



Type 2 Diabetes in Young Adults: A More Aggressive Disease Treated with an Older Playbook

Lucia Bermejo^{1*}, Rasmus Vinther² and Maja Perkovic³

¹Department of Diabetology, Galician Institute of Endocrinology, Vigo, Spain

²Department of Diabetes and Endocrinology, Limfjord University Hospital, Aalborg, Denmark

³Department of Epidemiology, Dalmatian University Hospital, Split, Croatia

*Correspondence to: Lucia Bermejo, Department of Diabetology, Galician Institute of Endocrinology, Vigo, Spain

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Abstract

Type 2 diabetes diagnosed in adolescence and young adulthood behaves differently from the adult-onset disease on which its treatment is modelled. In the principal randomised trial, 51.8 per cent of participants on metformin monotherapy reached treatment failure over about four years, and beta cell function declined at 20 to 35 per cent annually, faster than reported in adult studies. Complications appeared early: after a mean of 3.9 years, 33.8 per cent had hypertension, 16.6 per cent microalbuminuria and 13.7 per cent retinopathy, in a population still in its teens and twenties. The mechanistic finding matters most for treatment. Loss of control was driven by rapid beta cell failure rather than by worsening insulin sensitivity, and was not explained by adherence or body mass index, which is the opposite of the adult pattern. Adding structured lifestyle support to metformin was not superior to metformin alone, and the arm that performed best was subsequently withdrawn from use in this age group on safety grounds.

Keywords: Youth-onset type 2 diabetes; Beta cell function; Treatment failure; Metformin; Early complications

Introduction

Type 2 diabetes was until recently a disease of middle age, and its treatment algorithms were derived from adult populations [1,2]. Diagnosis in adolescence and young adulthood has become steadily more common, particularly in minority ethnic groups [3,4,20]. Baseline characterisation of the principal trial cohort describes the population in which most of this evidence was generated [24].

The condition in this age group resembles adult type 2 diabetes in its pathophysiology, being characterised by insulin resistance and non-autoimmune beta cell failure rather than autoimmunity [5,6,23]. Acute and chronic complications in this age group were described well before the trial evidence accumulated [31]. That resemblance has encouraged the assumption that the adult treatment approach transfers.

A consensus report characterising the condition concluded that it differs from adult disease in ways that matter clinically, notably in the speed of beta cell decline and in the accelerated development of complications [5]. Cohort analyses report an

inverse relationship between age at onset and both complication risk and mortality [32,33,34]. This review examines what the trial evidence shows and why the adult-derived approach performs poorly.

Material and Methods

Search strategy: PubMed and the archives of the major diabetes, paediatric and endocrinology journals were searched for studies of type 2 diabetes with onset in youth or young adulthood. Search terms combined youth-onset type 2 diabetes with beta cell function, treatment failure, metformin, complications and adult comparison. Reference lists of the consensus report [5] and the principal trial reports [7,8] were screened by hand for primary sources.

Eligibility: Studies were included if they reported glycaemic, beta cell or complication outcomes in populations with youth-onset type 2 diabetes, or compared youth with adults using the same protocol. Studies in adult populations are cited as the comparator and identified as such.

Data extraction and handling: Design, population, the definition of treatment failure and the reported estimate were extracted as published. Whether a comparison between youth and adults used a common protocol, or set separate studies alongside one another, is stated in each case, because the two support different strengths of inference. This review reports trial findings and makes no dietary, caloric, exercise or prescribing recommendations. No pooling or re-analysis was performed. Figures 1 to 6 and Tables 1 to 3 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

How often treatment failed: In the principal randomised trial, 51.8 per cent of participants receiving metformin monotherapy reached the primary outcome of treatment failure, defined as an HbA1c of 8 per cent or above or inability to wean from insulin after its initiation, over approximately four years (Figure 1) [7,8]. Metformin monotherapy therefore provided durable control in only about half of those treated.

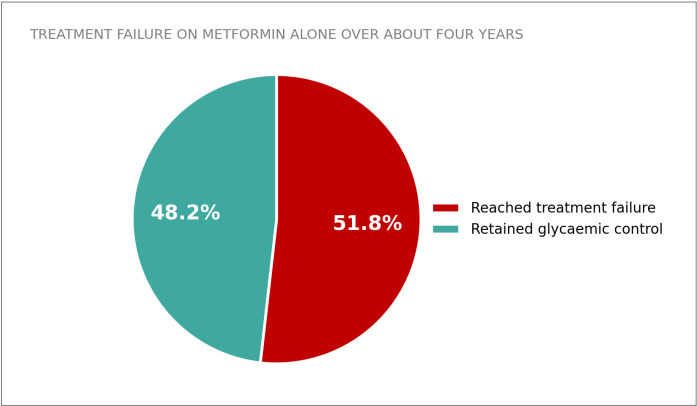


Figure 1: Treatment failure on metformin monotherapy over about four years [7,8]

What the trial arms showed: Combination of metformin with rosiglitazone gave better durability of glycaemic control, reducing sustained hyperglycaemia by 23 per cent, while metformin combined with intensive lifestyle intervention was intermediate and not superior to metformin alone (Figure 6) [7,9]. Rosiglitazone is no longer used in this age group because of safety concerns, so the most effective arm of the trial is not an available option [9,10].

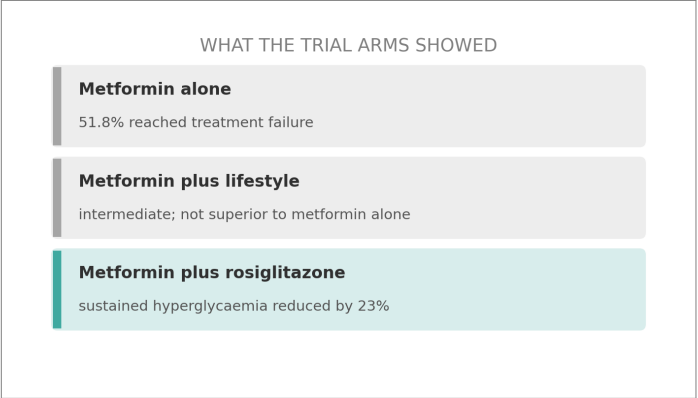


Figure 6: What the three trial arms showed [7,9]

Why control was lost: Deterioration in glycaemic control was associated with rapid loss of beta cell function rather than with worsening insulin sensitivity, and could not be explained by differences in adherence or body mass index (Figure 5) [7,11]. Beta cell function deteriorated at a rate of 20 to 35 per cent per year, described by the investigators as faster than in adult studies (Figure 2) [7,12].

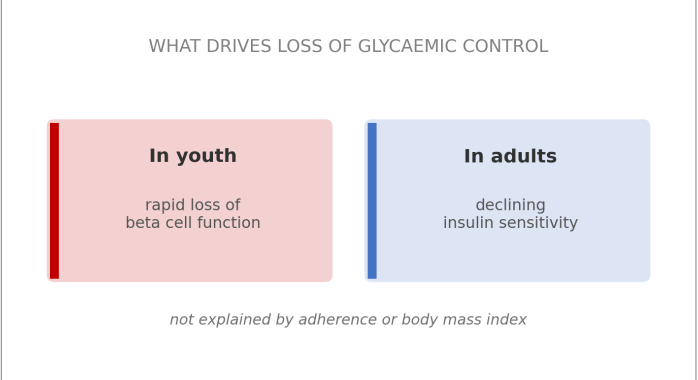


Figure 5: What drives loss of glycaemic control, by age of onset [7,11,13]

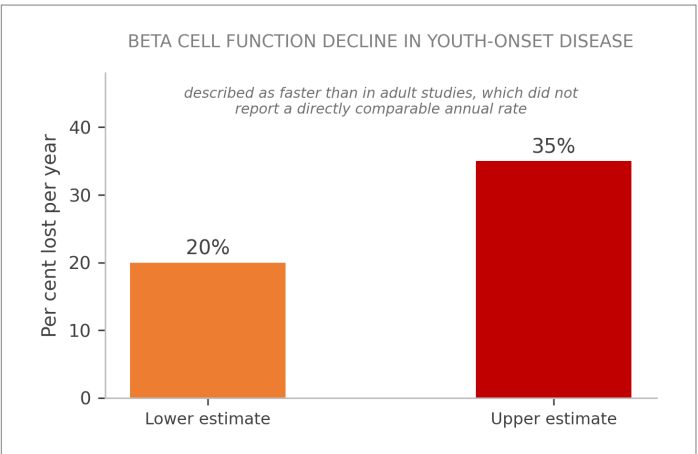


Figure 2: Reported annual decline in beta cell function in youth-onset disease [7,12]

The comparison under a common protocol: A study using hyperglycaemic clamps examined insulin sensitivity and beta cell function in adults and in youth with impaired glucose tolerance or recently diagnosed type 2 diabetes, at baseline, after 12 months of treatment and after a period off treatment. At baseline, youth had lower insulin sensitivity, lower insulin

clearance and considerably greater beta cell secretory responses than adults [13,14]. Beta cell function in youth declined markedly over 12 months of treatment, in contrast to adults, without significant differences between treatment groups [13,15]. In the same programme, lower insulin sensitivity was associated with loss of glycaemic control among adults, while poor beta cell function was the driving factor among youth [11,13].

Feature	Youth-onset	Adult-onset
Driver of loss of control	Beta cell failure	Insulin sensitivity
Beta cell decline	20 to 35% per year	Slower in adult studies
Response to treatment over 12 months	Marked decline	Not comparable decline
Baseline secretory response	Considerably greater	Lower
Baseline insulin clearance	Lower	Higher

Table 1: Differences between youth-onset and adult-onset disease as reported by the original investigators [11,13,14]

Complications appear early: After a mean of 3.9 years, 33.8 per cent of participants had hypertension, 16.6 per cent had microalbuminuria and 13.7 per cent had retinopathy (Figure 3) [7,16]. Only 55.9 per cent had an LDL cholesterol below 100 mg/dL after three years (Figure 4) [7]. Both of the large observational and randomised programmes in this field documented a more aggressive course of complications in youth-onset type 2 diabetes than in either type 1 diabetes or adult-onset type 2 diabetes [13,16,17].

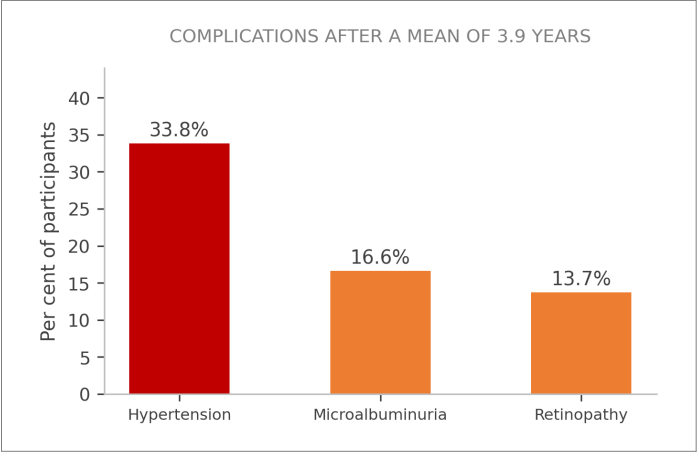


Figure 3: Complications present after a mean of 3.9 years [7,16]

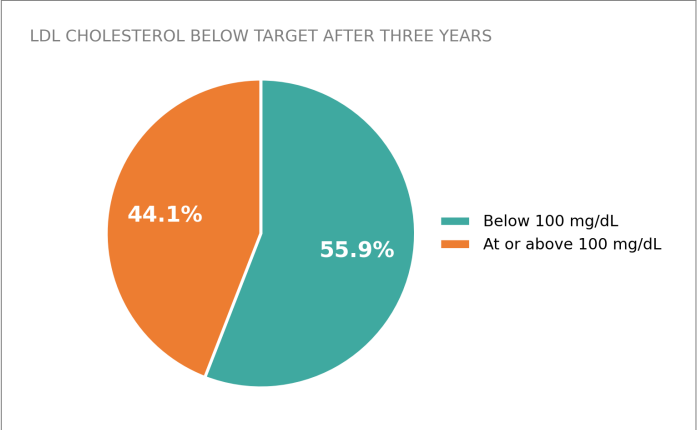


Figure 4: LDL cholesterol below target after three years [7]

Outcome	Reported value	Time point
Treatment failure on metformin	51.8%	About four years
Hypertension	33.8%	Mean 3.9 years
Microalbuminuria	16.6%	Mean 3.9 years
Retinopathy	13.7%	Mean 3.9 years
LDL below 100 mg/dL	55.9%	Three years

Table 2: Principal reported outcomes and the time point at which each was measured [7,16]

What treatment is available: The consensus report noted that treatment options for youth-onset type 2 diabetes were inadequate, being limited at that time to two approved drugs, insulin and metformin, alongside the promotion of healthy lifestyles [5]. Options for those under 18 have since increased [3,18,25]. Randomised trials of a glucagon-like peptide-1 receptor agonist and of a once-weekly agent have reported in this age group [26,28], and international consensus guidance has been updated [27]. Adding insulin to metformin in the setting of sustained hyperglycaemia produced a reduction in HbA1c of less than 0.5 per cent at six months [12,19]. An HbA1c of 6.3 per cent or above after starting metformin has been reported to predict sustained hyperglycaemia within the first 48 months [12].

Observation	Implication for the adult-derived approach
Metformin durable in about half	Monotherapy is not an adequate default [7]
Lifestyle plus metformin not superior	Adding behavioural support did not help here [7]
Beta cell failure drives decline	Insulin-sensitising logic is mismatched [11,13]
Complications at under four years	Delay in escalation is costly [16]
Best arm withdrawn on safety	The trial answer is unavailable [9,10]

Table 3: Why the adult treatment approach transfers poorly to this population

What long-term follow-up has added: Observational continuation of the trial cohort has reported complication rates well beyond the original period, and both the randomised programme and the parallel observational study documented a more aggressive course than in either type 1 diabetes or adult-onset type 2 diabetes [17,21,22]. Registry analyses outside

these programmes report an inverse relationship between age at diagnosis and both complication risk and mortality, so the pattern is not confined to trial populations [32,33,34].

What has changed since: Licensed options for those under 18 have widened. Randomised trials of a glucagon-like peptide-1 receptor agonist and of a once-weekly agent have reported in this age group, and international consensus guidance has been revised to reflect them [26,27,28]. Whether the newer agents alter the beta cell trajectory, as opposed to lowering glucose while it declines, has not been established [12,29].

Discussion

The clinical facts are not in dispute. Half of young people treated with metformin alone lost glycaemic control within about four years, and a third had hypertension before the end of the same period [7,16]. For a population in its teens and twenties, microvascular complications at under four years of disease duration represent a trajectory quite unlike the adult one on which management is modelled.

The mechanistic finding is what gives the title its point. In adults, loss of glycaemic control tracks declining insulin sensitivity; in youth it tracked beta cell function, and did so independently of adherence and body mass index [7,11,13]. Treatment algorithms built around improving insulin sensitivity are therefore addressing the wrong limiting factor in this group. That is a stronger claim than saying the disease is more severe, and the common-protocol comparison supports it, since the same measurements were made in both populations [13,14].

An uncomfortable observation follows about lifestyle intervention. Adding intensive lifestyle support to metformin was intermediate and not superior to metformin alone [7]. That result is frequently passed over, and it should not be, because behavioural intervention is what is most often offered when pharmacological options are limited. The trial does not show that lifestyle change is useless; it shows that this intervention, delivered at this intensity, did not improve durability of glycaemic control in this population.

The trial's most effective arm is unavailable. Metformin with rosiglitazone reduced sustained hyperglycaemia by 23 per cent, and rosiglitazone was subsequently withdrawn from use in this age group on safety grounds [7,9,10]. That leaves the field in an awkward position: the best-supported combination cannot be used, and the next-best options were until recently limited to two drugs.

The practical implication concerns timing rather than choice of agent. If beta cell function is declining at 20 to 35 per cent annually and an HbA1c above 6.3 per cent after starting metformin predicts sustained hyperglycaemia within four years, then the window in which escalation can act is short [7,12]. Guidance has moved in that direction, with a more stringent glycaemic target now recommended for this population than for adults [12,18]. Whether earlier escalation improves the

complication trajectory has not been demonstrated.

There is a further consideration about how this population is served. Adolescence and young adulthood are also the years in which engagement with services is most fragile, as the transition literature documents, and the trial delivered structured follow-up that routine care does not [7,19]. The complication rates reported here were therefore achieved under better-than-usual conditions, which makes them a floor rather than a ceiling.

It is also worth separating two claims. That youth-onset disease progresses faster is well supported by the clamp comparisons and the trial data [7,13,14]. That earlier or more aggressive escalation improves the complication trajectory is a reasonable inference and remains untested, since no trial has randomised young people to different escalation thresholds with complications as the endpoint [12,18].

Study limitations

The limitations belong to the underlying literature. The principal randomised trial recruited a specific population and its treatment failure definition, an HbA1c of 8 per cent or above or inability to wean from insulin, is one of several that could have been chosen and affects the reported rate [7,19]. Long-term follow-up of the same cohort has since reported complication rates well beyond the original trial period [21,22]. Comparisons between youth and adults are drawn from separate studies in most cases, and only the clamp programme used a common protocol across both, so the strength of inference differs between comparisons [13,14,29]. Durability of monotherapy in adults was assessed in a separate programme with a different design [30]. Beta cell function is estimated rather than measured directly, and the methods used differ between studies [11,13]. Rosiglitazone results cannot inform current practice since the agent is not used in this group [9,10]. Complication rates come from a trial population with structured follow-up and may understate what occurs in routine care [16]. Newer agents licensed for this age group since the trial reported are not covered by it [3,18]. And the populations studied are predominantly from one country, with a specific distribution of ethnicity and socioeconomic circumstance that bears on both risk and access [4,5].

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Conclusion

Type 2 diabetes with onset in youth is not adult type 2 diabetes arriving early. Half of those on metformin monotherapy lost control within about four years, beta cell function declined at 20 to 35 per cent annually, and a third had hypertension before four years of disease duration. The decisive difference is mechanistic: control was lost through beta cell failure rather than declining insulin sensitivity, independently of adherence and weight, which inverts the assumption the adult treatment sequence rests on. Intensive lifestyle support added to metformin was not superior to metformin alone, and the combination that worked best is no longer available in this age group. The playbook is older than the disease it is being used to treat.

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Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

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