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Energy homeostasis and appetite regulating hormones as predictors of weight loss in men and women

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ABSTRACT

Sex differences in weight loss are often seen despite using the same weight loss program. There has been relatively little investigation of physiological influences on weight loss success in males and females, such as energy homeostasis and appetite regulating hormones. The aims were to 1) characterise baseline plasma leptin, ghrelin and adiponectin concentrations in overweight and obese males and females, and 2) determine whether baseline concentrations of these hormones predict weight loss in males and females.

Subjects were overweight or obese (BMI 25–40 kg/m^2) adults aged 18–60 years. Weight was measured at baseline, and after three and six months participation in a weight loss program. Baseline concentrations of leptin, adiponectin and ghrelin were determined by enzyme-linked immunosorbent assay (ELISA). An independent t-test or non-parametric equivalent was used to determine any differences between sex. Linear regression determined whether baseline hormone concentrations were predictors of six-month weight change.

Females had significantly higher baseline concentrations of leptin, adiponectin and unacylated ghrelin as well as ratios of leptin:adiponectin and leptin:ghrelin. The ratio of acylated:unacylated ghrelin was significantly higher in males. In males and females, a higher baseline concentration of unacylated ghrelin predicted greater weight loss at six months. Additionally in females, higher baseline total ghrelin predicted greater weight loss and a higher ratio of leptin:ghrelin predicted weight gain at six months.

A higher pre-weight-loss plasma concentration of unacylated ghrelin is a modest predictor of weight loss success in males and females, while a higher leptin:ghrelin ratio is a predictor of weight loss failure in females. Further investigation is required into what combinations and concentrations of these hormones are optimal for weight loss success.

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1. Introduction

The prevalence of overweight and obesity increased dramatically in the past 30 years (World Health Organization, 2015) and although in some developed countries the rate appears to be plateauing, the prevalence in these countries remains very high with just over 40% of women and almost 50% of men overweight or obese (Ng et al.). There is variability in the effectiveness of different weight loss strategies, but there is also substantial variation in the extent of weight loss achieved within studies using the same intervention (Williams, Wood, Collins, & Callister, 2015). One contribution to this variability may be differences in weight loss achieved by males and females, as many studies report only the combined results (Ramage, Farmer, Apps Eccles, & McCargar, 2013), which may mask sex differences. Although research has focused on understanding the behavioural factors influencing weight loss in men and women (Williams et al., 2015), there has been relatively

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little investigation of possible physiological influences on weight loss, such as the energy homeostasis and appetite regulating hormones leptin, adiponectin and ghrelin (Ramel et al. 2010; Labayen et al. 2011).

The roles and functions of leptin, adiponectin and ghrelin in the regulation of body weight in healthy populations have been reported and their functions relatively undisputed (Holst & Schwartz, 2004, Trujillo & Scherer, 2005, Ahima, 2008). Leptin is primarily released from adipocytes in response to elevated fat stores and at normal plasma concentrations, suppresses appetite and increases energy expenditure (Ahima, 2008; Kelesidis, Kelesidis, Chou, & Mantzoros, 2010). Adiponectin is released from adipocytes when fat stores are low or reduced and stimulates appetite (Cnop et al. 2003). Ghrelin is primarily secreted from the gastric mucosa, particularly following periods of food deprivation, and this increase in ghrelin prior to meals stimulates intake. Additionally, plasma concentrations also increase with fat mass loss (Cummings, 2006; Soares & Leite-Moreira, 2008;). There are two main types of ghrelin; acylated, a 28-amino acid peptide with an 8-carbon fatty acid side chain, and unacylated ghrelin, where the 8-carbon fatty acid side chain has been cleaved (Callaghan & Furness, 2014). Until recently, it was thought that the main actions of ghrelin were due to the acylated form and that unacylated ghrelin was simply a degradation product. However, more recent evidence has shown that unacylated ghrelin may play an active role in appetite regulation, mainly through antagonising acylated ghrelin and therefore dampening the stimulation of appetite (Delhanty, Neggers, & van der Lely, 2012).

There are sex differences in the plasma concentrations of these hormones with overweight females having higher fasting concentrations of leptin, independent of fat mass (Nicklas, Katzel, Ryan, Dennis, & Goldberg, 1997; Ramel, Arnarson et al. 2010), adiponectin (Cnop, et al. 2003; Arita, 2012) and ghrelin (Makovey, Naganathan, Seibel, & Sambrook, 2007) than overweight males. Hence, although females may experience stronger appetite suppression secondary to higher leptin concentrations relative to males, this may in part be counteracted by greater appetite stimulation from ghrelin and adiponectin (Klok, Jakobsdottir, & Drent, 2007). This suggests that the physiological interactions and balance between these hormones may differ between males and females, making identification of their sex specific associations with weight regulation important to examine. However, the differences in energy homeostasis hormone concentrations between men and women may be further confounded by an individuals' weight status.

The concentrations of these hormones may fall outside of normal ranges in individuals with excess body fat, and the functions of these hormones, in particular leptin, appear to be compromised with the expected effects on appetite and energy expenditure lost or diminished (Pan, Guo, & Su, 2014). Resistance to leptin is observed in the obese, in association with elevated leptin concentrations (Myers, Cowley, & Münzberg, 2008; Pan et al., 2014). In response to weight loss, leptin concentrations decrease (Crujeiras et al. 2010) but ghrelin concentrations increase (Mason et al. 2014). These changes in hormone concentrations in response to weight loss have been investigated in a number of studies (Hansen et al. 2002; Abbenhardt et al. 2013) and their role(s) in influencing weight regain explored (Strohacker, McCaffery, Maclean, & Wing, 2014). In contrast, there has been little investigation of the influence of pre-weight-loss hormone concentrations on weight loss success (Ramel et al. 2010; Labayen et al., 2011). Labayen et al. (Labayen et al., 2011) found that women with higher leptin and lower ghrelin hormone profiles at baseline may be less likely to achieve weight loss success (Labayen et al., 2011). There is still limited understanding of whether these baseline hormone levels influence weight loss and whether there is a similar hormonal profile in males and females.

Weight loss of 5% or more is a common benchmark of success in weight loss interventions and leads to a clinically significant reduction in disease risk (Wing et al. 2011). The duration of interventions required for this level of weight loss may differ between males and females with some suggestion that in the early stages, weight loss in males exceeds that of females (Collins et al. 2012) but that over longer time periods men and women lose the same amount of weight (Williams et al., 2015). A potential explanation for this observation may be differences in baseline hormone profiles between men and women, or the changes in these hormones over time, influencing weight loss trajectory.

Therefore, the aims of the current study were to: 1) characterise baseline plasma leptin, ghrelin and adiponectin concentrations in i) males and females, ii) those classified at baseline as overweight and obese, and iii) those who lost $\geq$6% and <3% of initial weight; and 2) to determine whether baseline concentrations of energy homeostasis and appetite regulating hormones predict weight loss outcomes in males and females. It was hypothesised that baseline hormone concentrations of leptin, ghrelin and adiponectin would influence weight loss success in males and females.

2. Subjects and methods

2.1. Study population

Data were obtained from participants (53 males and 66 females) enrolled in a web-based weight loss randomised controlled trial (RCT) described in detail elsewhere (Collins et al. 2010; Collins et al. 2012). Briefly, overweight or obese (BMI 25–40 kg m^2) adults aged 18–60 years were recruited. Participants in this analysis were required to be allocated to an intervention arm of the RCT for the six months and to have complete baseline and six month weight and blood sample data. Ethics approval was obtained from the University of Newcastle Human Research Ethics Committee.

2.2. Weight loss program

The weight loss program provided daily calorie targets to facilitate 0.5–1 kg of weight loss per week. Features that were included in the program to assist participants in meeting this goal were weekly calorie-controlled, low-fat menu plans and grocery lists, a weekly physical activity plan tailored to exercise preferences, access to a web-based food and exercise diary to self-monitor energy intake, expenditure and balance, weekly educational tips, a weekly nutrition summary compared with recommended nutrient targets and self-monitoring of weight.

2.3. Menopausal status

Menopausal status of female participants is reported in two ways. Status based on self-report and symptoms and predicted menopausal status based on age for those with missing data as follows: <40 years pre-menopausal, $\geq$40 and < 55 years peri-menopausal, $\geq$55 years post-menopausal.

2.4. Anthropometric measurements

Weight was measured in light clothing, without shoes, on a digital scale to 0.01 kg (CH-150kp; A&D Mercury Pty Ltd, Adelaide, Australia). Height was measured to 0.1 cm using the stretch stature method (Coombes & Skinner, 2014) on a Harpenden portable stadiometer (Holtain Limited, Croswell, Pembrokeshire, UK). BMI was calculated as weight (in kilograms) divided by height (in meters)

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