Flexible, intensive vs. conventional insulin therapy in insulin-naive adults with type 2 diabetes - an open-label, randomized controlled cross-over clinical trial of metabolic control and patient preference

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Abbreviations: FIT, flexible, intensive insulin therapy; CIT, conventional insulin therapy; BPsys, systolic blood pressure; BPdias, diastolic blood pressure; GHb, glycosylated hemoglobin A₁c

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Introduction
Improving metabolic control can reduce complications in type 2 diabetes (1-4). Conventional (CIT) and flexible, intensive insulin therapy (FIT) are treatment options in insulin-dependent type 2 diabetes. In CIT, participants inject premixed human insulin (30% regular insulin, 70% NPH-insulin) before breakfast and dinner and follow individually adjusted diet plans with fixed amounts of carbohydrates (5). In FIT, blood glucose and desired carbohydrate intake adjusted human regular insulin becomes injected before main meals. When necessary, NPH-insulin is added at bedtime. CIT can be easy to handle and requires less active diabetes self-management. In FIT, patients benefit from dietary freedom and improvement in quality of life (6). In pilot studies, FIT has shown good metabolic control and low risk of hypoglycemia (7). FIT may have additional advantages due to better post-prandial blood glucose control (8).

Research design and methods
We tested the hypothesis that FIT and CIT in insulin-naive adults with type 2 diabetes are equally effective in regards to metabolic outcomes. We hypothesized that younger participants, in employment, would prefer FIT. The trial was designed as a clinical, prospective, randomized, open label, single center, cross-over study. The primary end-point was glycosylated hemoglobin A1c (GHB), secondary endpoints were mild and severe hypoglycemia, insulin dosage, blood pressure, BMI and therapy preference. Participants started insulin therapy either with CIT (group A) or FIT (group B), randomly. Individual insulin dosage and carbohydrate intake were determined over a four week run-in period with weekly visits. All visits were the same in both groups and held in the study center. In CIT, daily blood glucose self-control was performed before breakfast and dinner, in FIT before main meals. Oral anti-diabetic drugs were not permitted. The participants completed an out-patient Diabetes Treatment and Teaching Program with 5 lessons (90-120 minutes) during run-in (8, 9). The run-in was followed by an 8 week study sequence until cross-over. At cross-over, participants were given one structured teaching session for refreshing and switched from CIT to FIT or FIT to CIT. After an one week run-in period for insulin dose-adjustment, participants completed the second 8 week study sequence. At trial end, therapeutic preference was investigated with a structured interview. Eligible participants who failed therapeutic goals under oral anti-diabetic therapy were recruited consecutively (Outpatient Clinic, Friedrich-Schiller-University). Exclusion criteria were: not type 2 diabetes, diabetes duration <2 years, not insulin-naive, ineffective oral anti-diabetic therapy <3 months, GHB <7 or >11%, age <40 or >65 years. GHB was measured using HPLC-technique (TOSOH-Glykohämoglobin-Analyzer-HLC-723-GHbV, TOSOH CORPORATION, Tokyo, normal range 3.8-5.5%; mean 4.7%; SD±0.33). Mild hypoglycemia was defined as symptomatic neuroglycopenia or blood glucose readings <3.3 mmol/l. Severe hypoglycemia required intravenous glucose or subcutaneous/intramuscular glucagon injection.

To have a 90% chance of detecting as significant (at the two sided 5% level) a 0.5% difference between the two groups in GHB, with an assumed standard deviation of 0.8%, 38 participants were required. Intention-to-treat analysis was carried out according to a pre-established analysis plan. Means and standard deviations were calculated. The t-test for paired and non-paired samples was used where appropriate. For statistical analysis of
associations of GHb and participant’s characteristics, linear mixed-effects models were used. A \( p < 0.05 \) was regarded as statistically significant. Statistical analysis was performed with SPSS15.0 (SPSS Inc., Chicago). The study was approved by the local ethics committee and was performed according to the principles of the Helsinki declaration. Written informed consent was obtained before taking part. The trial was registered with ClinicalTrials.gov (NCT00440284).

Results
Baseline clinical data between groups were not significantly different [table 1, group A (first CIT, n=20) vs. group B (first FIT, n=19)]: age 56.6±7.3 vs. 54.7±6.6 years, diabetes duration 7.5±4 vs. 8.2±4.2 years, total cholesterol 5.3±1.1 vs. 5.3±1.1 mmol/l, creatinine 82±18.4 vs. 77±16.3 µmol/l, peripheral neuropathy 9 vs. 4 participants, in employment 12 vs. 15 participants. All participants completed both study sequences except for one person who refused to switch. After initiation of insulin therapy, GHb declined from 8.9±1.7 to 7.3±0.9% \( (p<0.0001) \), BMI increased from 29.4±4.4 to 30±4.2 kg/m² \( (p<0.01) \). Blood pressure and lipid profiles remained unchanged. There was no significant difference between CIT and FIT regarding GHb, BMI, BP, insulin dosage and hypoglycemia (table 1). In linear mixed-effects models, GHb after CIT and GHb after FIT were not associated with age, gender, diabetes duration, initial GHb, blood pressure, lipid profiles, co-morbidity and occupation.

20 participants preferred to continue CIT, 18 opted for FIT. Reasons to opt for FIT were: therapy flexibility \( (n=9) \), easier therapy \( (n=1) \), metabolic control \( (n=1) \). Arguments in favor of CIT were: easier therapy \( (n=8) \), fewer injections \( (n=8) \), metabolic control \( (n=3) \). In a binary logistic regression model 88% of therapy decisions were explained by the last therapy option. To add data on age, gender, diabetes duration, GHb after CIT/FIT, initial GHb, blood pressure, lipid profiles, co-morbidity and occupation did not improve the model.

Conclusions
Initiation of insulin therapy in type 2 diabetes was safe and effective. Metabolic control improved during the first study sequence in FIT and CIT but did not further improve in the second sequence. Participants did not reach GHb levels below 7%. After having practiced CIT and FIT for 8 weeks each, participants preferred their last therapy. This indicates that clinical advantages of CIT or FIT were of minor importance for participants irrespective of age or being employed or not. Interestingly, in contrast to patients with type 1 diabetes, gaining more dietary freedom seems not to be a prevalent motive in type 2 diabetes (6).

Limitations to consider include: The sample size of this RCT was too small and the study period too short to detect minor differences. Carry-over effects of the cross-over design can reduce the effect of the second trial sequence. The primary outcome measure of this trial (GHb) was a surrogate parameter. Comparison of side effects may be limited by different definitions of mild and severe hypoglycemia. Participants were young and had early manifestation of type 2 diabetes compared to general population (10). Older patients with impaired cognitive function might be unable to practice effective diabetes self-management using insulin therapy or might be disinterested in the clinical advantages of FIT and CIT (11).
References


11. Braun A, Muller UA, Muller R, Leppert K, Schiel R: Structured treatment and teaching of patients with Type 2 diabetes mellitus and impaired cognitive function--the DICOF trial. Diabet Med 21(9):999-1006, 2004
Table 1. Main outcomes (intention to treat analysis), participants were randomized to start insulin therapy either with CIT (group A) or FIT (group B), differences were not significant

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>First 8 week sequence</th>
<th>Second 8 week sequence</th>
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<tbody>
<tr>
<td></td>
<td>Group A</td>
<td>Group B</td>
<td>Group A CIT</td>
</tr>
<tr>
<td>GHb [%]</td>
<td>8.9 (1.5)</td>
<td>9.2 (2.1)</td>
<td>7.4 (1)</td>
</tr>
<tr>
<td>BMI [Kg/m²]</td>
<td>29 (4.1)</td>
<td>29.3 (4.8)</td>
<td>29.9 (3.7)</td>
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<tr>
<td>BP sys [mmHg]</td>
<td>137.3 (17)</td>
<td>137.6 (17.3)</td>
<td>138.3 (13.3)</td>
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<tr>
<td>BP dias [mmHg]</td>
<td>81 (10)</td>
<td>80.9 (8.9)</td>
<td>81.5 (8.9)</td>
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<tr>
<td>Insulin [IU/day]</td>
<td>0</td>
<td>0</td>
<td>34 (14)</td>
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<tr>
<td>Mild Hypo. [n]</td>
<td>0</td>
<td>0</td>
<td>2</td>
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<tr>
<td>Severe Hypo. [n]</td>
<td>0</td>
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