Treating obesity in type 1 diabetes mellitus – review of efficacy and safety

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Purpose of review
Obesity is an epidemic in the United States with serious concomitant co-morbid conditions; people living with type 1 diabetes mellitus (T1D) are not immune to the risk either. Weight gain in T1D is likely multifactorial, due to genetic, environmental and treatment-related factors. FDA-approved and other adjunctive weight loss therapies may benefit people living with T1D but there are risks to consider when providing recommendations or prescribing medications.

Recent findings
We performed a PubMed search of studies assessing clinical outcomes of both approved and off-label medications used in the treatment of type 1 diabetes. Search terms included 'type 1 diabetes, obesity' and the following: (1) metformin, (2) pramlintide, (3) glucagon-like peptide-1 (GLP-1) receptor agonists, (4) dual GLP-1 and gastric inhibitory polypeptide (GIP) agonists, (5) sodium-glucose cotransporter-2 (SGLT-2) inhibitors, (6) surgical treatment of obesity, (7) insulin pump, (8) insulin, (9) medical nutrition therapy, (10) diabetes self-management education, (11) exercise, (12) naltrexone-buproprion, (13) orlistat, and (14) phentermine-topiramate.

Summary
Weight loss treatments provide a wide-range of benefits in reducing both morbidity and mortality in those who are obese. Treatments also have varying adverse effect profiles which may impact T1D treatment. In this review, we aim to summarize study outcomes in people with T1D, including risks and benefits, of on- and off-label weight loss treatments.

Keywords
exercise, medical nutrition therapy, type 1 diabetes, weight loss medication, weight loss surgery

INTRODUCTION

In the United States, the rate of obesity in adults and children is climbing. The prevalence in the adult population during the years 1999–2000 was 30.5%; it rose to 41.9% in the years 2017–2020 [1]. In this same period, the prevalence of severe obesity increased from 4.7% to 9.2%. Unfortunately, people living with type 1 diabetes mellitus (T1D) are not immune to the risk of weight gain either. It is estimated that the rate of obesity, as defined by a BMI of 30 kg/m^2 or greater, in adults living in the United States with type 1 diabetes may be as high as 35.9% [2]. And these rates are now rising at a greater clip than the general population [3]. Young people living with T1D are also at risk as reported by the SEARCH for Diabetes in Youth Study. In this cohort, T1D had a higher prevalence of overweight (22.1% vs. 16.1%) in ages 3–19 years compared to those without diabetes [4].

In addition to genetics and environmental stimuli such as high caloric foods, chronic stress and short sleep duration, exogenous insulin is considered a key risk factor for weight gain in people living with T1D. Hypoglycemia and its treatment with carbohydrates can lead to weight gain. Despite advances in insulin formulations, glucose monitoring and pump technologies, hypoglycemia remains quite common. In one large retrospective review from the T1D Exchange, 6% of patients between 18–25 years, 7% 26–49 years and 10% 50 years of age and older experienced one or more severe hypoglycemic event in the prior 3 months [5]. Additionally, perturbations

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KEY POINTS

- People living with type 1 diabetes mellitus are at-risk for weight gain and obesity, similar to the general population. Environmental stimuli, such as high caloric foods, chronic stress and short sleep duration are risk factors. Exogenous insulin use is also a potential reason for rising rates.
- Medical nutrition therapy, exercise and behavioral modifications are first steps in the prevention or treatment of obesity but must be recommended with caution given risks related to hypoglycemia.
- Insulin formulations and methods of delivery have shown modest differences in weight gain.
- Current pharmacologic therapies used to treat weight loss in obesity have limited or mixed safety and efficacy data. People living with type 1 diabetes may be at-risk for hypoglycemia, diabetic ketoacidosis or other complications not generally seen when using medications in the general population.

in glucagon and amylin secretion may impact weight as well.

It is well known that obesity increases the risk of co-morbid conditions such as heart disease, stroke, cancer, arthritis, liver disease, and type 2 diabetes mellitus (T2D). People living with T1D are at higher risk for many of these conditions. Adults with T1D and obesity show greater progression of coronary artery calcium, a potential marker of atherosclerosis [6]. Weight gain also results in insulin resistance and higher insulin requirements impeding glycemic control and further increasing risk for microvascular complications [7]. The prevalence of the metabolic syndrome was shown to increase from 4.9% in normal weight to 35.3% among obese patients with T1D [8]. In the Diabetes Control and Complications Trial (DCCT), cardiovascular events in the group with the most weight gain were higher than those with minimal weight gain [6]. More recently, Wallace *et al.* reported that obesity was associated with increased odds of low estimated glomerular filtration rate (eGFR) in T1D [adjusted odds ratio – 1.52, 95% confidence interval (CI) 1.12–2.08] [9].

Promising new medications for the treatment of overweight and obesity are now available and have seen a dramatic rise in use; they may also provide weight loss benefits in people living with T1D. Yet dual treatment of obesity and T1D presents its own challenges. Weight loss in T1D may reduce insulin requirements and lead to an increase in hypoglycemia severity and frequency. Other concerns related to weight loss, include medication side effects such as euglycemic diabetic ketoacidosis, cardiovascular disease and depression [10]. In this review, we evaluate potential risks and benefits of weight loss therapies in people living with concomitant T1D and obesity.

METHODS

Relevant studies were identified by searching PubMed through August 2023 using the following search terms: 'Medical nutrition therapy obesity type 1 diabetes'; 'exercise obesity type 1 diabetes'; 'education obesity type 1 diabetes'; 'insulin obesity type 1 diabetes'; 'pramlintide type 1 diabetes'; 'metformin type 1 diabetes'; 'Glucagon like peptide-1 receptor agonist type 1 diabetes'; 'liraglutide type 1 diabetes'; 'dulaglutide type 1 diabetes'; 'semaglutide type 1 diabetes'; 'exenatide type 1 diabetes'; 'lixisenatide type 1 diabetes'; 'Dual glucagon like peptide–1 and gastric polypeptide agonist type 1 diabetes'; 'Tirzepatide type 1 diabetes'; 'SGLT inhibitor type 1 diabetes'; 'empagliflozin type 1 diabetes'; 'dapagliflozin type 1 diabetes'; 'canagliflozin type 1 diabetes'; 'sotagliflozin type 1 diabetes'; 'orlistat type 1 diabetes'; phentermine topiramate type 1 diabetes"; 'naltrexone buproprion type 1 diabetes'; 'surgical treatment of obesity type 1 diabetes.' Randomized controlled trials (RCTs), systematic reviews of RCTs and real-world observational studies were included in this review.

NUTRITION, EXERCISE AND DIABETES EDUCATION

The majority of weight loss programs include nutritional counseling. Generally, dietary intervention in obesity focuses on reducing total caloric intake. A reduction of 500–1000 kcal/day may lead to 0.5–1 kg/week or about 5% body weight loss over 6 months. Additionally, data suggests choosing a specific diet may be less impactful than finding one that is sustainable. Weight loss programs for people living with T1D have also shown benefit; focus on diets enriched with carbohydrates at a lower glycemic index and a higher fiber count may reduce the weight gain after bolus insulin [11]. Yet, there are no consistent randomized controlled trials demonstrating benefit of low carbohydrate or ketogenic diets over others in T1D [12]. Similarly, data are lacking for intermittent fasting programs in T1D; more so, these diets may increase the risk of significant hypoglycemia and impairment of the glucagon effect.

Physical activity on its own may be of only modest benefit in weight loss. Yet, it has shown benefit to cardiovascular and psychological health. Additionally, physical activity reduces risk of weight

re-gain [13]. Data also suggests patients with T1D may be less active [14]. The reasons behind less physical activity may be multifactorial; it is likely to include need for planning surrounding meals, insulin dosing and the risk of hypoglycemia. Currently, the American Diabetes Association (ADA) recommends 150 min or more of moderate to vigorous intensity exercise per week spread out over at least 3 days [15]. It is important to individualize physical activity recommendations.

Anxiety, depression, eating disorders, and the distress of a chronic disease may also lead to weight gain. Behavioral therapy may be required to assist in developing coping skills, stress reduction and stimulus control. Medications to treat anxiety or depression may be required but may also lead to further weight gain.

To achieve meaningful change in weight, the ADA recommends a multidisciplinary approach to weight management, including diabetes self-management education and support (DSMES) services [15]. In a retrospective review of a multidisciplinary approach, Mottalib *et al.* enrolled patients with T1D in a high-intensity face-to-face lifestyle intervention in a 12-week program which resulted in 6.4% body weight loss [16]. The intervention also led to a 0.4% hemoglobin A1c (HbA1c) reduction. The authors matched patients with a similar cohort (SC); the SC group showed no change in weight or HbA1c.

INSULIN FORMULATIONS AND PUMP THERAPY

Clinical trials comparing insulins head-to-head, including short- and long-acting formulations have reported modest differences in weight gain.

In 2015, Home *et al.* reported results from a head-to-head randomized clinical trial comparing insulin glargine 300 units/ml and glargine 100 units/ml [17]. Five hundred and forty-nine patients with type 1 diabetes with an average of 21 years duration and an average BMI of 27.6 kg/m^2 were recruited. The change in HbA1c was equivalent between the two insulins. At 6 months, glargine 300 units/ml participants gained 0.6 kg less weight than glargine 100 units/ml participants [confidence interval (CI) −1.1 to −0.03, $P = 0.037$].

In a separate study of patients with T1D and an average BMI of 26 kg/m^2, Heller *et al.* compared insulin degludec and glargine 100 units/ml [18]. After 1 year, HbA1c and overall confirmed hypoglycemia outcomes were similar between the two insulins. Mean weight gain was also similar in both treatment groups (1.8 kg insulin degludec vs. 1.6 kg with glargine 100 units/ml). Insulin degludec and glargine 100 units/ml were again compared in a head-to-head 26-week flexible dosing protocol [19]. Glycemic control was similar between the groups. Confirmed rates of hypoglycemia were similar between the two groups and weight gain was not statistically different at 52 weeks between degludec free-flex (1.3 kg) and glargine 100 units/ml (1.9 kg).

Weight gain has also been reported when comparing multiple daily insulin injections (MDI) and insulin pump therapy (CSII). In one retrospective review, annual changes in body weight, HbA1c and daily insulin doses over 6–10 years were compared in T1D adult patients either on CSII ($n = 90$) or MDI ($n = 90$) [20]. During a mean follow-up of 9.1 years, body weight increased on average 0.5 kg/year with no significant difference between groups. In a separate systematic review of 33 randomized clinical trials of children or adults comparing CSII and MDI with or without continuous glucose monitoring, Hsin-Chieh *et al.* reported HbA1c, hypoglycemia rates and other outcomes [21]. HbA1c was lower with CSII than MDI in all but one study; severe hypoglycemia events were no different. There was no difference in weight gain between the CSII and MDI groups. In a separate review by Fang *et al.*, efficacy and safety closed loop pump (CL) therapy was compared to sensor augmented pump (SAP) therapy [22]. Among 12 randomized trials, CL demonstrated lower HbA1c levels. CL was associated with fewer hypoglycemic events, which may portend weight benefit compared to SAP.

METFORMIN

Although society guidelines have modified recent recommendations, metformin has historically been first-line therapy for the treatment of T2D. It is not currently approved for use in T1D. Metformin reduces hepatic gluconeogenesis and improves peripheral insulin sensitivity [23]; it also decreases glucose absorption and does not increase the risk of significant hypoglycemia. Metformin has shown to be of modest HbA1c benefit in T1D. A meta-analysis of 19 RCTs, including 1540 patients, demonstrated that when metformin was added to insulin therapy in T1DM, HbA1c was reduced by 0.26% [24]. The effect was only observed for 3 months of use and not present for longer durations. In the same meta-analysis, daily insulin dosing and fat mass were both reduced. Additionally, metformin treatment resulted in a significant decrease in body weight (−2.24 kg) and BMI (−0.6 kg/m^2). There was a statistically significant increase in gastrointestinal side effects with metformin compared to placebo (relative risk 2.01, CI 1.35–3.00) but no difference in severe hypoglycemia, lactic acidosis or diabetic ketoacidosis.

PRAMLINTIDE

Amylin is a naturally occurring hormone co-secreted with insulin; it is deficient in T1D. Amylin increases satiety, slows gastric emptying and decreases postprandial glucagon secretion; it also reduces postprandial glucose levels [25]. Pramlintide is an amylin analog and the only currently available noninsulin adjunctive therapy approved for the treatment of T1D. At doses of 60 mcg three times daily, Pramlintide has been shown to improve HbA1c levels by 0.25% when compared to placebo [26]. A similar effect was seen at 30 mcg four times daily with a 0.27% HbA1c reduction compared to placebo [27]. At the end of the 52-week trial, compared to baseline, weight was reduced by 0.4 kg in the pramlintide group compared to 0.8 kg weight gain in the placebo group. Despite benefits, widespread acceptance and use has been limited due to increased rates of hypoglycemia, gastrointestinal adverse effects and the requirement for additional injections.

GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS

Glucagon-like peptide-1 (GLP-1) receptor agonists are approved for the treatment of T2D, and in individuals who are overweight with co-morbidities or who are obese. GLP-1 receptor agonists stimulate insulin secretion in a glucose-dependent manner, decrease glucagon release, slow gastric emptying and increase satiety [28]. They have also shown cardiovascular benefit in patients with T2D when compared to placebo [29–31].

GLP-1 receptor agonists are not approved for adjunctive treatment of T1D but have been evaluated for their impact on glucose control, body weight and side effects. In the Lira Pump Trial, adults with T1D on an insulin pump were randomized to adjunctive liraglutide 1.8 mg daily or placebo over a 26-week period [32]. HbA1c levels were lower (0.7%) in the liraglutide arm when compared to placebo and there were no differences in hypoglycemia rates. The average starting BMI in the study was 30 kg/m^2 in the active arm and 29 kg/m^2 in the placebo arm; body weight was reduced 6.3 kg more in the active liraglutide arm compared to placebo. Additionally, there were no episodes of diabetic ketoacidosis; gastrointestinal adverse effects occurred more commonly with liraglutide. The same group published a follow-up study presenting a secondary analysis focusing on body composition and change in food intake [33▪]. They reported reductions in total fat (−4.6 kg) and lean body (−2.5 kg) mass with the use of liraglutide; energy intake was also lower with liraglutide. Energy input from added sugars decreased by 27% in the liraglutide arm compared to a 14% increase with placebo.

The ADJUNCT ONE and TWO studies compared adjunctive liraglutide to placebo in individuals with T1D on insulin [34,35]. Once daily liraglutide was associated with significant HgA1c improvement. Mean body weight loss in ADJUNCT ONE was greater in all liraglutide groups compared to placebo (−4.9 kg, 3.6 kg, 2.2 kg for 1.8 mg, 1.2 and 0.6 mg doses, respectively). Body weight loss in ADJUNCT TWO was also greater (−5.1 kg, 4.0 kg, 2.5 kg for 1.8, 1.2, 0.6 mg doses, respectively) when compared to placebo (0.2 kg). Adverse events included more frequent symptomatic hypoglycemia in both ADJUNCT ONE and TWO; hyperglycemia with ketoacidosis was also reported.

In a meta-analysis by Park *et al.*, 24 randomized trials using four different GLP-1 receptor agonists with a total of 3377 T1D patients were reported [36▪]. Weight loss data were tallied in 17 studies; average weight loss from GLP-1 receptor agonists was 4.9 kg for liraglutide 1.8 mg dosing, 3.77 kg for liraglutide 1.2 mg dosing, 2.27 kg for liraglutide 0.6 mg dosing, and 4.06 kg for exenatide (all compared to placebo). Additionally, HbA1c was reduced by 0.09% with liraglutide compared to placebo; total daily insulin dose was also lower.

In a recently published real world study, Edward *et al.* reported on a retrospective chart review of GLP-1 receptor agonists and SGLT-2 inhibitors in the management of T1D [37▪]. They identified 76 patients who ever used a GLP-1 receptor agonist for more than 90 days. Patients experienced statistically significant reductions in weight compared to those not taking GLP-1 (90.5 vs. 85.4 kg). Additionally, HbA1c (7.7% vs. 7.3%), and total daily insulin doses (61.8 vs. 41.9 units) were lower. GLP-1 receptor agonists were discontinued due to adverse events in 26.9% of patients. In a second retrospective chart review of 54 patients with T1D on a GLP-1 receptor agonist, Mohandas *et al.* reported an average weight loss of 3.16 kg with use [38]. Mean GLP-1 receptor agonist use was 23.85 months and included semaglutide, dulaglutide, exenatide ER, and albiglutide. Additionally, mean HbA1c was reduced by 0.71%, time-in-range (70–180 mg/dl) increased by 12.15%; DKA admissions were also reduced.

DUAL HORMONAL AGONISTS

The newest class of medications used for the treatment of TT2DD are dual GLP-1/gastric inhibitor polypeptide (GIP) agonists. Significant benefits of weight loss [39] and HbA1c for T2D [40] have been reported in clinical trials. Currently, the only FDA

approved agent within the class is tirzepatide, which is approved for the treatment of T2D but not the treatment of obesity.

At this time, there are no clinical trials reporting head-to-head data on its use in T1D. One case report recently published by Mendoza and Pasiani [41] described a 23-year-old female with T1DM for 13 years duration, treated with an insulin pump; her HbA1c was 7.4% and BMI 38 kg/m^2. Weekly injectable tirzepatide was added; doses reached 7.5 mg weekly at time of reporting. Glycemic measures improved and weight had decreased from 195 to 188 pounds.

SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors decrease glucose reabsorption in the proximal renal tubule leading to increased glucose excretion by the kidneys [42]. In the United States, they are approved for the treatment of T2D, heart failure and chronic kidney disease. They are not approved for the treatment of obesity. Additionally, SGLT-2 inhibitors are not approved for the treatment of T1D in the United States; dapagliflozin and sotagliflozin are approved for use in Europe. Euglycemic diabetic ketoacidosis (DKA) has been a primary concern in preventing approval for its use in T1D. Real-world rates of DKA have been reported to be approximately 7.1 per 100 person-years in T1D [43].

A number of clinical trials have compared SGLT-2 inhibitors to placebo in T1D. When compared to placebo, SGLT-2 inhibitors spur weight loss. In the DEPICT-1 trial, dapagliflozin 5 mg or 10 mg was compared to placebo in 708 patients with T1D [44]. Body weight was reduced by 2.95% and 4.54% in 5 and 10 mg doses, respectively. Additional outcomes included a reduction in HbA1c by 0.33% and 0.36% with dapagliflozin 5 mg and 10 mg compared to placebo. Hypoglycemic events were comparable but DKA was higher in the active arms (4.0% dapagliflozin 10 mg, 3.4% dapagliflozin 5 mg and 1.9% placebo). In the DEPICT-2 trial, Mathieu *et al.* reported results from a similar trial design in patients from Asia, mostly from Japan [45]. In the study, 813 patients with T1D were randomized to dapagliflozin 5 mg, 10 mg or placebo. Mean percentage body weight loss was 4.42% and 4.86% with 5 mg and 10 mg dosing compared to placebo. HbA1c was reduced 0.2% and 0.25% with 5 mg and 10 mg dosing compared to placebo. More participants experienced DKA in the active arms (4.1% 5 mg, 3.7% 10 mg and 0.4% placebo).

The EASE trials evaluated the SGLT-2 inhibitor, empagliflozin, added to insulin therapy in 1707 patients with T1D [46]. Doses of empagliflozin of 2.5 mg, 10 mg and 25 mg daily reduced mean weight by 1.8 kg, 3.0 kg and 3.4 kg, respectively. Reductions in HbA1c, total daily insulin dose and systolic blood pressure were also reported; DKA occurred more frequently with empagliflozin 10 mg (4.3%) and 25 mg (3.3%) when compared to empagliflozin 2.5 mg (0.8%) and placebo (1.2%). In a separate trial, Garg *et al.* randomly assigned 1402 patients with T1D on insulin to treatment with the combined SGLT-1 and 2 inhibitor, sotagliflozin 400 mg daily or placebo [47]. When compared to placebo, patients in the active arm lost 2.98 kg of weight and had a reduced HbA1c of 0.46%. The rate of DKA was higher in the sotagliflozin group than placebo (3.0% vs. 0.6%).

Finally, in a real-world study evaluating efficacy and safety of SGLT-2 inhibitors, Palanca *et al.* reported results from a retrospective review of patients treated at two European centers [48▪]. Outcomes from 199 adults with T1D who initiated SGLT-2 inhibitors adjunct to insulin were collected. Mean body weight loss was 2.9 kg after 12 months of use; amongst patients with a BMI >27 kg/m^2, weight loss reached an average of 3.5 kg. Other outcomes included average reduction in HbA1c of 0.5%, 8.5% lower insulin dosing and an eGFR increase of 4.5 ml/min/1.73 m^2. Nearly 30% of patients reported adverse events; these included genital infections, ketosis and diabetic ketoacidosis.

ORLISTAT

Orlistat is approved for the treatment of obesity; it is a reversible inhibitor of lipases and reduces absorption of fat by approximately 30% [49]. A Cochrane database meta-analysis, that included 11 randomized controlled trials using 120 mg orlistat three times daily, reported a 2.9% greater weight loss compared to placebo [50]. Orlistat can lead to diarrhea, flatus and fecal urgency. Contraindications for use include chronic malabsorption, cholestasis and nephrolithiasis. There are no clinical trials evaluating the safety of orlistat use in people living with T1D.

NALTREXONE-BUPROPRION

Naltrexone–buproprion is also approved for the treatment of obesity. It combines an opioid receptor agonist (naltrexone) with dopamine and norepinephrine reuptake inhibition (buproprion) to reduce appetite. At the highest dosing, naltrexone–buproprion SR 32/360 mg, patients lose an average of 4.5% body weight when compared to placebo [11]. Common side effects include nausea,

constipation, headache, dizziness, dry mouth and diarrhea. Contraindications to use include uncontrolled hypertension, seizures, eating disorders, chronic opioid use, and concurrent use of monoamine oxidase inhibitors. There are no clinical trials evaluating the safety of naltrexone-bupropion use in people living with T1D.

PHENTERMINE–TOPIRAMATE

The phentermine–topiramate combination is approved for the treatment of weight loss in obesity. It includes phentermine, which is a sympathomimetic amine anorectic, first used for weight loss in 1959. Topiramate is an anticonvulsant that carries multiple properties augmenting appetite suppression. In the CONQUER and SEQUEL trials, the combination therapy reduced weight by 5.1% in low dose and 10.9% in high dose formulations [11]. Side effects may include paresthesias, dizziness, insomnia, constipation and dry mouth. Contraindications include glaucoma, hyperthyroidism, and concurrent use of monoamine oxidase inhibitors. There are no clinical trials evaluating the safety of phentermine-topiramate in people living with T1D.

SURGICAL TREATMENT OF OBESITY

Bariatric surgery may be an option in patients with T1D and obesity. The international federation for surgery of obesity supports procedures in T1D for patients with BMI $\geq$35 kg/m^2 with or BMI $\geq$40 kg/m^2 without co-morbidities [51]. The majority of safety and efficacy outcomes of bariatric surgery in T1D are published as small case reports. The largest retrospective review was published by Hoskuldsdottir *et al*. in 2020. They compared 387 age, sex, and BMI-matched patients with T1D with Roux-en-Y to those not undergoing the procedure [52]. In their nationwide cohort study, with follow-up of 9 years, surgery was associated with a lower risk of cardiovascular disease, cardiovascular death, hospitalization for heart failure and stroke. There was a higher risk of hypoglycemia after surgery. Patients in the surgical cohort lost an average of 38 kg of weight compared to 6 kg in the control group. In separate a retrospective review of 32 patients with T1D undergoing bariatric surgery, patients had a mean decrease in BMI of 9 kg/m [2,53]. Safety surrounding hypoglycemia, substance abuse and DKA are noted concerns.

CONCLUSION

People living with T1D are at-risk for the development of obesity due to multiple factors. Similar to the general population, weight loss may improve outcomes in T1D especially as they relate to cardiovascular health, kidney disease and mortality. Yet treatment does not come without risk, especially with T1D, and they may include hypoglycemia and diabetic ketoacidosis. At this time, more studies across all lines of treatment are needed to evaluate both efficacy and safety.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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