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Review on Chronopharmacology and Chronotherapeutics of Statins

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Abstract
Chronopharmacology uses the knowledge of biological rhythms to develop an optimal pharmacotherapeutic plan. A self-evident physiological feature of living organisms is the fact that biological phenomena are not invariable over time, but manifest rhythmicity at the systemic, organ, and cellular level. Circadian rhythms can influence important functions in our bodies, such as Hormone release, Eating habits and digestion and Body temperature. Chronotherapeutics refers to a treatment method in which in vivo drug availability is timed to match rhythms of disease in order to optimize therapeutic outcomes and minimize side effects. The liver clock is largely responsible for buffering the circadian fluctuation of blood glucose and cholesterol in response to an individual's eating habits. The conversion of cholesterol to mevalonate acid by HMGCoA reductase has been known to be circadian clock regulated. Studies found that atorvastatin showed no significant difference in lipid lowering effect between morning and evening administration whereas evening is the preferred time of administration for Simvastatin.

Keywords
Chronopharmacology, HMGCoA reductase

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CHRONOPHARMACOLOGY

Many functions of the human body vary considerably in a day. These variations cause changes both in disease state and in plasma drug concentrations. Chronopharmacology is the science dealing with the optimizations of drug effect and the minimizations of adverse effects by timing medications in relation to biological rhythm Goal is to improve our understanding of periodic and thus predictable changes in both desired effects and tolerance of medication.[1] Chronopharmacology uses the knowledge of biological rhythms to develop an optimal pharmacotherapeutic plan. A self-evident physiological feature of living organisms is the fact that biological phenomena are not invariable over time, but manifest rhythmicity at the systemic, organ, and cellular level. Biological rhythms are self-supporting oscillations of physiological phenomena generated and controlled by endogenic "biological clocks", characterized by repeatability. These rhythms are a manifestation of the adaptative capabilities of the body. They are activated to synchronize biological and behavioral functions with the dynamically changing and predictable conditions of the external environment, which affects the homeostatic status of the body [2–4,5].

Chronopharmacology is useful to solve problems of drugs optimization means to enhance the desired efficiency or to reduce its undesired effects. The chronopharmacologic approach

involves a lesser risk of errors or false information than the conventional homeostatic approach. Many seasonal psychopharmacological drugs are useful in seasonal affective disorders though diazepam has fewer adverse effects and other selected drugs like phenobarbitone, and chlorpromazine also have many adverse effects because of which they are leaving the market even though their pharmacological actions are potent. The need of the hour is to design strategies to ameliorate the side effects which make them more acceptable if the pharmacology and adverse effects of these drugs is

circadian time dependant, it can be modulated by altering the time of administration of drugs. Any dependence of these drugs on the circadian time may provide a clue to ameliorate the major drawback of drugs [6].

Types of rhythms

Ultradian (t<20h)
Circadian (20< t <28h)
Infradian (>28 h)
Circaseptan (t ~7d)
Circamensual (t~30d)
Circannual (t~1 yr)
Seasonal rhythms (such as seasonal affective disorders causing more depression in susceptible individuals in winter) [7]

Circadian Rhythm

An approximately 24-hour cycle of biological procedures in plants and animals. In humans, the circadian "clock" is found in the superchiasmatic nucleus, a cluster of cells sited in a part of the mind called the hypothalamus. The circadian rhythm inspirations asleep, eating, heart rate, blood pressure, body temperature, the levels of firm hormones, and the immune system. Biological clocks are organisms' natural timing devices, regulating the cycle of circadian rhythms. They're composed of specific molecules (proteins) that interact with cells throughout the body. Nearly every tissue and organ contains biological clocks. Researchers have identified similar genes in people, fruit flies, mice, plants, fungi, and several other organisms that make the clocks' molecular components.[8]

A master clock in the brain coordinates all the biological clocks in a living thing, keeping the clocks in sync. In vertebrate animals, including humans, the master clock is a group of about 20,000 nerve cells (neurons) that form a structure called the suprachiasmatic nucleus, or SCN. The SCN is in a part of the brain called the hypothalamus and receives direct input from the eyes.[8]

Beyond the neurotransmitters whose circadian output is directly or indirectly regulated by the SCN, numerous other hormones show diurnal regulation that significantly regulates physiology and pharmacology. Melatonin, a circadian hormone of the pineal gland, influences various aspects of retinal [9] and cardiovascular function [10], as well as affecting local clocks in diverse brain regions [11]. Circadian regulation of the adrenal gland results in diurnal secretion of glucocorticoid hormone, which in turn strongly influences metabolism, and in fact directly regulates 60% of the liver transcriptome [12]. Circadian regulation of gastrin, ghrelin, and somatostatin, as well as direct regulation by autonomous clocks within the gastrointestinal tract, mediate circadian influences upon digestive function [13].

More generally, autonomous circadian clocks not only within the GI tract, but also in numerous other tissues, have considerable influences upon physiology and metabolism. For example, ablation of clocks in pancreatic islets results in diabetes because of defects in coupling of β-cell stimulus to insulin secretion [14], and local clockwork controls expression of multiple ion channels and kinases in heart that influence cardiac function and triglyceride metabolism [15,16]. Recent transcriptome studies have identified widespread local
circadian regulation not only in heart, but also in skeletal muscle and fat, showing that clocks in these tissues directly regulate physiology [17].

A second prominent pharmacological target with strong circadian regulation is the immune system. Diurnal variations in white blood cell count and susceptibility to endotoxic shock have long been documented. However, recent research shows that cell-autonomous clocks within immune cells themselves direct variation in a large number of circadian immune parameters. For example, the response of T-cells to stimulation varies in circadian fashion [18], and macrophages in turn stimulate immune responses in equally diurnal fashion with their own clocks [19]. By contrast, far fewer reports exist of circadian B-cell activity, and indeed the oscillations documented in circadian gene expression in peripheral blood mononuclear cells is much lower in amplitude than that observed in other tissues such as the liver.

The consequences of pervasive circadian regulation of immune function are numerous, and range far beyond the aforementioned diurnal variation in infective susceptibility. For example, a pronounced circadian oscillation of blood clotting has long been known, and is supported by circadian variation in factors ranging from platelet aggregation and adhesion
[20] to actual expression of clotting factors like PAI-1 [21]. Circadian clocks also regulate circulation of many immune cells such as hematopoietic stem cells [22]. Finally, circadian immune regulation results in diurnal variations in related immune parameters like inflammation, which plays a strong role in circadian variation in many diseases [23].

Our body produce and maintain circadian rhythms. For humans, some of the most important genes in this process are the Period and Cryptochrome genes. These genes code for proteins that build up in the cell's nucleus at night and lessen during the day.

Studies in fruit flies suggest that these proteins help activate feelings of wakefulness, alertness, and sleepiness. However, signals from the environment also affect circadian rhythms. For instance, exposure to light at a different time of day can reset when the body turns on Period and Cryptochrome genes.[8]
Circadian rhythms can influence important functions in our bodies, such as:

- Hormone release
- Eating habits and digestion
- Body temperature

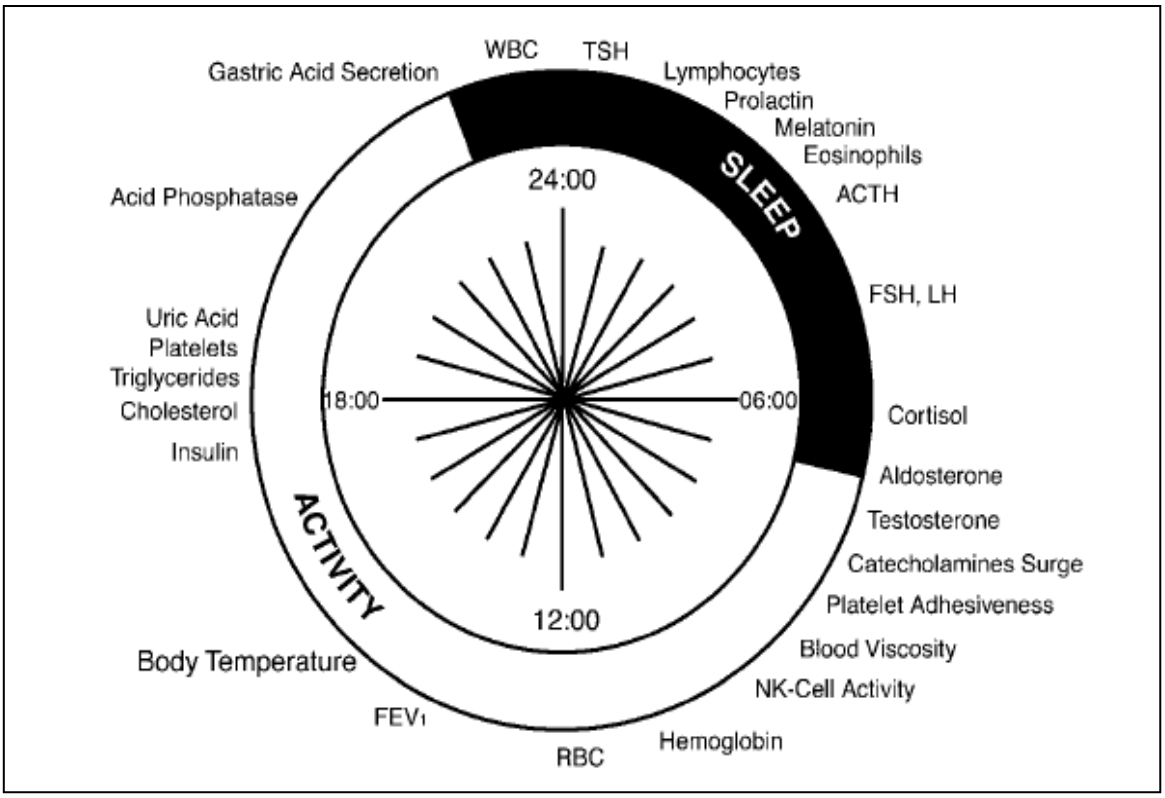
However, most people notice the effect of circadian rhythms on their sleep patterns. The SCN controls the production of melatonin, a hormone that makes you sleepy. It receives information about incoming light from the optic nerves, which relay information from the eyes to the brain.
Changes in our body and environmental factors can cause our circadian rhythms and the natural light-dark cycle to be out of sync.

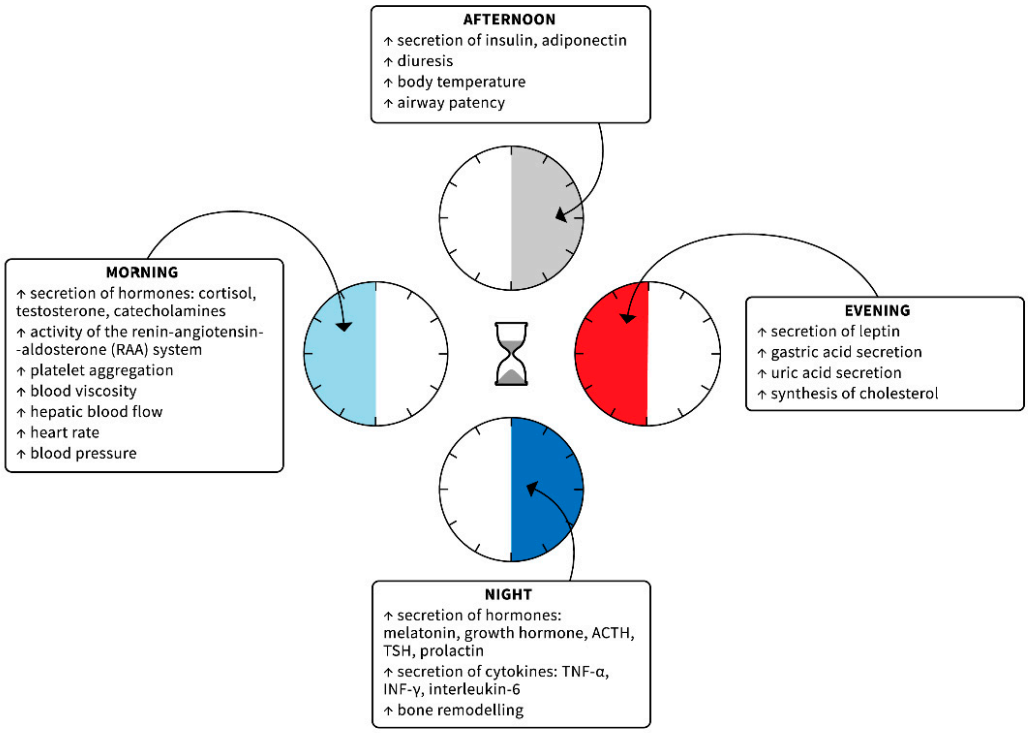
For example:

- Mutations or changes in certain genes can affect our biological clocks.
- Jet lag or shift work causes changes in the light-dark cycle.
- Light from electronic devices at night can confuse our biological clocks.

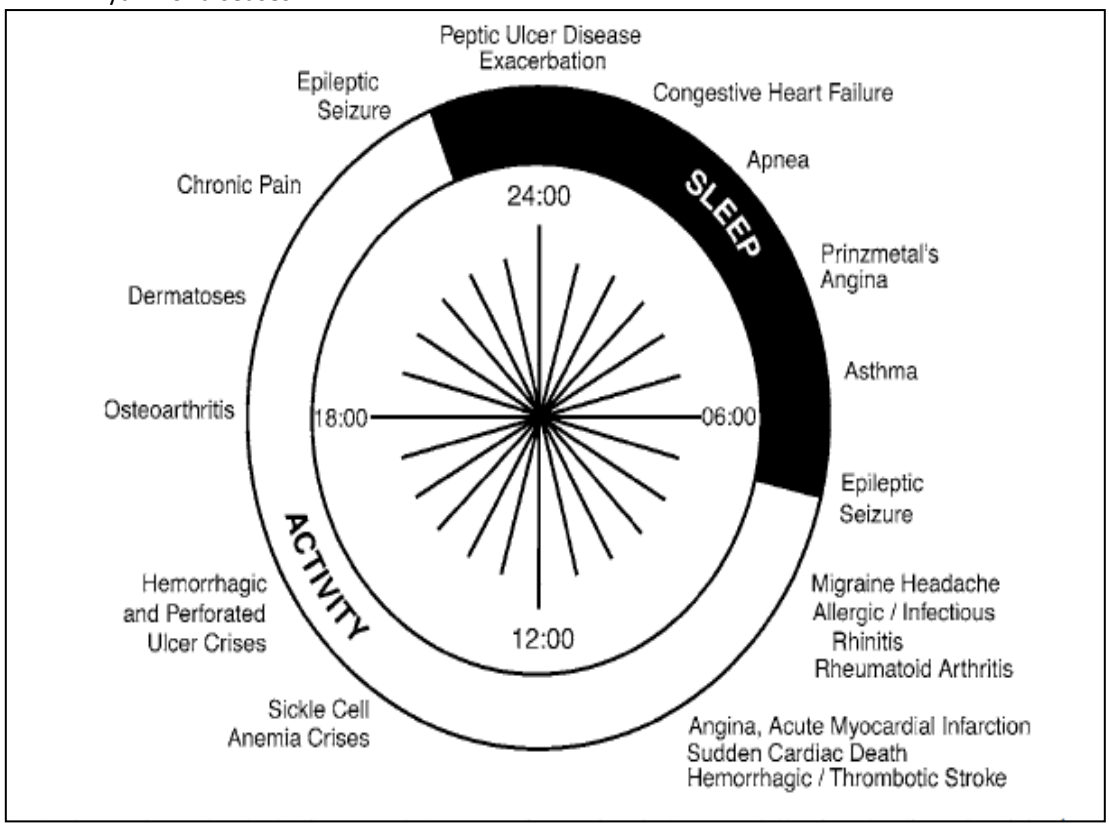
These changes can cause sleep disorders, and may lead to other chronic health conditions, such as obesity, diabetes, depression, bipolar disorder, and seasonal affective disorder. [8]
Some of the more mutual of these illnesses contain "jet lag" syndrome, consisting of certain circumstances called circadian rhythm conditions that can disrupt a person's wake-sleep cycle. Extreme tiredness and lack of day alertness in survey or some who cross time zones, shift-work sleep illness, which occurs in people who work at night modifications or rotating shifts, and delayed sleep-phase.

HUMAN CIRCADIAN STRUCTURE





CIRCADIAN rhythm of diseases



Chronopharmacology further deals with[24]

- Chronotherapeutics
- Chronokinetic
- Chronesthesy
- Chronergy
- Chronotoxicity

Chronotherapeutics: Chronotherapeutics refers to a treatment method in which in vivo drug availability is

timed to match rhythms of disease in order to optimize therapeutic outcomes and minimize side effects. It is based on the observation that there is an interdependent relationship between the peak-to through rhythmic activity in disease symptoms and risk factors, pharmacologic sensitivity, and pharmacokinetics of many drugs takes into account predictable administration time dependent variation in the pharmacokinetics of drugs as well as the susceptibility due to temporal organization of physiochemical process and function of body as circadian and other rhythms [25]. One approach to increase the efficiency of pharmacotherapy is the administration of drugs at times at which they are most effective and best tolerated [26].

Chronopharmacokinetics: It deals with the study of temporary changes in absorption (A), distribution (D), metabolism (M), excretion (E) and thus takes into account the influence of time of administration on these different steps. Temporal changes in drug absorption from GIT occurs due to circadian variations in gastric acid secretion and pH, motility, gastric emptying time, gastrointestinal blood flow, plasma protein binding and drug distribution and drug metabolism (temporal variations in enzyme).

Chronesthesy: It deals with circadian or other systemic changes in the susceptibility and sensitivity of the target system to a drug.

Chronergy: It deals with rhythmic difference in effects of drug on the organism as a whole which includes both desired and undesired effects.

Chrono toxicology: It is an aspect of chromodynamics; it refers specifically to dosing time i.e rhythm – dependent differences in the manifestations and severity of adverse effects and thus intolerance of patients to medication.[27]

Chronopharmacotherapy: - It is an area where the drug administration is synchronized with biological rhythms so as to maximize therapeutic effect. It involves both the investigation of drug effects as a function of biologic timing and the investigation of drug effects upon rhythm characteristics. Circadian changes in the effect of various chemical agents have been documented such as histamine, sodium salicylate, acetylcholine, halothane, prostaglandin F2alpha, reserpine, Cyproheptadine, ethanol, insulin, chlorothiazide, oxymetholone, orcinprenaline, Indomethacin, lignocaine, ACTH, cortisol and various synthetic corticosteroids.

Advantages of Chronopharmacotherapy –

1. It prevents an overdosing of any class of drug.
2. It makes the utilization of the drug more appropriate and thus the value of a drug is increased.
3. It reduces the unnecessary side effects of a drug and helps in caring out the treatment for only a particular or limited period of time.

Need For Chronopharmacotherapy

It is important to monitor therapy so as to limit the duration of therapy especially in cases where patients are already having compromised renal, cardiac and hepatic or any other function of the body. Any type of accumulation of drugs in these organs causes greater toxicity which may led to diminished function of the organ. Thus, the chrononpharmacotherapy becomes a very important part of treatment of several diseases particularly those effecting targeted body parts

Evaluation of chronopharmacology methodology

I. Identification of its occurrence: its cause should be identified so as to know which type of variation is seen. This step also clarifies the point that whether the affect is due to biological clock or not.

II. Determination of the parameter affected: the pharmacokinetic parameters which are affected need to be known. However, more than one parameter may be affected but a need arises to study for all the possible parameters.

III. Mechanism of non-linearity: there are different types of variations because of which non-linearity in pharmacokinetic profile is seen. To implement chronopharmacotherapy it is necessary to first identify the mechanism and then takemeasures to solve it.

Chronotherapeutics of Statin (Hyperlipidemic drug)

Hyperlipidemia is considered one of the major risk factors causing cardiovascular diseases (CVDs).CVDs accounts for one third of total deaths around the world, it is believed that CVDs will turn out to be the main cause of death and disability worldwide by the year 2020.[28,29]

Hyperlipidemia is an increase in one or more of the plasma lipids, including triglycerides, cholesterol, cholesterol esters and phospholipids and or plasma lipoproteins including very low-density lipoprotein and low-density lipoprotein, and reduced high-density lipoprotein levels. [30,31]

Hypercholesterolemia and hypertriglyceridemia are the main cause of atherosclerosis which is strongly related to ischemic heart disease (IHD).[32] There is a strong relation between IHD and the high mortality rate. Furthermore, elevated plasma cholesterol levels cause more than four million deaths in a year.[33]

Statins for the treatment of Hyperlipidaemia

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA)reductaseinhibitors (statins).

This class includes (Lovastatin, Simvastatin, Pravastatin, Fluvastatin, Atorvastatin and

Rosuvastatin). Statins are broadly prescribed in the treatment of hypercholesterolemia, can achieve 20%–50% reductions in cholesterol levels and have been linked to the reduced incidence of coronary morbidity and mortality in high-risk adults.[34]

Mechanism of action

These drugs are structural analogues of HMG-coenzyme A reductase. They act by inhibiting the rate limiting enzyme (HMG-coenzyme A reductase) in the biosynthesis of cholesterol in the liver. By inhibiting this enzyme, statins significantly reduce plasma levels of total cholesterol (TC), LDL and Apo B. Meanwhile, statins also cause a modest decrease in plasma triglycerides and a small increase in plasma level of HDL.[35]

Other HMG-CoA reductase inhibitors include the diallyl disulfide (DADS) and diallyl thiosulfinate. DADS, is an organosulfur compound derived from garlic, has been shown to reduce cholesterol synthesis by 10–25% at low concentrations. Diallylthiosulfinate, a metabolite of allicin, block the formation of 7-dehydrocholesteroland reduced the production of cholesterol. Bis-(3-(4-nitrophenyl) prop-2-ene) disulfide, a new derivatives of diallyldisulfide,is effective in reducing plasma total cholesterol.[36]

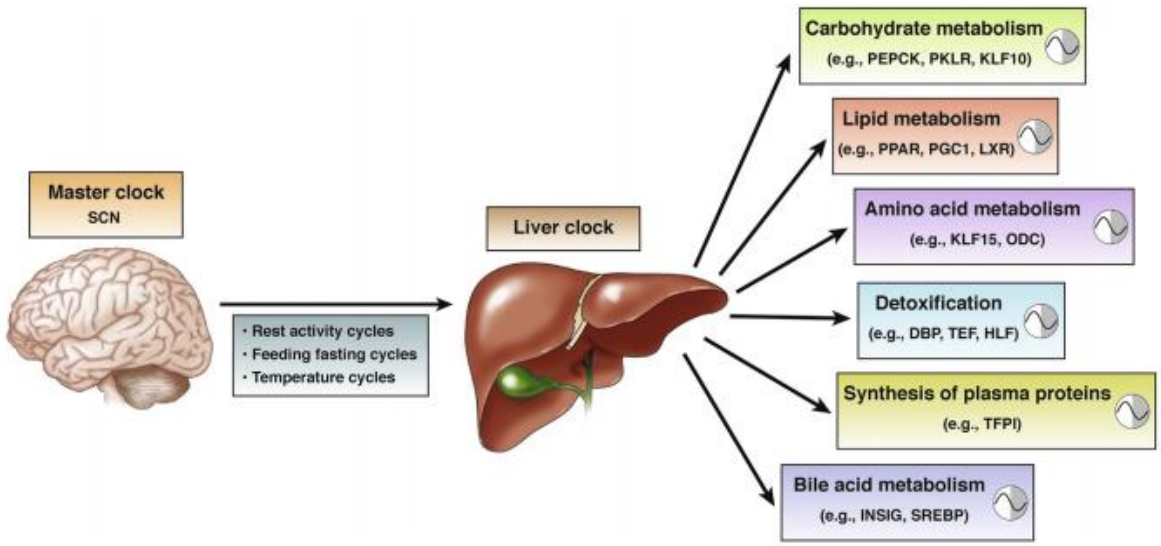
Side effects

Statins are frequently well tolerated with the most common adverse effects being transient gastrointestinal symptoms, headache, myalgia and dizziness. These symptoms are more common with higher doses and may solve if a different statin is used.[37]

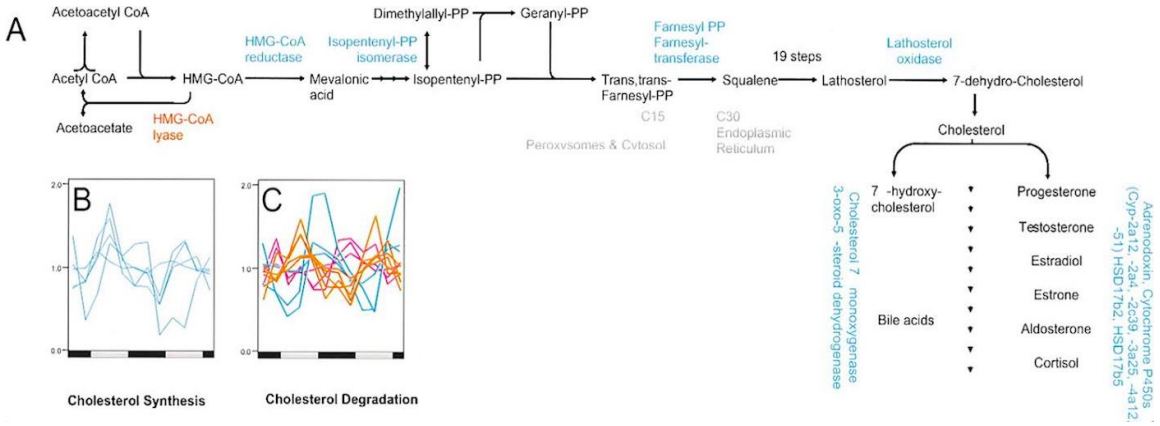
Statins also cause myopathy, rhabdomyolsis and an increase serum transaminase. These substances are harmful to the kidney and often cause kidney damage. Additionally, statins may cause cardiomyopathy [38]. Recent clinical trials showed that statin use has been linked to an increase in type 2 diabetes [39].

Circadian and diurnal variation in lipids in human plasma

The body's circadian clock is regulated by a master pacemaker in the superchiasmatic nucleus (SCN) in the hypothalamus, which receives it's time cues from light exposure through the retina hypothalamic tract. Secondary pacemakers in peripheral organs, such as the liver, get their cues through energy sensing systems like AMPK and metabolic feedback loops, making these clocks extremely responsive to metabolic cues and feeding behaviors. Reinke state that the peripheral clock within the liver can be efficiently entrained by an individual's fast/feed cycle to the point of being completely separate from the master rhythms generated by the SCN. [40]



The liver clock is largely responsible for buffering the circadian fluctuation of blood glucose and cholesterol in response to an individual's eating habits. The conversion of cholesterol to mevalonate acid by HMGCoA reductase has been known to be circadian clock regulated. Panda et al. demonstrated that many key enzymes in the cholesterol pathway exhibit coordinated expression; Enzymes responsible for cholesterol biosynthesis like HMGCoA reductase peak during the night, when dietary cholesterol is low, and enzymes of cholesterol degradation are expressed evenly at different times of the day. [41]



Many genes involved in lipid metabolism are regulated by the circadian clock. Lipids are synthesised and metabolised by enzymes. Hence, a growing number of studies have implemented approaches to conduct large-scale profiling of metabolites (i.e. metabolomics), including targeted analysis of lipids (i.e. lipidomics) [42]. These studies have revealed circadian regulation of different categories of lipids, including fatty acids, glycerolipids, glycerophospholipids, sphingolipids, sterol lipids and prenol lipids [43]. In human subjects, circadian regulation of the metabolome has been assessed in the laboratory using 'constant routine' procedures. Under these conditions, it was found that about 15 % of metabolites (forty-one out of 281) exhibited circadian variation [44]. The greatest proportion of circadian-oscillating metabolites were fatty acids (>75 %), which reached their highest concentrations near midday. In another study that used similar experimental procedures, several metabolites in the steroid hormone metabolism pathway exhibited circadian rhythms [45]. Other studies have revealed strong diurnal variation in acylcarnitines, which play a key role in intracellular fatty acid transport required for β-oxidation, as well as glycerophospholipids (in particular, phosphatidylcholine (PC) species) and sphingolipids [46,47].

One study has used targeted lipidomics approaches to examine the circadian time course of lipids in human plasma [48]. Using constant routine procedures, it was found that 13 % of lipid species examined (thirty-five out of 263 lipid species) showed a circadian rhythm in group-level analyses. Most circadian-oscillating lipids were TAG and diacylglycerols, which increased during the biological night and reached their highest levels near usual wake time. Several plasmalogen PC species were also rhythmic but cycled in antiphase to glycerolipids, reaching their peak levels in the afternoon and evening [49].

Chronotherapy of Statin

A review conducted on nine studies evaluated the chronotherapy of statins (atorvastatin and simvastatin).[50] Five out of nine studies supported the administration time dependency of the lipid lowering effect for statin use [51–55]. In the case of atorvastatin, a prospective randomised trial conducted with 152 people with hyperlipidaemia demonstrated statistically significant reductions in lipid concentrations for evening administration. The patients were randomised to receive their atorvastatin dose (40 mg/day for the first month and 10 mg/day ongoing regimen) either in the morning (Group I, n = 73) or in the evening (Group II, n = 79). Lipid profiles were compared between both the groups at baseline and six months of therapy. After six months, LDL-C concentration decreased by 5 mg/dL, and total cholesterol (TC) concentration decreased by 4 mg/dL in Group II, as compared to Group I (both $p < 0.05$) [51]. However, a study conducted by Plakogiannis et al. found that atorvastatin (40 mg) showed no significant difference in lipid lowering effect between morning and evening administration [56].

For simvastatin, the literature review of seven studies reported a chronotherapeutic benefit with evening administration.[50] A placebo-controlled, double-blind study compared the effectiveness of morning vs. evening administration of simvastatin for two different doses (2.5 and 5 mg) [52]. Hyperlipidaemic patients (n = 172) were randomised into five groups. After 12 weeks of treatment, the percent decrease in LDL-C concentrations when compared to baseline was greater in patients taking simvastatin in the evening than in the morning (_22.2% vs. _15.2% for simvastatin 2.5 mg and _28.5% vs. _19.3% for simvastatin 5 mg). The reduction in LDL-cholesterol concentration for evening administration was statistically significant for the 5 mg dose when compared to morning administration. In another study,Wallance et al. reported a significant increase of 10% in the LDL-C

concentration from baseline (95% CI 0.06–0.44; p = 0.012) in 57 hyperlipidemic patients switching simvastatin from evening to morning administration [53]. Similar results were obtained from other studies on simvastatin, including patients with coronary artery disease [54] and dyslipidaemia [55]. Collectively, these studies indicate that simvastatin has greater LDL-C concentration percentage reduction when taken in the evening. However, a trial comparing morning vs. evening administration for a controlled release (CR) simvastatin demonstrated no statistically significant differences between morning and evening treatment [57]. In fact, recent evidence has highlighted that morning administration of CR simvastatin is equivalent to that of evening administration of immediate-release (IR) simvastatin for lowering LDL-C, TC and TG (triglyceride) concentrations [58]. Similarly, simvastatin in combination with ezetimibe also did not show any significant differences in LDL-C concentration reduction, after morning (46%, p < 0.001 from baseline) or evening administration (48%, p < 0.001 from baseline) [59].

The FDA has approved evening administration for simvastatin. It is based on the rationale of the short half-life (2–3 h) of simvastatin [60]. Atorvastatin, its active metabolite and rosuvastatin all have long half-lives (14, 20 and 30 h, respectively), and the FDA approved "any time" administration for these medicines [60]. Given this definitive direction, the administration time evidence for simvastatin provided explicit advice that "evening" is the preferred time of administration, and that is consistent with the evidence from the reviewed studies for simvastatin.

CONCLUSION:

In conclusion a significant circadian variation has been known to characterize cholesterol and triglycerides, with predictably highest values at the end of the diurnal active hours, and lowest values after awakening [61]. It has thus been suggested that statins should be administered at the right time.

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