Effect of intensive insulin therapy on β-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial

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Summary

Background Early intensive insulin therapy in patients with newly diagnosed type 2 diabetes might improve β-cell function and result in extended glycaemic remissions. We did a multicentre, randomised trial to compare the effects of transient intensive insulin therapy (continuous subcutaneous insulin infusion [CSII] or multiple daily insulin injections [MDI]) with oral hypoglycaemic agents on β-cell function and diabetes remission rate.

Methods 382 patients, aged 25–70 years, were enrolled from nine centres in China between September, 2004, and October, 2006. The patients, with fasting plasma glucose of 7·0–16·7 mmol/L, were randomly assigned to therapy with insulin (CSII or MDI) or oral hypoglycaemic agents for initial rapid correction of hyperglycaemia. Treatment was stopped after normoglycaemia was maintained for 2 weeks. Patients were then followed-up on diet and exercise alone. Intravenous glucose tolerance tests were done and blood glucose, insulin, and proinsulin were measured before and after therapy withdrawal and at 1-year follow-up. Primary endpoint was time of glycaemic remission and remission rate at 1 year after short-term intensive therapy. Analysis was per protocol. This study was registered with ClinicalTrials.gov, number NCT00147836.

Findings More patients achieved target glycaemic control in the insulin groups (97·1% [133 of 137] in CSII and 95·2% [118 of 124] in MDI) in less time (4·0 days [SD 2·5] in CSII and 5·6 days [SD 3·8] in MDI) than those treated with oral hypoglycaemic agents (83·5% [101 of 121] and 9·3 days [SD 5·3]). Remission rates after 1 year were significantly higher in the insulin groups (51·1% in CSII and 44·9% in MDI) than in the oral hypoglycaemic agents group (26·7%; p=0.0012). β-cell function represented by HOMA B and acute insulin response improved significantly after intensive interventions. The increase in acute insulin response was sustained in the insulin groups but significantly declined in the oral hypoglycaemic agents group at 1 year in all patients in the remission group.

Interpretation Early intensive insulin therapy in patients with newly diagnosed type 2 diabetes has favourable outcomes on recovery and maintenance of β-cell function and protracted glycaemic remission compared with treatment with oral hypoglycaemic agents.

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Introduction

The UK Prospective Diabetes Study[1,2] has shown that β-cell function progressively deteriorates over time in people with type 2 diabetes mellitus, irrespective of lifestyle and existing pharmacological interventions. Notwithstanding, continued effort has been directed toward β-cell preservation or rejuvenation in an attempt to change or at least delay the natural course of type 2 diabetes.[3] Other studies have indicated that, in newly diagnosed patients, short-term intensive insulin therapies that target overall glycaemic control, such as multiple daily insulin injections (MDI) and continuous subcutaneous insulin infusion (CSII), could improve β-cell function and result in extended remissions in which only diet was needed to maintain normoglycaemia.[3–8] The results of our previous study[7] also suggest that the improvement of β-cell function, especially the restoration of the first-phase insulin secretion, could be responsible for the remission. Still unclear, however, is whether this disease-modifying effect is due to insulin therapy itself or the effects of simply eliminating glucotoxicity by achieving excellent glycaemic control, and which kind of initiation of early intensive therapy would be more beneficial.

We therefore did a multicentre, randomised, parallel-group trial to assess the efficacy of short-term intensive insulin therapy (including MDI and CSII) compared with oral hypoglycaemic agents on glycaemic control, remission rate, and β-cell function in patients with newly diagnosed type 2 diabetes. Several indicies were used for assessment of β-cell insulin-secretory capacity, including: HOMA B, which represents basal β-cell function; the first-phase insulin secretion after a glucose challenge, which represents the acute insulin response; and the ratio of plasma proinsulin to immunoreactive insulin (PI/IRI), which indicates β-cell secretory quality.[9]

Methods

436 patients with newly diagnosed type 2 diabetes, according to WHO diagnostic criteria (1999),[10] who had not received previous antihyperglycaemic therapy, were enrolled from nine centres in China between September, 2004, and October, 2006. The patients, aged 25–70 years, had levels of fasting plasma glucose between 7·0 mmol/L and 16·7 mmol/L. Patients were excluded if they had acute or severe chronic diabetic complications, severe intercurrent illness, or tested positive for glutamic acid decarboxylase antibody. Patients with maturity onset diabetes in youth and mitochondria diabetes mellitus were excluded.[11,12] There was a 3–7 days run-in period of diet alone. The protocol and informed consent document were approved by the research ethics board of the Sun Yat-Sen University. All patients gave written informed consent.

Study design

Patients were randomly assigned to one of three groups for antihyperglycaemic therapies: MDI, CSII, or oral hypoglycaemic agents. Sealed, opaque envelopes arranged in a computer-generated random order were prepared by the data-coordinating centre and distributed to each participating centre, where they were opened sequentially to determine the patients' treatment assignments.

Patients in the CSII group received human insulin (Novo Nordisk, Bagsværd, Denmark) with an insulin pump (H-Tron Plus V100; Disetronic Medical Systems). Patients in the MDI group were treated with pre-meal Novolin-R, and human insulin NPH (Novolin-N, Novo Nordisk) at bedtime. Initial insulin doses were 0·4–0·5 IU/kg and total daily doses were divided into 50% of basal and 50% of bolus injection in the CSII group and into 30%–20%–20%–30% in the MDI group. In the group treated with oral hypoglycaemic agents, patients with a body-mass index between 20 kg/m² and 25 kg/m² were initially treated with gliclazide (Servier, Tianjin, China) 80 mg twice a day, which was increased up to a maximum of 160 mg twice a day to achieve glycaemic control. Patients with a body-mass index of between 25 kg/m² and 35 kg/m² were initially treated with metformin (Glucophage, Bristol-Myers Squibb) 0·5 g twice a day and increased to a maximum of 2·0 g a day. A combination of gliclazide and metformin was used in patients who could not reach the glycaemic control goal with one oral hypoglycaemic agent or who had a fasting plasma glucose of 11·1 mmol/L or more at randomisation. The doses were titrated every day in the insulin groups and every 3 days in the hypoglycaemic agents group in order to attain the glycaemic goal. This goal was defined as a fasting capillary blood glucose of less than 6·1 mmol/L and capillary blood glucose at 2 h after each of three meals of less than 8·0 mmol/L. Treatments were maintained for 2 weeks after the glycaemic target was reached. Patients who did not achieve glycaemic control by CSII or MDI alone or by combined maximum dosage of oral hypoglycaemic agents within 2 weeks, or could not stand the side-effects of oral hypoglycaemic agents, were regarded as requiring additional or different therapy and were excluded from the efficacy analysis.

Fasting blood samples were collected for measurement of fasting plasma glucose, proinsulin, free fatty acids, and lipid profiles in all patients before and after treatment (2 days after insulin or hypoglycaemic agent cessation), immediately followed by an intravenous glucose tolerance test using 25 g of glucose (50 mL of 50% glucose), with serum samples obtained before and 1, 2, 4, 6, and 10 min after intravenous glucose load to measure insulin. 2-h postprandial (after breakfast) plasma glucose concentrations were assessed the day before the intravenous glucose tolerance test. The acute insulin response during the intravenous glucose tolerance test was used to assess the first-phase β-cell insulin secretion, which was calculated as the incremental trapezoidal area during the first 10 min. Homoeostasis model assessment was used to estimate basal β-cell function (HOMA B) and insulin resistance (HOMA-IR).[13] The following equations were used to calculate β-cell function and insulin resistance: HOMA B=20×fasting insulin/(fasting plasma glucose−3·5). HOMA-IR=fasting plasma glucose×fasting insulin/22·5. The PI/IRI ratio was also calculated.

Concentrations of insulin, proinsulin, and free fatty acids were assessed centrally at the Diabetes Center of First Affiliated hospital of Sun Yat-Sen University. Radioimmunoassay was used for measurement of insulin (3V Bio-engineering group, Weifang, China) and proinsulin (Linco Research, St Charles, MO, USA). Free fatty acids levels were assessed enzymatically with a Wako NEFA C test kit (Wako Chemicals, Dallas, TX, USA). Measurements of glycated haemoglobin A_{1c} (HbA_{1c}) levels and routine clinical laboratory tests were done in the central laboratory units of the nine participating centres. HbA_{1c} was assayed using the Bio-Rad Variant Hemoglobin A_{1c} assay.

After interventions were stopped, patients were instructed to continue diet and physical exercise only and were followed-up with glycaemic monitoring monthly during the initial 3 months and at 3-month intervals thereafter. Hyperglycaemia relapse was defined as either fasting plasma glucose of more than 7·0 mmol/L or 2-h postprandial plasma glucose of more than 10·0 mmol/L, which was confirmed 1 week later. The time of glycaemic remission was recorded, and patients with hyperglycaemic relapse were treated with oral hypoglycaemic agents or insulin, according to the guidelines of the International Diabetes Federation-Western Pacific Region. Patients who maintained optimum glycaemic control for at least 12 months without medication were defined as the remission group and those who relapsed during the 12 months of follow-up as the non-remission group. The above measures were repeated at 1-year follow-up.

The primary endpoint was the time of glycaemic remission and remission rate at 1 year after short-term intensive therapy in patients with newly diagnosed type 2 diabetes. The secondary endpoint was the effect of

different interventions including CSII, MDI, or oral hypoglycaemic agents on β-cell function in these patients.

Statistical analysis

As expected from our previous studies, 45% of patients who received insulin treatment (CSII or MDI) and 25% of patients treated with oral hypoglycaemic agents achieved long-lasting remission. With 89 patients in each group, the study had 80% power at 5% significance (2-sided) to detect a clinically significant difference (20%) in the remission rate between the insulin group and the group treated with oral hypoglycaemic agents. Since the average rate of not achieving glycaemic control by the intervention was about 20%, based on the results of previous studies, and the estimated dropout rate was 15%, at least 392 patients in total should be recruited. Efficacy analyses were done on the population who achieved 2 weeks of euglycaemic control during intensive intervention. Safety analyses were done on all randomly assigned patients who received study medication.

Data were analysed with the SPSS 11·0 program.[14] Normally distributed and continuous variables are presented as mean (SD), and non-normally distributed variables (triglycerides, acute insulin response, PI/IRI, HOMA B, and HOMA IR) expressed as median (IQR). For the assessment of differences between the treatment groups with regard to quantitative variables (ie, fasting plasma glucose, HbA_{1c}, lipid profile parameters, HOMA IR, PI/IRI), one-way analysis of variance (ANOVA) with multiple comparisons Scheffé post-test was used. The non-normally distributed variables have been log-transformed and then analysed with ANOVA. The comparison of β-cell function among the three groups was made using an ANCOVA model with treatment as fixed effects and sex, age, body-mass index, and baseline triglycerides as the covariates. A Kruskal-Wallis H or Friedman test was used to analyse the non-normally distributed variables (acute insulin response and the change of PI/IRI ratio from baseline to after interventions). Time-to-event distributions were summarised with Kaplan-Meier curves. The percentage reduction in risk was computed as 100×(1–hazard ratio), with the hazard ratio estimated from the Cox proportional-hazards model. χ^2 tests were done to analyse the differences of remission rates among the three intervention groups. Significance was defined as $p<0·05$.

This study was registered with ClinicalTrials.gov, number NCT00147836.

Role of the funding source

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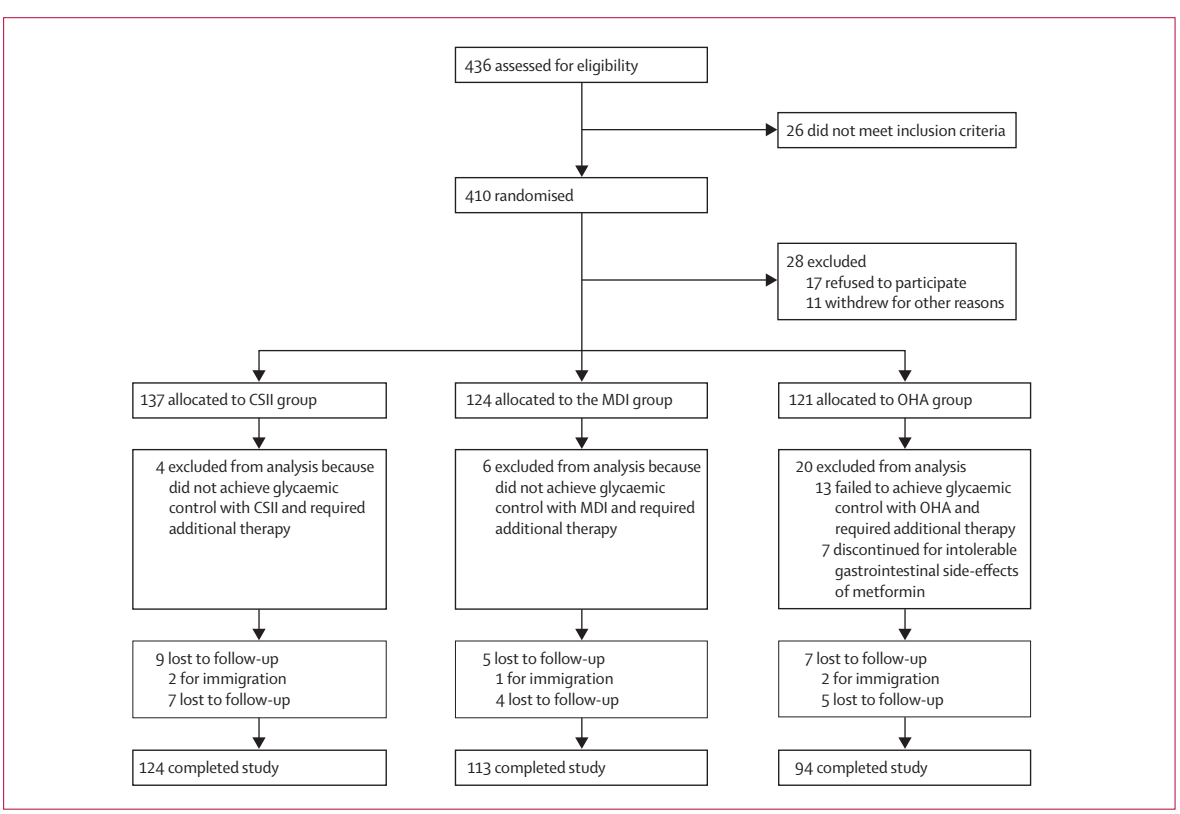

Figure 1: **Trial profile**
CSII=continuous subcutaneous insulin infusion. MDI=multiple daily insulin injections. OHA=oral hypoglycaemic agents.

sources had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

	CSII	MDI	Oral hypoglycaemic agents
Number	133	118	101
Men (n)	88	81	58
Age (years)	50 (11)	51 (10)	52 (9)
Body-mass index (kg/m²)	25·1 (3·0)	24·4 (2·7)	25·1 (3·3)
Fasting plasma glucose (mmol/L)			
Before therapy	11·3 (3·3)	11·5 (3·2)	10·8 (2·9)
After therapy*	6·6 (1·5)	6·8 (1·6)	6·5 (1·6)
2-h postprandial plasma glucose (mmol/L)			
Before therapy	16·1 (5·5)	17·5 (5·5)	16·6 (5·0)
After therapy*	7·5 (2·2) (n=113)	8·1 (2·9) (n=111)	8·2 (2·7) (n=90)
HbA_{1c} (%)			
Before therapy	9·8 (2·3)	9·7 (2·3)	9·5 (2·5)
After therapy*	8·0 (1·5)	8·0 (1·6)	7·9 (1·7)
Triglycerides (mmol/L)†			
Before therapy	1·7(1·4) (n=132)	1·7(1·4) (n=117)	1·8(1·1) (n=97)
After therapy*	1·3(0·7) (n=127)	1·3(0·8) (n=113)	1·4(1·0) (n=97)
Total cholesterol (mmol/L)			
Before therapy	5·2 (1·2) (n=128)	5·4 (1·2) (n=115)	5·4 (1·2) (n=100)
After therapy*	4·7 (1·0) (n=127)	5·0 (1·1) (n=113)	4·7 (0·9) (n=97)
HDL-C (mmol/L)			
Before therapy	1·2 (0·3) (n=132)	1·3 (0·4) (n=117)	1·3 (0·4) (n=96)
After therapy	1·2 (0·4†) (n=127)	1·3 (0·4) (n=113)	1·2 (0·4) (n=95)
p value	0·044	0·098	0·158
LDL-C (mmol/L)			
Before therapy	3·0 (1·0) (n=132)	3·2 (0·9) (n=117)	3·1 (0·8) (n=96)
After therapy	2·7 (0·8) (n=127)	2·8 (1·0) (n=113)	2·6 (0·7) (n=95)
p value	<0·0001	0·001	<0·0001
Free fatty acids (mmol/L)			
Before therapy	0·76 (0·39) (n=117)	0·70 (0·27) (n=101)	0·73 (0·22) (n=89)
After therapy	0·61 (0·20) (n=116)	0·62 (0·21) (n=99)	0·62 (0·19) (n=86)
p value	<0·0001	0·001	<0·0001
Acute insulin response (pmol/L per min)†			
Before therapy	−62 (421) (n=126)	−7 (347) (n=114)	−95 (452) (n=95)
After therapy*	889 (1087) (n=129)	793 (1150) (n=115)	736 (1289) (n=90)
PI/IRI (%)†			
Before therapy	23·8 (17·5) (n=123)	26·5 (22·6) (n=115)	28·4 (22·2) (n=95)
After therapy*	12·1 (11·8) (n=113)	16·8 (20·1) (n=105)	21·2 (20·7)‡ (n=90)
HOMA B†			
Before therapy	33·6 (45·6) (n=114)	38·3 (36·9) (n=108)	50·0 (60·6) (n=94)
After therapy*	87·5 (82·5) (n=113)	78·9 (65·2) (n=103)	102·3 (16·0) (n=90)
HOMA IR†			
Before therapy	6·0 (5·6) (n=114)	6·7 (5·7) (n=108)	6·9 (8·6) (n=94)
After therapy*	3·2 (2·8) (n=113)	3·1 (2·9) (n=103)	4·8 (4·8) (n=90)

Data are mean (SD) unless otherwise indicated. *p<0·0001 compared with before treatment. †Data are median (IQR). ‡p<0·05 compared with CSII.

Table 1: **Comparison of glucose control and β-cell function at baseline and after interventions**

Results

Of the 436 patients screened, 410 were eligible and were randomised. 28 patients withdrew before receiving interventions (figure 1). The remaining 382 patients (mean age 51 years [SD 10], body-mass index 25·0 kg/m² [3·0], and mean fasting plasma glucose 11·2 mmol/L [3·1]) were allocated to the CSII group (137), the MDI group (124), and the hypoglycaemic agents group (121).

Of these patients, 23 (four in the CSII group, six in the MDI group, and 13 in the oral hypoglycaemic agents group) did not reach the glycaemic control goals and seven patients in the oral hypoglycaemic agents group were withdrawn because of gastrointestinal side-effects of metformin. These 30 patients were therefore excluded from further analysis. Of the remaining 352 patients who completed transient intensive treatment, 331 completed 1-year visits and 21 (5·5%, nine in the CSII group, five in the MDI group, and seven in the oral hypoglycaemic agents group) dropped out because of immigration or were lost to follow-up (figure 1).

Clinical characteristics, glucose levels, and lipid profiles at baseline were similar between the three groups (table 1). 92·1% (352 of 382) of patients reached glycaemic goals in 7·9 days (SD 4·6) during the intervention period. More patients achieved target glycaemic control in the insulin groups (133 of 137 [97·1%] in CSII, and 118 of 124 [95·2%] in MDI) in less time (4·0 days [SD 2·5] in CSII and 5·6 days [3·8] in MDI) than those in the oral hypoglycaemic agents group (101 of 121 [83·5%], 9·3 [5·3] days; p<0·0001 *vs* CSII and p=0·01 *vs* MDI). The mean maximum daily doses were 0·68 IU kg^{-1} (SD 0·21) in the CSII group and 0·74 IU kg^{-1} (0·35) in the MDI group, and the median maximum daily doses in the oral hypoglycaemic agents group was gliclazide 160 mg plus metformin 1500 mg. 25 patients were treated with gliclazide alone and 27 with metformin alone.

Of the patients who reached glycaemic targets, the improvement of glucose control, represented by significant decrease of fasting plasma glucose, 2-h postprandial plasma glucose, and HbA_{1c}, did not significantly differ among the groups (table 1). Nor did the amelioration of lipid profile, indicated by decreased total cholesterol, LDL-C, triclycerides, and free fatty acid levels after intensive therapies.

The indicies of β-cell function and HOMA IR were similar between the three treatment groups before treatment (table 1). The acute insulin response was absent in all patients at that point. After 2–5 weeks of intensive treatment, the acute insulin response was partially restored and HOMA B was significantly increased in all patients (p<0·0001). The PI/IRI ratios were markedly decreased (p<0·0001), and HOMA IR also decreased (p<0·0001). When the data after therapy among three groups were compared, we found no significant difference in the improvement of acute

insulin response, HOMA B, and HOMA IR. But the decrease in the PI/IRI ratio was more obvious in both the insulin groups (median 8·7% [IQR 17·1%] in CSII, 10·8% [IQR 19·7%] in MDI) than in the oral hypoglycaemic agents group (4·1% [IQR 14·5%] *vs* CSII, p=0·038; *vs* MDI, p=0·011, respectively).

The remission rate at 1 year was 42·0% (148 of 352) in all patients who achieved glycaemic control during the intensive interventions. Figure 2 shows the remission rates at 1 year in the three groups: 51·1% (68 of 133) in the CSII group, 44·9% (53 of 118) in MDI group, and 26·7% (27 of 101) in the oral hypoglycaemic agents group. The remission rate was significantly higher in both insulin groups than in the oral hypoglycaemic agents group (p=0·0012). The risk of relapse was reduced by 44% (95% CI 0·40–0·78, p=0·001) with CSII and by 31% (95% CI 0·50–0·97, p=0·032) with MDI compared with oral hypoglycaemic agents.

The remission group had higher initial body-mass index, lower fasting plasma glucose and HbA_{1c}, and also achieved glycaemic control faster than the non-remission group (table 2). After short-term treatment, the remission group had a more marked reduction in fasting plasma glucose, 2-h postprandial plasma glucose, and HbA_{1c}.

The non-remission patients from different interventions were combined into one non-remission group in order to compare the acute insulin response between remission and non-remission patients. As a result, we found the increase of acute insulin response induced by CSII (median 1151 [IQR 1131] pmol/L per min), MDI (1065 [IQR 1158] pmol/L per min), or oral hypoglycaemic agents (968 [IQR 1752] pmol/L per min) was greater in the remission groups than in the non-remission group (601 [IQR 819] pmol/L per min; p<0·0001).

Among the remission groups, the increase of the acute insulin response was maintained after 1 year in CSII (809 pmol/L per min; p=0·235) and MDI groups (729 pmol/L per min; p=0·063) compared with immediately after the intervention. But it significantly declined in the oral hypoglycaemic agents group (335 pmol/L per min; p<0·0001). Acute insulin response in the oral hypoglycaemic agents group was significantly lower than that in the CSII group (p=0·006), whereas there was no difference between oral hypoglycaemic agents group and MDI group (p=0·097) at 1 year (figure 3).

There were no severe hypoglycaemic episodes—defined as an event requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative treatments—during the short-term intensive interventions. The proportion of patients with one or more minor hypoglycaemic episodes—defined as having classical symptoms of hypoglycaemia or blood glucose level below 3·1 mmol/L and prompt recovery after the patient self-administered carbohydrate—was higher, although not significantly, in the CSII (31%, 42 of 137) and the MDI (28%, 35 of 124) groups than in the oral hypoglycaemic agents group (19%, 23 of 121). No pump-related side-effects or injection site reactions were reported. Diarrhoea and other gastrointestinal side-effects

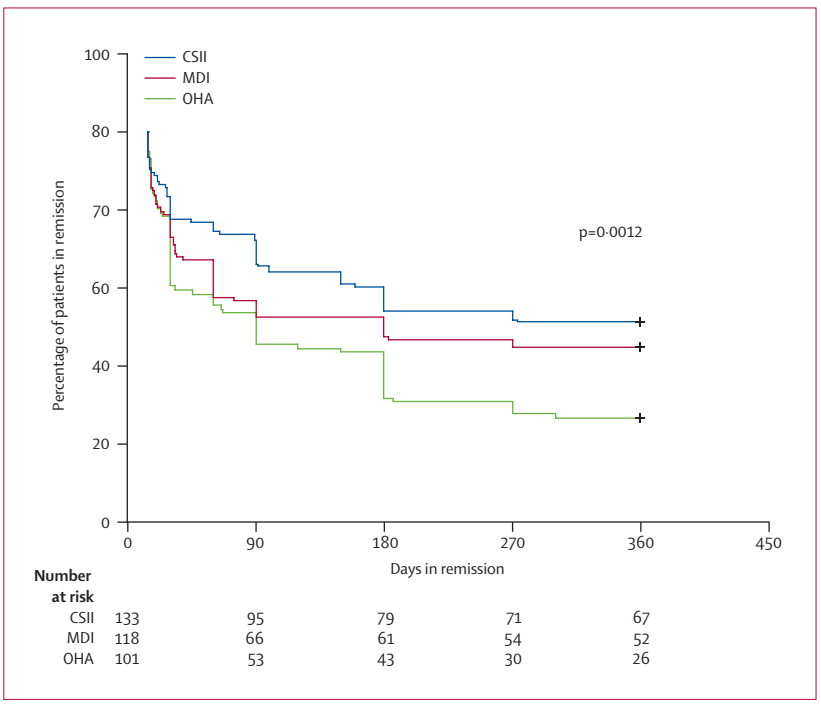

Figure 2: **Kaplan-Meier estimates of time to primary endpoint**

	Remission group	Non-remission group	p, compared between remission and non-remission group
Number	148	183	
Men (n)	104	110	0·055
Age (years)	50 (10)	52 (10)	0·0157
Body-mass index (kg/m²)			
Before treatment	25·5 (2·8)	24·3 (3·1)	<0·0001
Fasting plasma glucose (mmol/L)			
Before treatment	10·8 (3·2)	11·6 (3·1)	0·014
After treatment*	6·2 (1·0)	7·0 (1·9)	<0·0001
2-h postprandial plasma glucose (mmol/L)			
Before treatment	16·4 (5·6)	17·0 (5·1)	0·337
After treatment*	7·2 (2·0)	8·5 (2·8)	<0·0001
HbA_{1c} (%)			
Before treatment	9·2 (2·2)	10·0 (2·4)	0·004
After treatment*	7·7 (1·5)	8·1 (1·7)	0·029
Days of achieving euglycaemia	6·1 (4·1)	6·7 (3·5)	0·048

Data are mean (SD) unless otherwise indicated. *p<0·0001 compared with before treatment.

Table 2: **Comparison between remission group and non-remission group before and after treatment**

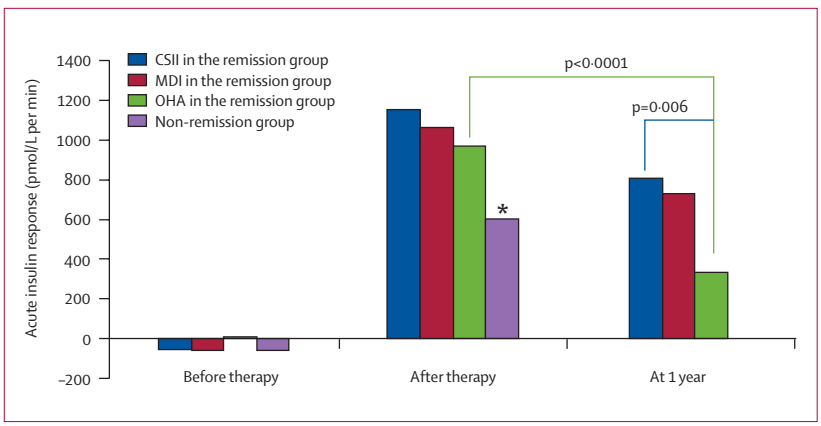

Figure 3: **Acute insulin response (shown as median) before and after different interventions and at 1 year**
*p<0·05 in the non-remission group compared with that in each intervention in the remission group (after treatment).

were reported in 14 patients in the hypoglycaemic agents group, all of whom were using metformin, and seven of these patients withdrew because of intolerance. The mean bodyweight of patients was unchanged after transient treatments in all groups. No other severe adverse events were reported during the study period.

Discussion

Our results show that excellent glycaemic control could be successfully achieved in 7·9 days (SD 4·6) in most patients with mean fasting plasma glucose of 11·2 mmol/L (SD 3·1), irrespective of the use of CSII, MDI, or oral hypoglycaemic intervention. Of those patients who reached glycaemic targets, both fasting plasma glucose and 2-h postprandial plasma glucose concentrations rapidly corrected to near physiological range after treatment, and HbA_{1c} was greatly improved after only 2–5 weeks.

In our study, the acute insulin response was absent before treatment and was restored partially in patients after short-term treatments. HOMA B was also significantly increased. The PI/IRI ratios were markedly decreased, indicating the improvement of qualitative insulin secretion. Additionally, the decline in HOMA-IR and amelioration of the lipid profile without the use of lipid-adjusting agents were also indicators of the reduction in glucotoxicity. Besides these improvements, 148 (42·0%) of 352 responsive patients achieved more than 1-year remission in which only diet control and exercise were necessary to maintain optimum glycaemic control. Hence, in patients newly diagnosed with type 2 diabetes, any kind of early intensive glycaemic control—either induced by insulin or oral hypoglycaemic agents—could rescue β-cell function and induce longterm glycaemic remission in almost half of patients, most likely through eliminating the effects of acute glucotoxicity and related pathogenesis factors.

The glucotoxicity generated by hyperglycaemia is commonly thought to be the fundamental acquired factor causing continuous decline of β-cell function in type 2 diabetes.[3,15] Thus, optimum metabolic control, especially early intensive glycaemic control, can eliminate the deleterious effects of hyperglycaemia and rescue injured β cells, avoiding irreversible loss of β-cell secretory function and β-cell mass that leads to the worsening of diabetes.

Comparing the effects of different interventions in those patients who achieved 2 weeks of euglycaemic control during intensive intervention, we found that more patients in the insulin groups achieved the glycaemic control goal earlier than did patients in the hypoglycaemic agents group. The average times to achieve euglycaemia were 4·0 days (SD 2·5) in the CSII group, 5·6 days (SD 3·8) in the MDI group, and 9·3 days (SD 5·3) in the oral hypoglycaemic agents group. These findings suggest that more patients would benefit from insulin treatment for near-normoglycaemic control, and would have a shorter period of antecedent glucotoxicity. The results are consistent with a previous study.[6]

Notably, insulin replacement could provide a type of β-cell rest and reduce excessive secretory demands on damaged β cells.[3,16] However, despite the similar improvement of glycaemic control and lipid profile and the magnitude of basal and stimulated insulin secretion among groups after treatments, the decrease in the PI/IRI ratio was more obvious in the two insulin groups than in the oral hypoglycaemic agents group, suggesting attenuated β-cell overstimulation with insulin treatment. In particular, the maintenance of improved acute insulin response was much better in the insulin groups, especially in the CSII group, than in the oral hypoglycaemic agents group at 1 year. A more profound β-cell rest by intensive insulin therapy could possibly have an extended beneficial effect. Other insulin effects such as anti-inflammatory[17] and anti-apoptosis effects,[18,19] and the more recent finding of normalised glucose-dependent insulinotropic polypeptide responsiveness by intensive insulin treatment, could also have contributed to the long-lasting beneficial effects of insulin.[20] Thus, all these distinct effects could reasonably be thought of as contributing to the large difference in 1-year remission rate between the groups. Compared with oral hypoglycaemic agents, insulin therapy, including CSII and MDI, has obviously increased remission rates (26·7% for hypoglycaemic agents *vs* 51·1% for CSII and 44·9% for MDI). The risk of hyperglycaemia relapse was reduced by 44% with CSII and by 31% with MDI compared with oral hypoglycaemic agents. From these observations, we conclude that early aggressive insulin treatment has unique effects on the recovery and maintenance of β-cell function and has more potential to induce glycaemic remission in patients with newly diagnosed type 2 diabetes than with oral hypoglycaemic agents.

Sulphonylurea drugs can exert negative effects by over-stimulating β-cells, offsetting its effects in

alleviating of glucotoxicity.[21,22] Alvarsson and colleagues[23] reported that early insulin versus glibenclamide treatment temporarily prolonged endogenous insulin secretion and promoted better metabolic control in a 2-year prospective study. Metformin is known to lower the fasting glucose level by reducing basal hepatic glucose production and can augment glucose-mediated glucose uptake to enhance the tissue sensitivity to insulin. Metformin has no stimulatory effects on insulin secretion.[24] We also found a slightly higher remission rate in the metformin group than in the sulphonylurea group. However, we could not draw a conclusion here because only a small proportion of patients with a mean fasting plasma glucose of 11·2 mmol/L (SD 3·1) achieved euglycaemia on one oral hypoglycaemic agent. Assessed together, the results of these studies suggest that early rigorous glycaemic control by intensive insulin intervention could have more persistent beneficial effects on β-cell function and protracted glycaemic control than treatment with oral hypoglycaemic agents, by affecting the metabolic memory, impeding the progression from metabolic abnormalities to irreversible cellular and epigenetic alterations. These effects might further alter the natural history of diabetes and ultimately prevent or reduce development and progression of diabetes-related complications.[25]

The characteristics of patients with type 2 diabetes who achieved near-normoglycaemic remission in our study were moderate obesity, had a shorter time to euglycaemia, and had relatively lower glucose levels at baseline than did non-remission patients. Those who went into remission had significant improvement in glycaemic control and greater recovery of acute insulin response after treatment than those who did not achieve remission during the 1-year study period. Many of these factors could indicate a shorter duration of diabetes. We should note that a new diagnosis of type 2 diabetes is not equivalent to a new onset of the disease. In this study, all patients were drug-naive and might have different duration of diabetes, although all were newly diagnosed. The patients who achieved near-normoglycaemic remission might possibly have had a shorter duration of diabetes. Due to uncertainty in disease duration, we could infer, but cannot conclude, that patients who did better had a shorter duration of diabetes.

In our study, several factors could limit the extent to which the results can be generalised. First, the range of fasting plasma glucose (7·0–16·7 mmol/L), age (25–70 years), and body-mass index (25·0 kg/m² [SD 3·0]) of our patients were appreciably wide, so the group was heterogeneous. However, the distribution in the three groups was even, and the subgroup analysis (fasting plasma glucose 7·0–11·1 mmol/L and 11·1–16·7 mmol/L) showed the same trends as the whole group (data not shown). Second, 28 patients withdrew before receiving interventions, resulting in imbalanced sample size among the three groups. Those 28 patients shared the same clinical characteristics with the whole group. We were concerned that some of the variations might have affected our results, but they had little effect on our conclusions.

In conclusion, early intensive insulin interventions in patients with newly diagnosed type 2 diabetes have favourable outcomes with regard to recovery and maintenance of β-cell function and prolonged glycaemic remission compared with treatment with oral hypoglycaemic agents. Our findings support the initiation of early transient intensive insulin treatment in those patients.

Contributors

YL wrote the first draft. JL, ML, and WX contributed to compilation of data and did the statistical analysis. JW designed and organized the study and co-wrote the first draft. YL, LS, DZ, ZZ, HT, ZL, L Yan, LZ, L Yang, WX, JL, QZ, YH, XY, XR, JX, FL, YC, and SY contributed to data collection, identification, and assessments of the primary data sources for each participating study centre. HC and ZF were members of the scientific committee for the study and contributed to manuscript discussion.

Conflict of interest statement

Sun Yat-Sen University has an unrestricted research grant from Novo Nordisk (China) and Roche Diagnostics (Shanghai). The authors declare that they have no conflict of interest. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors have seen and approved the final text.

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