Type 2 Diabetes and Obesity: Evolving Treatment Strategies

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PATHOGENESIS OF TYPE 2 DIABETES

HGP = hepatic glucose production.

Islet β-cell

Impaired Insulin Secretion

Increased HGP

Decreased Glucose Uptake

Metformin

SUs

Insulin

Su/sulfonylurea; TZDs/thiazolidinediones; T2DM/type 2 diabetes.

Type 2 Diabetes
Evolving Treatment Strategies

ACCORD All-Cause Mortality and Primary Outcome Event Curves

HbA1c (%)

Pre-DCCT 9.0%
9
8
7
6
5
1980s 1990s 2000s

SU = sulfonylureas; TZDs = thiazolidinediones; T2DM = type 2 diabetes.
Design of Intensive Glycemia Intervention

<table>
<thead>
<tr>
<th>Group</th>
<th>A1C Targets</th>
<th>A1C</th>
<th>&gt; 50% of SMBG Results/4 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive</td>
<td>&lt; 6%</td>
<td>5.9%</td>
<td>50% of SMBG Results/4 Days</td>
</tr>
</tbody>
</table>

Rx was reduced in the presence of significant hypoglycemia. Even if the A1C is <6.0

ACCORD Subgroup Analyses

Mortality vs Treatment

Death Rate vs Drop in A1C

Diabetes Management Strategies
Making Sense of ACCORD

No drop in A1C = higher death rate
Pathogenesis of Type 2 Diabetes

HGP = hepatic glucose production.

**Impaired Insulin Secretion**

- Increased HGP
- Decreased Glucose Uptake

**Neurotransmitter Dysfunction**

- Decreased Glucose Uptake

**Islet β-cell**

- Impaired Insulin Secretion

**Islet α-cell**

- Increased Glucagon Secretion
- Increased Lipolysis
- Increased Glucose Reabsorption
- Increased HGP
- Decreased Incretin Effect

**Failing β-cell**

- Insulin resistance

**Functional β-cell**

- Insulin resistance

**Metabolic syndrome**

- Hyperglycemia

**CVD**

- Cancer

**Nephropathy**

**Retinopathy**

**Neuropathy**

Heine RJ, Splekman AM. 2006.

Type 2 Diabetes: A Heterogeneous Disorder
**DIABETES/OBESITY**
Management Strategies

- Insulin Resistance
  - Metabolic Syndrome
  - Energy Storage
- Insulin Supply
  - Beta Cell Dysfunction
  - Hyperglycemia

**Prevention**
- Intensive management of insulin resistance
- β cell dysfunction
- CVD risks

**Damage Control**
- Less intensive glycemic goals
- Avoid hypoglycemia

Adapted from CDC, Minneapolis, MN

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**History of Diabetes Therapy:**
What More Could We Possibly Want?

The End of Protocol Driven Therapy


11βHSD1 inhib
SGLT-2 inhib
Liraglutide
Degludec
Glucagon R antagonists
Diabides
Pramlintide
Sitagliptin
Bromocriptine
Saxagliptin
Bexarotene
Glibenclamide
Lifestyle
Insulin
Metformin
Lisinopril
Human Insulin
Animal Insulin

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**Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach**

Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)
3. ANTI-HYPERGLYCEMIC THERAPY

- Glycemic targets
  - HbA1c < 7.0% (mean PG ≈ 150-160 mg/dl [8.3-8.9 mmol/l])
  - Pre-prandial PG < 130 mg/dl (7.2 mmol/l)
  - Post-prandial PG < 180 mg/dl (10.0 mmol/l)
  - Individualization is key:
    - Tighter targets (6.0 - 6.5%) - younger, healthier
    - Looser targets (7.5 - 8.0%) - older, comorbidities, hypoglycemia prone, etc.
  - Avoidance of hypoglycemia

PG = plasma glucose

Figure 1

Approach to management of hyperglycemia.

Irrelevant, routine, self-care capacities
Quite relevant, self-care capacities
Essential self-care capacities
Full self-care capacities

Healthy eating, weight control, increased physical activity

Initial drug monotherapy

Two drug combinations

Three drug combinations

Further complex insulin strategies

Diabetes Care, Diabetologia. 19 April 2012 [Epub ahead of print]

4. OTHER CONSIDERATIONS

• Weight
  - Majority of T2DM patients overweight / obese
  - Intensive lifestyle program
  - Metformin
  - GLP-1 receptor agonists
  - ? Bariatric surgery
  - Consider LADA in lean patients
Incretins: GLP-1 Agonists vs. DPP-IV Inhibitors

**Differential Effects:**
Glycemic Control
Energy Balance

Pharmacology vs Physiology
DPP-IV – increases endogenous GLP-1
GLP-1 agonist – super physiologic effect

...Not quite that simple

**Differential Effects:**
Glycemic Control
Energy Balance

T2DM – Treatment Strategies

Islet β-cell
Impaired Insulin Secretion

Neurotransmitter Dysfunction
Decreased Glucose Uptake

Islet α-cell
Increased Glucagon Secretion

Increased Lipolysis
Increased Glucose Reabsorption

Increased HGP
Decreased Incretin Effect
GLP-1 > DPP-IV (A1c, FPG, β-cell function)

**Incretins (Exenatide): Sustained Efficacy- Improved Beta Cell Function**

*Improvements in β-cell function and insulin sensitivity at 4 years:*
- HOMA-β 28%±5%
- HOMA-8 13%±3%

Buse et al., Oct 2012, EASD, Berlin
T2DM – Treatment Strategies

Islet β-cell

Impaired Insulin Secretion

Neurotransmitter Dysfunction

Decreased Glucose Uptake

Islet α-cell

Increased Glucagon Secretion

Increased Lipolysis

Increased Glucose Reabsorption

Hyperglycemia

Increased HbA1c

Decreased GLP-1 > DPP-IV (A1c, FPG, β-cell function)

GLP-1 > DPP-IV

Incretin Therapy

Effect on Energy Homeostasis

The 56-week SCALE™ – Maintenance study investigated the use of lixivulitide in obese adults without diabetes

Main inclusion criteria
- BMI ≥30 kg/m² or ≥27 kg/m² with comorbidities
- FPG <7 mmol/l (<136 mg/dl) at week -12
- Age ≥18 years
- Stable body weight during 3 months prior to screening

Main exclusion criteria
- Diagnosis of type 1 or type 2 diabetes
- Previous treatment with GLP-1 receptor agonists
- History of medications - within 3 months prior to screening - that can affect weight change
- Participation in programmes or surgery that can lead to significant weight loss
In the 56-week SCALE™ Maintenance study, liraglutide promoted weight maintenance and additional weight loss in obese adults

Change in body weight by week

Incretins: Expanding Role in Treatment Strategies
Pediatric Type 1 Diabetics (n=8)

Insulin dose reduced 20% with exenatide dosing – mixed meal
Incretins (DPP-IV inhibitors): Special Populations: Geriatrics

**Pharmacology Recommendations**

- Metformin – still first line for most
- Less effective in many
- GFR  - <30 – no, 30-50 reduce dose
- Glyburide – never
- DPP-IV inhibitors - recommended

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**Diabetes in Older Adults**

ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

4. OTHER CONSIDERATIONS

- Comorbidities
  - Coronary Disease
  - Heart Failure
  - Renal disease
  - Liver dysfunction
  - Hypoglycemia

- Metformin: CVD benefit (UKPDS)
- Avoid hypoglycemia
- ? SUs & ischemic preconditioning
- ? Pioglitazone & ↓ CVD events
- ? Effects of incretin-based therapies

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**Peptide Therapeutics: Incretins (GLP-1 and GIP)**

- Cardiovascular Outcome Trials
  - TECOS - sitagliptin
  - EXSCEL – weekly exenatide
  - LEADER – liraglutide
  - ELIXA – lixisenatide
  - SAVOR - saxagliptin
4. OTHER CONSIDERATIONS

- Comorbidities
  - Coronary Disease
  - Heart Failure
  - Renal disease
  - Liver dysfunction
  - Hypoglycemia

- Metformin: CVD benefit (UKPDS)
- Avoid hypoglycemia
- ? SUs & ischemic preconditioning
- ? Pioglitazone & CVD events
- ? Effects of incretin-based therapies

Glyburide (and older) – Should never be used
Glimepiride or Glipizide if any SU
4. OTHER CONSIDERATIONS

- Comorbidities
  - Coronary Disease
  - Heart Failure
  - Renal disease
  - Liver dysfunction
  - Hypoglycemia

> Emerging concerns regarding association with increased mortality
> Proper drug selection in the hypoglycemia prone

Adapted Recommendations: When Goal is to Avoid Hypoglycemia

T2DM – Treatment Strategies
PROactive: Pioglitazone Reduced “Hard” Coronary Heart Disease Endpoints

Type 2 Diabetes: Benefits vs Risks of TZDs

PROactive: Pioglitazone Reduced “Hard” Coronary Heart Disease Endpoints

Type 2 Diabetes: Benefits vs Risks of TZDs
**New Basal Insulins: insulin degludec**

**molecular structure**

BEGIN®

- **DesB30 LysB29(No-y-glu-hexadecandioyl) human insulin**
- **Degludec (Tresiba)**

**A chain**

- **B chain**

- **desB30 Insulin**

- **Hexadecandiyl**

- **L-g-Glu**

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**Diabetes Care, Diabetologia. 19 April 2012 [Epub ahead of print]**

**The Ominous Octet – Treatment Strategies**

- Impaired Insulin Secretion
- Neurotransmitter Dysfunction
- Decreased Glucose Uptake
- Islet ß-cell Dysfunction
- Increased Glucagon Secretion
- Increased Lipolysis
- Increased Glucose Reabsorption
- Increased HGP
- Decreased Incretin Effect

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**T2DM Anti-hyperglycemic Therapy: General Recommendations**
Multi-hexamer formation after injection

Insulin degludec in pen

Injection site

Long multi-hexamer chains assemble

[Phenol; Zn²⁺]

Insulin degludec multi-hexamers

Main picture shows elongated IDeg structures in absence of phenol; inset (white box) shows absence of elongated IDeg structures in presence of phenol.

Following injection

Subcutaneous depot

Insulin degludec multi-hexamers

As zinc slowly diffuses out of the multi-hexamers, insulin degludec monomers are formed

Monomers are absorbed from the depot into the circulation

Jonassen I et al. Diabetes. 2010;59(suppl 1):A11


Kurtzhals P. EASD 2011; 092-P #1049 (MoP + NN1250-1993)
Clamp profile in type 2 diabetes: ultra-long, flat and consistent

Glucose infusion rate (mg/(kg*min))

Treatment
- IDeg 100 U/mL 0.4 U/kg
- IDeg 100 U/mL 0.6 U/kg
- IDeg 100 U/mL 0.8 U/kg

Nosek L et al. ADA 2011;49-LB (NN1250-1987)
Nosek L. EASD 2011; 093-P #1055 (NN1250-1987)

Consistently lower within-subject variability over time for insulin degludec

Heise et al. Diabetes 2011;60(Suppl. 1):A263c
**Inclusion criteria**

- Type 2 diabetes ≥ 6 months
- Insulin naïve treated with metformin ± SU, DPP-4 or acarbose for ≥ 3 months
- HbA1C 7.0–10.0%
- BMI ≤ 40 kg/m²
- Age ≥ 18 years

**Study design**

ONCE LONG (3579)

Randomized 3:1 (IDeg OD:IGlar OD)
Open label

**Nocturnal confirmed hypoglycemia**

ONCE LONG (3579)

36% lower rate with IDeg OD:
\[ p < 0.05 \]

**Pre-specified hypoglycemia meta-analyses Type 1 & type 2 diabetes**

Reduction in confirmed hypoglycemia with degludec (All IDeg vs. IGlar studies, maintenance period)

- **Nocturnal**
  - T1 and T2: 32%*
  - T2 basal only: 49%*
- **Overall**
  - T1 and T2: 16%*
  - T2 basal only: 28%*

*statistically significant improvement
Graph is picture. SDM will source slide with graph as graph.

Jackson, Meryn, 2/23/2012
Treatment Strategies for Type 2 Diabetes
(My Approach – T2DM + Metabolic Syndrome)

Islet \( \beta \)-cell Impaired Insulin Secretion

Neurotransmitter Dysfunction

Decreased Glucose Uptake

Islet \( \alpha \)-cell Increased Glucagon Secretion

Increased Lipolysis

Increased Glucose Reabsorption

Increased HGP

Decreased Incretin Effect

GLP-1

Insulin

TZDs

Exercise

Metformin

Energy Balance and Body Weight:
Simple Right?

Energy In (Caloric Intake) → Body Weight → Energy Out (Metabolism)

ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

4. OTHER CONSIDERATIONS

• Weight
  - Majority of T2DM patients overweight / obese
  - Intensive lifestyle program
  - Metformin
  - GLP-1 receptor agonists
  - ? Bariatric surgery
  - Consider LADA in lean patients

[Diabetes Care, Diabetologia, 19 April 2012 [Epub ahead of print]]
Evolving Treatment Strategies: The Complexity of Energy Homeostasis

The Science of Willpower

Visceral Fat Cell

Visceral Fat Cell

Energy Homeostasis - Metabolic Syndrome
Set Point Theory

Body Mass Index

Kcal 24 Hours

Energy Intake

Energy Expenditure

(*) Energy Balance

(−) Energy Balance

Energy Homeostasis - Metabolic Syndrome
Set Point Theory

Evolving Treatment Strategies:
The Complexity of Energy Homeostasis

Artificial sweeteners lead to weight gain?

Figure 1. Time line of artificial sweetener use and obesity, United States. In 1966, information on the use of sugar substitutes was collected for the first time in the United States. Ships were stopped at port; customs officers counted the number of cases of artificial sweeteners coming into the country. Since that time, the consumption of artificial sweeteners has increased, and obesity has increased. Source: Whitehouse, New York Times, 1996. Bar graph below illustrates the trend and variability of artificial sweetener use in the United States over time. Source: Kruger et al. 38.
Energy Balance and Body Weight: What is Metabolism?

Energy In (Caloric Intake) → Body Weight → Energy Out (Metabolism)

Energy Homeostasis: The Quick Fix?

The Diet Strategy
Failure Rate of Diet Alone 90-98%

New Set Point
Baseline

Weight ↓ 5-10%

Counter-Regulation
Weight Management
Counter-Regulation and the Failure of the “Diet” – HCG Diet

<table>
<thead>
<tr>
<th>First author (reference)</th>
<th>Duration of intervention (week)</th>
<th>Changes</th>
<th>Change in body weight (kg)</th>
<th>Weight loss (kg)</th>
<th>Authors’ conclusion</th>
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<tbody>
<tr>
<td>Lane (26)</td>
<td>12</td>
<td>yes</td>
<td>+6.8 (5.9-7.7)</td>
<td>+6.8 (5.9-7.7)</td>
<td>negative</td>
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<tr>
<td>Young (26)</td>
<td>8</td>
<td>yes</td>
<td>+5.6 (4.0-7.2)</td>
<td>+5.6 (4.0-7.2)</td>
<td>negative</td>
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<tr>
<td>Hiley (21)</td>
<td>6</td>
<td>yes</td>
<td>+5.8 (4.6-7.1)</td>
<td>+5.8 (4.6-7.1)</td>
<td>positive</td>
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<tr>
<td>Hump (21)</td>
<td>6</td>
<td>yes</td>
<td>+5.8 (4.6-7.1)</td>
<td>+5.8 (4.6-7.1)</td>
<td>positive</td>
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<tr>
<td>Berardis (21)</td>
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<td>+5.8 (4.6-7.1)</td>
<td>+5.8 (4.6-7.1)</td>
<td>positive</td>
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<tr>
<td>Bech (22)</td>
<td>5</td>
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<td>-3.5 (5.1-6.9)</td>
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<tr>
<td>Gritsenko (24)</td>
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<td>Adler (25)</td>
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<td>-3.5 (5.1-6.9)</td>
<td>negative</td>
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<tr>
<td>Craig (25)</td>
<td>4</td>
<td>no</td>
<td>-3.5 (5.1-6.9)</td>
<td>-3.5 (5.1-6.9)</td>
<td>negative</td>
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<tr>
<td>Borowiak (27)</td>
<td>2</td>
<td>no</td>
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<td>-3.5 (5.1-6.9)</td>
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<tr>
<td>Miller (27)</td>
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<td>no</td>
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<td>-3.5 (5.1-6.9)</td>
<td>negative</td>
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<tr>
<td>Reck (28)</td>
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<td>no</td>
<td>-3.5 (5.1-6.9)</td>
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<tr>
<td>Lebow (29)</td>
<td>2</td>
<td>no</td>
<td>-3.5 (5.1-6.9)</td>
<td>-3.5 (5.1-6.9)</td>
<td>negative</td>
</tr>
</tbody>
</table>

Weight Loss
Counter-Regulation and the Failure of the “Diet” – Ideal Protein

Energy Balance and Body Weight: What is Metabolism?
Low Metabolism
How Do I Fix It? – “Get Your Ducks in a Row”

- Sleep Problems – Sleep Apnea
- Vitamin D Deficiency
- Thyroid
- Vitamin B12
- Low Testosterone (male)
- Medications (centrally acting)
Energy Homeostasis: The Search for the Magic Pill?

Substrates
- Glucose
- Aminoacids
- Free Fatty Acids
- Lipids

Hormones
- Insulin
- Leptin
- Ghrelin
- PYY
- CCK
- Adiponectin

Mechanical
- Gastric Distension

Neural
- Vagal Afferents

Psychological
- Pleasure
- Reward
- Visual
- Olfactory
- Taste

Hypothalamus
- Dopamine, Cannabinoids
- Norepinephrine, NPY
- Serotonin, POMC, GABA etc...

Sibutramine (Meridia)
Topiramate (Topomax)
Phentermine
Rimonobant
Qsymia (phentermine + topiramate)
Contrave (bupropion + naltrexone)
Energy Balance Center
Belviq
Lorcaserin (5HT2C)

Weight Loss Pills
Empatic (bupropion + zonisamide)
Tesofensine (NS2330)

4-8% Total body weight loss
Not sustainable
20-30% Non-response rate

Belviq
N=8,000 52-104 weeks
Weight Loss: 3-3.7% over placebo
47% loss >5%
Dosing: 10mg BID

Qsymia
N=3,700 52-104 weeks
Weight Loss: 6.7-8.9% over placebo
70% loss >5%
Dosing: 3.75/23mg, 7.5/46mg, 11.25/69mg, 15/92mg

The Ominous Octet – Treatment Strategies

Surgery?

- Impaired β-cell Insulin Secretion
- Decreased Glucose Uptake
- Increased α-cell Glucagon Secretion
- Increased Lipolysis
- Increased HGP
- Increased Glucose Reabsorption
- Decreased Glucose Uptake

ADA Clinical Practice Recommendations 2011: Changing Treatment Paradigms

Bariatric surgery
- Bariatric surgery should be considered for adults with BMI ≥35 kg/m² and type 2 diabetes, especially if the diabetes or associated comorbidities are difficult to control with lifestyle and pharmacologic therapy. (B)
Energy Homeostasis: A Role for Surgery?

- Lap Band
  - Restriction of caloric intake

- Gastric Bypass (Roux-En-Y)
  - Restriction of caloric intake
  - Malabsorption of nutrients

Gastric Bypass: Five Operations

1. Isolation of gastric cardia
2. Exclusion of distal stomach

3. Exclusion of duodenum and proximal jejunum

4. Exposure of distal jejunum to undigested nutrients
Gastric Bypass: Five Operations

5. Partial vagotomy

Energy Homeostasis: A Role for Surgery?

Sleeve Gastrectomy
Stomach becomes a “sleeve”
Alters signaling mechanisms
Independent glycemic effect

Metabolic Surgery: The STAMPEDE Trial
Type 2 DM, A1c > 7.0%, BMI 27 - 43

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Medical Therapy (N=50)</th>
<th>Gastric Bypass (N=50)</th>
<th>Sleeve Gastrectomy (N=50)</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>Duration of diabetes (yr)</td>
<td>5.6±0.8</td>
<td>5.4±0.3</td>
<td>5.1±0.8</td>
<td>0.67</td>
</tr>
<tr>
<td>Use of insulin — no. (%)</td>
<td>22 (44)</td>
<td>22 (44)</td>
<td>22 (44)</td>
<td>1.00</td>
</tr>
<tr>
<td>Age — yr</td>
<td>49.9±7.4</td>
<td>45.1±8.4</td>
<td>47.9±8.0</td>
<td>0.06</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>15 (30)</td>
<td>20 (40)</td>
<td>19 (39)</td>
<td>0.08</td>
</tr>
<tr>
<td>Body mass index</td>
<td>36.8±5.0</td>
<td>37.6±5.3</td>
<td>38.1±5.9</td>
<td>0.42</td>
</tr>
<tr>
<td>&lt;50 — no. (%)</td>
<td>19 (38)</td>
<td>14 (28)</td>
<td>18 (36)</td>
<td>0.34</td>
</tr>
<tr>
<td>Body weight — kg</td>
<td>105±14.7</td>
<td>197±24.3</td>
<td>100±12.4</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Primary Outcome: Proportion with A1c < 6.0% at 12 months
THE END

Metabolic Surgery: The STAMPEDE Trial - Results

<table>
<thead>
<tr>
<th>Table 1: Pre and Secondary Endpoints at 12 Months*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>End Point</strong></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Glucose mg/dL</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Body weight (kg)</td>
</tr>
</tbody>
</table>

*Data represent mean±standard deviation.