

Daily rhythms in hormonal markers of diabetes and obesity: effect of weight and Type 2 diabetes

Cheryl Isherwood, Daniella T. Otway, Simone Mäntele, Benita Middleton, John Wright, M. Denise Robertson, Debra J. Skene, Michelle Gibbs and Jonathan D. Johnston
Faculty of Health and Medical Sciences, University of Surrey, Guildford, GU2 7XH, UK

Concentrations of some circulating hormones associated with energy metabolism and homeostasis are under the influence of the 24 hour circadian timing system, controlled by the central oscillator in the suprachiasmatic nuclei (SCN) of the hypothalamus and peripheral clocks, including those in endocrine organs along the alimentary canal and in adipose tissue. Circulating concentrations of these hormones are also influenced by feeding, weight and type 2 diabetes mellitus (T2DM). To date, however, 24-hour rhythmicity has only been investigated for a small number of relevant hormones.

The aim of this study was to investigate the effect of weight and T2DM on the concentration and rhythmicity of these hormones across a 24 h day under highly controlled laboratory conditions.

Men aged between 45–65 years were recruited into lean ($n = 8$), overweight (OW) ($n = 10$) or OW with T2DM ($n = 7$) groups⁽¹⁾. They followed a strict sleep-wake and diet regime for 1 week before the laboratory session. During the laboratory session, they were kept in a controlled light-dark environment, remained semi-recumbent throughout and received identical hourly Fortisip meal replacement milkshakes calculated at 1.5 times BMR from 15:30 h on day 1 to 06:30 h on day 3 during waking hours (06:30 h – 22:30 h). Hourly blood samples were taken from 07:00 h on day 2 until 07:00 h on day 3, collected in di-potassium EDTA-coated tubes. Plasma C-peptide, insulin, ghrelin, leptin, GIP, GLP-1, glucagon, PAI-1, resistin and visfatin were measured using the Bio-Plex Pro™ Diabetes Assay. The table below compares average hormone concentrations across the 24-hour period in the 3 groups.

	Lean		OW		T2DM		P value		
	mean pg/ml	SEM	mean pg/ml	SEM	mean pg/ml	SEM	lean: OW	lean: T2DM	OW: T2DM
C-peptide	1319	204	1624	81	1811	118	0.004	<0.001	
Insulin	491	58	1122	105	1487	214	<0.001	<0.001	<0.001
Ghrelin	1087	159	1316	110	1107	71	<0.001		<0.001
Leptin	1433	286	8533	1602	7871	1730	<0.001	<0.001	
GIP	709	94	1044	120	1295	410	0.023	<0.001	
GLP-1	223	46	338	31	362	32	<0.001	<0.001	
glucagon	269	16	450	14	437	27	<0.001	<0.001	
PAI-1	5064	556	8671	772	5571	351	<0.001		<0.001
Resistin	3104	263	3697	302	3859	477		0.016	
visfatin	7669	1184	7408	1004	26360	15139		<0.001	<0.001

P value shows the significant difference between groups (one way ANOVA followed by post hoc Tukey HSD)

To determine daily rhythmicity, each data point was expressed as a percentage of the 24-h mean for each analyte. Cosinor analysis was then performed on the grouped data to assess the fit of a cosine curve. The results indicated significant ($p < 0.05$) rhythmicity for C-peptide, insulin, ghrelin, leptin, GIP and GLP-1 in one or more groups, with C-peptide, insulin and leptin showing a diurnal rhythm in all 3 groups. Ghrelin displayed a clear diurnal rhythm in the lean group but not in OW and T2DM. As expected, concentrations of C-peptide, insulin, leptin, GIP, GLP-1, glucagon, were significantly increased in the OW and T2DM groups (see table).

In conclusion, our data show plasma concentrations were significantly different in the OW and T2DM groups compared with the lean group in 6 of the 10 analytes. Some analytes (6 of the 10) exhibited daily rhythmicity in one or more of the groups.

This work was funded by Diabetes-UK (grant 08/0003607), EU FP7-HEALTH-2011 EuRhythDia (grant 278397), BBSRC (grant BB/I019405/1), BBSRC (grant BB/D526853/1) and Stockgrand Ltd.

1. Mäntele S, Otway DT, Middleton B, *et al.* (2012) PLoS ONE 7(5): e3.