phosphorylation, nuclear translocation, and protein degradation (molecular clock), to ensure that they oscillate in an appropriate phase to each other (Kalsbeek et al., 2006; Schibler, 2009; Welsh et al., 2010). The molecular clock is based on the activity of two positive elements, CLOCK and BMAL1: their dimerization activates the rhythmic transcription of Per and Cry genes. PER and CRY proteins dimerize and migrate to the nucleus where they inhibit the CLOCK-BMAL1 dimerization, resulting in the inhibition of Per and Cry transcription. This molecular clock regulates the expression of several clock-controlled genes which are responsible for the rhythmicity of many physiological processes (Dibner et al., 2010).

On the other hand, the SCN is in turn synchronized with the environment by external factors called “zeitgebers” (the German word for ‘time-givers’) or “synchronizers”. The synchronizers could be classified as primary or secondary depending on the extent of their influence on the SCN. The most potent and primary synchronizer for the body clock is, with no doubt, the light–dark cycle. The light gives information to the SCN passing from retinal ganglion cells via a direct pathway, the retinohypothalamic tract (Castel et al., 1993), and, consequently, the central clock is able to synchronize the peripheral clocks by neuro-normal signalling. In addition, other secondary synchronizers are, to a lesser degree, the social routine, physical activity (PA) and food uptake (Mrosovsky et al., 1989). The correct expression of circadian rhythmicity is crucial for the body homeostasis and humans, in general, perform optimally when all biological rhythms are in synchrony (Haus et al., 2006). A circadian disruption results in desynchronization between the cellular oscillators in the SCN and the ones in the peripheral tissues.

Chronodisruption and chronodisruptors

As mentioned before, a very large number of biological and physiological variables in humans are ruled by circadian rhythmicity. For instance, adrenal and gonadal stress steroids, such as C, T, or dehydroepiandrosterone, showing significant effects on metabolism, glucose utilization, adipose tissue, body mass, physical function, and/or performance, are secreted with a specific

circadianicity (Collomp et al., 2014; Edwards et al., 2001). Acrophases of C and T circadian rhythm, in healthy subjects, occur in the morning, specifically with C showing a peak about 30-45 minutes after waking, while the lowest values are registered in the evening (Chung et al., 2011). The desynchronization of a 24-h rhythm in a chronic manner has been recently defined “chronodisruption” or “circadian disruption” (CD) (Erren et al., 2009). CD is considered a new health concern in the 21st century and it can determine a reduction in rhythm amplitude or in phase differences between the SCN and peripheral clocks. Several factors or pathological conditions, called “chronodisruptors” (CDs), strongly influence the diurnal patterns of different hormones resulting in negative health effects (Lac et al., 2006). CDs can be considered both exogenous and endogenous effectors disrupting the timing of physiological functions; the most common CDs include light at night, frequent flying across time zones, jet-lag, social jet-lag, shift works, disturbed eating pattern, low levels of physical exercise, nocturnal training, and also clock gene polymorphisms (Garaulet et al., 2013). The altered circadian rhythm of steroids may lead to several pathological conditions (cancer, obesity, metabolic syndrome) (Garaulet et al., 2010; Pauley, 2004), decrease the metabolic function or accelerate the aging process (Depner et al., 2014; Nedeltcheva et al., 2014). To confirm this, it has been shown that older subjects had a flattened C rhythm, with lower amplitude, higher evening levels and decreased morning acrophase (Ferrari et al., 2001).

Circadian disruption in metabolic pathologies and cancer

In order to limit the subject of this review, here we will considerate obesity, T2DM, metabolic syndrome (MS) and cancer that cover the majority of the main causes of death above mentioned (2009). Epidemiological studies have highlighted a surprisingly strong association between metabolic diseases and an increased risk of multiple types of cancer (Calle et al., 2004a; Calle et al., 2004b; Gallagher et al., 2011). It has been proposed that a molecular mechanism of tumorigenesis in obesity involves secretion of adipokines (leptin, adiponectin, and increased inflammatory cytokines) together with the induction of anabolic pathways (Khandekar et al., 2011). In other terms, obesity leads to a diabetogenic and pro-inflammatory status that favours tumorigenesis in several tissues and cell types (Mazzarella, 2015). CD is a common feature in obesity. In this case, a leading cause is represented by high fat diet (HFD): rats fed by HFD show a disruption of the rhythms of insulin, adiponectin, IL-1, IL-6, tumour necrosis factor (TNF)- α , leptin, ghrelin, and monocyte chemoattractant protein (MCP)-1 (Cano et al., 2009). Similarly, humans assuming 3 high-fat meals during a day shown a deregulation of the rhythms of insulin and leptin. Specifically, while insulin was lowered, diurnal fluctuations of leptin were impaired and this would eventually be the cause for obesity development (Havel et al., 1999). One week HFD in mice, other than increasing the food intake during the normal resting phase (Kohsaka et al., 2007), affected the expression and cycling of clock (Clock, Bmal1, Per2) and clock-related genes in fat and liver (Barnea et al., 2009; 2010). Moreover, HFD-induced obesity affects the cyclical fluctuations in gut microbiome composition leading to dysbiosis (Leone et al., 2015; Zarrinpar et al., 2014). Similarly, there are increasing evidence linking CD with tumorigenesis and tumour progression. This is not surprising since the molecular clock regulates the cell cycle and also affects the repairing response to DNA damages (Sahar et al., 2009). Night-shift, and the number of hours spent working at night (Hansen, 2001; Schernhammer et al., 2001) and possibly, although still debated, the exposure at light during night and the subsequent reduction in melatonin production (Schernhammer et al., 2008; Stevens, 2005; Travis et al., 2004) have been associated with risk of breast cancer in women.

Furthermore, mutations and deregulations of genes involved in the molecular clock are associated with tumorigenesis: CLOCK variants and the methylation status of its promoter have been associated with breast cancer risk, in human (Hoffman et al., 2010); Bmal1 overexpression increases the sensitivity of colorectal cancer to drugs (Zeng et al., 2014); Per2 mutations increase the Ras-mediated expression of the cell cycle gene p21 and cyclin D thus favouring tumorigenesis (Pluquet et al., 2013).

Circadian disruption of steroids in metabolic pathologies and cancer

It is crucial to highlight that CD and pathologies have a reciprocal relationship: pathological conditions, such as obesity or breast cancer, can lead to the desynchronization of the human's circadian system and, vice versa, CD, such as the altered sleep-wake cycle, can promote several pathological conditions (Laermans et al., 2016). In the present paragraph, we will present the altered circadian pattern of adrenal and gonadal stress steroids, especially C and T, in several metabolic diseases: obesity, T2DM, MS, and cancer.

Obesity

In obese mammals a decrease in the amplitude of several clock genes and loss of rhythmicity in the expression of several adipocyte-specific factors, such as adiponectin and resistin (Ando et al., 2005). Two study on humans confirmed this statement: a flatter rhythm with lower amplitude for C has been observed in men and women with higher Body Mass Index (BMI) (Champaneri et al., 2013; Incollingo Rodriguez et al., 2015), nonetheless these findings have not been totally confirmed and they are not fully exhaustive (Incollingo Rodriguez et al., 2015; Steptoe et al., 2004). In addition, obese subjects have a larger acute response of stress-related C with an upregulation of this hormone in the adipose tissue (Incollingo Rodriguez et al., 2015). Other studies reported decreased free testosterone levels in males with visceral obesity while increased levels were observed in obese women (Diaz-Arjonilla et al., 2009; Kaplan et al., 2006; Tchernof et al., 2004). Few studies focused the attention on T circadian pattern and it was just reported that obese subjects had lower amplitude of T rhythm, with lower levels in the morning, compared to healthy

controls (Guimard et al., 2013).

Obesity is also associated with increased risk of cardiovascular disease (Poirier et al., 2006). Blood pressure, heart rate, and cardiac output are controlled by the circadian system. Noteworthy, the major cardiovascular adverse events (e.g., acute myocardial infarction, sudden cardiac death, stroke) show a peak incidence between 6 a.m. and 12 a.m. (Takeda et al., 2011).

T2DM and MS

Lower levels of T in obese male individuals are greater and more frequent with the presence of T2DM (Cap, 2012) while results concerning C levels in diabetic subjects are still controversial. A flatter slope of C circadian rhythm and significantly greater bedtime levels of this hormone were detected in a cohort of 3508 participant with diabetes, both males and females, compared to healthy subjects. A flatter slope in cortisol patterns in diabetics could be partially justified by the higher evening values (Hackett et al., 2014) and to the blunted cortisol awakening response levels reported (Bruehl et al., 2009). In addition, a recent study highlighted that subjects with diabetes, of both genders, had a slower early cortisol decline than individuals without diabetes while no difference were detected in the late cortisol decline (Champaneri et al., 2012). For what concerns adult subjects affected by MS, defined as a cluster of cardiac and metabolic risk factors (Johnson et al., 2006; O'Neill et al., 2015), similar results have been reported. Most studies highlighted the association between metabolic alterations and reduced levels of C in the morning and/or higher diurnal levels of cortisol in middle-aged adults (Kuehl et al., 2015; Lasikiewicz et al., 2008). To confirm this, Vreeburg and colleagues (2009) observed higher overall morning peaks with steeper C circadian rhythm in physically active and working persons compared to subjects with MS and a higher evening C level was associated with older age too (Vreeburg et al., 2009). Other authors reported opposite trends: no positive association has been observed between morning levels of C and any of the cardio-metabolic variables associated with MS (Kajantie et al., 2004); furthermore, the circadian rhythm of this hormone seems to show significantly different characteristics according to the gender of the individuals with MS with women reporting larger variations compared to men

(Bengtsson et al., 2010).

Cancer

Several studies widely demonstrated that a large number of patients with advanced cancer had flattened C circadian rhythm with altered peaks along the days (Collomp et al., 2016; Mormont et al., 1997). The association between C dysregulation and accelerated tumour growth has been reported in patients with breast (Zeitzer et al., 2014), colon (Rich et al., 2005) ovarian (Schrepf et al., 2015), prostate (Bartsch et al., 1994), and lung cancer (Sephton et al., 2013). In a study conducted with women with advanced breast cancer, the flattened C diurnal pattern was also associated with higher levels in the evening and during the night hours (Zeitzer et al., 2014). In addition, fatigued cancer survivors had a significantly flatter cortisol slope with a slower decline in the evening and higher measures of systemic inflammation than non-fatigued survivors (Bower et al., 2005; Lutgendorf et al., 2008). It is therefore crucial to underline that some variables, such as sleep problems and poor social or emotional habits, which are common in cancer patients and that negatively affect their quality of life, are also strongly linked to altered circadian rhythm of C (Rich et al., 2005; Roveda et al., 2017b). Data concerning testosterone are not exhaustive. It has been showed that patients with lower T levels had more aggressive disease and worse prognosis while T circadian rhythm in subjects with prostate cancer had a lower amplitude than age-matched controls (Lissoni et al., 1998; Ribeiro et al., 1997).

Physical activity and the circadian rhythm

PA is part of our evolutionary history: the sustainment of the human being has been indissolubly bound to the physical performances in terms of both resistance and power. Endurance has been a basis for human activities over millions of years, determining the natural selection of the metabolic profiles specifically addressed at satisfying the energetic requirements (Bramble et al., 2004). First of all, the modern human-like body shape, firstly appeared in *Homo erectus*, was associated with the improved walking performance (Wood et al., 1999). Compared to other mammals (e.g. equines, bovines, caprine), even elite human sprinters are comparatively slow and less efficient in energy usage terms. Instead, endurance running (ER, i.e., aerobic long-lasting running) represents a peculiarity for human among primates and non-primates species (Isbell et al., 1998; Taylor et al., 1982). Humans have developed several adaptations to improve long-distance walking performance such as: long legs, large hind-limb and vertebral joint surface, narrow waist with a low, wide and decoupled shoulder girdle, short toes, as well as extensive system of spring in leg and foot maximizing the storage-release cycle of elastic energy during running, hypertrophied gluteus maximum and spinal extensor muscles stabilizing trunk during running, and multiple specializations for shedding excessive body heat (e.g., sweating, hairlessness, cranial cooling systems) (Bramble et al., 2004; Pontzer, 2017; Rolian et al., 2009). The recent (in evolutionary terms) shift towards a sedentary lifestyle is one of the main cause of the exponentially increased prevalence of a wide panel of diseases [e.g., metabolic disorders, type 2 diabetes (T2D), obesity, cardiovascular diseases, cancers, and neurodegenerative disorders] all associated with suboptimal level of PA or inactivity (Sansoni et al., 2017). The effects of exercise on circadian rhythm are several since it serves a nonphotic signal for the circadian clock, hence, PA is often considered a part of chronotherapeutic path accompanying the classical pharmacological treatment (Laermans et al., 2016). For example, according to a series of epidemiological studies, prolonged and regular exercise is associated with better nocturnal sleep and lower daytime tiredness (Van Someren et al., 2007). Time-imposed PA entrains behavioural rhythms in humans (Yamanaka et al., 2014) but also

in rodents (Yamanaka et al., 2013) in which it has also been observed that voluntary wheel running causes a phase-shifting on peripheral clocks (Pendergast et al., 2014; Yasumoto et al., 2015). Furthermore, a recent pilot study demonstrated that PA improved night-eating syndrome (NES) and its related symptoms (e.g., anxiety, depression, perceived stress) a typical circadian rhythm deregulation-related condition (Vander Wal et al., 2015). Schroeder and colleagues first demonstrated that free access to a running wheel improve the power of diurnal rhythms in mice. The timing of the voluntary wheel access, either early (in the first 6 h) or late (in the latter 6 h) of the active phase, altered the normal diurnal rhythms in heart rate and body temperature: late exercise shifted the time of peak heart rate and body temperature to a later time of day (Schroeder et al., 2012).

Physical activity as chrono-enhancer and synchronizer

As previously mentioned, standardized sleep-wake cycle, meals timing, social habits, and physical exercise too are some of the synchronizers for humans' circadian system. Specifically, in this chapter, we will show the role and the acute and chronic effects of PA on circadian steroids secretion, both in athletes and in subjects with pathological conditions.

It is largely known that salivary C increases, as marker of stress, independently of the time of the day and of the kind of sport performed, both during and immediately after an acute session of relative high-intensity physical exercise (Kraemer et al., 1992; Passelergue et al., 1995) and the same C response-to-exercise was observed in obese and diabetic individuals (Baillot et al., 2011). Nevertheless, it is crucial to emphasize that a single acute session of PA is not able to significantly affect steroids circadian rhythm, neither for athletes, healthy subjects, nor for individuals with cardio-metabolic diseases (Labsy et al., 2013). On the contrary, medium-to-long term training, intended as chronic exercise, seems to play a key role as synchronizer for the whole circadian system even if specific data on C diurnal pattern are sparse and contradictory. In tennis athletes, for instance, a blunted C awakening response was observed after 16 weeks of training (Filaire et al., 2013), while, conversely, other authors reported an increase in both morning and midnight values of

this hormone in gymnasts after 7 days of training; for the latter reason, they concluded that chronic strenuous exercise abolished the circadian rhythm of salivary C (Minetto et al., 2008). Moreover, no C circadian variation after 5 weeks of chronic training was detected in elite judo athletes (Georgopoulos et al., 2011) and, with reference to T circadian pattern, most studies reported no difference after time-of-day specific training in athletes (Georgopoulos et al., 2011; Sedliak et al., 2007; Shariat et al., 2015). Due to the lack of clear evidence on the effects of vigorous chronic PA on C and T circadian profile in athletes, further studies seem to be necessary to study if exercise can really exert a significant influence on the diurnal pattern of these hormones.

For what concerns the synchronizing effect of PA on steroids circadian rhythm in pathological conditions, it can be stated that, nowadays, the literature is still scarce. It has been showed, for instance, that moderate chronic PA positively influence sleep behaviour and the activity-wake circadian rhythm in cancer patients (Innominato et al., 2014; Roveda et al., 2017b) while, to the best of our knowledge, few data are available on C and T daily pattern. As mentioned before, subjects with cardio-metabolic diseases or tumour displayed elevated C levels with erratic diurnal fluctuations that lead to a down-regulation of the immune response as a result of stress (Cohen et al., 1991; Spiegel et al., 1998). These modifications could also be attributable to the physical and psychological stress of having the pathology (Mormont et al., 1997). It seems that low-intensity chronic physical exercise could be an effective intervention/treatment to decrease morning C levels. It has been showed that participation in a yoga training program for 6 or 8 weeks determined a decrease in evening C levels, self-reported anxiety, depression, and perceived stress in breast cancer patients (Banasik et al., 2011; Vadiraja et al., 2009). In addition, a study by Matousek et al., highlighted positive effects of a mindfulness-based stress reduction program on C rhythm with a prolonged increase after awakening (Matousek et al., 2011). Nevertheless, the results are contradictory. It was reported that an 8-week yoga program mixed with daily home practice did not affect C levels in individuals with breast and prostate cancer (Carlson et al., 2004). In conclusion, also patients with MS showed a significant decrease in C levels along the day after a 6-month

intervention of low-impact stretching (Corey et al., 2014) while, unfortunately, no study yet evaluated the influence of chronic moderate-intensity PA on T altered rhythm.

Conclusions and perspectives

Alterations of steroids circadian rhythm are determined by a multitude of chronodisruptors, such as light at night, shift works, disturbed eating pattern or meal composition, social jet-lag, fatigue, and depression too (Beccutti et al., 2017; Kabia et al., 2016). The chronodisruption of C and T circadian pattern can be largely observed in many pathologies but the literature is still sparse and contradictory and several future investigations are needed in order to clarify the reciprocal relationship between these circadian alterations and the various cardio-metabolic or endocrine diseases.

Moreover, the scientific literature is trying to understand if chronic PA has to be considered as a strong “zeitgeber” and if it is able to modify and synchronize the circadian system in humans in several conditions, involving trans meridian travels, shift-works, or pathologies; nevertheless, now, this question still remains to be answered (Atkinson et al., 2007). It is crucial, in future longitudinal studies, to control for potential confounding factors, such as competing synchronizers, non-controlled diet, environmental conditions, exercise characteristics (time of day, mode, intensity and duration), and inter-individual variability with the aim to reduce the methodological bias. With reference to the inter-individual variability, it results essential to highlight that the subjects’ chronotype is able to largely influence and affect behavioural, physiological, and bio-psychological characteristics and, consequently, the circadian system in general (Adan et al., 2012; Bonato et al., 2017a; Bonato et al., 2017b; Montaruli et al., 2017; Rossi et al., 2015; Roveda et al., 2017a; Vitale et al., 2013; Vitale et al., 2015; Vitale et al., 2017a; Vitale et al., 2017b; Vitale et al., 2017c; Vitale et al., 2017d). The correct chronobiologic approach to the problem and the standardization of all confounding factors are needed to reach more clear evidence-based results.

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Conflict of interests

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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