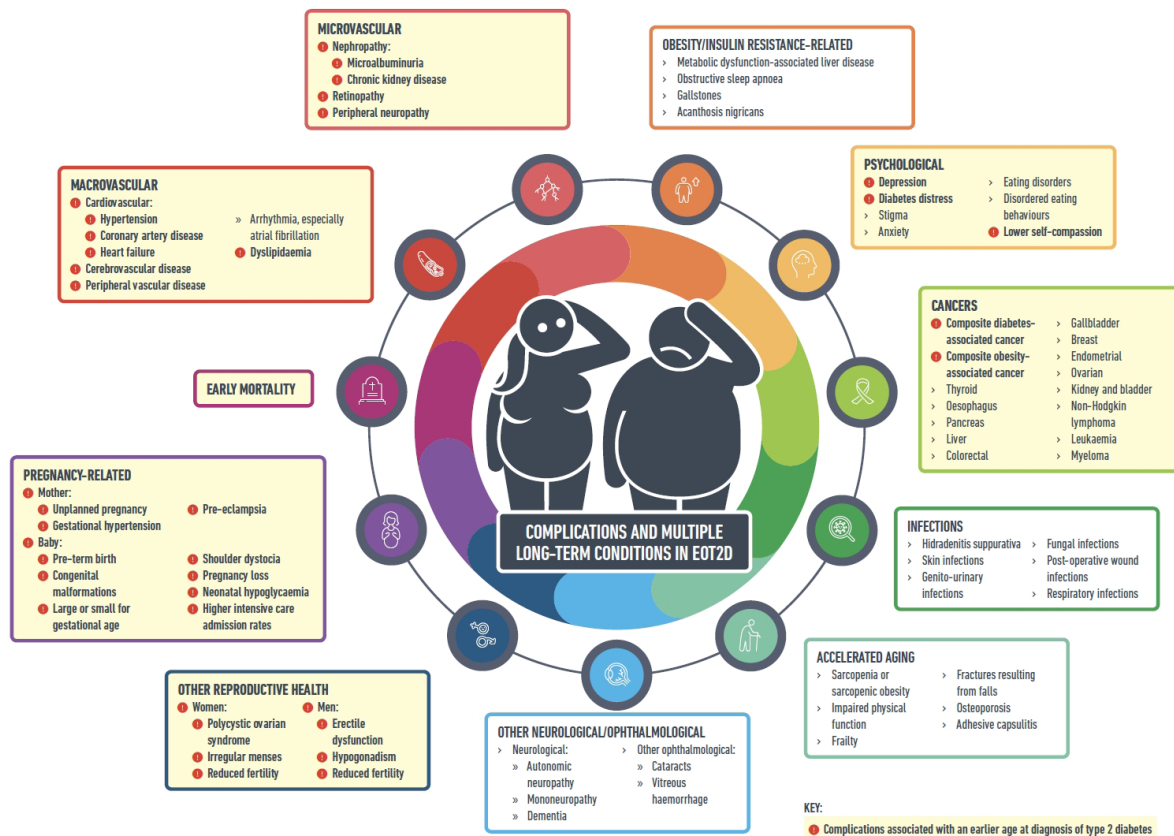


Management of Early-Onset Type 2 Diabetes in Adults: Current Evidence and Future Directions

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Highlights

- EOT2D is increasing globally and linked to more complications and premature mortality.
- Individuals with EOT2D face stigma, clinical inertia, and competing life demands.
- Key targets include weight, β -cell function, cardiometabolic risk, and mental health.
- Bariatric surgery, tirzepatide, and lifestyle programs show potential benefit.
- Digital and educational interventions are promising but require further RCT evidence.

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Management of Early-Onset Type 2 Diabetes in Adults: Current Evidence and Future Directions

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The global prevalence of early-onset type 2 diabetes (EOT2D) is rising rapidly. Adults with EOT2D represent a high-risk population characterised by increased rates of microvascular and macrovascular complications, adverse psychological wellbeing and psychiatric comorbidities such as depression, and premature mortality compared to those with later-onset type 2 diabetes mellitus. This emerging population faces unique challenges, including high levels of diabetes-related stigma, clinical inertia, and competing life demands, such as starting a family. This review synthesises current evidence on the clinical management of EOT2D. Key therapeutic targets include weight reduction, preservation of β -cell function, cardiometabolic risk management, and psychological support. Overall, there are few randomized controlled trials (RCTs) undertaken specifically in adults with EOT2D. However, we summarise early data from the few RCTs that do report outcomes specific in young adults, with bariatric surgery, tirzepatide and intensive lifestyle interventions emerging as particularly effective treatments. There is a strong rationale that technology-based inventions and structured education programs may prove to be effective treatments but data from RCTs is lacking. We provide broad recommendations for future research and clinical practice based on the current evidence. In conclusion, substantial further research is required to inform tailored, evidence-based guidelines and improve long-term outcomes in this underserved population.

Keywords: Bariatric surgery; Diabetes mellitus, Type 2; Lifestyle; Pharmacology; Randomised controlled trials; Technology; Weight loss; Young adult

INTRODUCTION

Historically, type 2 diabetes mellitus (T2DM) has been considered a disease affecting middle-to-older aged adults; although the prevalence of 'early-onset type 2 diabetes' (EOT2D; diagnosis of T2DM aged <40 years [1,2]), is rapidly increasing [3]. Young adults currently constitute 15% to 20% of all adults diagnosed with T2DM worldwide [1,4-6]. This is particularly alarming as EOT2D is characterised by a high-risk phenotype, with diagnosis of T2DM at an earlier age associated with a higher risk of micro- and macrovascular disease [1,7-10], accelerated ageing [11], and increased risk of mortality in compar-

ison to later-onset T2DM [7,8,12,13]. As well as physical complications, EOT2D is associated with greater burden of mental illness, such as anxiety, depression, and diabetes-related distress [14,15]. There is also evidence that despite the high risk of complications, health systems may not be meeting the needs of individuals with EOT2D: compared with later-onset T2DM, EOT2D is associated with lower rates of attendance at health-care appointments [16,17], suboptimal medication-taking behaviors [18,19], as well as a lower proportion achieving treatment targets [20]. This may be related to competing stressors associated with young adulthood, including early-careers, education, lower income or having a younger family [21].

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Despite the increasing prevalence of EOT2D and its associated risks, there is a severe lack of clinical research in this population. Indeed, a recent review identified that young adults aged 18 to 39 years represent <5% of total participants included in prominent clinical trials [22]. It is therefore unsurprising that there are no specific clinical guidelines for the management of EOT2D. Given the high-risk phenotype associated with EOT2D as well as unique life circumstances associated with EOT2D, it cannot be assumed that guidelines and evidence for older adults with T2DM will be relevant to adults with EOT2D.

This review aims to provide an overview of evidence-based treatment targets and interventions for the management of EOT2D in adults, focusing on data from randomized controlled trials (RCTs), to guide current clinical practice and identify directions for future research.

It is important to note that children are outside the scope of this review, due to physiological differences and differences in licenced medication between adults and children, and because there are already specific guidelines available for the management of T2DM in children [23,24]. For similar reasons, the management of T2DM during pregnancy was not included within the scope of this review.

TREATMENT TARGETS

Considering the more aggressive disease course in adults with EOT2D compared with later-onset T2DM (Fig. 1), and the unique life circumstances associated with young adulthood, we highlight several treatment targets which are of particular therapeutic importance for adults with EOT2D.

Weight reduction

Excess body weight has long been established as a causal factor in the development of T2DM [25], and weight reduction is crucial in managing the condition, regardless of the age of diagnosis. Notably, magnitudes of weight loss exceeding 10% can lead to remission of T2DM [26-29]. The benefits of weight loss also far exceed those related specifically to glucose control, with demonstrable improvements observed in cardiometabolic risk factors and quality of life [30]. A younger age at T2DM diagnosis has consistently been associated with a higher body mass index (BMI) and excess visceral adiposity [4,31-36]. As such, it is likely that excess adiposity is a key aetiological driver in developing T2DM at a younger age, and likely contributes to increase rates of obesity-associated complications for individuals

with EOT2D as compared to older-onset (Fig. 1). Consequently, interventions targeting weight reduction in those living with overweight and obesity are essential in this group, as they are likely to reverse the aetiological processes of T2DM, but also reduce the risk of obesity-associated complications [37,38].

Preserving β -cell function

EOT2D is associated with a rapid decline in β -cell function [39-42]. The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study found that youth (aged 10 to 17 years) with T2DM experienced a 20% to 35% annual decline in β -cell function, which is significantly higher than the ~7% decline seen in older individuals [43-45]. β -Cell dysfunction is associated with impaired glycaemic control and a greater likelihood of treatment failure in both younger and older adults with T2DM [43,46]. Furthermore, β -cell function has been shown to be modifiable, as early tight glycaemic control can improve and maintain β -cell function in older populations [47]. Given the critical role of β -cells in regulating blood glucose, early and intensive interventions are likely to preserve β -cell function, delay disease progression, and reduce the long-term risk of diabetes-related complications in adults with EOT2D.

Cardiometabolic management

EOT2D is also associated with higher cardiovascular morbidity [8], often related to the coexistence of metabolic abnormalities such as high blood glucose, dyslipidemia, and hypertension (Fig. 1) [36,48,49]. Indeed, throughout the disease course individuals with EOT2D have consistently higher glucose levels than those with later-onset T2DM, leading to a more than three-fold increase in cumulative glycaemic exposure by the age of 75 years [50]. Hypertension and dyslipidemia are also commonly associated with EOT2D [2], with concerning implications. For instance, each decade earlier that hypertension is diagnosed increases the risk of cardiovascular disease by 11% [51]. Even with statin therapy for dyslipidemia, individuals with EOT2D continue to exhibit a significant burden of atherogenic apolipoprotein particles compared to those with later-onset T2DM, though the long-term consequences remain unknown [52]. Managing hyperglycemia, hypertension, and dyslipidemia are likely to be essential in preventing complications associated with EOT2D.

Psychological wellbeing

Individuals diagnosed with EOT2D face a disproportionately

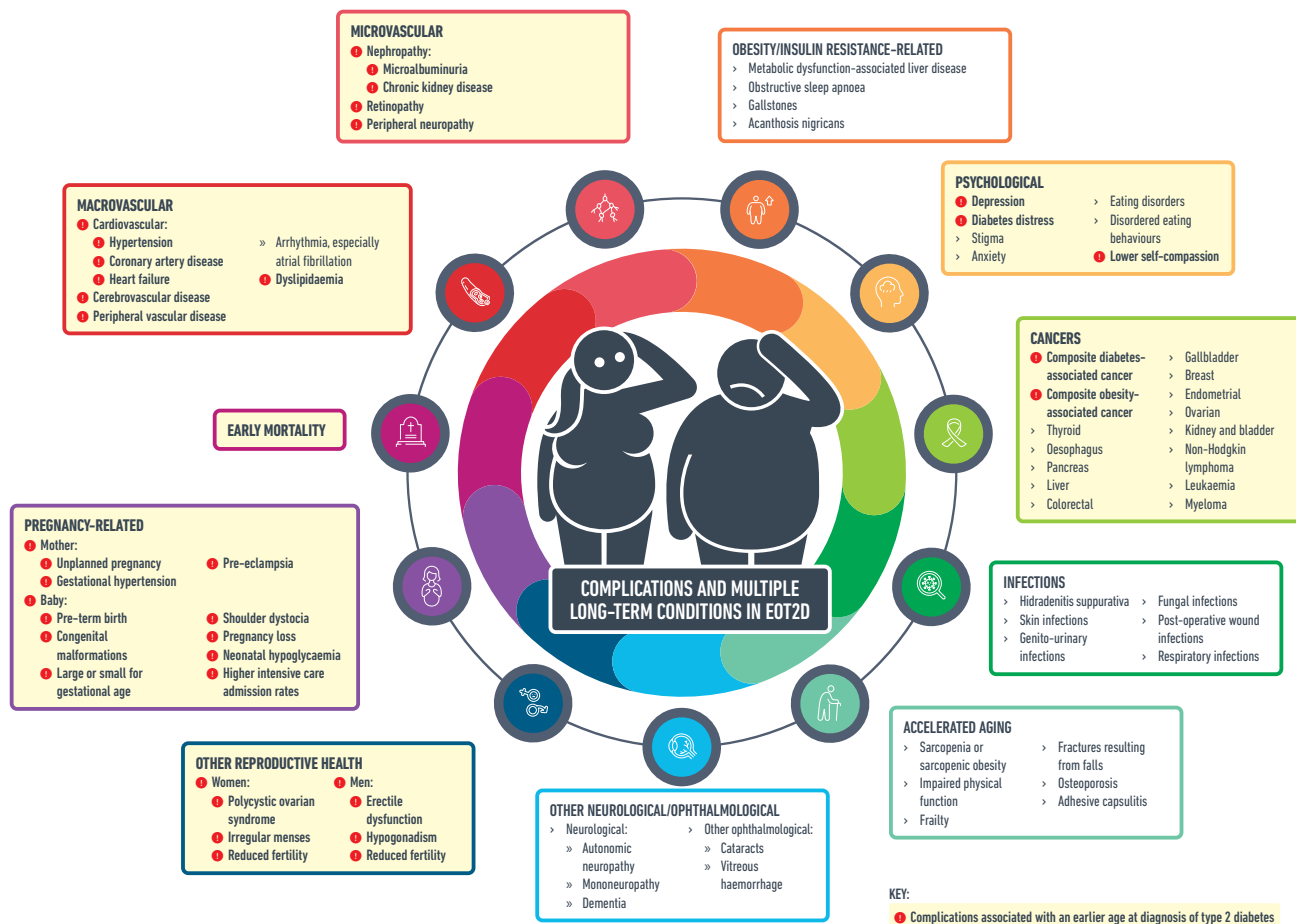


Fig. 1. Illustrates the broad range of complications and coexisting long-term conditions observed in individuals with early-onset type 2 diabetes (EOT2D). Conditions for which stronger evidence suggests increased severity or prevalence in EOT2D as compared to later-onset type 2 diabetes (LOT2D) are highlighted using a red '!' and bold text.

high burden of adverse psychological and mental-health complications compared to those with later-onset disease. Rates of hospitalisation due to mental illness are significantly higher among those with EOT2D [53], and there is a greater prevalence and severity of depressive symptoms [54]. Diabetes-specific distress is markedly more common, with 50% of adults with EOT2D reporting moderate-to-high levels, compared to 19% among individuals diagnosed with T2DM aged ≥ 60 years [54]. Moreover, people with EOT2D report increased feelings of self-judgment and social isolation, along with lower levels of self-compassion [54]. These psychological difficulties are strongly associated with poorer quality of life, suboptimal glycaemic control, and a heightened risk of diabetes-related complications [55]. The psychological burden associated with EOT2D can be exacerbated further by stigma or negative so-

cial judgement, which is frequently reported by individuals with EOT2D [56,57]. This can ultimately lead to heightened feelings of shame, self-blame, embarrassment and exclusion from society [57]. As such, improving mental wellbeing is an essential treatment target for individuals with EOT2D and is likely to improve quality of life and engagement with care.

INTERVENTIONS TO IMPROVE OUTCOMES IN ADULTS WITH EOT2D

A summary of RCTs to assess the effectiveness of interventions to improve outcomes in adults with EOT2D is provided in Table 1.

Pharmacological interventions

In the last two-decades, there has been a substantial increase in

Table 1. Summary of RCTs to assess the effectiveness of interventions to improve outcomes in adults with early-onset type 2 diabetes mellitus

Types of intervention	Study	Country(s)	Sample size	Sample description	Duration of follow-up	Investigated treatments	Primary outcome	Summary of findings
Pharmacological	Chan et al. (2021) [65] (VERIFY study sub-analysis)	Global	EOT2D n=186; LOT2D n=1,815	EOT2D Age 35.8±4.2 years BMI 30.5±5.1 kg/m ² LOT2D Age 56.2±7.5 years BMI 31.1±4.7 kg/m ²	5 yr	Metformin up to 1,000 mg twice daily alone or in combination with vildagliptin 50 mg twice daily	Treatment failure (HbA1c ≥ 7.0%) at two consecutive scheduled visits following randomization	Participants with EOT2D receiving combination therapy experienced reduced risk of treatment failure (50.5%) compared to monotherapy (73.3%). Those with EOT2D experienced higher rates of treatment failure compared with participants with later-onset T2DM when receiving both methods of treatment (42.9% combination therapy & 61.0% monotherapy).
			Zeidler et al. (2024) [66] (SURPASS study sub-analysis)	Global	EOT2D n=762; LOT2D n=3,030	EOT2D Age (yr) SURPASS-1: 38.5±8.5 SURPASS-2: 45.1±9.6 SURPASS-3: 45.4±9.2 BMI (kg/m ²) SURPASS-1: 33.7±7.5 SURPASS-2: 35.4±7.8 SURPASS-3: 34.5±6.2 LOT2D Age (yr) SURPASS-1: 58.0±9.0 SURPASS-2: 59.7±8.2 SURPASS-3: 60.1±8.1 BMI (kg/m ²) SURPASS-1: 31.4±6.3 SURPASS-2: 33.9±6.6 SURPASS-3: 33.3±6.0	12 mo	Tirzepatide alone (5, 10, or 15 mg once weekly) or tirzepatide combined with metformin
	Middleton et al. (2022) [68]	Australia	n=20	Age 29.4±7.2 yr BMI 37.0±13.0 kg/m ²	12 mo	Rapid treatment intensification with metformin (1–2 g/day), empagliflozin (10–25 mg/day)+ liraglutide (0.6–1.8 mg/day)	HbA1c and ISSI-2 after 12 months	9/10 (90%) participants achieved glycemic control (defined as HbA1c < 6.5%) after 6 weeks of RTI and 5 (50%) were on mono or dual therapy at 12 months. 44% of RTI participants (4/9) and 33% of SOC participants (2/6) showed improved ISSI-2 compared to baseline after 12-months.

(Continued to the next page)

Table 1. Continued

Types of intervention	Study	Country(s)	Sample size	Sample description	Duration of follow-up	Investigated treatments	Primary outcome	Summary of findings
Bariatric surgery	Aung et al. (2016) [26]	Taiwan	EOT2D n=339; LOT2D n=219	EOT2D Age 33.5 ± 7.5 yr BMI 39.4 ± 8.5 kg/m ² LOT2D Age 50.6 ± 6.5 yr BMI 36.7 ± 7.5 kg/m ²	5 yr	Bariatric surgery (Roux-en-Y gastric bypass or sleeve gastrectomy)	Achievement of sustained diabetes remission (defined as HbA1c <6.0%) after 5 years	EOT2D patients had higher diabetes remission rates (65.3% vs. 54.2%) and greater percentage weight loss than LOT2D (30.4% vs. 21.6%) 5 years following surgery.
Lifestyle	Taheri et al. (2020) [75] (DIADEM-I study)	Qatar	n = 147	Age 42.1 ± 5.6 yr BMI 34.9 ± 5.5 kg/m ²	12 mo	12-week intervention including a low-energy diet (800–820 kcal/day) and physical activity support (target of 10,000 steps per day, with gradual progression to 150 min/week of unsupervised structured exercise)	Weight loss at 12 months following starting the intervention. Diabetes remission rates after 12 months (defined as HbA1c <6.5%)	Weight loss was greater in the intervention group (–12.0 kg) compared to the control group (–4.0 kg) after 12 months. 61.4% of participants in the intervention group achieved diabetes remission compared to 11.6% of those in the control group.
DSMES	Li et al. (2025) [110]	China	n = 120	Age 28.8 ± 0.8 yr BMI 27.0 ± 0.6 kg/m ²	12 mo	Internet-based platform with CGM-linked personalised feedback, education, remote support	Change in HbA1c at 12 months following baseline	Those in the intervention group had significantly greater reductions in HbA1c compared to the control group (–1.8% vs. –1.2%). Participants in the intervention also saw greater improvements in fasting blood glucose, insulin resistance, and β-cell function compared to those in the control group.

RCT, randomized controlled trial; VERIFY, Vildagliptin Efficacy in combination with metformin For early treatment of type 2 diabetes; EOT2D, early-onset type 2 diabetes; LOT2D, later-onset type 2 diabetes; BMI, body mass index; HbA1c, glycosylated hemoglobin; T2DM, type 2 diabetes mellitus; ISSI-2, insulin secretion-sensitivity index-2; RTI, rapid treatment intensification; SOC, standard of care; DIADEM-I, Diabetes Intervention Accentuating Diet and Enhancing Metabolism; DSMES, diabetes self-management education and support; CGM, continuous glucose monitoring.

the number of medications licenced for management of T2DM which reduce cardiovascular and renal risk, and enhance weight loss [58-60]. These medications include sodium-glucose cotransporter 2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs), both of which also have established efficacy in lowering glucose in youth (<18 years) with T2DM [61-63]. These medications may be of particular relevance for adults with EOT2D given the high risk of associated-cardiorenal complications. In particular GLP-1 RAs have potent anorexigenic and weight-lowering effects [64], which may be of particular importance given the high BMI associated with an earlier diagnosis of T2DM.

Currently, only two RCTs have reported data surrounding the effectiveness of pharmacological treatment in adults with EOT2D in sub-analyses of larger RCTs [65,66]. The Vildagliptin Efficacy in combination with metfoRmIn For early treatment of type 2 diabetes (VERIFY) RCT sub-analysis compared treatment outcomes between adults with EOT2D ($n=186$; 9.3%), and later-onset T2DM ($n=1,815$; 90.7%), who were randomized to either metformin monotherapy, or early combination therapy with metformin plus vildagliptin (a dipeptidyl peptidase-4 inhibitor) [65,67]. In adults with EOT2D, a reduced proportion experienced treatment failure (glycosylated hemoglobin [HbA1c] $\geq 7.0\%$) with early combination therapy (metformin and vildagliptin; 50.5%) compared to monotherapy (metformin only; 73.3%) over 5 years. Failure rates in both treatment groups were higher in the EOT2D population compared to the later-onset T2DM population (42.9% with early combination therapy; 61.0% with monotherapy) [65,67]. While the VERIFY RCT suggests that combination therapy with conventional treatments (such metformin and vildagliptin) may be an effective treatment for adults with EOT2D, it may be less effective than in older adults due to the observed higher rates of treatment failure with combination therapy in younger adults as compared to older adults.

Further evidence comes from a *post hoc* analysis of the SURPASS programme of RCTs, which examined the efficacy of subcutaneous tirzepatide—a dual GLP-1 RA and glucose-dependent insulinotropic polypeptide receptor agonist—in doses of 5, 10, and 15 mg on various metabolic outcomes [66]. Specifically, data come from the SURPASS-1 (vs. placebo), SURPASS-2 (vs. subcutaneous semaglutide), and SURPASS-3 (vs. insulin degludec) RCTs. The SURPASS-2 trial included the largest number of individuals with EOT2D, comprising ~22.0% of the total study sample ($n=1,878$), which is considerably

greater than the ~5.0% reported previously [22]. In this study, large HbA1c improvements were seen after 40 weeks: -2.6% (95% confidence interval [CI], -2.9 to -2.4) with 15 mg subcutaneous tirzepatide vs. -1.9% (95% CI, -2.1 to -1.7) with 1 mg subcutaneous semaglutide. Furthermore, 93.5% of participants achieved an HbA1c $<7.0\%$ with 15 mg tirzepatide, versus 75.3% with 1 mg semaglutide. There were also greater improvements in other cardiometabolic markers with tirzepatide versus semaglutide in individuals with EOT2D, respectively these were: -14.0% (95% CI, -15.3 to -12.6) vs. -5.4% (95% CI, -6.8 to -3.9) body weight reduction; -10.4 cm (95% CI, -12.5 to -8.4) vs. -5.7 cm (95% CI, -7.9 to -3.5) change in waist circumference; -6.0 mm Hg (95% CI, -8.2 to -3.8) vs. -5.2 mm Hg (95% CI, -7.5 to -2.8) change in systolic blood pressure; -26.1% (95% CI, -32.3 to -19.9) vs. -11.8% (95% CI, -19.7 to -3.8) change in triglycerides; 7.2% (95% CI, 3.7 to 10.6) vs. 3.1% (95% CI, -0.5 to 6.7) change in high-density lipoprotein cholesterol; -26.1% (95% CI, -19.9 to -32.3) vs. -5.6% (95% CI, -11.7 to 0.4) change in low-density lipoprotein (LDL) cholesterol. There were dose-response improvements in all metabolic markers with increasing tirzepatide dosages, with comparable improvements in these markers also seen in the SURPASS-1 and SUPPASS-3 RCTs. Observed improvements were similar between adults with EOT2D and later-onset T2DM, and there were no clear differences in the rates of adverse events between cohorts. The SURPASS programme of trials provides clear evidence that tirzepatide may be similarly effective at improving glucose control (in addition to a range of metabolic markers) in both individuals with EOT2D and later-onset T2DM.

Additionally, a small ($n=20$) open-label pilot RCT in Australian adults with EOT2D demonstrated that rapid titration of medication (metformin [1 g/day–2 g/day] \pm empagliflozin [10 mg/day–25 mg/day] \pm liraglutide [1.2 mg/day–1.8 mg/day]), guided by the use of continuous glucose monitoring (CGM), improved β -cell function (measured using the insulin secretion-sensitivity index-2) at 6 and 12 months, when compared with standard care [68]. This suggests that preserving or even improving β -cell function may be a realistic treatment target in adults with EOT2D, although trials in more individuals are needed.

Taken together, these studies highlight that both early combination therapy utilising traditional glucose-lowering medications, and more novel SGLT2i and GLP-1-based therapies, may be effective for managing T2DM. However, despite advances in medical management of T2DM generally, there re-

mains a distinct lack of data from RCTs in adults with EOT2D [22]. This is particularly concerning given the elevated metabolic burden and increased lifetime cardiovascular risk associated with EOT2D. As such, more dedicated trials in adults with EOT2D are needed to identify the most effective pharmacological combinations, and to understand the long-term health implications of these medications in this population.

Bariatric surgery

Bariatric surgery has consistently demonstrated high efficacy in promoting weight loss, improving glycemic control, and alleviating comorbidities in individuals with T2DM and in older adults with obesity [69]. Emerging evidence indicates that the effectiveness of bariatric surgery may be even greater in younger populations. Individuals with EOT2D tend to exhibit higher rates of diabetes remission and more substantial weight reduction following bariatric surgery, suggesting a heightened therapeutic benefit in this subgroup [26,70].

Specifically, one observational study demonstrated that those with EOT2D were more likely to achieve T2DM remission compared to those with later-onset T2DM 1 year (56.9% vs. 50.2%) and 5 years (65.3% vs. 54.2%) following bariatric surgery [26]. Additionally, individuals with EOT2D also achieved a greater percentage weight loss after 5 years compared to those with later-onset T2DM (30.4% vs. 21.6%). This is consistent with an additional observational study showing that 86% of adolescents (aged 13 to 19 years) achieved T2DM remission 5 years following bariatric surgery, compared to 53% of adults (aged 25 to 50 years) [70]. Importantly, these results remained unchanged even when diabetes duration was factored into the analysis. Indeed, bariatric surgery is now recommended when pharmacological and lifestyle interventions fail to achieve adequate glycemic control or address related comorbidities in youth (aged <18 years) with obesity and T2DM [24].

Given these data, the benefits of bariatric surgery for adults with EOT2D are clear. Further work is now required to understand the longer-term implications of bariatric surgery in adults with EOT2D.

Lifestyle interventions

Lifestyle modifications (i.e., changes to 24-hour physical behaviors, such as physical activity, sedentary time, sleep, structured exercise, and diet) are also fundamental components of T2DM management [71-73]. Indeed, intensive interventions incorporating very-low energy diets and increased physical ac-

tivity have been increasingly recognised as effective methods of improving T2DM management in adults and children [74]. However, there remains a dearth of studies investigating the impact of lifestyle interventions in adults with EOT2D [22].

To date, only one RCT has assessed the impact of an intensive lifestyle intervention on diabetes-related outcomes in adults with EOT2D. The Diabetes Intervention Accentuating Diet and Enhancing Metabolism (DIADEM-I) study combined a low-energy diet (through a total dietary replacement protocol; 800 to 820 kcal/day) with physical activity support (target of 10,000 steps per day, with gradual progression to 150 min/week of unsupervised structured exercise) for 12 weeks, with a further 12-week structured food reintroduction in individuals with T2DM (aged 18 to 50 years, T2DM duration <3 years) [75]. Weight loss after 12 months was greater in the intervention group (-12.0 kg; 95% CI, -9.7 to -14.2) compared to the control group who received standard care (-4.0 kg; 95% CI, -2.8 to -5.2) [75]. Additionally, 61.4% of intervention participants achieved diabetes remission, in comparison to 11.6% in the control group.

Despite the promising short-term results from DIADEM-I, evidence suggests that the durability of such outcomes may be limited. For example, in the Diabetes Remission Clinical Trial (DiRECT), which employed a similar low-energy diet approach, diabetes remission was observed in 46% of participants at 1 year, but dropped to only 12.9% after 5 years (7% following intention-to-treat-analysis) [28]. These findings highlight the potential for intensive lifestyle interventions to drive short-term improvements in diabetes outcomes, while also underscoring the challenge of sustaining those benefits over the long term [76,77]. Given the extended lifetime disease burden faced by individuals with EOT2D, further research into the effectiveness of longer-duration lifestyle interventions is essential, an area currently being explored through studies such as RESET for REMISSION [78].

Technology-driven approaches

Device technologies, including CGM sensors, insulin pumps, and closed-loop insulin therapy, have been recommended internationally for individuals with type 1 diabetes mellitus based on robust evidence supporting their effectiveness in improving glycemic control and quality of life [79-83]. In contrast, international guidelines for T2DM have yet to recommend these technologies broadly, with CGM recommendations typically restricted to patients in special circumstances (e.g., pregnancy

or those requiring insulin therapy with multiple-daily dosing regimens) [84-87]. This conservative stance is likely due to a historical lack of large, well-powered RCTs in the T2DM population. However, growing evidence suggests these technologies may also offer considerable benefits for individuals with T2DM, including those with EOT2D.

Indeed, a recent umbrella review demonstrated with moderate evidence certainty that CGM improves glycemic outcomes in T2DM (HbA1c mean difference with CGM, -0.40% [95% CI, -0.54 to -0.25]), irrespective of age and insulin-use status [88]. Additionally, a small number of studies in older adults have demonstrated that using CGM can also enhance weight loss, wellbeing, and health and lifestyle behaviors compared to self-monitoring of blood glucose [89-94], although data in adults with EOT2D is lacking. Notably, a few small RCTs (sample size ≤ 24 participants) in paediatric populations and young adults (aged ≤ 21 years) have demonstrated that consistent CGM use for ≤ 3 months may be beneficial for improving glycemic control and quality of life, with no increase in disease burden with technology use [95-97].

There is also growing evidence to suggest that insulin pumps and insulin closed-loop therapy can have positive effects for T2DM management, although largely in trials in older individuals. The OpT2mise RCT, which included adults with EOT2D amongst older participants aged 30 to 75 years (mean age \pm standard deviation = 55.5 ± 9.7 years), demonstrated that insulin pump therapy led to marked reductions in mean total daily insulin dose and improvements in HbA1c, compared to multiple-dose injection therapy [98].

Technological interventions such as CGM, insulin pumps, and closed-loop insulin delivery have demonstrated clear benefits for glycemic control, lifestyle outcomes, and treatment satisfaction in broader T2DM populations. However, despite the emerging evidence in older adults and preliminary data in younger age groups, there remains a complete absence of RCTs evaluating the use of these technologies specifically in adults with EOT2D. While technology shows promise for improving the management of EOT2D, individuals with EOT2D may face multiple barriers to adopting diabetes-related technologies (e.g., insulin pump therapy and CGM), including psychosocial concerns, stigma associated with device use, limited digital health literacy, and financial constraints related to device costs [99]. Effectively addressing these challenges will require coordinated, multisectoral collaboration involving technology developers, healthcare providers, research institutions, and

policymakers [99]. Crucially, the inclusion of individuals with lived experience throughout the development, implementation, and evaluation processes is essential to ensure that interventions are both patient-centered and contextually relevant [100]. This approach may support the advancement of precision medicine strategies aimed at identifying and mitigating individual-level barriers, while also promoting equitable, non-judgemental access to diabetes technologies by healthcare professionals [100].

Diabetes self-management education and support

Diabetes self-management education and support (DSMES) is widely regarded as a crucial element of interventions aimed at improving diabetes-related outcomes and plays a central role in establishing and implementing principles of care [74]. Indeed, evidence from studies largely in older adults suggests that traditional, face-to-face DSMES programmes are cost-effective and can improve knowledge and understanding, boosting patient confidence in managing diabetes, stabilising glycemic levels, improving behavioral outcomes, and increasing psychosocial wellbeing [101-103].

In an increasingly digital world, the use of digital-based DSMES programmes have become commonplace [104,105], accelerated by restrictions on face-to-face interventions during the coronavirus disease 2019 (COVID-19) pandemic [106]. Digital-based DSMES can support people to 'live well' with diabetes [107], showing promising and often comparable outcomes to face-to-face programmes [108,109]. Such digital-based programmes may be more appropriate for those with EOT2D given that reasons such as inconvenient timing, competing priorities, and diabetes-related stigma have been reported to limit attendance at face-to-face DSMES programmes [16,17].

To date, only one RCT has examined the effectiveness of an internet-based management system on diabetes-related outcomes in Chinese young adults newly-diagnosed with T2DM (aged 18 to 40 years, T2DM duration ≤ 6 months) [110]. The internet-based platform utilised participants' blood glucose data (captured in real-time via CGM) and changes in BMI to deliver personalised dietary and exercise recommendations. In addition, participants received weekly health reports summarising trends in glycemic control, had access to a library of educational resources, and were able to remotely communicate with healthcare professionals for tailored feedback. After 12 months, results demonstrated that participants receiving the

intervention ($n=60$) achieved significantly greater reductions in HbA1c compared to those receiving standard care ($n=60$) (-1.8% vs. -1.2% , $P<0.001$). Compared to participants in the control group, those receiving the intervention also had greater improvements in a plethora of secondary outcomes including fasting blood glucose, homeostasis model assessment of insulin resistance, homeostatic model assessment of beta-cell function, fasting C-peptide, triglycerides, LDL cholesterol, and patient-reported outcome measures such as the Short Form-36 (SF-36) and Patient Health Questionnaire (PHQ-9). Finally, a greater proportion of participants in the intervention achieved diabetes remission in comparison to those receiving standard care (60% vs. 37% , $P=0.03$).

While encouraging, the generalisability of the study's findings is limited, as the trial was conducted exclusively in Chinese young adults. Moreover, people with EOT2D remain underrepresented in research focused on DSMES [22]. Questions also persist regarding the long-term sustainability and effectiveness of such interventions [110]. Consequently, the evidence supporting DSMES for adults with EOT2D remains limited.

BARRIERS TO EFFECTIVE TREATMENT IN ADULTS WITH EOT2D

Severe underrepresentation of young adults in diabetes-related research means that treatment guidelines for these groups are often based on data from older adults [22]. However, existing methods of treatment may not be suitable for younger populations, where there may be differences in underlying risk factor profiles and rates of progression [2,31]. Furthermore, individuals with EOT2D experience unique challenges in adhering to medication and lifestyle therapies compared to older adults [18,19,76,77,111]. This is driven by a multitude of factors including complex and busy lifestyles (e.g., starting a family, education, and employment responsibilities) that may make accessing care in current health-systems difficult [15,112,113].

A lack of appropriate treatment methods may also contribute to higher levels of 'clinical inertia.' Defined as 'failure to initiate or intensify therapy according to clinical guidelines' [114], clinical inertia is a prominent issue experienced by up to two-thirds of individuals with T2DM in the UK [115]. Clinical inertia can occur because of clinician-, patient-, or system-level factors [116], and the young age of people with EOT2D may exacerbate patient-level barriers. Indeed, there is evidence to suggest that younger individuals with T2DM are less likely to

be prescribed cardioprotective, antihypertensive, or lipid-lowering therapies, as compared to older adults with T2DM [117].

Barriers to effective treatment may be further exacerbated when attempting to access newer medications such as tirzepatide. National formulary inclusion, prescribing restrictions, healthcare system infrastructure, and socioeconomic disparities may limit affordability and availability, particularly in underserved populations [118]. While the high number of emerging medications may increase availability and drive down costs over time [119], the current relatively high cost of these therapies limits integration into standard care [118]. Furthermore, concerns about the potential teratogenic effects of current and experimental treatments often lead to the exclusion of women of childbearing age from clinical trials [120], resulting in underrepresentation of this group in research. To mitigate these barriers, targeted strategies that aim to improve access to treatment, reduce delays in treatment intensification, and consider lifestyle-related challenges are required to deliver care that meets the specific needs of those with EOT2D.

RECOMMENDATIONS

As highlighted by the 2022 American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) consensus report, dedicated studies in adults with EOT2D are essential to enhance understanding of how to optimise management strategies that will ultimately reduce the health risks associated with the disease [74]. The current review emphasises this further and highlights the dearth of high-quality data available in this population. To enhance evidence in the area, specific recommendations for future research are highlighted in Fig. 2. Broadly, we call for research to investigate hard clinical outcomes associated with the interventions discussed in this review, in particular, dedicated trials investigating therapies proven to be disease-modifying in older populations given the high-risk nature of EOT2D. We further highlight that psychological wellbeing and quality of life are particularly important outcomes for future research, and emphasise that future research, and models of care, need to be adapted to meet the needs of individuals with EOT2D, as these are likely to be different to older populations.

The current lack of high-quality data in individuals with EOT2D means that age-specific, clinical guidelines are not forthcoming. Using the available evidence synthesised throughout this review, broad recommendations for clinical practice



Fig. 2. Recommendations for future research in adults with early-onset type 2 diabetes (EOT2D). RCT, randomized controlled trial; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

are outlined in Fig. 3. Our broad recommendations emphasise that the best quality RCT data exists for tirzepatide and bariatric surgery, albeit it that long-term data and hard clinical outcomes are lacking, and so these interventions should be preferentially considered. Intensive lifestyle intervention involving a low-energy diet should also be considered given data from DIADDEM-I; however, data in older population suggests the clinical benefits are likely to be short-lived. Given the high risk of complications for individuals with EOT2D, we further recommend intensive management of cardiometabolic risk factors including hypertension, dyslipidemia, and obesity. Additionally, based on the importance of preserving β -cell function and euglycemia in adults with EOT2D, we recommend early intensification of glucose-lowering therapies in this population. Although the VERIFY RCT demonstrates that early combination therapy with metformin and vildagliptin is more effective in

reducing HbA1c than metformin alone, the magnitude of metabolic improvement remained lower than that observed with tirzepatide or bariatric surgery. However, direct comparisons are limited due to differences in the populations studied. We therefore avoid specific recommendations about combination therapy in lieu of more robust evidence.

CONCLUSIONS

The rising prevalence and associated complications of EOT2D is a prominent global issue. Adults with EOT2D remain significantly underrepresented in research and current treatment options often fail to consider the unique challenges and circumstances associated with T2DM during young adulthood. Given the heightened risk of poor physical and mental health outcomes in this group, there is a clear need for more tailored

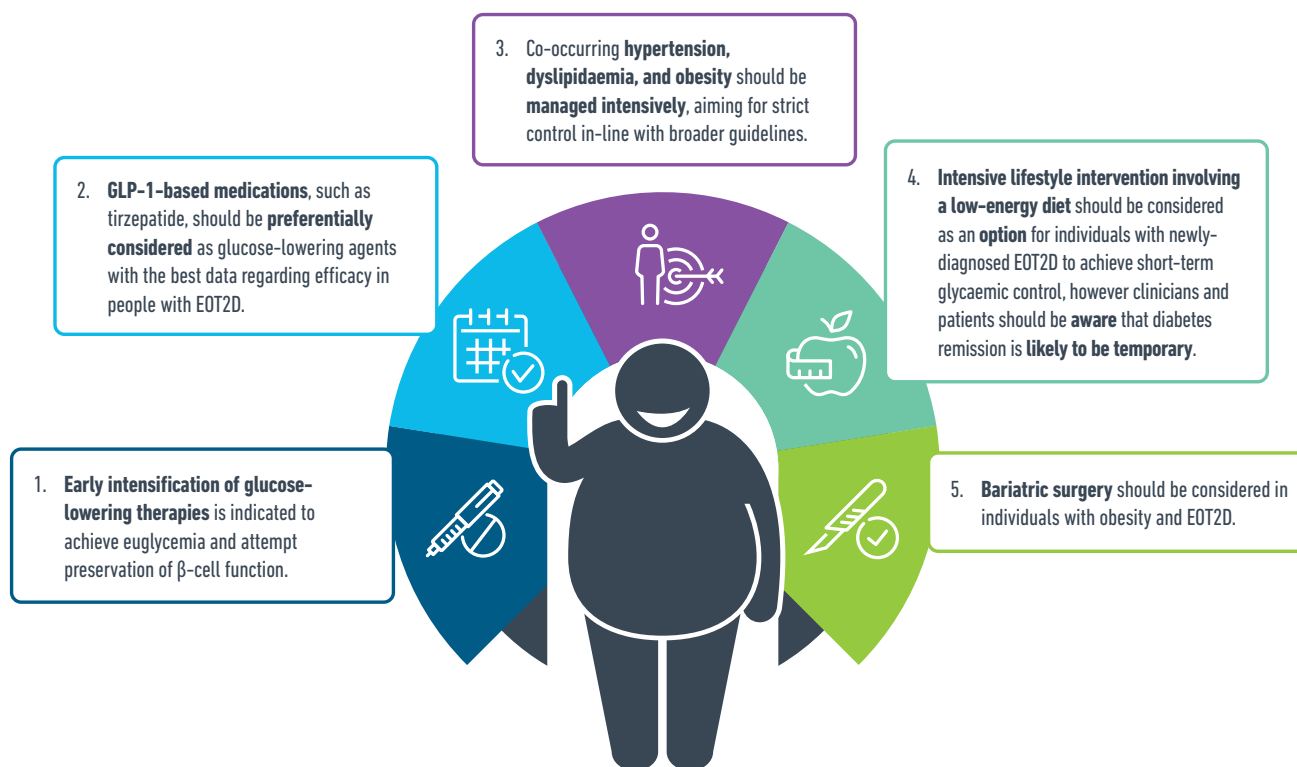


Fig. 3. Recommendations for clinical practice for adults with early-onset type 2 diabetes (EOT2D). GLP-1, glucagon-like peptide-1.

and effective interventions. While early findings from a small number of RCTs are promising, particularly for bariatric surgery, tirzepatide, and intensive lifestyle approaches, high-quality trials across all therapeutic areas are urgently needed to close the evidence gap and improve outcomes for this population.

CONFLICTS OF INTEREST

Professor Melanie J. Davies has acted as a consultant/advisor and speaker for Eli Lilly, Novo Nordisk and Sanofi, has attended advisory boards for AbbVie, Amgen, AstraZeneca, Biomea Fusion, Carmot/Roche, Daewoong Pharmaceutical, Sanofi, Zealand Pharma, Regeneron, GSK and EktaH and as a speaker for AstraZeneca, Boehringer Ingelheim and Zuellig Pharma. She has received grants from AstraZeneca, Boehringer Ingelheim and Novo Nordisk.

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