Letters to the Editor

Near-normoglycaemia and microvascular complications

Dear Editor,

In their review article on "Diabetic control and microvascular complications: the near-normoglycaemic experience", Hanssen and coworkers [1] draw the conclusion that "The benefits of the best possible metabolic control for Type 1 diabetic patients are well documented and proven; the methods on how to achieve this goal remain a matter of further investigation and trial."

Their statement reads as if intended to suggest a conclusively achieved, once and for all, final result which from now on not only justifies but demands (near-)normoglycaemia for the young diabetic patient. At the same time it implies that any further study which randomizes patients to less than the best possible treatment must be regarded as unethical.

As much as we appreciate and agree with the authors' perception, it is disturbing that their conclusion is little more than an almost verbatim repetition of what has strongly and continuously been put forward for many years by a number of leading diabetologists [2–7].

Without a doubt, some of the recently published and reviewed investigations [1] on this subject have added scientifically and elegantly to the already extensive literature, proving again what has been known for decades, i.e. that lower blood glucose levels, even though still far from normal, are less harmful than higher blood glucose levels; and, not really surprisingly, that this also holds true for the human body already moderately injured by a previous overabundance of glucose in the blood. What additionally may be re-learned from these studies is that the destructive effects of moderate hyperglycaemia may not become clinically obvious after observation periods as short as 6 or 12 months; in fact, patients must be followed for several years until reliable and meaningful data may be published. This appears particularly relevant to those studies which have been performed on patients with more advanced stages of diabetic late complications. The deleterious consequences of leaving these patients without optimal metabolic control may well become apparent only after several years. This point is not to be disregarded today, when life expectancy is predicted to become considerably prolonged in those patients when they receive adequate medical care. In addition, it must be taken into account that, although one organ may already be severely damaged and may thus

not further be harmed by hyperglycaemia, this does not necessarily hold true for other tissues in the same body.

What really is distressing in all these randomized prospective studies which aim to investigate the influence of near-normoglycaemia on the development and progression of diabetic microangiopathy is that (near-)normoglycaemia (i.e. glycosylated haemoglobin levels in the upper normal range) had, in fact, *not* been achieved, even though patient groups were usually small and medical attention presumably intensive. Thus, one wonders if the initial premises of the protocols had ever been fulfilled, i.e. the comparison of patients with near-normalization of blood glucose (with a possibly increased risk of severe hypoglycaemia) with patients in so-called *good* metabolic control, a prerequisite put forward to ethically justify this kind of research. In fact, during follow-up in all these studies, glycosylated haemoglobin levels of the patient groups randomized to some kind of intensive insulin therapy were on average still somewhere between 1.3 and 1.4 times the respective normal mean values (Table 1), and mostly not more than 1–2% lower in comparison to the "untreated" patients. Nevertheless, the benefits of even minor improvements of metabolic control were substantial and thus of tremendous importance for the prognosis of the diabetic patient.

Most interestingly, comparably good or even better metabolic control has been achieved in "non-research" routine patients at diabetes centres where, as standard therapy, every patient is offered an intensive diabetes treatment and teaching programme (Table 2). Thus, for example, mean values of glycosylated haemoglobin of "research patients" randomized to near-normoglycaemia in the Diabetes Control and Complications Trial (DCCT) [8] actually achieved the same degree of metabolic control as consecutive routine patients participating in an intensive and structured diabetes treatment and teaching programme in the Bucharest-Düsseldorf study [16]. Based on these observations, the suspicion arises that all these investigations have really compared modern insulin treatment plus adequate patient training with the lack of such an intervention.

Relying on the authors' concluding remarks [1], one might feel confident that their own research studies have definitely been terminated, and that the medical teams have, by now, intensified their care

Table 1. Research studies including patients randomized to intensive treatment

Centre or study name	Study design	Intervention	n	Glycosylated haemoglobin ^a			Reference
				Before	After 1 year	Net decrease	
DCCT-Trial	Prospective Controlled	CSII ^b , ICT ^c	146	1.87	1.39	0.48	8
Steno Memorial Hospital	Prospective Controlled	CSII	18	1.79	1.34	0.45	9
Oslo Study	Prospective Controlled	CSII	15	1.55	1.34 (2 years)	0.21	10
University of Aarhus	Prospective Controlled	CSII	12	1.70	1.33	0.37	11

^a Expressed as times the respective normal mean values; ^b continuous subcutaneous insulin infusion; ^c intensified conventional therapy

Table 2. Studies including consecutive patients participating in an intensive diabetes treatment and teaching programme (DTTP) as standard therapy

Centre or study name	Study design	Intervention	n	Glycosylated haemoglobin ^a			Reference
				Before	After 1 year	Net decrease	
University of Düsseldorf	Uncontrolled	DTTP	98	1.69	1.39	0.30	12
	Uncontrolled	DTTP + CSII ^b	50	1.63	1.28	0.35	13
University of Vienna	Uncontrolled	DTTP + NIS ^c	80	1.55	1.26 (2 years)	0.29	14, 15
Bucharest-Düsseldorf Study	Prospective Controlled	DTTP	100	1.89	1.43	0.46	16

^a Expressed as times the respective normal mean values; ^b continuous subcutaneous insulin infusion; ^c near-normoglycaemic insulin substitution

of the control groups, restoring as much as possible what has been withheld from those patients during the past several years, namely metabolic control as good as possible.

However, we are still doubtful whether there really is reason to hope that from now on all efforts will concentrate on *how* to improve metabolic control, or whether these most recent studies will ultimately become more ugly heads of Medusa, which, as soon as being severed, initiate the immediate growth of many more. Such heads would again randomize patients into groups to whom good metabolic control is refused. Undoubtedly these same heads would argue that the benefits of good metabolic control still may not be 100% proven, necessitating studies to re-confirm the previous results on a greater number of patients, still better characterized with respect to age, duration of diabetes, presence or absence of early or late complications, presence or absence of other vascular risk factors, for longer observation periods, applying even a greater number of even better, more sophisticated methods – what else?

We feel deeply obligated to discourage such research. Instead, we want to re-draw our colleagues' attention to (what we are convinced has always been and still is the answer to) their question on how to best and most safely improve metabolic control, not only for "research patients" but for all patients. This is achieved by intensive and structured diabetes training aimed at motivating and enabling the individual patient to take personal responsibility for a modern insulin therapy: the ability to achieve blood glucose levels as normal as possible, and at the same time a flexibility in life style as great as possible [12–16].

Yours sincerely,

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