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Abbreviations used in this issue:

BMI = body mass index; GLP-1 = glucagon-like-peptide-1; PTH = parathyroid hormone; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; SGLT = sodium glucose co-transporter.

Welcome to the third issue of Obesity Research Review.

A topical paper included in this issue reports on the impact of BMI in patients admitted in intensive care for SARS-CoV-2. The French retrospective study found the proportion of patients who required mechanical ventilation increased with BMI. Results from a prospective, longitudinal study conducted at a high-volume bariatric unit in Singapore suggest that different bariatric procedures have specific nutritional deficiencies. Another retrospective multicentre cohort study found bariatric surgery was associated with a reduced risk of fracture.

A MRI substudy evaluated the efficacy and safety of dapagliflozin plus saxagliptin versus glimepiride in patients with type 2 diabetes on metformin background. The authors reported there was a significant reduction from baseline in liver fat and adipose tissue volumes with dapagliflozin plus saxagliptin plus metformin versus glimepiride plus metformin. A randomised controlled trial found licogliflozin treatment induced a dose-dependent reduction in body weight in Japanese patients with obesity. The authors noted licogliflozin was safe and well tolerated.

The concluding article assessed exenatide treatment in adolescents with severe obesity. Extended-release exenatide led to a modest reduction in BMI metrics and improvement in glucose tolerance and cholesterol.

I hope you find the research in this issue useful to you in your practice and I look forward to your comments and feedback.

Kind Regards,

Professor Joseph Proietto
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Effect of telehealth extended care for maintenance of weight loss in rural US communities a randomized clinical trial

Authors: Perri MG, et al

Summary: Participants were randomised to individual telephone counselling (n = 149), group telephone counselling (n=143), and email education control (n =153). All participants received 18 modules with post-treatment recommendations for maintaining lost weight delivered over 4 months. In the telephone-based interventions, health coaches provided individual or group sessions focused on problem solving for obstacles to the maintenance of weight loss. Mean baseline weight was 99.9 kg and mean weight loss after the initial intervention was 8.3 kg. The authors reported mean weight regains at follow-up were 2.3 kg in the individual telephone counselling group, 2.8 kg for the group telephone counselling group, and 4.1 kg for the control group. They noted there was a significantly smaller weight regain in the individual telephone counselling group versus control group.


Reference: JAMA Netw Open 2020 Jun 1;3(6):e206764

Abstract
Associations of bariatric interventions with micronutrient and endocrine disturbances

Authors: Syn NL, et al

Summary: This prospective, longitudinal study was conducted at a high-volume bariatric unit in Singapore. A total of 688 patients were included, of whom 499 underwent laparoscopic sleeve gastrectomy and 189 underwent one-anastomosis gastric bypass or Roux-en-Y gastric bypass. The researchers performed serial assessment of 13 biochemical parameters at 12 time points for up to 5 years after bariatric procedure. They found no differences during follow-up among patients who underwent laparoscopic sleeve gastrectomy versus those who underwent one-anastomosis gastric bypass or Roux-en-Y gastric bypass in intact parathyroid hormone (PTH) levels, serum 25-hydroxyvitamin D levels, or phosphate levels. Haemoglobin levels were a mean 0.63 g/dL higher among patients who underwent laparoscopic sleeve gastrectomy compared with those who underwent one-anastomosis gastric bypass or Roux-en-Y gastric bypass (P < .001), despite no differences in iron concentration levels, total iron-binding capacity, or ferritin levels. Compared with patients who underwent laparoscopic sleeve gastrectomy procedures, patients who underwent one-anastomosis gastric bypass or Roux-en-Y gastric bypass had higher folate levels (mean difference, 2.376 ng/mL; P < .001) but lower serum magnesium levels (mean difference, -0.25 mg/dL; P < .001) and zinc levels (mean difference, -7.58 μg/dL; P < .001).

Comment: Bariatric surgery is currently the most effective way to lose weight and keep the weight off long term. However, one of the key ongoing issues following bariatric procedures is long term follow up of patients. Arguably the most important long-term issue is to avoid nutritional deficiencies. This study finds that the different procedures have specific nutritional deficiencies. Thus the popular sleeve gastrectomy procedure resulted in the same PTH and 25-OH vitamin D level, phosphate levels and iron status but had higher haemoglobin levels and lower folate than Roux-en-Y gastric bypass. This study will be useful to all HCP’s who look after post bariatric surgery patients.

Reference: JAMA Netw Open 2020 Jun 1;3(6):e205123

Abstract

Association of bariatric surgery with risk of fracture in patients with severe obesity

Authors: Khalid SI, et al

Summary: This retrospective multicentre cohort study included bariatric surgery-eligible patients who did not undergo weight loss surgery (n = 16,37), patients who had undergone Roux-en-Y gastric bypass (n = 16,37), and patients who had undergone sleeve gastrectomy (n = 16,37). The authors reported patients undergoing Roux-en-Y gastric bypass had a significantly reduced risk of fractures compared to those who did not have surgery, once adjusted for age, sex, smoking, alcohol consumption, and comorbidities. The fat mass and obesity associated gene, FTO, is also associated with osteoporosis phenotypes. PLoS ONE;6:e27312 2011; Tencerova M, et al. Obesity-Associated Hypermetabolism and Accelerated Senescence of Bone Marrow Stromal Stem Cells Suggest a Potential Mechanism for Bone Frailty. Cell Rep;27:2050–2062 2019). It is interesting that weight loss with Roux-en-Y bypass surgery did not reduce the risk of fractures. It is not clear why Roux-en-Y is detrimental to bone. Whatever the mechanism, it seems to be mitigated by exercise (Murai IH, et al. Exercise Mitigates Bone Loss in Women With Severe Obesity After Roux-en-Y Gastric Bypass: A Randomized Controlled Trial. J Clin Endocrinol Metab 104:4639–50 2019).

Comment: This study found that weight loss caused by sleeve gastrectomy reduced the risk of fractures compared to those who did not have surgery, once again confirming that obesity can weaken bones (Liu P-Y, et al. New insight into fat, muscle and bone relationship in women: Determining the threshold at which body fat assumes negative relationship with bone mineral density. Int J Prev Med;5:1452–63 2014). Several mechanisms have been proposed (Guo Y, et al. The fat mass and obesity associated gene, FTO, is also associated with osteoporosis phenotypes. PLoS ONE;6:e27312 2011; Tencerova M, et al. Obesity-Associated Hypermetabolism and Accelerated Senescence of Bone Marrow Stromal Stem Cells Suggest a Potential Mechanism for Bone Frailty. Cell Rep;27:2050–2062 2019). It is interesting that weight loss with Roux-en-Y bypass surgery did not reduce the risk of fractures. It is not clear why Roux-en-Y is detrimental to bone. Whatever the mechanism, it seems to be mitigated by exercise (Murai IH, et al. Exercise Mitigates Bone Loss in Women With Severe Obesity After Roux-en-Y Gastric Bypass: A Randomized Controlled Trial. J Clin Endocrinol Metab 104:4639–50 2019).

Reference: JAMA Netw Open 2020 Jun 1;3(6):e207419

Abstract

Maternal obesity and risk of cardiovascular diseases in offspring: A population-based cohort and sibling-controlled study

Authors: Razaz N, et al

Summary: The investigators used data from live singleton births (n = 2,230,115) without congenital malformations recorded in the Swedish Medical Birth Register. They calculated maternal body mass index (BMI) in early pregnancy from self-reported height and weight measurements at the first prenatal visit. Overall, 1,741 (0.08%) offspring were diagnosed with a cardiovascular disease between ages 1 and 25 years. Cardiovascular disease rates by maternal BMI categories were 0.57 per 10,000 child-years (BMI 18.5-24.9 kg/m2; normal weight), 0.61 per 10,000 child-years (25.0-29.9 kg/m2; overweight), 0.67 per 10,000 child-years (30.0-34.9 kg/m2; obesity grade I), 1.02 per 10,000 child-years (35.0-39.9 kg/m2; obesity grade II), and 1.38 per 10,000 child-years (≥40.0 kg/m2; obesity grade III). Compared with offspring of mothers with normal BMI, HRs of cardiovascular diseases were 1.10 for overweight, 1.16 for obesity grade I, 1.84 for obesity grade II, and 2.51 for obesity grade III. The investigators concluded risks of cerebrovascular diseases increased with maternal obesity severity and were partly mediated through asphyxia-related neonatal complications.

Comment: The authors followed a large cohort of singleton births including 2.23 million children, for cardiovascular disease including ischaemic heart disease, heart failure, and cerebrovascular diseases. It is unusual to find these disorders in young people and indeed only 0.08% of the offspring had cardiovascular disease. There may be a mechanism to explain the presence of vascular disease in the young, through asphyxia-related neonatal complications. This may be the mechanism as it is well known that obesity increases the risk of both maternal and childhood complications (Callaway LK, et al. The prevalence and impact of overweight and obesity in an Australian obstetric population. Med J Aust;184(2):56–92 2006) that could lead to poor oxygenation. However, as a commentator for the Lancet Diabetes and Endocrinology said, “whether these findings reflect actual causal associations through direct intrauterine mechanisms or are explained by shared family-based sociodemographic, lifestyle, and genetic factors is still unknown.”


Abstract

Independent commentary by Professor Joseph Proietto

Joseph Proietto is Professor Emeritus at the University of Melbourne in the Department of Medicine Austin Health and an endocrinologist specialising in diabetes and obesity. He established the first obesity clinic in Victoria at the Royal Melbourne Hospital and is now Head of the Weight Control Clinic at Austin Health. Professor Proietto was the inaugural Sir Edward Dunlop Medical Research Foundation, Professor of Medicine, and Head of the Metabolic Disorders Research Group in the Department of Medicine, Austin Health. He is currently on the executive of World Obesity and is Chair of the Clinical Care Committee. Professor Proietto has published over 200 articles and several book chapters on obesity and diabetes. He is the Author of “Body Weight Regulation: Essential Knowledge to Lose Weight and Keep It Off”.

Reference: JAMA Netw Open 2020 Jun 1;3(6):e207419

Abstract
Most of your patients with obesity have the will.¹
You can offer them a way.²

Saxenda® delivers significant and sustained weight loss with a well-established safety profile.²⁻⁴ Consider it for your patients with obesity today.²

At 1-year: 11.2%* mean weight loss with Saxenda® in early responders²⁻⁵

*65% pooled population with ≥5% weight loss at 12 weeks on 3 mg, post-hoc analyses

PBS Information: This product is not listed on the PBS.

References:


Dapagliflozin plus saxagliptin add-on to metformin reduces liver fat and adipose tissue volume in patients with type 2 diabetes

Authors: Johansson L, et al

Summary: This was a randomised trial that evaluated the efficacy and safety of dapagliflozin plus saxagliptin versus glimepiride in patients with type 2 diabetes on metformin background. Glimepiride was performed on 59 patients; liver fat and adipose tissue volumes were analysed for 59 and 57 patients, respectively. The authors reported there was a significant >30% reduction from baseline in liver fat (P = 0.007) and >10% reduction in adipose tissue volumes (P < 0.01) with dapagliflozin plus saxagliptin plus metformin at week 52 versus glimepiride plus metformin.

Comment: This study shows that even modest weight loss is associated with reduced liver fat. This is useful as fatty liver may lead to non-alcoholic steato-hepatitis (NASH), which can progress to cirrhosis. Cirrhosis causes multiple problems including jaundice, bleeding problems and eventually, in some, hepatic and hence energy loss. Saxagliptin, a DPP4 inhibitor, increases secreted GLP-1 levels by inhibiting the enzyme that degrades it (DPP4). GLP-1 only stimulates insulin secretion if the glucose is high. In contrast, sulfonylureas such as the comparator in this study, glimepiride, stimulate insulin secretion at any glucose level. The resulting hyperinsulinaemia can cause mild weight gain and hypoglycaemia. In addition, sulfonylureas may speed up the progression of beta cell failure in type 2 diabetes. (Aston-Mourney K. et al. Too much of a good thing: why it is bad to stimulate the beta cell to secrete insulin. Diabetologia 51:540-5 2008). Treatment guidelines and the PBS should stop advising sulfonylureas as the next medication following metformin in the treatment of type 2 diabetes. However, sulfonylureas are cheap!

Reference: Diabetes Obes Metab 2020 Jul;22(7):1094-1101

Dose-dependent reduction in body weight with LIK066 (licogliflozin) treatment in Japanese patients with obesity

Authors: Yokote K, et al

Summary: This was a randomised, double-blind, placebo-controlled trial of licogliflozin, a dual sodium glucose co-transporter (SGLT) 1/2 inhibitor. Japanese patients with obesity (n = 126) were treated with licogliflozin 2.5, 10, 25 and 50 mg once daily for 12 weeks. The mean percentage change in body weight from baseline at week 12 was -1.99, -3.00, -3.54 and -3.91% in licogliflozin 2.5, 10, 25 and 50 mg once-daily dose groups, respectively. The proportion of responders with ≥3% reduction in body weight in the licogliflozin 2.5, 10, 25 and 50 mg once-daily dose groups were 15.8%, 55.6%, 50.0% and 56.7%, respectively, versus placebo (7.1%; P <0.002 for all except the 2.5 mg once-daily group (P = 0.39)). Significant dose-dependent reductions were reported in haemoglobin A1c, uric acid, fasting plasma glucose and potentially in the waist circumference, diastolic blood pressure and visceral fat area.

Comment: SGLT2 inhibitors have been shown to be effective drugs for the treatment of type 2 diabetes. Not only do they lower blood glucose and reduce the risk of heart failure, they are also associated with a modest weight loss due to the energy loss caused by the glycosuria. This is the first study of these agents as obesity drugs in individuals who do not have diabetes. They show that the weight losses are about the same as seen in the studies on the treatment of diabetes. Is there a problem with this approach to weight loss in non-diabetic individuals? Potentially, yes. In a study in rats, Chris Nolan in modelling the insulin resistance of pregnancy, was able to reproduce the metabolic derangements of pregnancy by inducing glycosuria with the basic molecule of all SGLT2 inhibitors, phlorizin. (Nolan CJ, et al. The fetoplacental glucose steal phenomenon is a major cause of maternal metabolic adaptation during late pregnancy in the rat. Diabetologia 37: 976-84 1994). We therefore may be inducing insulin resistance if we prescribe SGLT2 inhibitors to patients who do not have diabetes.

Reference: Diabetes Obes Metab 2020 Jul;22(7):1102-1110

High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation

Authors: Simonnet A, et al

Summary: The retrospective cohort study included 124 patients admitted in intensive care for SARS-CoV-2 in a single French centre. Among the study cohort obesity (BMI > 30) and severe obesity (BMI > 35) were present in 47.6% and 28.2% of cases, respectively. Overall, 66.8% of patients required invasive mechanical ventilation. The authors reported the proportion of patients who required mechanical ventilation increased with BMI categories and it was greatest in patients with BMI > 35 (85.7%). In addition, the need for mechanical ventilation was significantly associated with male and BMI, independent of age, diabetes, and hypertension. The odds ratio for mechanical ventilation in patients with BMI > 35 versus patients with BMI < 25 was 7.36 (P = 0.02).

Comment: This is a very topical study as we are still in the midst of the pandemic. It shows that patients with obesity had more severe disease with more individuals requiring invasive ventilation. It is assumed that the reason for more ventilation is the mechanical problem of moving the diaphragm when there is a large abdomen. Piper AJ. Obesity hyperventilation syndrome—the big and the breathless. Sleep Med. Rev. 15:79-89 2011). The other possibility is that the immunological response to the virus may be impaired in obesity (Mancuso P. Obesity and respiratory infections: does excess adiposity weight down host defence? Palm Pharmacol Ther 26:412-9 2013).

Either way, we must warn our patients with severe obesity to safeguard themselves much like we tell our elderly patients to do.

Reference: Obesity (Silver Spring) 2020 Jul;28(7):1195-1199

Overweight and obesity impair academic performance in adolescence: A national cohort study of 10,279 adolescents in China

Authors: Ma L, et al

Summary: Self-reported weight and height were collected from 10,279 Chinese adolescents each year from seventh grade to ninth grade. All adolescents with overweight and obesity had lower academic performance than their counterparts without overweight (β = -0.46 to -0.08; P < 0.05), except for school-life experience for boys. It was also noted those who developed overweight and obesity after having normal weight had poorer school-life experiences (β = -0.55 to -0.25; P < 0.05).

Comment: The adverse consequences of obesity continue to mount. We can now add impaired academic performance. It is not clear what the mechanisms might be, but one can speculate that undiagnosed sleep apnoea could lead to sleep deprivation and resultant reduced academic performance. Another mechanism could be anoxia during childbirth as adolescents with obesity after having mothers with obesity. As discussed above, obesity increases the risk of childbirth complications.

Reference: Obesity (Silver Spring) 2020 Jul;28(7):1301-1309

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Active travelling to school is not associated with increased total daily physical activity levels, or reduced obesity and cardiovascular/pulmonary health parameters in 10–12-year olds: A cross-sectional cohort study

Authors: Zhang X, et al.

Summary: The study cohort comprised of 432 children, aged 10-12, from three primary schools in North East Scotland. All children had height, weight, blood pressure levels and lung function measured. Physical activity was also measured by actigraph accelerometers. The researchers defined active travellers as children who used active transport modes for >70% of their journeys to school over the week and passive travellers as those who used active transport modes <30%. They found actively commuting children (70% walking) had significantly higher activity levels than passive commuters during the 30 min that encompassed their journey to and from school. However, there were no significant differences between active and passive school travellers in total daily physical activity, BMI SDS, and both systolic and diastolic blood pressure and lung function.

Comment: This study confirms a study published in the BMJ some years ago (Mallam KM, et al. Contribution of timetabled physical education to total physical activity in primary school children: cross sectional study. BMJ 327:592-593 2003), showing that children that are made to exercise at school move around less when they are home, while those that move less at school spontaneously move more when at home. This is another reason why education-based public health measures will never work to tackle the obesity epidemic. The main reason why public measures can’t work is that the body vigorously defends weight. (Sumithran P, et al. Long-term persistence of adaptive thermogenesis in subjects who have maintained a reduced body weight. Am J Clin Nutr 88:906-910 2008).


A 6-month randomized, double-blind, placebo-controlled trial of weekly exenatide in adolescents with obesity

Authors: Weghuber D, et al

Summary: The objective of the study was to investigate the effect of exenatide, a glucagon-like-peptide-1 (GLP-1) receptor agonist, on BMI-SDS in adolescents with obesity. The study cohort included 44 adolescents (10-18 years, 50% females), with BMI-SDS > 2.0 or age-adapted-BMI > 30 kg/m². Participants received lifestyle intervention and were randomised 1:1 to exenatide extended release 2 mg or placebo subcutaneous injections given once weekly. Exenatide reduced (P < .05) BMI-SDS (-0.09; -0.18, 0.00), subcutaneous adipose tissue (-552 cm²; -989, -114), 2-hour-glucose during oral glucose tolerance tests (-15.3 mg/dL; -27.5, -3.1), total cholesterol (11.6 mg/dL; -21.7, -1.5), and BMI (-0.83 kg/m²; -1.68, 0.01) without significant change in liver fat content (-1.36; -3.12, 0.4; P = .06) in comparison to placebo.

Comment: This is one of the rare studies on pharmacotherapy-treated obesity in adolescents (10-18 years old). They tested weekly injection of long acting exenatide. As with treatment of adults in diabetes treatment studies, exenatide only gives modest weight loss. Liraglutide and semaglutide, also GLP-1 analogues, cause more weight loss (Heimburger S M, et al. Efficacy and safety of exenatide once weekly in patients with type 2 diabetes Expert Opin Pharmacother. 20: 501- 510 2019). GLP-1 analogues should be safe as GLP-1 is one of our own hormones, provided the dose is not too high.


Abstract