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Probing the diurnal regulation of glycaemic control

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Diurnal variation in human glycaemic control was reported by several authors in the 1960s. The classic study carried out by Jarrett and Keen giving oral glucose in the morning and evening established that increased glucose intolerance and insulin resistance occurs later in the day (Jarrett & Keen, 1969), a phenomenon often referred to as "afternoon diabetes". However, despite our long-standing knowledge of this phenomenon, its underlying mechanisms are still not well understood.

The cause of diurnal variation in glycaemic control is likely to be multi-factorial. Tissue-specific disruption of mouse circadian rhythms has identified major roles of peripheral clocks in glucose homeostasis (Lamia et al., 2008; Marcheva et al., 2010; Dyar et al., 2014). The clock in the murine adrenal cortex is also likely to contribute to glucose regulation by gating glucocorticoid production in response to ACTH (Oster et al., 2006). Precise temporal control of behavioural rhythms has revealed that endogenous circadian time is also a powerful determinant of glycaemic response in humans (e.g. Morgan et al., 1998; Scheer et al., 2009; Leproult et al., 2014). It is well established that human diurnal rhythms of glucose tolerance are influenced by number of factors including sleep, hormones such as cortisol, prior meal composition, lipid clearance (reviewed in Van Cauter et al., 1997; Morgan et al., 2003) and possibly fatty acid metabolism (Yoshino et al., 2014). Additional contributory mechanisms are likely to include the daily variation of incretin hormones secreted from the gastrointestinal tract (e.g. Elliott et al., 1993).

This issue of the *Journal of Diabetes and its Complications* contains a paper that further investigates mechanisms of diurnal glycaemic control in human prediabetes (Sonnier et al., 2014). Volunteers were subjected to two oral glucose tolerance tests (OGTT) in a single day, twelve hours apart. The first occurred at 07:00 following a 10-hour overnight fast and the second was administered at 19:00 after an 8-hour fasting period during the day. In addition to monitoring glucose, the investigators measured concentrations of additional endocrine and metabolic factors in the fasting samples at the

start of each OGTT. Consistent with the literature, the authors found reduced glucose tolerance, insulin sensitivity and OGTT-stimulated insulin concentration in the evening. However the main strength of the paper lies in the analysis of putative mechanisms driving diurnal changes of glucose tolerance. In brief, it appears that the amplitude of the diurnal cortisol rhythm, which peaks in the morning and declines during the day, may be a major contributor to temporal glycaemic control. Specifically, individuals with a smaller evening decline in serum cortisol had a greater decline in glucose tolerance. The authors therefore propose that increased understanding of the cortisol circadian rhythm and its abnormalities may have important consequences for the glycaemic control across the day, but this putative mechanism requires further elucidation.

As with any study, the work presented by Sonnier et al has some limitations. From a circadian viewpoint, it is impossible to measure the exact phase and amplitude of rhythmic parameters when they are assessed at only two time points during the day. Compounding this problem is the lack of circadian synchronisation of subjects prior to entering the laboratory. The pulsatile, ultradian nature of cortisol secretion is also likely to cause variation in the data that could obscure interpretation, especially in a small sample size. Nonetheless, while keeping these caveats in mind, the work presented here contains some interesting findings that should inform future studies and may provide beneficial insight into glucose homeostasis in humans.

In addition to their insight into mechanisms of glucose tolerance, the data presented by Sonnier et al have other noteworthy aspects. The observation that changes in the amplitude of diurnal glucose tolerance and cortisol rhythms seemingly occur in opposite directions is itself an important one. Some previous studies have reported decreased amplitude rhythms from lean to obese to obese-insulin resistant subjects (Sinha et al., 1996; Ando et al., 2005). However, it is clear that not all rhythms follow this pattern (Otway et al., 2011; Mantele et al., 2012). It is therefore important not to over-simplify by suggesting that metabolic dysregulation associates with reduced rhythm

amplitude per se, but to appreciate that rhythms alter in a specific manner, depending on the nature of the rhythm and/or the tissue(s) concerned. Such a level of complexity may be expected given the number of contributing mechanisms, described above, to glycaemic control.

Finally Sonnier et al suggest a strategy of predominantly eating early in the day to counteract the evening decline in glucose tolerance. Their data from OGTT are in agreement with a recent study on low glycaemic index foods that established lower postprandial glycaemic responses when consumed in the early part of the day (Gibbs et al., 2014). Emerging data indicate that a shift in the timing of calorie consumption towards the start of the day can enhance weight loss (Garaulet et al., 2013; Jakubowicz et al., 2013b) and improve insulin sensitivity (Jakubowicz et al., 2013a). In some cultures, a change in people's perception of main meal timing will be required to translate these findings into the widespread community. However timed meal strategies may represent an important future intervention that builds upon the robust daily changes in glucose tolerance and wider metabolic physiology (Johnston, 2014).

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