Intensive insulin therapy in newly diagnosed type 2 diabetes

The natural history of type 2 diabetes is characterised by worsening hyperglycaemia and progressive deterioration in function of the insulin-secreting pancreatic β cells.[1] Despite intense investigative efforts, the pathophysiological basis underlying β-cell dysfunction (and the concomitant loss of β-cell mass) remains unclear. Nevertheless, the central importance of declining β-cell function in type 2 diabetes is underscored by its correlation with a progressive loss of glycaemic control, which typically occurs over time.[2,3] Although β-cell dysfunction contributes to worsening glycaemia, hyperglycaemia itself further undermines β-cell function. This so-called glucotoxicity is apparent in the observation that the first-phase component of normal biphasic insulin secretion is abolished when the blood glucose concentration exceeds 6·4 mmol/L.[4] Accordingly, early in the course of type 2 diabetes (ie, when sufficient residual β-cell mass still exists), the glucose-lowering effect of antidiabetic therapy can be amplified by improved endogenous insulin secretion secondary to the elimination of hyperglycaemia. Unfortunately, however, this effect is ultimately transient, because no oral antidiabetic agent has yet been shown to profoundly change the inexorable β-cell deterioration and worsening glycaemia in type 2 diabetes.[5]

Insulin therapy is usually instituted late in the course of type 2 diabetes, when glycaemic control can no longer be maintained with oral antidiabetics. Interestingly, however, as shown in limited studies up to now (table), early implementation of a short course of intensive insulin therapy by continuous subcutaneous insulin infusion or multiple daily injections can induce sustained euglycaemia (ie, off any antidiabetic therapy) in patients with type 2 diabetes.[6–9] The "remission" of type 2 diabetes achieved in these studies persists for 1 year after the cessation of insulin therapy in about 40% of patients. Furthermore, Li and colleagues[6] reported that patients who maintained euglycaemia off antidiabetic therapy for 1 year showed greater recovery of β-cell function than their counterparts, when assessed immediately after 2 weeks of continuous subcutaneous infusion.[6] The suggestion has therefore been made that an improvement in β-cell function, especially restoration of first-phase insulin secretion, might be responsible for the ability of intensive insulin therapy to induce sustained euglycaemia.

In today's *Lancet*, Jianping Weng and colleagues[10] extend these concepts by reporting a randomised trial that compares the effects of temporary (2–5 weeks) intensive insulin therapy (continuous subcutaneous infusion or multiple daily injections) versus oral antidiabetics (ie, metformin, gliclazide, or, in most patients, both) on remission of diabetes and β-cell function in 382 newly-diagnosed patients with type 2 diabetes in nine centres in China. Glycaemic control was rapidly achieved (mean 7·9 days [SD 4·6]) in 92·1% of patients. When assessed 2 days after stopping therapy, first-phase insulin secretion (measured by acute insulin response on an intravenous glucose-tolerance test) was significantly increased with all three regimens. Importantly, remission at 1 year after therapy was significantly higher in the insulin groups (continuous infusion, 51·1%; multiple injections, 44·9%) than in the oral antidiabetic group (26·7%). Moreover, in patients in remission, the decline in the acute insulin response

Study	N	Mean age (years)	Mean body-mass index (kg/m²)	Duration of type 2 diabetes	Baseline HbA$_{1c}$ (%)	Type of therapy	Duration of therapy (days)	Patients who achieved euglycemia with therapy (%)	Patients with euglycemia at 6 months (%)	Patients with euglycemia at 1 year (%)
Li[6]	138	49	25	Newly diagnosed	10·1	CSII	14	91	67	47
Ilkova[7]	13	50	26·9	Newly diagnosed	11·0	CSII	14	92	69	N/A
Park[8]	91	54	NA	Mean 7·2 years	13·2	CSII	Mean 53·6 (SD 39)	34	~34	~34
Ryan[9]	16	52	30·8	Newly diagnosed	11·8	MDI	14–21	88	N/A	44
Weng[10]	382	51	25·0	Newly diagnosed	~9·7	CSII	14–35	97	N/A	51
Weng[10]	382	51	25·0	Newly diagnosed	~9·7	MDI	14–35	95	N/A	45
Weng[10]	382	51	25·0	Newly diagnosed	~9·7	OAD	14–35	84	N/A	27

NA=not available. CSII=continuous subcutaneous insulin infusion. MDI=multiple daily injections. OAD=oral antidiabetic agent.

Table: Previous studies of insulin therapy

over 1 year in the insulin groups did not reach statistical significance, whereas the group on oral antidiabetics showed a significant decrease in this response over the same period, suggesting that preservation of first-phase insulin secretion probably contributed to the greater remission achieved with either insulin regimen.

Although certain limitations of this study need to be noted (including: limited description of β-cell function and glycaemic control during the year; absence of clinical characterisation of the remission and non-remission groups at 1 year; and the single ethnic group under study), these findings are intriguing. In particular, the comparison of intensive insulin and oral therapy is an important novel feature of this trial, because earlier studies only assessed continuous insulin infusion or multiple daily injections. Indeed, although both insulin and oral drugs lowered glucose concentrations, the apparent beneficial effect of intensive insulin therapy on remission and preservation of first-phase insulin secretion suggests that other factors beyond the elimination of glucotoxicity might be relevant. In this context, insulin therapy would be expected to decrease the secretory demand for endogenous insulin placed on the β cells (by contrast with the β-cell stimulatory effect of the sulphonylurea gliclazide, which most patients in the oral-antidiabetic group received). As such, these data might support the concept of a beneficial effect of "β-cell rest" with insulin therapy.

Alternatively, other biological actions of insulin might be contributory, including anti-inflammatory activity and the potential direct effects of insulin-receptor signalling on β-cell growth and survival. Although the relevant biological mechanisms and target tissues contributing to preferential improvement in β-cell function remain unclear, these data suggest that the use of intensive insulin therapy early in the course of type 2 diabetes warrants further clinical investigation.

Furthermore, an increased mechanistic understanding of the specific effects of early insulin therapy on the survival and function of β cells over time might provide new insights into the pathophysiology of progressive β-cell deterioration in type 2 diabetes.

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Novel cardiac therapies and innocent bystanders

The oxidation hypothesis of atherosclerosis is an attractive explanation of why high concentrations of LDL cholesterol result in ischaemic cardiovascular events in some, but not all, individuals. This theory is supported by several large epidemiological studies suggesting an inverse association between the intake of antioxidant vitamins and cardiovascular events.[1] However, no randomised trials of antioxidant (principally vitamin) therapy have shown cardiovascular benefit.[2] This lack of positive findings might be because the antioxidants have been started too late in the disease process, because there is no accurate, readily available test that facilitates targeting treatment to those with increased oxidative stress, or because antioxidant vitamins are not potent