Obesity

Addressing beta-cell mass in obesity and type 2 diabetes

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Pancreatic islet beta-cell failure has been proposed to be an important process within the pathophysiological pathway of obesity and type 2 diabetes. Prevention of beta-cell decline could be a key therapeutic approach in these conditions. Animal studies showing that glucagon-like peptide-1 analogues may have a beta-cell-preserving effect have not been confirmed in humans. It is likely that other molecules will be discovered that are key to beta-cell preservation and may serve as therapeutic targets.

Recently, betatrophin has been identified as a potential target for beta-cell preservation. In animal models of insulin resistance and obesity, such as the leptin-deficient *ob/ob* mouse, beta-cell proliferation is observed (Flier et al, 2001). This suggests that there are unknown factors that regulate beta-cell proliferation. Another piece of evidence for such factors is through the study of liver-specific insulin receptor-knockout mice, which demonstrate increased beta-cell mass (Michael et al, 2000). Parabiosis experiments (connecting the circulation of these knockout mice with wild-type [normal] mice) confirmed that a circulating factor was responsible, since wild-type mice also developed increased beta-cell mass (El Ouaamari et al, 2013).

That work also highlighted the important role of the liver in the pathophysiology of type 2 diabetes. Indeed, the resolution of diabetes was recently reported in a patient who underwent liver transplant (Pallayova et al, 2013). Yi et al (2013) used an insulin receptor antagonist to block insulin action, resulting in insulin resistance. With this approach, they observed beta-cell proliferation that was independent of direct pancreatic exposure to the insulin receptor antagonist. They also observed that a messenger RNA (betatrophin) was induced in liver and white adipose tissue in response to insulin receptor antagonism. Increased betatrophin expression was also observed in *ob/ob* mice. Another group examining responses to high-fat diets and fasting in mice discovered lipasin, an inhibitor of lipoprotein lipase, which regulates triglyceride levels (Zhang, 2012). It turns out that betatrophin and lipasin are the same.

In humans, the main site of betatrophin expression is the liver. Interestingly, betatrophin gene-knockout mice have normal blood glucose levels (Wang et al, 2013). However, another study has cast doubt on the role of betatrophin in beta-cell proliferation. Betatrophin (also called angiopoietin-like protein 8) overexpression in the liver was shown not to affect beta-cell proliferation (Gusarova et al, 2014). It was suggested that this compound is more important for triglyceride metabolism.

The role of betatrophin in humans remains to be determined. Several groups have measured betatrophin in the circulation, with conflicting results. Furthermore, levels of circulating betatrophin differ according to the various assays that measure different betatrophin epitopes. Gómez-Ambrosi and colleagues (their study summarised alongside) measured serum betatrophin in obese participants with normoglycaemia, impaired glucose tolerance and diabetes. They observed that betatrophin levels were decreased in obesity and further decreased when obesity was complicated by insulin resistance and diabetes. A negative linear relationship between betatrophin levels and degree of obesity (BMI and waist circumference) was observed. There was a positive linear association of betatrophin levels with HDL-cholesterol levels and a negative association with triglyceride levels. The levels of betatrophin were also higher in women.

The physiological role of betatrophin is controversial in animal models. Unfortunately, the matter is not straightforward in humans either, as another group has reported increased levels of betatrophin in newly diagnosed patients (Hu et al, 2014). Thus, its levels will differ depending on the patient populations studied and the disease stage. These studies were all cross-sectional; prospective studies will be more informative. There are likely to be further discoveries of factors that regulate beta-cell (and alpha-cell) proliferation. Betatrophin may not be this elusive agent, but we have entered a new era of discovery of beta-cell trophic factors for tackling the metabolic pathophysiology of obesity and insulin resistance. ■

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J Clin Endocrinol Metab

Reduced betatrophin levels in obesity and T2D

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓

1 Betatrophin is a 22-kDa hormone expressed in the liver and adipose tissue. In mice models of insulin resistance, it promotes beta-cell proliferation and mass, as well as improving glucose tolerance.

2 The role of this hormone in human insulin resistance is less well understood; therefore, the authors evaluated serum betatrophin concentrations in obese people with impaired glucose tolerance or T2D.

3 The authors recruited 153 white participants, of whom 33 had a normal weight and normoglycemia, 75 were obese and normoglycemic, 30 were obese with impaired glucose tolerance (IGT) and 15 were obese with T2D.

4 Compared with the lean participants, betatrophin levels were reduced by 40% in normoglycaemic obese people, 59% in those with IGT and 70% in those with T2D ($P<0.001$ for all).

5 Betatrophin levels were significantly higher in women than in men (mean, 34.1 vs 21.1 ng/mL; $P<0.001$), and they were more closely related to BMI in the former; this could underlie the observed gender difference in the risk of developing diabetes.

6 The authors conclude that serum betatrophin levels are decreased in obese people and decrease further as insulin resistance increases.

7 Further studies to determine the pathophysiological regulators of betatrophin and to identify its receptor will bring to light the role of this hormone in obesity, insulin resistance and T2D.

Gómez-Ambrosi J, Pascual E, Catalán V et al (2014) Circulating betatrophin concentrations are decreased in human obesity and type 2 diabetes. *J Clin Endocrinol Metab* **99**: E2004–9

Obes Surg

Bariatric surgery results in less coronary calcification

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓

1 Coronary artery calcium (CAC) scores, as quantified using non-contrast computed tomography, are a measure of atherosclerosis and can predict coronary events and long-term survival more accurately than Framingham risk scores.

2 While obesity is associated with rapid progression of CAC scores over time, it is not known whether weight loss can slow CAC development; therefore, the authors sought to determine the effects of bariatric surgery in a group of 149 obese participants.

3 CAC scores were compared between 65 participants who underwent gastric bypass surgery and the 84 who did not.

4 At the 6-year follow-up, the surgery group had lost an average of 40.5 kg, whereas the control group had gained 1.3 kg. Metabolic risk factors for coronary artery disease also improved in the former but not the latter group.

5 The surgery group had a lower mean CAC score after 6 years, as well as a greater proportion of participants with no measurable CAC (70% vs 49%; P=0.003).

6 Gender, age at CAC measurement, baseline BMI and baseline LDL-cholesterol level were significantly associated with the presence of CAC; after adjustment for these variables, the odds ratio of having any CAC was 0.39 (95% confidence interval, 0.17–0.90) in the surgery group.

7 The authors conclude that the marked weight loss associated with bariatric surgery results in reduced coronary calcification independently of changes in LDL-cholesterol.

Priester T, Ault TG, Davidson L et al (2014) Coronary calcium scores 6 years after bariatric surgery. *Obes Surg* 15 Jun [Epub ahead of print]

Diabetes Care

Ethnic-specific diabetes risk: UK Biobank data

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓

1 The current authors used data from the UK Biobank to determine the relationship between adiposity and diabetes prevalence across different ethnic groups.

2 A total of 490 288 participants were evaluated, of whom 471 174 (96.1%) were white, 9631 (2.0%) were South Asian, 7949 (1.6%) were black and 1574 (0.3%) were Chinese. Overall, 5.2% of the cohort had diabetes.

3 Diabetes was more prevalent and the association between adiposity and diabetes prevalence was stronger in all non-white populations compared with the white population, even after adjustment for age and socioeconomic status.

4 Compared with white women with a BMI of 30, the prevalence of diabetes was equivalent at a BMI of 22.0 in South Asian women, 26.0 in black women and 24.0 in Chinese women. In men, the equivalent BMIs were 21.6, 26.0 and 26.0, respectively.

5 The authors conclude that obesity should be defined at lower thresholds than the current World Health Organization guidelines in non-white populations, and that lower thresholds should be applied in South Asians compared to Chinese people.

Ntuk UE, Gill JM, Mackay DF et al (2014) Ethnic-specific obesity cutoffs for diabetes risk: cross-sectional study of 490,288 UK biobank participants. *Diabetes Care* **37**: 2500–7

Obes Surg

Laparoscopic sleeve gastrectomy versus Roux-en-Y for obesity

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓

1 In this meta-analysis of 21 studies involving 18 766 morbidly obese people, laparoscopic sleeve gastrectomy was compared with laparoscopic Roux-en-Y gastric bypass.

2 The two procedures were equal in terms of weight loss at 0.5–1.5 years postoperatively, but thereafter, Roux-en-Y was superior.

3 Roux-en-Y was superior in terms of achieving T2D remission but there was no difference in terms of resolving other comorbidities of obesity.

4 However, Roux-en-Y was associated with nearly twice as many major complications, although both procedures were generally safe.

Zhang Y, Ju W, Sun X et al (2014) Laparoscopic sleeve gastrectomy versus laparoscopic Roux-en-Y gastric bypass for morbid obesity and related comorbidities: a meta-analysis of 21 studies. *Obes Surg* 5 Aug [Epub ahead of print]

Obes Surg

Predictive factors of T2D remission with bariatric surgery

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓

1 The aim of this meta-analysis was to determine the factors associated with remission in a total of 1753 people with T2D who underwent bariatric surgery.

2 T2D remission was more likely in people with a younger age, shorter diabetes duration, no insulin use and lower HbA_{1c} at baseline.

3 Overall, gender and BMI were not predictive of T2D remission; however, in Asian people only, high BMI and C-peptide levels were associated with remission.

4 These results indicate a number of criteria that could be used to select bariatric surgery recipients.

Wang GF, Yan YX, Xu N et al (2014) Predictive factors of type 2 diabetes mellitus remission following bariatric surgery: a meta-analysis. *Obes Surg* 8 Aug [Epub ahead of print]

"The authors conclude that obesity should be defined at lower thresholds than the current World Health Organization guidelines in non-white populations, and that lower thresholds should be applied in South Asians compared to Chinese people."

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