Raised Circulating Fetuin-A After 28-Day Overfeeding in Healthy Humans

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Fetuin-A is a liver secretory glycoprotein that has been linked to the development of insulin resistance in animal models (1). Recent work suggests that free fatty acids (FFAs) and fetuin-A interact to induce insulin resistance in animal models (1) and humans (2). However, short-term overfeeding increases peripheral insulin resistance without significant increases in the levels of circulating FFAs in healthy humans (3,4). Thus, short-term overfeeding studies provide an ideal model with which to evaluate the relationships between fetuin-A and insulin resistance, independent of FFAs.

We examined the effects of 28-day overfeeding (1,100 ± 100 kcal/day above baseline energy requirement, increasing mean [±SEM] dietary fat intake from 34 ± 1% to 45 ± 1% of energy intake) on circulating levels of fetuin-A, FFAs, and proinflammatory markers in healthy men and women (BMI 25.6 ± 0.6; age 37 ± 2 years; $n = 40$ [20 men]). The study protocol was described in detail previously (3) and approved by the Human Research and Ethics Committee at St. Vincent's Hospital (Sydney, New South Wales, Australia). Metabolic studies were performed at baseline and after 28-day overfeeding, and included 2-h euglycemic (5 mmol/L) hyperinsulinemic (60 mU/m^2) clamp to evaluate insulin sensitivity, dual-energy X-ray absorptiometry (Lunar DPX; Lunar Corp., Madison, WI) to evaluate body fat composition, and computed tomography (Gemini GXL; Phillips) to evaluate abdominal fat distribution and liver density. Fasting circulating concentrations of fetuin-A (BioVendor, Brno, Czech Republic), FFAs (Wako, Osaka, Japan), monocyte chemoattractant protein-1 (MCP-1; R&D Systems, Minneapolis, MN), and high-sensitivity C-reactive protein (CRP; Beckman Coulter Inc., Sydney, New South Wales, Australia) were also measured at baseline and in response to overfeeding. Statistical analyses included repeated-measures ANOVA to evaluate the change in end points with overfeeding and linear regression models to evaluate the relationships among variables, with age and sex as independent variables.

Weight, body fat mass, and visceral and subcutaneous abdominal adipose tissue increased, whereas liver density (inversely proportional to liver fat) decreased (Fig. 1). The glucose infusion rate necessary to maintain euglycemia during the hyperinsulinemic clamp decreased, and the homeostasis model assessment of insulin resistance increased, indicating reduced insulin sensitivity with overfeeding (Fig. 1). Circulating levels of fetuin-A and the inflammatory markers CRP and MCP-1 were all increased with overfeeding (Fig. 1). Consistent with other short-term overfeeding studies in healthy individuals (4), fasting FFA levels were not elevated ($P = 0.4$; Fig. 1). Moreover, the insulin sensitivity response to overfeeding was not explained by FFA response ($\beta = -0.15$, $P = 0.9$), fetuin-A response ($\beta = -0.08$, $P = 0.9$), or their interaction ($\beta = -0.09$, $P = 0.9$).

Interestingly, baseline circulating levels of fetuin-A were correlated with those of MCP-1 ($\beta = 0.36$, $P = 0.04$), and MCP-1 response to overfeeding was explained by fetuin-A response ($\beta = 0.39$, $P = 0.02$), demonstrating a link between fetuin-A and low-grade inflammation in healthy humans.

In conclusion, opposite to findings concerning caloric restriction and weight loss (5), caloric excess and weight gain resulted in significant elevations in circulating levels of fetuin-A in humans. Relationships between fetuin-A and MCP-1 provide support for the notion that fetuin-A may be involved in an inflammatory response. However, our study suggests that this may have occurred

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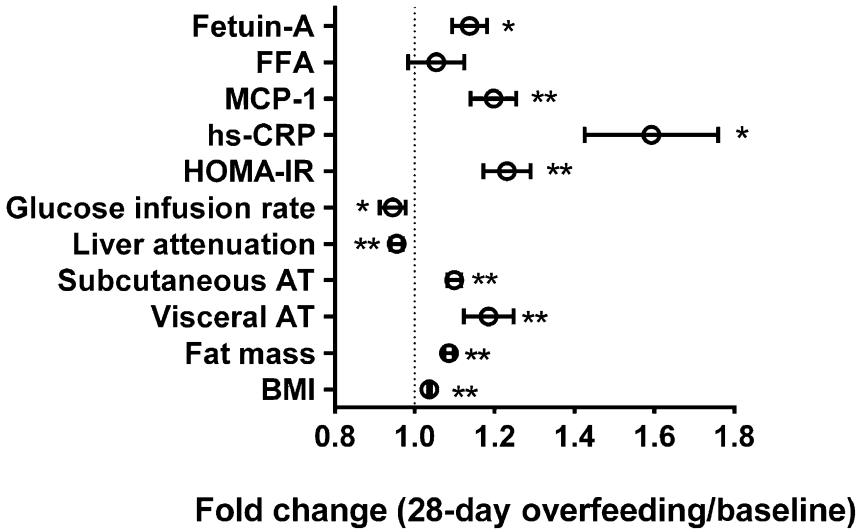

Figure 1—Effects of 28-day overfeeding on BMI, fat distribution, insulin sensitivity, and circulating levels of proinflammatory markers, FFAs, and fetuin-A in healthy humans. Data are the mean fold change ± SEM ($n = 40$; 20 men/20 women). *$P < 0.05$, **$P < 0.01$, compared with baseline levels by repeated-measures ANOVA. CRP, MCP-1, FFA, and fetuin-A data were log-transformed prior to statistical analysis. AT, adipose tissue (at the L4/L5 disc space); HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high-sensitivity CRP.

independent of FFA, although detailed studies of fatty acid utilization were not performed. Further study is needed to elucidate the role of fetuin-A in weight gain–associated insulin resistance in humans.

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