Summary

• Sultan – 12 yr old with T2DM
• Childhood T2DM is different from adult T2DM?
• Treatments for T2DM
• Published clinical trials in childhood T2DM
• Treatment guidelines for T2DM
• Future studies
BBC Panorama – diabetes the hidden killer
https://youtu.be/dWhSzQEePMQ
Sultan

• Presented aged 12 years with foot pain
• Weight 96kg – above 99.6 centile for age and gender
• Random glucose 16mmol/L, HbA1c 8.5%
• Raised urate – gout – allopurinol
• Intensive input - dietetic and exercise advice
• Started metformin – increased dose to 1 gramme 12 hourly
• Enrolled into clinical trial of GLP-1 agonist – more intensive input
• Rescue basal insulin therapy
• Significant psychological issues
How common is T2D in children?

T2D incidence per 100,000 person-years in children and adolescents (0–19 years)*

- **Canada**: 1.54
- **USA**: 5.28
- **UK**: 0.53–1.5
- **Austria**: 0.14–0.34
- **Sweden**: 3.1
- **Japan**: 1.41–3.23
- **Taiwan**: 6.5
- **Australia**: 0.2–2.5
- **New Zealand**: 0.1–2.5

Variation related to study population (including age, region, ethnicity), calendar period and study methodology

*as of 2013

T2D, type 2 diabetes

Adapted from Fazeli Farsani S et al. *Diabetologia* 2013 56:1471–1488 (systematic review of reported studies up to February 2013).

- **2006**
  - 0.35/100,000/year (white UK)
  - 1.25/100,000/yr S Asian UK
  - 57% girls
  - 43% ethnic minorities
  - 83% obese,
  - 57% acanthosis nigricans, 84% family history of diabetes
  - 50% asymptomatic at diagnosis

- **2016**
  - 0.44/100,000/year (white UK)
  - 2.92/100,000/yr S Asian UK
  - 67% female

30% increase in white UK
Doubling in S Asian UK

(Candler T et al. Diabet Med 2018)
(Haines L et al. Diabetes Care 2007)
Children and adolescents with diabetes are different from adults with diabetes

Physiological and psychological burdens of adolescence

Diabetes care in school

Exercise and eating

Fear of hypoglycaemia

Dependence on caregivers

Difference in presentation of T2D between adults vs children and adolescents

*Not the case in the Asian population
†Among children and adolescents with T2D in the SEARCH study (n=1425) DKA prevalence was 5.7% in 2008–2010 (decreased from 11.7% in 2002–2003). Higher prevalence of DKA was associated with younger age at diagnosis, minority race/ethnicity, and male gender.

Glycosurial without ketonuria
Unexplained

May have other clinical features of insulin resistance at diagnosis: Hypertension, dyslipidaemia, PCOS, acanthosis nigricans

Overweight/obese*

Weight loss

Asymptomatic and detected through screening

Polydipsia, polyuria

Susceptibility to infections

Blurred vision

Ketoacidosis/DKA†

In response to stress or infection

Sometimes with polyphagia

Sometimes with polyphagia

Very often/ High proportion

Often

Sometimes

Rarely

Very often/ High proportion

Often

Sometimes

Rarely

Very often/ High proportion

Rarely

Sometimes

Often

Very often/ High proportion

Unexplained

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May have other clinical features of insulin resistance at diagnosis: Hypertension, dyslipidaemia, PCOS, acanthosis nigricans

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Beta cell failure rates in adults vs youth in T2DM

Nadeau K et al. Diabetes Care 2016
ADOPT, A Diabetes Outcome Progression Trial; Met, metformin; TODAY, Treatment Options for type 2 Diabetes in Adolescents and Youth; US DOD, U.S. Department of Defense Database; UKPDS, United Kingdom. Prospective Diabetes Study.
Natural history of T2D in children and adolescents

- Faster progression from insulin resistance to T2D than adults, particularly associated with obesity
- Early onset associated with complication risk similar to adults and more rapid than in adolescents with T1D
- High risk for early complications during most productive years of life
- High risk for rapid loss of glycaemic control in adolescents if unable to attain a non-diabetes range HbA$_{1c}$ on metformin initially

HbA$_{1c}$, glycosylated haemoglobin; T1D, type 1 diabetes; T2D, type 2 diabetes

Disposition index

Disposition Index (DI) = Insulin sensitivity \times 1^{st} phase insulin

Obese, insulin resistant with compensatory hyperinsulinemia

Normal Glucose Tolerance

Impaired Glucose Tolerance - Prediabetes

Type 2 Diabetes

Lean, insulin sensitive

First-Phase INSULIN SECRETION

Low INSULIN SENSITIVITY High

Hannon T et al Ann NY Acad Sci
Young people are more insulin resistant than adults, and insulin hypersecretors

First phase insulin response to glucose

RISE consortium, Diabetes Care 2018;41:1696-1706
Reduced insulin responses from IGT to diabetes

First phase insulin response to glucose

Insulin sensitivity

RISE consortium, Diabetes Care 2018;41:1696-1706
Treatments for children and young people with T2DM
## Treatment options of type 2 diabetes in children

<table>
<thead>
<tr>
<th>Modality</th>
<th>Glycaemia reduction</th>
<th>-cell enhancing</th>
<th>Insulin resistance lowering</th>
<th>Use</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet and Exercise</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>First line</td>
</tr>
<tr>
<td>Insulin</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Safe, used in children</td>
</tr>
<tr>
<td>Metformin</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Safe</td>
</tr>
<tr>
<td>Sulphonylure as Meglitinides</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>?</td>
<td>Safe in adults</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Yes</td>
<td>?</td>
<td>Yes</td>
<td>?</td>
<td>Little safety data</td>
</tr>
<tr>
<td>Acarbose or orlistat</td>
<td>?</td>
<td>No</td>
<td>No</td>
<td>?</td>
<td>Little used</td>
</tr>
<tr>
<td>Surgical treatment</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>?</td>
<td>Side effects</td>
</tr>
</tbody>
</table>

Children and young people should have at least 60 minutes of moderate to vigorous physical exercise a day.

Most of this exercise should be aerobic. Vigorous-intensity activities should be incorporated, including those that strengthen muscle and bone, at least 3 times a week.
Moderate to vigorous physical activity associated with lower cardiometabolic risk factors in children

- Data from 20,871 children collected between 1998 and 2009
- All studies from International Children’s Accelerometry Database
- Data on time spent in moderate, vigorous physical activity, sedentary time
- Related to waist circumference, systolic BP, fasting TG’s, HDL cholesterol, insulin

- Longer spent in moderate to vigorous physical activity by children was associated with better cardio-metabolic risk profiles regardless of the time spent sedentary

*(Ekelund U et al JAMA 2012;307(7):704-712)*
Physical activity associated with lower markers for metabolic syndrome

<table>
<thead>
<tr>
<th></th>
<th>Waist circumference (cm)</th>
<th>Systolic Blood Pressure (mmHg)</th>
<th>Insulin (pmol/L)</th>
<th>Triglycerides (mg/dl)</th>
<th>HDL-Cholesterol (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total PA (CMP)</td>
<td>-0.35 (-0.50; -0.16)</td>
<td>-0.10 (-0.26; 0.05)</td>
<td>-0.026 (-0.033; -0.020)</td>
<td>-0.021 (-0.026; -0.016)</td>
<td>0.19 (-0.11; 0.48)</td>
</tr>
<tr>
<td>MVPA (min/d)</td>
<td>-0.52 (-0.76; -0.28)</td>
<td>-0.15 (-0.30; -0.06)</td>
<td>-0.028 (-0.038; -0.017)</td>
<td>-0.017 (-0.025; -0.009)</td>
<td>0.25 (-0.034; 0.53)</td>
</tr>
<tr>
<td>Sedentary (min/d)</td>
<td>0.13 (-0.094; 0.358)</td>
<td>-0.043 (-0.21; 0.20)</td>
<td>0.012 (0.0029; 0.022)</td>
<td>0.014 (-0.0031; 0.030)</td>
<td>-0.064 (-0.24; 0.12)</td>
</tr>
<tr>
<td>MVPA adjusted for Sedentary (min/d)</td>
<td>-0.54 (-0.79; -0.30)</td>
<td>-0.17 (-0.30; -0.04)</td>
<td>-0.030 (-0.043; -0.017)</td>
<td>-0.014 (-0.023; -0.0046)</td>
<td>0.31 (0.036; 0.59)</td>
</tr>
<tr>
<td>Sedentary adjusted for MVPA (min/d)</td>
<td>-0.12 (-0.32; 0.09)</td>
<td>-0.10 (-0.21; 0.02)</td>
<td>-0.009 (-0.026; 0.008)</td>
<td>0.006 (-0.010; 0.023)</td>
<td>0.096 (-0.098; 0.29)</td>
</tr>
</tbody>
</table>

Meta-analysis 20,851 children

*(Ekelund U et al JAMA 2012;307(7):704-712)*
Oral anti-diabetic drugs: Metformin

• Biguanide: decreases hepatic gluconeogenesis, increases peripheral utilisation of glucose
• Needs circulating insulin to work.
• Insulin sensitiser, associated with lower incidence of weight gain, lower plasma insulin levels
• Gastro-intestinal side effects: abdo pain, nausea
• Contraindications: renal impairment; pregnancy
Metformin in children with type 2 diabetes:

Randomised controlled trial in 82 children 10-16yrs for up to 16 weeks.
Multicentre: 35 in US, 9 Eastern Europe

Included if: FPG 7.0-13mmol/L; HbA1c ≥ 7.0%, C-peptide ≥ 0.5nmol/L, BMI > 50th centile
Excluded if: diabetes antibodies; DKA; on insulin; hepatic dysfunction

(Lee Jones et al, Diabetes Care; 2002: 89-94).
Screened healthy children with known risk factors

Trial stopped early due to convincing efficacy of metformin
Glycaemic control measurements at baseline and last double-blind visit

<table>
<thead>
<tr>
<th>Variable</th>
<th>Metformin</th>
<th>Placebo</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline FPG</td>
<td>9.0 +/- 2.7</td>
<td>10.7 +/- 2.7</td>
<td></td>
</tr>
<tr>
<td>Last visit</td>
<td>7.0 +/- 2.2</td>
<td>11.5 +/- 4.5</td>
<td></td>
</tr>
<tr>
<td>Change</td>
<td>-2.4 +/- 0.5</td>
<td>1.2 +/- 0.5</td>
<td>-3.6 +/- 0.8*</td>
</tr>
<tr>
<td>Baseline HbA</td>
<td>8.2 +/- 1.3</td>
<td>8.9 +/- 1.4</td>
<td>-1.2 +/- 0.2*</td>
</tr>
<tr>
<td>Last visit</td>
<td>7.2 +/- 1.2</td>
<td>8.9 +/- 1.6</td>
<td></td>
</tr>
<tr>
<td>Adjusted mean</td>
<td>7.5 +/- 0.2</td>
<td>8.6 +/- 0.2</td>
<td></td>
</tr>
</tbody>
</table>

* P<0.001
TODAY study design

Eligibility at screening
- T2DM duration <2 years
- Age 10-17 years
- GAD-65 and IA-2 antibody negative (absent pancreatic autoimmunity)
- BMI ≥85th percentile
- Fasting C-peptide >0.6 ng/mL
- Willing to participate with a familiar support person

n = 1211

Run-in period (n=927)
- Metformin monotherapy
- HbA1c <8%

Randomisation n=699
- Metformin 1000 mg BID*
- Metformin 1000 mg BID* and rosiglitazone 4 mg BID
- Metformin 1000 mg BID* and lifestyle therapy†

Minimum 2 years’ follow up

End of study Primary outcome:
Failure of initial therapy
- HbA1c ≥8% for 6 months‡

Primary outcome

- Survival curves for freedom from glycaemic failure
  - HbA$_{1c}$ $\geq$ 8.0% for 6 months or persistent metabolic decompensation

HbA1c, glycosylated haemoglobin; TODAY, Treatment Options for type 2 Diabetes in Adolescents and Youth TODAY Study Group. *N Engl J Med.* 2012;366:2247-56
**Ellipse Study: efficacy and safety of Liraglutide in children with type 2 diabetes**

- The ELLIPSE study was conducted to **meet the unmet medical need** for treatment of adolescents with T2D and to **satisfy regulatory requirements** from the EMA and FDA.

- A phase 2 study of the **GLP-1RA liraglutide** demonstrated that approved adult dose ranges may also be appropriate for a paediatric population\(^1\).

- The ELLIPSE study subsequently investigated the efficacy and safety of liraglutide as a new treatment option for children and adolescents with T2D.

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EMA, European Medicines Agency; FDA, Food and Drug Administration; GLP-1RA, glucagon-like peptide-1 receptor agonist
\(^1\) Klein DJ et al. *Diabetes Technol Ther* 2014;16:679–687
307 patients screened

134 patients treated
• Multicentre trial
• Stratified according to sex and age at end of treatment†

**Ellipse: trial design**

<table>
<thead>
<tr>
<th>Screening 2 weeks</th>
<th>Metformin titration 3–4 weeks</th>
<th>Maintenance 8 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/12-week metformin run-in</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Patients with a stable dose of metformin at screening advanced directly to randomisation (no run-in period)**

<table>
<thead>
<tr>
<th>Liraglutide s.c. 0.6, 1.2 or 1.8 mg + metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo 0.6, 1.2 or 1.8 mg + metformin</td>
</tr>
<tr>
<td>Metformin</td>
</tr>
</tbody>
</table>

**Run-in period**

**Baseline, randomisation (1:1)**

**Double-blind period (26 weeks)**

**Open-label period (26 weeks)**

**FU W53**

**W52**

**End of trial**

---

**Key inclusion criteria**

- T2D
- Children and adolescents aged 10 to <17 years at randomisation
- HbA$_1c$
  - ≥7.0% and ≤11% if diet and exercise-treated
  - ≥6.5% and ≤11% if treated with metformin ± insulin
- BMI >85$^{th}$ percentile (with age- and sex-matched population as reference)

**Key exclusion criteria**

- Type 1 diabetes
- Maturity-onset diabetes of the young
- Fasting C-peptide <0.6 ng/mL
- History of pancreatitis or a personal or family history of MTC or MEN

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†(≤14; >14 years). BMI, body mass index; FU, follow-up; s.c., subcutaneous; MEN, multiple endocrine neoplasia 2; MTC, medullary thyroid cancer; T2D, type 2 diabetes; W, week
Study endpoints

Primary endpoint

• Change from baseline in HbA$_{1c}$ at 26 weeks$^\dagger$

Secondary endpoints (assessed at week 26)$^\dagger$

• Change from baseline in FPG
• Percentage of patients reaching HbA$_{1c}$ < 7%
• Change from baseline in BMI SDS

Safety was assessed throughout the trial

$^\dagger$Also measured at week 52. BMI SDS, body mass index standard deviation score; FPG, fasting plasma glucose
Baseline characteristics (1/2)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Liraglutide (N = 66)</th>
<th>Placebo (N = 68)</th>
<th>Total (N = 134)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – years</td>
<td>14.6±1.7</td>
<td>14.6±1.7</td>
<td>14.6±1.7</td>
</tr>
<tr>
<td>Female sex – %†</td>
<td>62.1</td>
<td>61.8</td>
<td>61.9</td>
</tr>
<tr>
<td>Age of 10 to 14 years at end of trial – no. (%)</td>
<td>21 (31.8)</td>
<td>19 (27.9)</td>
<td>40 (29.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Region – no. (%)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia</td>
<td>6 (9.1)</td>
<td>6 (8.8)</td>
<td>12 (9.0)</td>
</tr>
<tr>
<td>Europe</td>
<td>24 (36.4)</td>
<td>21 (30.9)</td>
<td>45 (33.6)</td>
</tr>
<tr>
<td>North America</td>
<td>28 (42.4)</td>
<td>35 (51.5)</td>
<td>63 (47.0)</td>
</tr>
<tr>
<td>Rest of the world</td>
<td>8 (12.1)</td>
<td>6 (8.8)</td>
<td>14 (10.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
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<th>Placebo (N = 68)</th>
<th>Total (N = 134)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race or ethnic group – no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>42 (63.6)</td>
<td>45 (66.2)</td>
<td>87 (64.9)</td>
</tr>
<tr>
<td>Black</td>
<td>9 (13.6)</td>
<td>7 (10.3)</td>
<td>16 (11.9)</td>
</tr>
<tr>
<td>Asian</td>
<td>10 (15.2)</td>
<td>8 (11.8)</td>
<td>18 (13.4)</td>
</tr>
</tbody>
</table>

| American Indian or Alaska Native                    | 2 (3.0)              | 1 (1.5)          | 3 (2.2)         |
| Native Hawaiian or Other Pacific Islander           | 0                    | 0                | 0               |
| Other                                               | 3 (4.5)              | 7 (10.3)         | 10 (7.5)        |

Data are mean ± standard deviation, or proportion of patients (%). †Fulfilling regulatory requirement of including ≥40% females.
Adapted from Table 1, Tamborlane et al., Liraglutide in Children and Adolescents with Type 2 Diabetes, N Engl J Med 2019;381:637–46. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.
### Baseline characteristics (2/2)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Liraglutide (N = 66)</th>
<th>Placebo (N = 68)</th>
<th>Total (N = 134)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic or Latino ethnic group − no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16 (24.2)</td>
<td>23 (33.8)</td>
<td>39 (29.1)</td>
</tr>
<tr>
<td>No</td>
<td>50 (75.8)</td>
<td>45 (66.2)</td>
<td>95 (70.9)</td>
</tr>
<tr>
<td>Duration of diabetes − years</td>
<td>1.9±1.7</td>
<td>1.9±1.3</td>
<td>1.9±1.5</td>
</tr>
<tr>
<td>Body weight − kg</td>
<td>93.3±31.0</td>
<td>89.8±22.1</td>
<td>91.5±26.8</td>
</tr>
<tr>
<td>BMI</td>
<td>34.55±10.87</td>
<td>33.27±7.36</td>
<td>33.90±9.25</td>
</tr>
<tr>
<td>BMI SDS score</td>
<td>3.03±1.47</td>
<td>2.86±1.11</td>
<td>2.94±1.30</td>
</tr>
<tr>
<td>HbA(_{1c}) − %</td>
<td>7.87±1.35</td>
<td>7.69±1.34</td>
<td>7.78±1.34</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Liraglutide (N = 66)</th>
<th>Placebo (N = 68)</th>
<th>Total (N = 134)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma glucose − mg/dl</td>
<td>156.8±52.2</td>
<td>146.8±38.3</td>
<td>151.7±45.8</td>
</tr>
<tr>
<td>Blood pressure − mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>118.4±11.4</td>
<td>115.3±12.0</td>
<td>116.8±11.8</td>
</tr>
<tr>
<td>Diastolic</td>
<td>73.2±8.5</td>
<td>71.2±7.6</td>
<td>72.2±8.1</td>
</tr>
<tr>
<td>Metformin dose at baseline − mg</td>
<td>1912±286</td>
<td>1877±384</td>
<td>1894±339</td>
</tr>
<tr>
<td>Basal insulin use at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%) of patients</td>
<td>15 (22.7)</td>
<td>10 (14.7)</td>
<td>25 (18.7)</td>
</tr>
<tr>
<td>Mean dose − U</td>
<td>29.6±19.5</td>
<td>29.6±17.7</td>
<td>29.6±18.4</td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation, or proportion of patients (%). Adapted from Table 1, Tamborlane et al., Liraglutide in Children and Adolescents with Type 2 Diabetes, *N Engl J Med* 2019;381:637–46. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.
Change from baseline in HbA$_{1c}$

Error bars: ± standard error (mean). Means are estimated from MMRM containing treatment, sex and age group as fixed effects and baseline value as covariate, all nested within visit, during the 52-week trial period. For MMRM results, data collected after initiation of rescue medication were handled as missing data. Liraglutide: all doses of liraglutide. CI, confidence interval; ETD, estimated treatment difference from the PMM; MMRM, mixed model repeated measurements; PMM, pattern mixture model. Adapted from Figure 2, Tamborlane et al., Liraglutide in Children and Adolescents with Type 2 Diabetes, *N Engl J Med* 2019;381:637–46. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.
Change from baseline in FPG

Error bars: ± standard error (mean). Means are estimated from MMRM containing treatment, sex and age group as fixed effects and baseline value as covariate, all nested within visit during the 52-week trial period. For MMRM results, data collected after initiation of rescue medication were handled as missing data. Liraglutide: all doses of liraglutide. CI, confidence interval; ETD, estimated treatment difference from the PMM; FPG, fasting plasma glucose; MMRM, mixed model of repeated measurements; PMM, pattern mixture model.

Adapted from Figure 2, Tamborlane et al., Liraglutide in Children and Adolescents with Type 2 Diabetes, N Engl J Med 2019;381:637–46. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.
Proportion of patients who attained HbA1c <7.0% at week 26

*P<0.001. Liraglutide: all doses of liraglutide.
Adapted from Suppl Figure 3, Tamborlane et al., Liraglutide in Children and Adolescents with Type 2 Diabetes, N Engl J Med 2019;381:637–46. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.
Change from baseline in BMI SDS

Error bars: ± standard error (mean). Means are estimated from MMRM containing treatment, sex and age group as fixed effects and baseline value as covariate, all nested within visit during the 52-week trial period. For MMRM results, data collected after initiation of rescue medication were handled as missing data. Liraglutide: all doses of liraglutide. BMI SDS, body mass index standard deviation score; CI, confidence interval; ETD, estimated treatment difference from the PMM; MMRM, mixed model of repeated measurements; PMM, pattern mixture model.

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## Key treatment-emergent AEs – entire 52-week study period

<table>
<thead>
<tr>
<th></th>
<th>Liraglutide n=66</th>
<th>Placebo n=68</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Events, n (%)</strong></td>
<td>56 (84.8)</td>
<td>55 (80.9)</td>
</tr>
<tr>
<td><strong>SAEs, n (%)</strong></td>
<td>9 (13.6)</td>
<td>4 (5.9)</td>
</tr>
<tr>
<td><strong>MESIs, n (%)</strong></td>
<td>6 (9.1)</td>
<td>3 (4.4)</td>
</tr>
<tr>
<td><strong>AEs leading to treatment discontinuation, n (%)</strong></td>
<td>1 (1.5)†</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td><strong>Key AEs (≥5%), n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>19 (28.8)</td>
<td>9 (13.2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17 (25.8)</td>
<td>6 (8.8)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>15 (22.7)</td>
<td>11 (16.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>14 (21.2)</td>
<td>13 (19.1)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12 (18.2)</td>
<td>5 (7.4)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>11 (16.7)</td>
<td>19 (27.9)</td>
</tr>
</tbody>
</table>

†One patient on liraglutide with hyperglycaemia AE leading to treatment discontinuation was withdrawn due to non-compliance. Liraglutide: all doses (0.6, 1.2 and 1.8 mg). AE, adverse event; MESI, medical event of special interest; SAE, serious adverse event. Adapted from Suppl Table 5, Tamborlane et al., Liraglutide in Children and Adolescents with Type 2 Diabetes, *N Engl J Med* 2019;381:637–46. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.
Hypoglycaemic episodes – entire 52-week study period

<table>
<thead>
<tr>
<th>Hypoglycaemia</th>
<th>Liraglutide n=66</th>
<th>Placebo n=68</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor, † n (%)</td>
<td>16 (24.2)</td>
<td>7 (10.3)</td>
</tr>
<tr>
<td>All hypoglycaemic episodes ‡</td>
<td>30 (45.5)</td>
<td>17 (25.0)</td>
</tr>
<tr>
<td>Severe</td>
<td>0 (0.0)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Documented symptomatic</td>
<td>19 (28.8)</td>
<td>6 (8.8)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>21 (31.8)</td>
<td>12 (17.6)</td>
</tr>
</tbody>
</table>

†Minor: symptomatic or asymptomatic hypoglycaemic episode with plasma glucose <3.1 mmol/L. ‡ADA classification. Liraglutide: all doses (0.6, 1.2 and 1.8 mg). ADA, American Diabetes Association. Adapted from Suppl Table 5, Tamborlane et al., Liraglutide in Children and Adolescents with Type 2 Diabetes, N Engl J Med 2019; 381:637–46. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.
ELLIPSE study summary

- At Week 26 and Week 52, liraglutide demonstrated reductions in HbA$_1c$ and FPG compared with placebo; superiority* was confirmed at Week 26.
- The percentage of participants achieving HbA$_1c$ <7% at Week 26 was superior* with liraglutide compared with placebo.
- >50% of participants reached liraglutide doses up to 1.8 mg.
- Overall, the safety profile of liraglutide is similar to that in adults, although the frequency of hypoglycaemic events was higher in liraglutide than in placebo.
- No episodes of severe hypoglycaemia were observed in liraglutide-treated participants.

Liraglutide at doses up to 1.8 mg/day (when added to metformin ± basal insulin) offers a new, efficacious and durable treatment option, with an acceptable safety profile, for children and adolescents with T2D in need of improved glycaemic control.

*Superiority testing only pre-specified for confirmatory endpoints at Week 26.
What about bariatric surgery?
Weight change following bariatric surgery in young people

T2DM remission after 3 years:
94% (gastric bypass)
68% (sleeve gastrectomy)

Ongoing clinical trials – SGLT2 inhibitor Dapagliflozin
New-Onset Diabetes in Overweight Youth
Initiate lifestyle management and diabetes education

A1C < 8.5%
No acidosis or ketosis
- Metformin PO b.i.d.
  - Titrate up to 2,000 mg per day as tolerated

A1C ≥ 8.5%
No acidosis with or without ketosis
- Basal insulin: start at 0.5 units/kg/day and escalate every 2–3 days based on meter glucose
- Metformin
  - Titrate up to 2,000 mg per day as tolerated

Acidosis and/or DKA and/or HHNK
- Manage DKA or HHNK
- I.V. insulin until acidosis resolves, then subcutaneous, as for type 1 diabetes until antibodies are known

Pancreatic autoantibodies

NEGATIVE
- Continue metformin
- Wean insulin guided by meter glucose values
- A1C goals not met
  - Initiate add-on insulin or continue insulin therapy—basal insulin to maximum 1.5 units/kg/day
  - A1C goals not met

POSITIVE
- Continue or initiate MDI insulin or pump therapy, as for type 1 diabetes
- Consider other drug therapy (see Table 3; not currently approved for <18 years old)

(Arslanian S et al Diabetes Care 2018;Nov 13)
Summary

• Type 2 diabetes in childhood an emerging health problem in UK
• T2DM a more aggressive disease in children than in adults
• First line treatment always lifestyle, exercise and diet + metformin
• Second line treatment – are now licensed alternatives to insulin
• All children under 16yrs should be seen in secondary care, managed in partnership with primary care colleagues
Thankyou!

t.g.barrett@bham.ac.uk