ISSN 2349-7203
IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals

Human Journals
Review Article
May 2017 Vol.:9, Issue:2

Chronopharmacology: Recent Advancements in the Treatment of Diabetes Mellitus through Chronotherapy

ISSN 2349-7203
IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals

Sagar Singh Jough*, Shashi Pratap Singh, Yatendra Singh, Dakshina Gupta, Preeti Saxena, Saumya Gupta, Ankit Singh, Akash Srivastva

Advance Institute of Biotech and Paramedical Sciences, Kanpur.

Submission: 5 May 2017
Accepted: 10 May 2017
Published: 25 May 2017

HUMAN JOURNALS
www.ijppr.humanjournals.com

Keywords: Chronopharmacology, Circadian rhythm, Diabetes mellitus, Chronotherapy

ABSTRACT

Chronopharmacology is the study of how the effects of drugs vary with biological timing and endogenous periodicities. The goal is to improve our understanding of periodic and thus predictable (e.g. circadian) changes in both desired effects (Chrono effectiveness) and tolerance (Chrono tolerance) of medications. In the management of diabetes, the target is to maintain the patient in normoglycemia. Chronopharmacological aspects are highly relevant in the management of diabetes mellitus since time of day, patient activities and timing of medication may impact on the risk of occurrence of peaks and troughs in blood glucose levels. It is well known that shift workers have increased diabetes and obesity, worse glucose control, and higher rates of cardiovascular disease and mortality. Endocrinologists and other health professionals who work with diabetic patients have long been aware that blood glucose levels vary with the time of day, even independently of eating habits and insulin use. Many people with diabetes experience what is known as a dawn phenomenon, in which the liver releases large amounts of glucose into the bloodstream just before dawn. The blood sugar can be as much as is contained in two cans of regular soda. This can cause problems for people with diabetes that is difficult to manage. In addition, diabetics are advised not to eat high carb meals late at night, as this often causes higher blood glucose levels than the same foods would cause at other times of the day. The major objective of this study is to know the role of biological clock and Chrono pharmacology to human health and diabetes and to monitor rhythmic markers such as clock variations which may be useful to choose the most appropriate time of day for administration of drug that may increase therapeutic effects and reduce side effects by chronotherapy.

INTRODUCTION

Chronopharmacology is the study of how the effects of drugs vary with biological timing and endogenous periodicities. The goal is to improve our understanding of periodic and thus predictable (e.g. circadian) changes in both desired effects (Chrono effectiveness) and tolerance (Chrono tolerance) of medications.[1] Many functions of the human body vary day by day and these type of variations cause the changes in both in disease state and in normal state.[2] Cardiovascular functions such as heart rate and blood pressure show 24 hours variation. The incidence of cardiovascular diseases such as acute myocardial infarction, strokes and arrhythmia also exhibits clear diurnal oscillation since most of these disorders can induce fatal or severe outcomes. It is the most important to elucidate the precise mechanism of the onset of this disease.[3] The dependence of our body functions in the certain diseased state depends on the circadian rhythm.[2] The science dealing with the phenomenon of biological rhythmicity in living organism is called chronobiology. The branch dealing with the pharmacological aspects of chronobiology is termed as Chronopharmacology which may be subdivided into chronotherapy, chronopharmacokinetics and Chrono toxicity.[3]

In the management of diabetes, the target is to maintain the patient in normoglycemia. Chronopharmacological aspects are highly relevant in the management of diabetes mellitus since time of day, patient activities and timing of medication may impact on the risk of occurrence of peaks and troughs in blood glucose levels. It is well known that shift workers have increased diabetes and obesity, worse glucose control, and higher rates of cardiovascular disease and mortality.[4] Changing the clocks back in spring is associated with increased myocardial infarctions. Supporting these observations are short-term experimental studies showing that misalignment of behavioral and circadian cycles results in adverse cardiometabolic endpoints including higher arterial blood pressure, glucose, insulin, ghrelin, cortisol, and catecholamines.[5] Genetic studies point to molecular mechanisms based on highly conserved controllers of periodicity or Zeitgeber. These molecular clocks are located in the central nervous system and in peripheral tissue, communicating with each other and responding to a great number of inputs presumably designed to maintain homeostasis of the entire organism relative to changing environments.[6-7] In type, I diabetes the circadian rhythms of insulin and its action are of physiological interest and clinical importance. So, insulin is released in pulsatile fashion but sometimes it is irregular. Insulin can show its cyclic rhythmicity of 8-30 min which can show the optimal action. The modulators of insulin release and action are secreted in a circadian pattern and impress the mode of insulin release. So difference between maximum and minimum plasma insulin concentration has short-term rhythmicity and complex secondary circadian rhythm is variable early-morning and late afternoon insulin resistance. [2]

Circadian Rhythm

An approximately 24-hour cycle of biological processes in plants and animals. In humans, the circadian “clock” is found in the suprachiasmatic nucleus, a cluster of cells located in a part of the brain called the hypothalamus. The circadian rhythm influences sleeping, eating, heart rate, blood pressure, body temperature, the levels of certain hormones, and the immune system.[8]

Levels of both insulin and the counterregulatory hormones, which work against the action of insulin, are influenced by a circadian rhythm. The counterregulatory hormones, which include glucagon, epinephrine (also known as adrenaline), growth hormone, and cortisol, raise blood glucose levels when needed. In the middle of the night, there is a surge in the amount of growth hormone the body releases, followed by a surge in cortisol, which increases blood glucose production by the liver. In people who don’t have diabetes, these processes are offset by increased insulin secretion by the pancreas, so blood glucose levels remain relatively stable. However, in people with Type 1 diabetes, whose pancreases don’t make insulin, and in people with Type 2 diabetes, whose livers may not respond to insulin well enough to stop glucose production, changes in blood glucose levels during sleep can have a powerful effect on morning blood glucose levels. Blood glucose levels typically rise between 4 am and 8 am, an event dubbed the “dawn phenomenon.” [8]

Some of the more common of these disorders include “jet lag” syndrome, consisting of certain conditions called circadian rhythm disorders can disrupt a person’s wake-sleep cycle. Excessive sleepiness and lack of daytime alertness in travelers who cross time zones, shift-work sleep disorder, which occurs in people who work night shifts or rotating shifts, and delayed sleep-phase syndrome, in which people fall asleep very late and wake up very late. Research findings suggest that not getting enough sleep or having poor quality of sleep can disrupt blood glucose control in people with diabetes.[9]

Chronopharmacology further deals with[11]

- Chronotherapeutics
- Chronokinetic
- Chronesthesy
- Chronergy
- Chronotoxicity

Chronotherapeutics: Knowledge of day-night and other prediction in time variations in the symptoms intensity and risk of acute exacerbation of disease coupled with evidence of circadian rhythms in the kinetics, effects and safety of medications constitutes the rationale for new pharmacologic approach to treatment. It deals with increase of the efficiency and safety of medications by proportioning their concentrations during the 24 hrs in synchrony with biological rhythm determinants of disease.

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.[12]

Circadian rhythms, insulin action, and glucose homeostasis.

Accumulating evidence supports a role for the circadian clock in the development of metabolic disease. We discuss the influence of the circadian clock on glucose homeostasis, intermediary factors in this relationship, and potential therapies for the prevention or attenuation of metabolic disease associated with circadian misalignment. Murine studies with tissue-specific deletion of core clock genes in key metabolic tissues confirm a mechanistic relationship between the circadian clock and the development of metabolic disease. Circadian misalignment increases insulin resistance and decreases pancreatic function.[13] Clock gene polymorphisms or altered expression of clock genes induced by circadian misalignment appear to play a role in the development of obesity and diabetes in humans. Circadian disruption caused by exposure to light at night is associated with lower nocturnal melatonin, which in turn seems to affect glucose metabolism. Potential therapies for circadian misalignment include entraining the central pacemaker with timed light exposure and/or melatonin and restricting food intake to the biological day.[13-14]

Circadian Clock Controls Sugar Metabolism

Humans' 24-hour circadian clock plays a leading role in glucose tolerance. Researchers in Boston have found that, because of body's circadian rhythm, human glucose tolerance is reduced during the evening hours, even when "day" and "night" times are experimentally reversed.

"In a prior [human] study, we found that when behavior cycles of feeding and sleeping are not in normal alignment with the internal body clock, that this negatively affects the regulation of blood sugar and especially glucose tolerance," said neuroscientist Frank Scheer from the Division of Sleep and Circadian Disorders at the Brigham and Women's Hospital in Boston. People who work night shifts are more prone to type 2 diabetes and obesity, he noted.

In an attempt to understand the independent effects of eating and sleeping behaviors versus the circadian clock on glucose tolerance, Scheer and his colleagues mimicked night-shift work in 14 healthy individuals under controlled laboratory conditions. Participants spent eight days on a typical day-shift schedule, eating breakfast at 8:00 a.m., dinner at 8:00 p.m., and sleeping during the night. Several weeks later, the same individuals had their days reversed: they then ate breakfast at 8:00 p.m., had dinner at 8:00 a.m., and slept during the day.[15]

"We showed that glucose levels after identical meals were 17 percent higher [indicating lower glucose tolerance] in the evening than in the morning, independent of when a participant had slept or had their meals".[15]

Circadian Variation of the Blood Glucose, Plasma Insulin and Human Growth Hormone Levels in Response to an Oral Glucose Load in Normal Subjects

Circadian variations in blood glucose, plasma insulin and human growth hormone response were studied in six healthy males who received 100 gm. oral glucose loads at 6 a.m., noon, 6 p.m., and midnight. The tests were conducted at seven day intervals, and each was preceded by a ten hour fast. During the three days before each test the subjects received meals containing no less than 300 gm. carbohydrate per day. Blood samples were drawn at 0, 15, 30, 60, 90, 120, and 180 minutes. A clear circadian variation occurred in the blood glucose levels, with lower values in the morning and higher values at 6 p.m. and midnight. The insulin profiles showed a trend toward lower afternoon and night values, with a noon peak. The afternoon insulin-glucose ratios were significantly lower. HGH values were inconsistent and tended toward higher afternoon and night basal levels. The results confirm the existence of a circadian variation in the blood glucose response to oral glucose loads in healthy men. This might in turn result from a circadian variation in the insulin response, probably secondary to changes in the pancreatic β cell sensitivity to glucose. This basic mechanism is believed to sustain the conditioning influence of other hormones, HGH being one of them.[16]

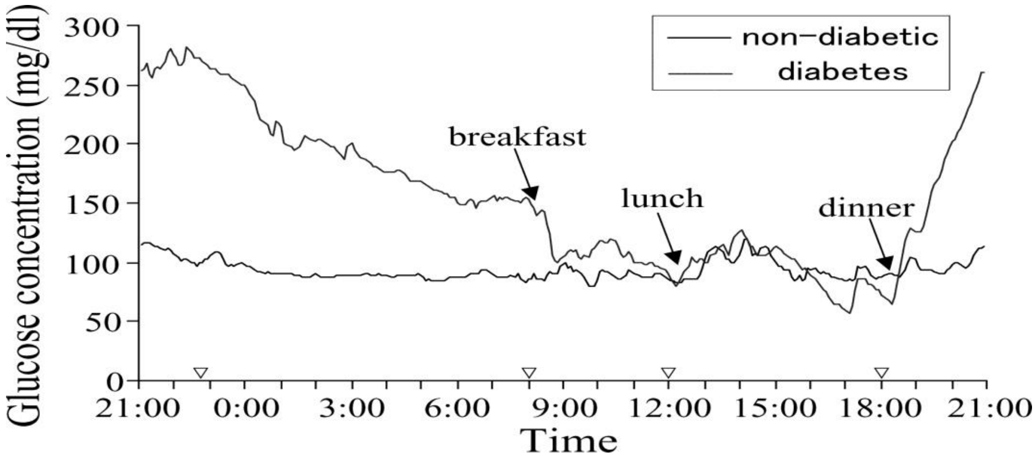

Fig-2 Biological clock shows variation in blood glucose level.[24]

Circadian Clock Controls Insulin and Blood Sugar in Pancreas

A new Northwestern Medicine study has pinpointed thousands of genetic pathways an internal body clock takes to dictate how and when our pancreas must produce insulin and control blood sugar, findings that could eventually lead to new therapies for children and adults with diabetes.

The body's circadian clocks coordinate behaviors like eating and sleeping, as well as physiological activity like metabolism, with the Earth's 24-hour light-dark cycle. There's a master clock in the brain, as well as peripheral clocks located in individual organs. When genetics, environment or behavior disrupt the synchrony of these clocks, metabolic disorders can develop.[17]

Blood Glucose and the Circadian Rhythm

Endocrinologists and other health professionals who work with diabetic patients have long been aware that blood glucose levels vary with the time of day, even independently of eating habits and insulin use. Many people with diabetes experience what is known as a dawn phenomenon, in which the liver releases large amounts of glucose into the bloodstream just before dawn. The blood sugar can be as much as is contained in two cans of regular soda. This can cause problems for people with diabetes that is difficult to manage. In addition, diabetics are advised not to eat high carb meals late at night, as this often causes higher blood glucose levels than the same foods would cause at other times of the day.[15]

Eating, Sleeping and Shift Work

In the study, a group of people lived under laboratory conditions that were rigidly controlled. Their diets and time spent sleeping were kept identical. However, schedules were modified to see their effect on health when all other factors are the same.

For eight days, study participants had a normal daily rhythm with breakfast in the morning, dinner in the evening and sleep at night. This schedule was then reversed for four weeks. The participants ate breakfast in the evening, worked all night, ate dinner in the morning, and slept all day. Blood glucose levels were tracked throughout the experiment, with surprising results. Post-meal blood glucose levels were higher by 17 percent in the evening than in the morning, even after identical meals. This occurred regardless of what shift the study participant's worked.[18]

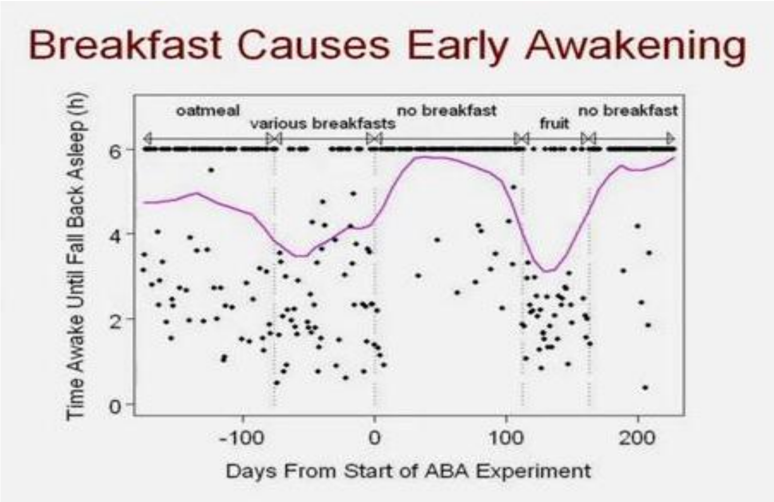

Fig-3 Reason of Why Breakfast Cause Early Awekening[23]

It's Not Just What You Eat, but when this new information offers a possible explanation for the fact that shift workers are more likely to develop diabetes. Breakfasts are higher in carb content than dinners in the Western world; eating this type of meal in the evening can lead to sustained blood sugar fluctuations that eventually cause insulin resistance. When people live lives that are not attuned to the natural rhythm of their endocrine system, blood glucose levels may become unstable enough to contribute to the development of diabetes. This is likely the cause of higher levels of diabetes in shift workers.[18-19]

Recent Advancements in Treatment of Diabetes Mellitus through Chronotherapy

Ideal characteristics of Chronotherapy:

- Non-toxic within approved limits of use.
- Should have a real-time and specific triggering biomarker for a given disease state.
- Should have a feedback control system (e.g. self-regulated an adaptative capability to circadian rhythm and individual patient to differentiate between awake – sleep status).
- Biocompatible and biodegradable, especially for parenteral administration.
- Easy to manufacture at economic cost.
- Easy to administer into patients in order to enhance compliance to dosage regimen.[25]

Advantages of Chronotherapy:

- Chronotherapy is drug-free.

- It is more effective when a person sleeps for several hours.
- While Chronotherapy patients often fall asleep this improves their condition and confidence as well.
- It is different from other treatments because it got the beginning, middle, and an end. So one can predict easily the point at which it will work.
- It gives a new schedule like getting up and sleeping early which will be quite unusual for some days but it will give a period to adjust psychologically.

Disadvantages of Chronotherapy:

- It develops a non 24 hours sleep wake syndrome after the treatment as the person sleeps for over 24 hours during the treatment. It's not quite common but the degree of risk is not known.
- Person may also be deprived of sleep sometimes.

- Person becomes less productive during chronotherapy and staying awake till the other schedule might be bit uncomfortable.

- Person will have to take some time off from your busy normal schedule as its time taking therapy.

- Medical supervision is mandatory for this therapy and regular consulting of sleep specialists is recommended.

- Person has to keep himself awake till the next sleep schedule so he has to get himself busy so that he stay awake till the other schedule.

- Person undergoing therapy may feel unusually hot or cold sometimes.

- Patient needs to consult the doctor regularly to avoid side effects.[26-27]

The Future of a Diet Based on Chronobiology

The challenges of modern life are not going to disappear, but they can be managed to be in better alignment with our circadian rhythm. For example, higher carb meals can be eaten in midday rather than at night and thus have less effect on blood glucose. Shift workers and other people who cannot sleep at normal hours can use light therapy and melatonin supplementation to align their circadian rhythm with the rhythm of their life and eating habits. In fact, medical professionals are already holding research trials to determine whether scheduling food intake at certain times may have immense positive health effects even for people who work a normal day shift.

Our internal clocks clearly are linked to blood glucose levels and the many diseases associated with uncontrolled blood glucose. Modern people will certainly benefit from knowing how they can make simple lifestyle changes to improve their overall health.[20]

Chronotherapy of diabetes

Both insulin secretion by pancreatic cells and insulin sensitivity in the insulin target organs exhibit daily rhythmicity, which may be involved in maintaining homeostasis of glucose metabolism. Because these rhythms are impaired in patients with diabetes, the correction of these abnormalities is necessary for effective treatment.[20]

At present, there are few studies showing chronotherapy of insulin sensitizers (thiazolidinediones and biguanides). On the other hand, several classes of medications which are used for the treatment of impaired insulin secretion, including glinides and rapid- and long-acting insulin analogs, have the merit of chronotherapeutic approach. These medications are useful not only for improving glycemic control but for the risk reduction of prolonged hypoglycemia and body weight gain.

Recently, we showed that circadian clock is impaired in patients with type 2 diabetes. Because the association between clock gene expression and glucose tolerance is also detected in subjects without diabetes, favorable lifestyles (e.g. awake time, bedtime, drinking) to maintain circadian clock function are important for the prevention of type 2 diabetes. However, lifestyles which may affect the biological clock are common. Because it is difficult to alter such a lifestyle in modern societies, a therapeutic agent for the correction of the impaired clock is strongly desired.[20-21]

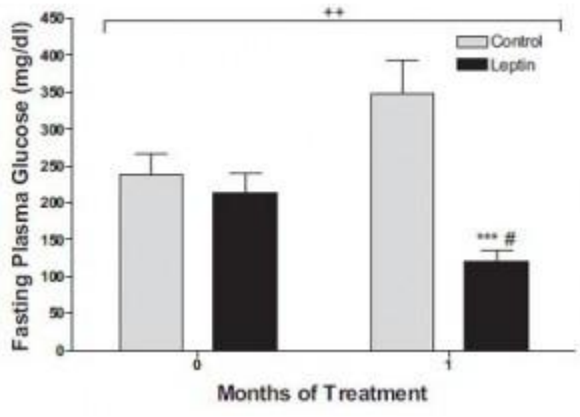

Fig-4 Graph represents the Fasting plasma glucose level according to time.[23]

Effects of aspirin standard therapy and chronotherapy on circadian organization of hemocoagulation in patients with insulin-dependent diabetes mellitus.

24-h profile of hemocoagulation was assessed in 30 patients with insulin-dependent diabetes mellitus type 1 aged 17-37 years. The patients were randomized into 2 groups, 15 patients each.

Patients of group 1 received aspirin by conventional scheme: 125 mg 3 times a day for 16 days. Patients of group 2 received aspirin as preventive chronotherapy: once a day in a dose 125 mg for 16 days two hours before the acrophase of platelet aggregation rhythm--at 22 p.m. Parameters of plasmic and platelet hemostasis in blood samples were measured at 3.00, 7.00, 11.00 a.m., 15.00, 19.00, 23.00. The above chronobiological information was processed by Kosinor-analysis according to F. Halberg. Before the treatment, hypercoagulation with night rise as well as external and internal desynchronism of the hemostasis circadian rhythms were observed. Conventional aspirin treatment improved hemostasis but influenced acrophases minimally. Aspirin chronotherapy promoted normalization of circadian organization of hemocoagulation.[22]

CONCLUSION

The Major objective of this study is to know the role of biological clock and Chrono pharmacology to human health and diabetes and to monitor rhythmic markers such as clock variations which may be useful to choose the most appropriate time of day for administration of drug that may increase therapeutic effects and reduce side effects.

REFRENCES

1. http://www.annualreviews.org/doi/abs/10.1146/annurev.pa.32.040192.000411?journalCode=pharmtox.
2. Maurya K.K, Semwal B.C., Chronopharmacology: A tool for therapy of diseases. International research journal of pharmacy 2012;3-5.
3. Pandit V, Suresh S. Emerging role of biorhythms in optimizing treatment of disease. Indian.J novel drug delivery 2009; 1:2-10.
4. Karlsson B, Knutsson A, Lindahl B, Is there an association between shift work and having a metabolic syndrome? Results from a population based study of 27,485 people. Occup Environ Med 2001;**58**:747–752.
5. Scheer FA, Hilton MF, Adverse metabolic and cardiovascular consequences of circadian misalignment. Proc Natl Acad Sci USA 2009; **106:4453**–4458.
6. Maury E, Ramsey KM, Circadian rhythms and metabolic syndrome: from experimental genetics to human disease. Circ Res 2010;**106**:447–462.
7. Silva CM, Sato S, Margolis RN., No time to lose: workshop on circadian rhythms and metabolic disease. Genes Dev 2010;**24**:1456–1464
8. https://www. diabetes self management.com/diabetes-resources/definitions/circadian-rhythm/
9. Jin X. A molecular mechanism regulating rhythmic output from the suprachiasmatic circadian clock. Cell, 1999; 96:1–20.
10. https://www.google.co.in/webhp?sourceid=chrome-instant&ion=1&espv=2&ie=UTF-8#q=chronopharmacology+and+its+branches.
11. Wal P, Wal A, Rai AK, Saxsena A. Chronopharmaceutics as a novel approach for drug delivery. J Pharma. Sci. & tech, 2009; 1(2): 59-62.
12. NasreenSulthana, Ayesha Sultana, B. Bindu Madhavi., The Clock Which Times Us- Chronobiology, Chronopharmacology And Chronotherapeutics WJJ Volume 4, Issue 12, 400-419 P.

13. Tan E, Scott EM, Frequency of the dawn phenomenon in type 2 diabetes: implications for diabetes therapy. Diabetes Technol Ther, 2002; 4: 595– 605.
14. Portaluppi F, Tiseo R, Smolensky MH, Hermida RC, Ayala DE, Fabbian F. Circadian rhythms and cardiovascular health. Sleep Med Rev, 2012; 16: 151-66.
15. Frank Scheer, MD**,** Félix E Puchulu, MD**,** Huapí 2170, Buenos Aires, Boston. Diabetes 1974 Feb; 23(2): 132-137.
16. Dr. Grant Barish, Mark Perelis, Juvenile Diabetes Research Foundation grants 17-2013-511, 1-INO-2014-178-A-V and 1-INO-2015:23.
17. Carroll MF, Hardy KJ, Burge MR, Schade DS. Frequency of the dawn phenomenon in type 2 diabetes: implications for diabetes therapy. Diabetes Technol Ther, 2002; 4: 595–605.
18. Dr. Wenyu Huang, Chiaki Omura Map of thousands of genes suggests new therapeutic targets for diabetes 2015 Nov;24(3): 36-38.
19. Prajapati B, Solanki H. Recent Techniques for Oral Time Controlled Diabetic Technology. The Internet Journal of Third World Medicine, 2008; 8(1):1-7.
20. Portaluppi F, Tiseo R, Smolensky MH, Hermida RC, Ayala DE, Fabbian F. Recent advancement and cardiovascular health. Sleep Med Rev, 2012; 16: 151-66.
21. Somogyi M. Chronotherapy of diabetes by excess insulin action. Am J Med, 1959; 26: 169–191.
22. Zaslavaskaia Rm *et al.* Controlled release approach to novel multiparticulate drug delivery system. Int J Pharm Pharm Sci, 2012; 4(3):757-763.
23. https://www.google.co.in/search?q=CIRCADIAN+RHYTHM+IN+BLOOD+GLUCOSE&espv=2&source=lnms&tbm=isch&sa=X&ved.
24. https://www.google.co.in/search?q=Circadian+Variation+of+the+Blood+Glucose,+Plasma+Insulin+and+Human+Growth+Hormone+Levels+in+Response+to+an+Oral+Glucose+Load+in+Normal+Subjects&espv=2&site=webhp&source.
25. Srinivas P, Sandeep G, Pridhvi AR and Soujanya Y: Chronotherapy- Clock Of Curing, International Journal of Pharma and Bio Sciences, Vol 2/ Issue 3/ Jul-Sept 2011.
26. Martin RJ, Banks-Schlegel S. Chronobiology of asthma, Am J Respir Crit Care Med. 1998; 158: 1002– 1007.
27. Muller JE, Tofler GH, Stone PH. Circadian variation and triggers of onset of acute cardiovascular disease. Circulation 1989; 79:733–743.