Drug-Induced Diabetes May Not Be Harmful But Should Be Prevented

Jeffrey A. Cutler, MD, MPH
Overview

• Focus on thiazide-like diuretics (not BB)
• Diuretic-induced versus diuretic-associated diabetes
• Role of potassium balance
• Associations of diuretic-associated diabetes with CVD outcomes
• Overall relative benefits of different classes in diabetic persons
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ALLHAT analyses

Among participants who were non-diabetic at baseline:

• Compared the effects of 1st-step antihypertensive drug therapy with chlorthalidone, amlodipine, or lisinopril on fasting glucose (FG) levels and incident diabetes

• Determine risks for CV and renal disease associated with elevated FG and incident diabetes in the three treatment groups.
Follow-up Fasting Glucose
126+ mg/dL

% FU Fasting Glucose 126+ mg/dL

2 Years 4 Years 6 Years

<table>
<thead>
<tr>
<th></th>
<th>2 Years</th>
<th>4 Years</th>
<th>6 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlor</td>
<td>9.3</td>
<td>11.0</td>
<td>13.8</td>
</tr>
<tr>
<td>Amlod</td>
<td>7.2</td>
<td>9.3</td>
<td>12.0</td>
</tr>
<tr>
<td>Lisin</td>
<td>5.6</td>
<td>7.8</td>
<td>11.0</td>
</tr>
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* p<.05 compared to chlorthalidone

10/11/2006
Assuming CCB is metabolically neutral, 85% (9.3% vs 11.0%) of DM at 4 years on chlorthalidone was not chlorthalidone-induced.
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Hypotheses: Glucose, Potassium, CVD

• Glucose intolerance/hyperglycemia ("dysglycemia") with thiazide use largely attributable to potassium depletion.
• Dysglycemia correctable/preventable by K+ repletion/maintenance.
• Any ↑ CVD risk with thiazide-induced dysglycemia attenuated by K+ repletion.
Potassium and glucose: Types of evidence

• 5 small (total N=42) depletion studies
  --Normal human subjects
  --K+ ↓ by diet, diuretic, or cation exchange
  --Short-term follow-up (10 d – 6 wk)
• Long-term observational studies in treated hypertensive patients.
• Secondary analyses of clinical trials.
First clinical study: Saglidi, 1961

- 3-period sequential design (11-14 days).
- 5 healthy young men on prepared diet.
- Combined glucose tolerance (GT)/insulin responsiveness test before potassium depletion via K+ exchange resin, right afterward, and following recovery.
- Results: reduced GT followed by recovery.
- No insulin resistance (IR).

Other clinical studies (I)

- Rapoport 1964
  - 16 subjects with + family history or IFG
  - In 7, CTZ rx → ↓GT in week 1, normalized with K+ repletion during week 2.
- Gordon 1973
  - In 5/5 healthy MF, 2 wks K+ depletion → ↓GT; 2 wks K+ repletion normalized 4/5.
  - Mechanism: delayed INS release, no IR.

Other clinical studies (II)

• Rowe 1980
  -- 7 healthy M, low K+ intake + resin, for 1 week.
  -- Mild (mean 5%) depletion of total K+ $\rightarrow \downarrow$ GT proportional to $\downarrow$ INS release; no IR.

• Helderman 1983
  -- 9 healthy men, 100 mg HCTZ for 10 days.
  -- In 7, also KCl (80 meq then adjusted for losses) $\rightarrow$ no changes in GT, INS sensitivity, etc.
  -- In 2, no KCl $\rightarrow$ sig. hypokalemia, $\downarrow$ GT, $\downarrow\beta$ cell rsp

Long-term study of treated hypertensives: Murphy 1982

- 34 weight-stable patients on high-dose thiazides had 4 GTTs over 14 years.
- 7 patients developed IGT; persistently low K+ assoc. with IGT:
  --<3.6 mm/l x 3→↑2h gluc by 2.7 mm/l
  --3.6+ mm/l x 3→↑2h gluc by 0.1 mm/l
- 7 mo post-thiazide, FG↓10%, 2h gluc ↓25%
- So thiazide-associated IGT is preventable and reversible.

Long-term study of treated hypertensives: Andersson 1991*

- 53 pts randomized to 2.5-5 mg BFMZ, with 8-16 meq KCl.
- In exams at 1 (n=53), 6 (n=49), and 10 years (n=45):
  --Mean serum K+ 4.0-4.2 meq/l at each visit, no ↓ total body K+.
  --No deterioration on OGTT overall, only one patient developed DM.

*1 arm of RCT described in Bergland 1986.

Systematic Overview of Glucose and Potassium Changes

• Across 59 trials using thiazides, large inverse correlation (-0.54, p<0.01) between potassium & glucose change.
• Magnitude=10 mg/dl FG per 1 mEq/l K+
• Both potassium and glucose Δs smaller in subset of trials with K+ supplements or K+-sparing agents.

Trial arms are plotted on the horizontal axis in descending order according to the change in potassium

\[ R = -0.54 \ (P<0.01) \]
Perspective from N. Kaplan

“The potentiation of diabetes by diuretics is likely a reflection of their potassium wasting effect, and may be overcome with lower doses of diuretic or either extra potassium or concomitant renin inhibition.”

Diuretics, Potassium, Glucose

Conclusions

• Potassium depletion appears to be a major intervening factor between thiazide treatment and dysglycemia.

• Both reduced insulin release and decreased insulin sensitivity have been demonstrated; findings not consistent.

• Evidence is incomplete; no RCT designed to test dysglycemia prevention by adequate K+ management.
“In the diuretic-treated patient hypokalemia is likely to be intermittent, due to dietary and drug adherence variation, and potassium-sparing therapeutic intervention. This may also translate to dysglycemia that is intermittent …and thus confer little risk of diabetic complications.”

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New diabetes and CVD risk

- 795 treated HTs, median FU 6 yrs.
- Diuretic rx (low-mod dose HCTZ or CLTD) independently predictive of new diabetes.
- Adjusted* RR (95% CI) of CVD-renal event (n=63)
  - BL DM, 3.57 (1.65, 7.73)
  - New DM, 2.92 (1.33, 6.41)
- Results for specific regimens not given, & only 11% on diuretic/β blocker alone.

“Adverse Prognostic Significance of New Diabetes in Treated Hypertensive Subjects”

“... the use of diuretics, albeit predictive of new diabetes, did not show any independent relation with the subsequent cardiovascular events.”

New diabetes and CVD risk

15-y follow-up of 686 middle-age hypertensive adults treated with diuretic

– Diabetes at baseline significantly associated with CHD—RR 2.1 (1.1, 4.1)

– Incident diabetes was not significantly associated with CHD—RR 1.5 (0.4, 6.0).


Cardiovascular Death (%) 14.3 yrs Follow up

PLACEBO

ACTIVE

B-L DM | F-U DM | NO DM

30* | 27* | 19

22* | 16 | 19

* p< 0.05 vs no diabetes
Effect of ΔFG & Incident Diabetes on Outcomes – Summary

• No significant overall effect of change in FG on any of the study endpoints in the combined treatment groups or the chlorthalidone group separately

• Incident DM increased risk of CHD only
  – Statistically significant for total group & lisinopril
  – In chlorthalidone group, increase in risk was smallest and not significant
### Effect of Incident Diabetes on CHD & Heart Failure by Treatment Group*
(Cox Regressions Beginning at 2 Years)

<table>
<thead>
<tr>
<th></th>
<th>Incident Diabetes / No Diabetes</th>
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<th>P for interaction</th>
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<tbody>
<tr>
<td></td>
<td>HR (95% CI), p</td>
<td></td>
<td></td>
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<tr>
<td><strong>CHD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1.64 (1.15 – 2.33), 0.006</td>
<td>0.21</td>
<td></td>
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<tr>
<td>Chlorthalidone</td>
<td>1.46 (0.88 – 2.42), 0.14</td>
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<tr>
<td>Amlodipine</td>
<td>1.71 (0.87 – 3.34), 0.12</td>
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<tr>
<td>Lisinopril</td>
<td>2.23 (1.07 – 4.62), 0.03</td>
<td></td>
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<tr>
<td><strong>Heart Failure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1.37 (0.84 – 2.24), 0.21</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>0.96 (0.46 – 2.00), 0.91</td>
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<tr>
<td>Amlodipine</td>
<td>1.29 (0.53 – 3.10), 0.58</td>
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<tr>
<td>Lisinopril</td>
<td>3.66 (1.30 – 10.32), 0.01</td>
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</tbody>
</table>

* In patients without diabetes at baseline. Adjusted for age, treatment group, race, gender, smoking, baseline FG, baseline BMI, 2-year BP, 2-year serum potassium, 2-year atenolol & statin treatment.
### Effect of Incident Diabetes on Total Mortality by Treatment Group*

(Cox Regressions Beginning at 2 Years)

<table>
<thead>
<tr>
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<th>Incident Diabetes / No Diabetes</th>
<th>HR (95% CI), p</th>
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<tbody>
<tr>
<td>Total</td>
<td></td>
<td>1.31 (0.95 – 1.81), 0.10</td>
<td>0.19</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td></td>
<td>1.05 (0.66 – 1.67), 0.83</td>
<td></td>
</tr>
<tr>
<td>Amlodipine</td>
<td></td>
<td>1.92 (1.07 – 3.44), 0.03</td>
<td></td>
</tr>
<tr>
<td>Lisinopril</td>
<td></td>
<td>1.31 (0.64 – 2.70), 0.46</td>
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* In patients without diabetes at baseline. Adjusted for age, treatment group, race, gender, smoking, baseline FG, baseline BMI, 2-year BP, 2-year serum potassium, 2-year atenolol & statin treatment.

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- Focus on thiazide-like diuretics
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Outcomes in the Blood Pressure Component of ALLHAT
DIABETIC GROUP

<table>
<thead>
<tr>
<th>Condition</th>
<th>Amlodipine / Chlorthalidone</th>
<th>Lisinopril / Chlorthalidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>0.97 (0.86 - 1.10)</td>
<td>0.97 (0.85 - 1.10)</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>0.95 (0.86 - 1.05)</td>
<td>0.99 (0.89 - 1.09)</td>
</tr>
<tr>
<td>Combined CHD</td>
<td>1.02 (0.93 - 1.12)</td>
<td>1.03 (0.94 - 1.13)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.89 (0.74 - 1.06)</td>
<td>1.06 (0.89 - 1.26)</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>1.39 (1.22 - 1.59)</td>
<td>1.15 (1.00 - 1.32)</td>
</tr>
<tr>
<td>Combined CVD</td>
<td>1.06 (0.98 - 1.14)</td>
<td>1.07 (0.99 - 1.15)</td>
</tr>
<tr>
<td>ESRD</td>
<td>1.27 (0.97 - 1.67)</td>
<td>1.09 (0.82 - 1.46)</td>
</tr>
</tbody>
</table>

Favors
Amlodipine
Chlorthalidone
Lisinopril
Chlorthalidone

10/11/2006
Outcomes in the Blood Pressure Component of ALLHAT

IMPAIRED FASTING GROUP

Amlodipine / Chlorthalidone

<table>
<thead>
<tr>
<th>Condition</th>
<th>Hazard Ratio (95% CI)</th>
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<tbody>
<tr>
<td>CHD</td>
<td>1.73 (1.10 - 2.72)</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>0.93 (0.66 - 1.34)</td>
</tr>
<tr>
<td>Combined CHD</td>
<td>1.37 (1.00 - 1.87)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.68 (0.35 - 1.29)</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>1.66 (0.98 - 2.80)</td>
</tr>
<tr>
<td>Combined CVD</td>
<td>1.13 (0.88 - 1.45)</td>
</tr>
<tr>
<td>ESRD</td>
<td>0.52 (0.11 - 2.60)</td>
</tr>
</tbody>
</table>

Favors Amlodipine

Lisinopril / Chlorthalidone

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<th>Condition</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>CHD</td>
<td>1.16 (0.71 - 1.89)</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>1.07 (0.76 - 1.50)</td>
</tr>
<tr>
<td>Combined CHD</td>
<td>1.12 (0.82 - 1.55)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.91 (0.52 - 1.61)</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>1.20 (0.69 - 2.09)</td>
</tr>
<tr>
<td>Combined CVD</td>
<td>1.09 (0.85 - 1.39)</td>
</tr>
<tr>
<td>ESRD</td>
<td>1.50 (0.48 - 4.66)</td>
</tr>
</tbody>
</table>

Favors Lisinopril

Favors Chlorthalidone
Conclusions

• Most diuretic-associated DM is not diuretic-induced.
• Diuretic-induced DM is reversible and probably preventable.
• Diuretic-associated DM appears to confer less risk than other DM.
• Diuretics are valuable agents for BP control and preventing CVD events.