Twenty-Four–Hour Pattern of Hunger Sensation in Obesity Complicated by Type 2 Diabetes Mellitus: A Pattern Recognition by Spectral Analysis

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Hunger sensation (HS) in humans physiologically shows intraday (circadian) and within-day (ultradian) recursivity. This intrinsic periodicity was investigated by applying the cosinor method and spectral analysis to the 24-hour profile of HS (orexigram) derived by a self-rating score (from 1 to 10 hunger units [HU]) recorded every half-hour. The study of circadian and ultradian recursivity on the orexigram was performed in 30 diabetic obese patients ([DOPs], 14 men and 16 women aged 22 to 62 years; body weight, 77 to 130 kg; body mass index, 31-47). The control group consisted of 30 clinically healthy subjects ([CHS], 15 men and 15 women aged 21 to 60 years; body weight, 65 to 72 kg; body mass index, 23 to 25). DOPs showed two types of orexigrams in which hunger was felt with limitation to the diurnal part of the day or with extension to the night, respectively. The type 1 orexigram was characterized by a normal spectrum and circadian rhythm. The type 2 orexigram was characterized by subsidiary ultradian components associated with an abnormal elevation of the circadian mesor and a significant delay of the circadian phase, as the spectral analysis was indicative of a structural difference in the frequencies that sustain the intraday and within-day recursivity of the HS. Accordingly, DOPs can be recognized by their orexigram as "eurectic" or "hyperrectic" to indicate subjects with a normal or an exaggerated HS, respectively, during the 24-hour span.

HUNGER SENSATION (HS) in human beings is a physiological signal that shows a repetitiveness within the day (ultradian recursivity) and every day (circadian recursivity), suggesting a multifrequency regulation of its daily pattern. Accordingly, HS can be investigated by spectral analysis[1] and the cosinor method[2] to identify the frequency components that sustain its daily recursivity.

Spectral analysis is a procedure for which the 24-hour curve of HS (orexigram, orectigram, or hungergram) can be transformed from its temporal domain to its frequency domain, via a spectrum of harmonics (periodogram or spectrogram) fitted according to Fourier's principle. Importantly, the resolved periodogram can be compared with an expected frequency spectrum (reference spectrogram) preventively derived from control subjects (in this circumstance, subjects not suffering from disorders in eating behavior and somatic features) to decipher whether it shows a physiological recursivity over the 24-hour period (pattern recognition). Cosinor analysis, in turn, can be used for validating the orexigram in its circadian rhythm and quantifying the rhythmometric parameters via the waveform profile (cosinorgram) that covers the 24-hour period.

Using both the spectral analysis and cosinor method, daily HS has already been studied by our research group in clinically healthy subjects (CHS) with respect to age, menstrual cycles, and shifts in work.[3] The research was extended to obese patients (OPs), documenting that their daily HS may show three varieties (orectic or orexic chronotypes) in terms of the entity and recursivity.[4-6] These chronotypes were termed "eurectic or eurexic," "hyperrectic or hyperrexic," and "hyporectic or hyporexic," ie, individuals whose HS shows a daily pattern that is compatible with a physiological, an exaggerated, or a diminished signal during the day-night period, respectively.

From clinical experience, HS is magnified by a condition of hyperglycemia not associated with a ketotic status. This clinical observation caused our research group to apply the spectral analysis and cosinor method to the orexigram of OPs who developed a manifest type 2 diabetes mellitus as a consequence of being overweight. The aim was to detect which orectic chronotypes can be found in diabetic (D)OPs.

SUBJECTS AND METHODS

Subjects and Protocol

The study was performed in 30 DOPs (14 men and 16 women aged 22 to 62 years; body weight, 77 to 130 kg; body mass index, 31 to 47). The control group consisted of 30 CHS (15 men and 15 women aged 21 to 60 years; body weight, 65 to 72 kg; body mass index, 23 to 25).

All subjects were asked to subjectively graduate the intensity of their HS every 30 minutes along a scale that varied from 1 to 10, as reported elsewhere.[3-6] The basal score was set at 1 instead of 0, to avoid division by zero in the computerized analysis. Each point of the scale was regarded as a hunger unit (HU). The scale was word-anchored at either extremes ("How hungry do you feel?": not at all hungry = 1 HU; as hungry as I have ever felt = 10 HU). Subjects were requested to plot within-day ratings of their perceived hunger on a bidimensional diagram (chronogram) to construct their orexigram, ie, the 24-hour profile of HS at 30-minute intervals. For the compilation, they were instructed to fill in the diagram during the night only in the case that they were not sleeping. It was assumed that the HS score in sleeping subjects was equal to 1 HU (not at all hungry). The day of recording, they were requested not to change their ordinary life-style, particularly with regard to eating behavior, motor-resting activity, and sleeping-awake alternation. Females were requested to start recording between the first and second week of the menstrual cycle. In this study, diurnal and nocturnal portions of the day-night cycle correspond to the time spans of (6:30 AM to 11:00 PM) and (11:00 PM to 6:30 AM), respectively.

Importantly, DOPs at the time of recruitment all had fasting hyperglycemia (blood glucose, 145 to 165 mg/dL) without glycosuria and ketonuria. Fasting insulin levels were increased, ranging from 40 to 85 μIU/mL.

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Data Analysis

The individual time series of each group were arranged as a matrix in which columns and rows represented sampling times and individual values, respectively. Therefore, each cell of the matrix was occupied by the individual score at that given sampling time. The mean chronogram of the time series of each group was obtained by computing, column by column, the time-qualified mean values of the pertinent matrix.

In a first approach, the mean chronogram of each was analyzed for macroscopic biometry, ie, a daily, diurnal, and nocturnal mean ± SD.

In a second approach, the mean chronogram was analyzed for circadian recursivity by means of the single cosinor method, a regression analysis that can detect the circadian rhythmicity of a given biological chronogram by fitting a 24-hour cosine function.[2] The single cosinor method not only provides the optimal oscillatory curve of the circadian rhythm (cosinorgram), but also quantifies the rhythmometric parameters, ie, the oscillatory level (mesor), oscillatory extent (amplitude), and oscillatory crest (acrophase) as time lag from the local midnight. Both the mesor and amplitude are measured in HU, and the acrophase is given in negative sexagesimal degrees that can be converted into hours and minutes considering that 360 degrees are equal to 24 hours, 15 degrees are equal to 1 hour, and 1 degree is equal to 4 minutes. The rhythmometric parameters are expressed with their dispersion from the central location, ie, the standard error of the mean.

In a third approach, the mean chronogram of each group was further investigated by means of least-squares spectral analysis,[1] a method that resolves each time data series in harmonic components. The method used consists of iterating the periodic regression analysis of the time data series under scrutiny, with periods increasing unitarily from the ultradian (periodicities <20 hours) to the circadian (periodicities of 20 to 28 hours) domain. For this reason, the method is said to be linear in period. As a function of their period (TAU), the amplitudes of all the fitted harmonics constitute the power spectrum of resolution, ie, the periodogram or spectrogram, which is strictly pertinent to that given time data series. Importantly, the least-squares spectral analysis lets us perform a statistical control of the significance of each fitted wave in order to detect those harmonic components that play the role of "formants" for the temporal recursivity of that given time series. The formants are the waves (significant waves) whose oscillatory amplitude (power) is found to be wide enough to reject the null hypothesis of zero amplitude at a P level of .05 or less. The formants are clearly visible on the periodogram as the waves whose amplitude is expressed by a vertical point positioned beyond a transversal line whose level represents the minimal amplitude requested for rejecting the zero-amplitude assumption.

As already mentioned, the spectral analysis can be used for pattern recognition, since the periodogram is thought to be specific in that, by the laws of probability, it is highly statistically unlikely that a different time data series might show a spectrogram constituted by the same configuration of n significant harmonics with that given period, amplitude, and phase. The pattern recognition of the eventual disorders in daily HS recursivity may be obtained by comparing the orectic periodogram under scrutiny with a reference spectrogram provided by normoponderal control subjects in clinical good health not suffering from disorders of eating behavior.

For reasons explained later, the comparison can be statistically validated by applying a χ^2 test between the formants and nonformants that appear in two subdomains of the ultradian components, respectively, with cycles with a period ranging from 2 to 12 hours (11 cycles) and from 13 to 19 hours (seven cycles). According to the reference spectrogram, the first subdomain should be almost lacking in ultradian formants that are eminently relegated to the second subdomain juxtaposed to the circadian components.

RESULTS

CHS

Figure 1 displays the mean chronogram of HS in CHS along with the pertinent mean cosinorgram and mean periodogram.

The mean orexigram shows the presence of three peaks during the day, each grossly corresponding to meal times, and the lack of signal during the night (diurnal orexigram). The mean cosinorgram shows a significant circadian rhythm

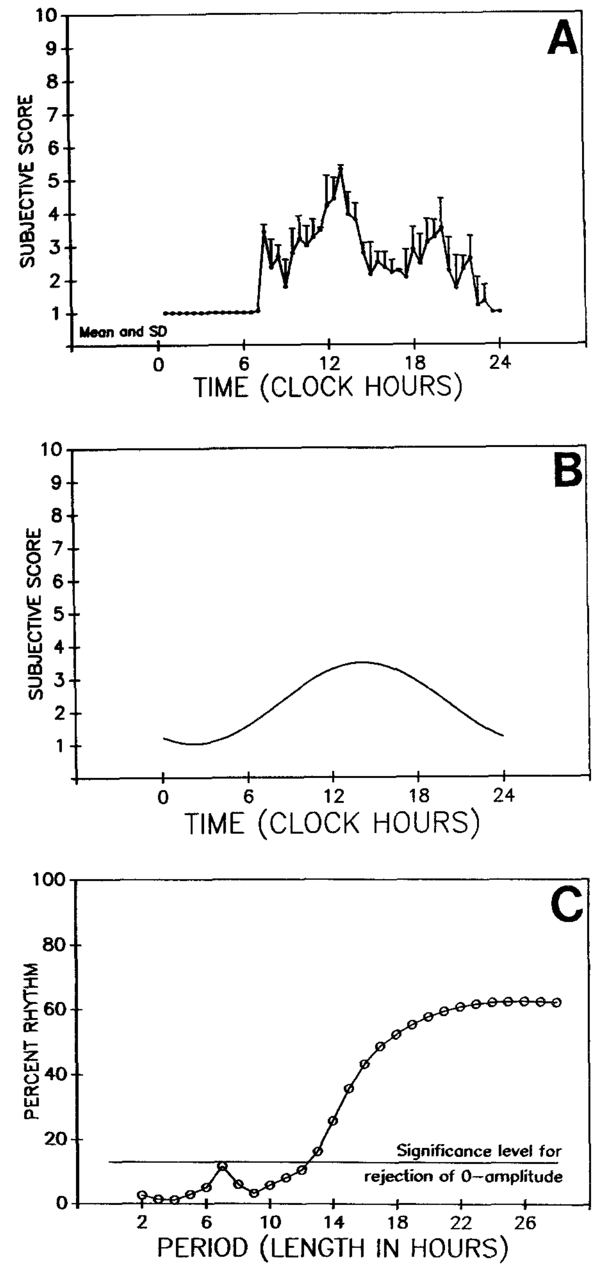

Fig 1. Mean chronogram (A), cosinorgram (B), and periodogram (C) of self-rated HS scoring in normoponderal individuals.

with an oscillatory level of 2.26 ± 0.10 HU and an amplitude of 1.23 ± 0.14 HU, with the acrophase timing at 14:08 ± 0.28. The mean periodogram shows a spectrum of harmonics in which the formants are a few ultradian components plus the totality of the circadian components. Interestingly, the ultradian formants are characterized by a period of oscillation ranging from 13 to 19 hours, thus showing a recruitment in the last part of their frequency domain just before the circadian domain. Accordingly, the ultradian spectrum of a physiological orectic spectrogram can be divided into two subdomains, assuming that any subsidiary, unexpected, unphysiological ultradian formant should unavoidably occur in the first part, the one related to the oscillatory components with a period ranging from 2 to 12 hours. As a consequence, a χ^2 test between the formants and nonformants of the two ultradian subdomains can be used to decipher whether a given spectrogram is compatible with a physiological orexigram. For the reference orectic spectrogram, the χ^2 test of the 2 × 2 contingency table containing the formants/nonformants in the first (0/11) and second (7/0) ultradian subdomain gave a significant result ($P < .001$).

Importantly, the prevalent power of the circadian formants may be regarded as evidence supporting the conception that the repetitiveness of daily HS in humans is principally regulated on a circadian period. Because of this prevalent periodicity, the orectic signal is lacking during the nocturnal hours.

DOPs

Individual orexigrams in DOPs did not show a homogenous profile. The chronogram showed three preprandial peaks in the absence of any signal during the night (diurnal orexigram) in some cases, and exaggerated diurnal peaks associated with a signal during the nocturnal hours (diurnal-nocturnal orexigram) in other cases. These two types of orexigrams were analyzed apart to verify whether they represented specific chronotypes.

DOPs With a Diurnal Orexigram

Figure 2 displays the mean chronogram of HS in DOPs with a diurnal orexigram, along with the pertinent mean cosinorgram and mean periodogram.

The mean chronogram shows a smoothed increase coinciding with breakfast, and two other peaks concomitant with lunch and dinner. The orectic signal is lacking during the night. The mean cosinorgram shows a significant circadian rhythm characterized by a mesor of 2.74 ± 0.12 HU, an oscillatory amplitude of 1.57 ± 0.17 HU, and an acrophase timing at 16:04 ± 00:24. The mean periodogram shows some ultradian formants and a prevalence of circadian harmonic components. A χ^2 test for the 2 × 2 contingency table, arranged with the formants and nonformants in the first (4/7) and second (7/0) ultradian subdomain, gave a significant result ($P = .010$), suggesting that the periodogram in this group of DOPs is in some way comparable to that of CHS. Moreover, the prevalent power of the circadian components demonstrates that the 24-hour

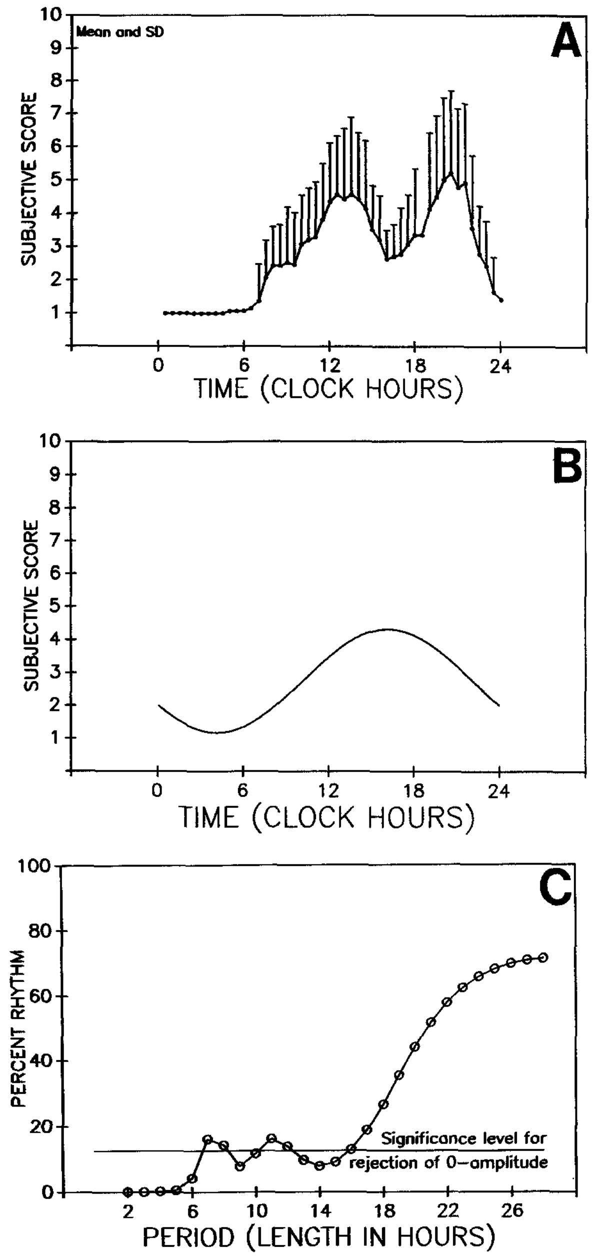

Fig 2. Mean chronogram (A), cosinorgram (B), and periodogram (C) of self-rated HS scoring in eurectic DOPs.

regulation of daily HS is preserved, explaining the lack of an orectic signal during the nocturnal hours in this group.

Because of the within-day peaks that were not exaggerated in number, height, and timing, the normal mesor and amplitude, the unshifted acrophase, and the spectrum not substantially different from that of CHS, the DOPs of this group were considered eurectic individuals.

DOPs With a Diurnal-Nocturnal Orexigram

Figure 3 displays the mean chronogram of HS in DOPs with a diurnal-nocturnal orexigram, along with the pertinent mean cosinorgram and mean periodogram.

The mean chronogram shows a smoothed prebreakfast

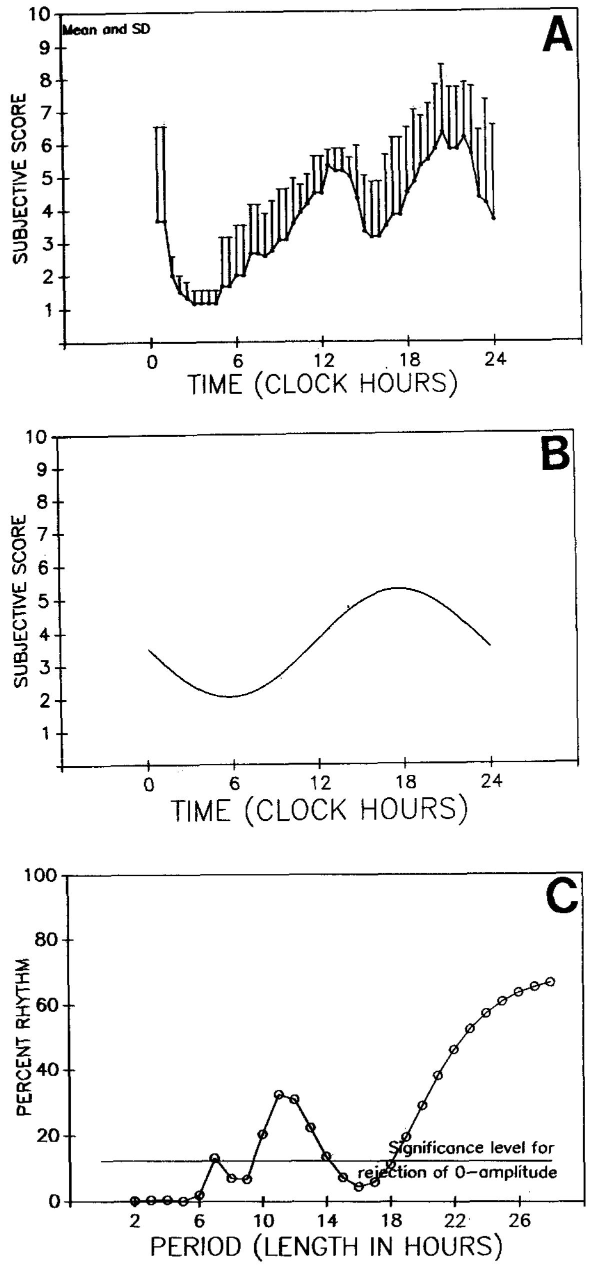

Fig 3. Mean chronogram (A), cosinorgram (B), and periodogram (C) of self-rated HS in hyperrectic DOPs.

increase and two preprandial peaks, the second of which was characterized by a higher increase. The orectic signal is detectable until late in the night (diurnal-nocturnal orexigram). The mean cosinorgram shows a significant circadian rhythm whose mesor is 3.66 ± 0.15 HU, with an amplitude of 1.61 ± 0.20 HU, and an acrophase timing at 17:36 ± 00:28. The mean periodogram shows the presence of wide ultradian formants even in the first part of their domain. The circadian formants, by contrast, appear to be less pronounced in their oscillatory power. A χ^2 test for the 2 × 2 contingency table containing the formants and nonformants in the first (4/7) and second (3/4) ultradian subdomains gave a nonsignificant result ($P > .05$), suggesting that the periodgram in this group is not comparable to that of the reference group. The relative increase in oscillatory power of the ultradian components demonstrates that the circadian regulation of daily HS in this group is no more dominant, explaining the occurrence of the orectic signal during the night.

Given the exaggerated diurnal peaks, the nocturnal prolongation of the orectic signal, the increased daily mean level, the relevant phase shift, and the relative prevalence of the ultradian-sustaining components, the DOPs of this group were regarded as hyperrectic individuals.

DISCUSSION

This study provides evidence that HS shows two different types of daily patterns in OPs who have developed a manifest nonketotic type 2 diabetes mellitus. As a matter of fact, the recorded orexigrams in DOPs documented that HS was perceived only in the daytime in one group, and also at night in another group.

These two types of orexigrams underwent a structural analysis of recursive components by means of the spectral analysis and cosinor method, to establish a pattern recognition along with a validation and quantification of the rhythmic properties.

It must be reemphasized that the spectral pattern recognition allows us to recognize temporal signals, in that the resolution of a time data series in its frequency spectrum is itself exhaustive, the resulting periodogram being specific for the pattern from which it has been derived.[7-12]

The importance of the spectral pattern recognition is well documented in the present study. Its application allowed us to understand that the physiological behavior of the daily HS in humans is mainly regulated by a circadian recursivity that causes the signal not to appear during the night. The identifiers of this daily regulation are clearly visible in the reference orectic spectrogram in which the circadian components are the formants dominating in numbers and oscillatory power.

Looking at the pattern recognition from this angle, one can argue that spectral analysis of the orexigram in DOPs may be used as a concrete tool for understanding whether daily HS shows a physiological structure in its recursive behavior. As a matter of fact, the spectrogram will indicate an unphysiological behavior in a given orexigram in which the ultradian components will be supranumerous and/or the circadian harmonics will show a loss in oscillatory power.

Importantly, such a type of periodogram was detected in the orexigram of DOPs, who recorded their HS in both the diurnal and nocturnal parts of the 24-hour period. This means that the unexpected occurrence of ultradian components along with the relative weakness of the circadian formants may be seen as the identifier of a derangement in HS from its daily physiological recursivity. Such a deviation is further demonstrated by cosinor analysis, the results of which documented a substantial shift to evening hours of the time at which HS reaches the highest circadian oscillation. Additionally, the rhythmometric estimates by cosinor analysis documented another consistent change in the orexigram of DOPs who had HS also at night. The mean level of the circadian oscillation was found to be substantially increased, suggesting that not only the recursivity but also the intensity of HS is exaggerated in these DOPs. Accordingly, it can be said that the orexigram of these DOPs identifies a daily pattern in HS that can be related to the hyperrectic chronotype.

This study documented in DOPs another type of orexigram, in which the pattern recognition was not able to identify abnormal ultradian and circadian domain components. Cosinor analysis, in turn, was not able to document unphysiological properties in HS circadian rhythm. Accordingly, it can be concluded that the orexigram of these DOPs identifies a daily pattern in HS that is compatible with the eurectic chronotype.

The identification of these two orectic chronotypes in DOPs raises a question: Are the differences in daily HS dependent on a configuration of the sleep-wake pattern in eurectic and hyperrectic subjects, or vice versa? It must be stressed that the answer to this question in this context is possible only in theoretical terms. It is true that eating behavior in mammals is strictly linked to the sleep-wake pattern not only on a circadian basis but also on a circannual basis, as demonstrated by lethargic animals. However, this linkage does not necessarily imply that sleeping is the factor that causes the nocturnal phase of anorexia. Assuming a cause-effect interaction would mean that sleeping has to be regarded as the promoter of the circadian rhythm in HS, and indirectly in eating behavior. With respect to this, it must be realized that biological rhythms are endogenous by nature, being regulated by biological clocks that are provided by a proper functional autonomy. There is chronobiological evidence that a nutritional pacemaker is located within the suprachiasmatic nuclei of the anterior hypothalamus.[13-19] As a matter of fact, the irreversible lesion of these nuclei causes the circadian rhythm of food intake to be irremediably lost in experimental animals. On the other hand, subjects suffering from insomnia do not invariably complain of HS during the night. In fatal insomnia syndrome, patients become anorectic. Finally, it is important to reemphasize that spectral analysis is able to detect the intimate structure of any recursive signal. Its resolution spectrum may thus be relevant for affirming whether the recursive signal is modified in its intrinsic properties. Given the intimate changes in the spectrum of daily HS in hyperrectic DOPs, it is disputable as to whether the nocturnal persistence of the orectic signal is a phenomenon that depends secondarily on a primary disorder in the sleeping pattern. Conversely, it seems more reasonable that the nocturnal HS might depend primarily on an intrinsic derangement of its repetitive structure. Mutatis mutandis, it is more likely that the changes in the sleeping pattern of hyperrectic DOPs might be secondary to the disturbance in HS.

As mentioned at the outset, the aim of this study was to decipher whether glucose intolerance can exert stimulatory effects on HS in OPs who develop a type 2 diabetes mellitus. To answer this question, it is important to take into account previous studies by our group in nondiabetic OPs,[4-6] in which the spectral analysis and cosinor method demonstrated three different types of orexigrams. The first two orexigrams and their analysis were perfectly superimposable on those detected in this study. Interestingly, the third one was characterized by a low orectic signal with intermittent peaks, a low mesor, and the exclusive presence of ultradian components within the first part of their spectral domain. OPs showing an orexigram with these chronobiometric characteristics were classified as hyporectic individuals.

Importantly, the third type of orexigram was not observed in this study. The lack of hyporectic DOPs is indirect evidence that nonketotic hyperglycemia may exert a stimulatory effect on mechanisms involved in the regulation of the within-day and intraday recursivity of HS in humans. However, the coexistence of eurectic and hyperrectic individuals suggests that the glycemic interference with the nutritional pacemaker in some way influenced by other intercurrent factors, which should be identified by more detailed investigation into the metabolic disorders that characterize obesity complicated by type 2 diabetes mellitus.

APPENDIX

The following is a glossary of the methodological and technical terms used in the article:

CHRONOBIOMETRIC PROCEDURES: Methods of statistical-mathematical analysis applied to temporal series of biological data to objectively detect, statistically validate, and biometrically estimate the occurrence and the pertaining properties of cycling patterns.

CHRONOGRAM: A bidimensional plane graph with values reported on the ordinate as a function of time expressed on the abscissa.

COSINOR METHOD: A method of periodic regression analysis developed by Halberg et al,[1] which is used worldwide for statistically validating and biometrically estimating biorhythmic events whose period is "a priori" known. It consists of best-fitting a cosine function to experimental time data series by minimizing the sum of residuals by the least-squares method.

COSINOGRAM: The optimal waveform profile fitted to experimental time data series by means of the cosinor method.

EURECTIC (or eurexic) SUBJECTS: The term "eurectic or eurexic" derives from the combination of two Greek roots, "eu," which means "normal," and "orexis," which means "hunger." A eurectic is thus the subject who is characterized by a normal HS during the day-night period.

FORMANTS: The harmonic components whose oscillatory amplitude (power) has been validated as statistically significant in the spectrum of periodicities detected in a time data series by means of the chronobiometric procedures (least-squares spectral analysis). Because of their significant power, the formants are the waves with a role of constituents in the construction of the wave resulting from the sinusoidal sum of all the significant cyclic components. The resultant wave returned by the formants represents the periodic trend of the time data series as it is expressed by its significant spectrum of resolution.

HARMONIC COMPONENTS: The cycles of a given period that can be found in a time series of biological data by adopting the chronobiometric procedures for detecting and validating bioperiodicities.
HUNGERGRAM: see OREXIGRAM.
HUNGER UNIT: A self-rated measure corresponding to 1 cm of 10 cm in a visual analog scale anchored between the extremes 1 and 10.
HYPERRECTIC (or hyperrexic) SUBJECTS: The term "hyperrectic or hyperrexic" derives from the combination of two Greek roots, "hyper," which means "increased," and "orexis," which means "hunger." A hyperrectic is thus the subject who is characterized by an exaggerated HS during the day-night period.
HYPORECTIC OBESITY: The term "hyporectic" derives from the combination of two Greek roots, "hypo," which means "reduced," and "orexis," which means "hunger." A hyporectic is thus the subject who is characterized by a reduced HS during the day-night period.
OREXIGRAM: A bidimensional plane graph with self-rated scores of HS recorded at regular intervals on the ordinate as a function of the 24-hour period expressed on the abscissa.
ULTRADIAN COMPONENTS: Cyclicities with a period less than 20 hours that can be found in a time data series by applying chronobiometric procedures for detecting and validating periodic recursivities in biological events.

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