Adjunctive inhaled insulin before meals improved glycemic control more than adjunctive metformin in type 2 diabetes mellitus


**Clinical impact ratings:** GIM/TP/GP ★★★★★★★ Endocrinology ★★★★★☆☆

**Question:** In patients with type 2 diabetes mellitus poorly controlled with sulfonylurea monotherapy, is adjunctive inhaled human insulin (INH) better than adjunctive metformin?

**Methods**
- **Design:** Randomized controlled trial.
- **Allocation:** Concealed.*
- **Blinding:** Unblinded.*
- **Follow-up period:** 24 weeks.
- **Setting:** 13 centers in Europe, South Africa, Israel, and Brazil.
- **Patients:** 427 patients 35 to 80 years of age (mean age 60 y, 53% men) who had type 2 diabetes mellitus ≥ 6 months, were poorly controlled on sulfonylurea ≥ 2 months, and had normal pulmonary function test results.
- **Outcomes:** Change in HbA1c for patients achieving HbA1c < 7%, Fasting plasma glucose for patients achieving HbA1c < 8%, Change in HbA1c for patients achieving HbA1c < 9.5%, Change in FEV1 for patients with HbA1c > 9.5%, and Patients achieving HbA1c < 7%.
- **Exclusion criteria:** Previous 6 months; concomitant therapy with obstructive pulmonary disease; smoking in the previous 6 months; concomitant therapy with hypoglycemic agents or agents that may affect glycemic control; fasting C-peptide ≤ 0.2 nmol/L; and major organ system disease.
- **Intervention:** Premal INH (dose was adjusted weekly to achieve a mean fasting glycemic target of 4.4 to 7.8 mmol/L [80 to 140 mg/dL]) (n = 225) or metformin (1 g twice daily) (n = 202). All patients maintained sulfonylurea therapy.
- **Outcomes:** Change from baseline in hemoglobin (Hb) A1c. Secondary outcomes included proportion of patients achieving HbA1c levels ≤ 7% and ≤ 8%, changes in fasting plasma glucose and 2-hour postprandial glucose, Fasting plasma glucose for patients achieving HbA1c < 9.5%, Change in FEV1 for patients with HbA1c > 9.5%, and Patients achieving HbA1c < 7%.

**Main results**
- **Relative risk (CI):**
  - Hypoglycemic events (events/patient-mo) 0.31 0.17 1.86 (1.56 to 2.22)
  - 2-h postprandial glucose (mg/dL) 162.9 171.7 −11.40 (−18.60 to −4.19)

**Conclusion**
- Patients with type 2 diabetes mellitus that was poorly controlled with sulfonylurea monotherapy had better glycemic control but more hypoglycemic events after the addition of premeal inhaled insulin than did those after the addition of metformin.

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*See Glossary.

**Adjunctive inhaled human insulin (INH) vs metformin in patients with type 2 diabetes mellitus poorly controlled with sulfonylurea at 24 weeks†**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>INH + sulfonylurea</th>
<th>Metformin + sulfonylurea</th>
<th>Difference in adjusted mean change (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in HbA1c, ≤ 9.5%</td>
<td>−2.06%</td>
<td>−1.83%</td>
<td>−0.22% (−0.40 to −0.05)</td>
</tr>
<tr>
<td>Change in HbA1c, &gt; 9.5%</td>
<td>−1.94%</td>
<td>−1.87%</td>
<td>−0.07% (−0.33 to 0.19)</td>
</tr>
<tr>
<td>Change in FEV1, &gt; 9.5%</td>
<td>−2.17%</td>
<td>−1.79%</td>
<td>−0.38% (−0.63 to −0.14)</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dL)</td>
<td>172.0</td>
<td>169.0</td>
<td>2.39 (−5.81 to 10.59)</td>
</tr>
<tr>
<td>2-h postprandial glucose (mg/dL)</td>
<td>162.9</td>
<td>171.7</td>
<td>−11.40 (−18.60 to −4.19)</td>
</tr>
</tbody>
</table>

**Commentary**

Patients’ inability to modify their lifestyle for a disorder attributed to sedentary lifestyle, limited long-term efficacy of current antihyperglycemic medications, and objection to the use of such medications as insulin may contribute to poor glycemic control in type 2 diabetes. Poor glycemic control may be caused by an unacceptable route of medication (e.g., parenteral) and fear of hypoglycemia. Therefore, inhaled insulin preparations are an interesting addition to the therapeutic armamentarium. Limitations of the study by Barnett and colleagues include different titration schedules for the 2 groups and more contact between providers and patients in the INH group, lack of blinding, and important loss to follow-up.

Where do we stand with regard to treatment of type 2 diabetes? Monotherapy choices include metformin, sulfonylureas, thiazolidinediones, meglitinides, and α-glucosidase inhibitors. When a second medication is required, exenatide, long- and intermediate-acting insulin preparations, and now INH are options. Patients and clinicians can choose combinations based on comorbid conditions and patient preference. The combination of metformin and exenatide seems most attractive, given its efficacy, safety (no hypoglycemia), and favorable weight changes (1). INH use in practice will require considering additional training of providers to instruct patients on its use, unknown long-term effects on lung function, unknown significance of insulin antibodies, unknown relation of insulin antibodies to hypoglycemic episodes, and limited portability of the inhalation device (2).

**References**