LETTERS TO THE EDITOR

Omentectomy, Visceral Fat, and Insulin Resistance

John M. Evans[1]

TO THE EDITOR: The study by Lottati and colleagues on the effect of omentectomy on insulin resistance provides more evidence for the sinister role of visceral fat (1). Although there is a strong association between excess visceral, as opposed to subcutaneous, fat and insulin resistance and related cardiovascular diseases, no clear mechanism for this association has been established (2).

A possible explanation for this could lie in the recent observation that adipocytes in white body fat are often poorly perfused with blood and that adipocyte hypoxia is common. In response to this hypoxic stress, the adipocytes secrete a spectrum of pro-inflammatory cytokines, or adipokines. These adipokines are intimately linked to the genesis of insulin resistance, type 2 diabetes, and cardiovascular disease (3). Excess visceral fat is associated with increased circulating adipokines (4).

Omental fat, like all intra-abdominal visceral fat, and unlike subcutaneous fat, is subject to the intra-abdominal pressure. In man, this is normally about 7 mm Hg but rises to ≥18 mm Hg in morbid obesity (5). This intra-abdominal pressure will reduce the arterial perfusion pressure gradient of the visceral fat by an equivalent amount. Relative to a typical mean arterial blood pressure of 85 mm Hg, this reduction could be as much as 20%. The lower perfusion pressure will decrease blood flow and oxygen flux to the visceral fat. In turn, this will lead to more adipocyte hypoxia. Consequently visceral adipocytes may tend to be more hypoxic than subcutaneous adipocytes.

This mechanism could explain the increased adipokine secretion of visceral adipocytes and could account for the association of increased visceral fat mass with insulin resistance, type 2 diabetes and cardiovascular disease. Thus, the reduction in visceral fat mass by omentectomy could bring about a reduction in excess adipokine secretion with consequent improvement in insulin sensitivity as observed by Lottati *et al.*

DISCLOSURE

The author declared no conflict of interest.

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Genetic Variation in the *FAAH* Gene and Metabolic Syndrome–related Phenotypes

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TO THE EDITOR: We read with great interest the article "Variants in the *CNR1* and the *FAAH* Genes and Adiposity Traits in the Community" by Lieb *et al.* about a lack of association of common variants of the *CNR1* and *FAAH* genes with surrogate measures of adiposity in a large community-based sample of individuals (1). The authors performed a comprehensive analysis of common variation across these two genes and observed no evidence for association of any variant with BMI, waist circumference, and visceral adipose tissue volume. In a smaller ($n = 420$) but well-characterized sample of adult men of self-reported European ancestry (aged 34.4 ± 0.4 years, mean ± s.e.), selected from a population-based study in Argentinean people, we explored the role of the C/T rs6703669-*FAAH* variant in the genetic susceptibility of metabolic syndrome–related phenotypes. The variant was selected as a tagSNP capturing common variation in the promoter region of the gene (pair-wise approach at $r^2 = 0.8$, minor allele frequency >10%). Genotyping was performed by allele-specific PCR and genotypes were in Hardy–Weinberg equilibrium. In agreement with Lieb *et al.*, we found no evidence of association between the variant and any of the obesity-related phenotypes: BMI as a continuous trait (logarithmically transformed) $P = 0.9$, waist circumference $P = 0.25$, obesity status as a discrete trait $P = 0.24$, and measurement of body fat content by bioelectrical impedance $P = 0.4$. Nevertheless, when we analyzed the serum lipid variables in relation to the rs6703669, a significant association was observed with plasma levels of triglycerides: homozygous CC 105.1 ± 5.9, heterozygous CT 131.3 ± 7.5 and homozygous TT 119.2 ± 15.5 mg/dl, $P < 0.015$, adjusted by log-transformed age and BMI. Accordingly, hypertriglyceridemia evaluated as a discrete trait (plasma triglycerides ≥150 mg/dl), also showed significant association with the variant (OR per T allele: 1.31, 95% CI 1.04–1.66, $P < 0.022$). Finally, we evaluated the possible association of the rs6703669 and other metabolic syndrome–related phenotypes and observed a significant association with arterial hypertension (dichotomized as a discrete trait): OR per T allele: 1.43, 95% CI 1.06–1.95, $P = 0.01$,

after adjusting by log-transformed age and BMI. Similarly, the quantitative trait diastolic arterial blood pressure was significantly associated with the variant ($P < 0.023$): homozygous CC: 74.2 ± 0.6, heterozygous CT: 76.2 ± 0.7 and homozygous TT: 78.1 ± 1.7 mm Hg. In summary, the findings of Lieb *et al.* can also be generalized to Argentinean population, as an example of replication in a different group of European descent. However, these results do not exclude other possible effects of the variants of the *FAAH* on metabolic syndrome–related phenotypes, for instance arterial blood pressure or plasma triglycerides. These data, which need to be confirmed in larger samples, may be of interest because the use of *FAAH* as a therapeutic target in hypertension is under evaluation not only because of the potential beneficial effect of endocannabinoid-related drugs on arterial blood pressure but also on the development of the hypertensive cardiac hypertrophy (2,3).

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DISCLOSURE

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Copper Deficiency After Gastric Bypass Surgery

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TO THE EDITOR: Recently, Griffith and co-workers, in their article "Acquired Copper Deficiency: A Potentially Serious and Preventable Complication Following Gastric Bypass Surgery," have reported on two cases of severe copper deficiency after Roux-en Y gastric bypass surgery (RYGB) that have led to severe neurological and hematological alterations which were in part irreversible (1). As stated by the authors, so far little information on copper depletion after RYGB is available (2,3); therefore, studies assessing the incidence and prevalence of copper deficiency after RYGB appear to be highly desirable.

Here we report on serum copper concentrations in 78 patients (71.8% women, age mean ± s.d.: 45.8 ± 9.9 years) that were assessed by atomic absorption spectrophotometry 1.3 ± 0.9 years (range: 0.3–5.1 years) after RYGB surgery. After the surgery, all patients received a standard micronutrient supplementation regime consisting of 100–200 mg iron per day (p.d.), 15–30 mg zinc p.d., 1.5 g calcium combined with 1,200 IU vitamin D_3 p.d., a vitamin B combination twice a week, intramuscular injections of 1,000 µg vitamin B_{12} every 3 months, and a multivitamin combination containing 0.45 mg copper p.d. Because micronutrient deficiencies are frequently found in severely obese patients even before a bariatric surgery (4), we additionally assessed serum copper levels in 77 severely obese patients (BMI ≥40 kg/m^2, 71.4% women, age: 41.2 ± 11.7 years) in our Interdisciplinary Obesity Center who were evaluated for obesity treatment but had not undergone a bariatric surgery. All patients gave written informed consent, and the protocol was approved by the local ethics committee. Data were analyzed by Student's *t*-test or χ^2 test as appropriate and is provided as mean ± s.d. values.

RYGB patients have lost on average 48.4 ± 20.7 kg after the surgery with a BMI reduction from 48.2 ± 7.7 to 31.1 ± 4.9 kg/m^2 ($P < 0.001$). Their preoperative BMI was roughly comparable to that of the nonoperated obese control patients (BMI: 46.4 ± 4.9 kg/m^2, $P = 0.09$). Serum copper levels were significantly lower in the RYGB group than in the obese control group (16.6 ± 4.0 vs. 20.1 ± 4.8 µmol/l; $P < 0.001$) (**Figure 1**). None of the obese control patients displayed a copper deficiency as defined by a level below the lower limit of the reference range (<13 µmol/l) whereas 15.4% of the RYGB patients showed a deficiency of this trace element (χ^2; $P < 0.001$).

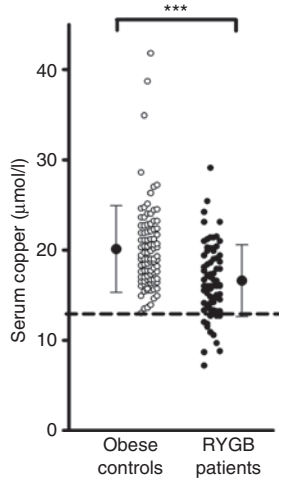

Figure 1 Individual as well as mean ± s.d. serum copper levels in 78 patients after gastric bypass surgery (filled circles) and 77 severely obese control patients without surgery (open circles). Dashed horizontal line indicates the lower limit of the reference range (13 µmol/l). ***$P < 0.001$.

As suggested by Griffith and co-workers (1), our data show an increased rate of copper deficiency after RYGB surgery. Fortunately, the decrease in copper concentrations was rather mild and even cases with a clearcut deficiency were not associated with any obvious symptoms. Copper deficiency after RYGB may be an effect of the exclusion of the duodenum and proximal jejunum from the passage of nutrients and prescribed supplements (5,6). On the other hand, it may also result from a inhibitory effect of iron, zinc, and calcium—all of which were administered at rather high doses in our patients—on copper absorption (7,8). In summary, our results support the notion that serial copper status monitoring as well as regular neurological examinations should be performed in RYGB patients.