Increased insulin dose requirement of long-acting insulin analogues in obese patients with type 2 diabetes

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Received: 6 August 2009 / Accepted: 19 August 2009 / Published online: 24 September 2009
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Keywords Hyperinsulinaemia · Insulin dose requirement · Long-acting insulin analogues · Obesity · Type 2 diabetes

To the Editor: Obesity, type 2 diabetes, insulin resistance and hyperinsulinaemia are associated with an increased risk of some types of cancer, and recent epidemiological data have refuelled discussions on the safety of insulin therapy [1]. The data published in the last issue of *Diabetologia* raise concern but do not provide evidence that any of the specific insulin preparations cause harm; there are too many confounders for which adjustment remains imperfect. Whether the potential risks of insulin preparations with increased affinity to type 1 IGF receptors are acceptable remains a matter of debate. We wish to point out that (apart from the intrinsic properties of an insulin preparation) higher levels of continuous insulin exposure resulting from the choice of insulin preparation should also be considered as a potential drawback.

A similar (unit-based) glucose-lowering efficacy of NPH insulin and the long-acting analogues has been suggested,

but it remains unclear whether this is also true for obese patients with type 2 diabetes.

In our recently published prospective study comparing the effect of NPH insulin, insulin detemir (NN304) [B29Lys(ε-tetradecanoyl),desB30 human insulin] and insulin glargine (A21Gly,B31Arg,B32Arg human insulin) injected at bedtime in patients with type 2 diabetes [2], each patient was sequentially treated with all three long-acting insulin preparations. Comparable predefined glucose targets were achieved at midnight (00:00 hours) and in the morning (at 07:00 hours) with all three insulin preparations tested; none of them could totally prevent the rise of glucose between 05:00 and 08:00 hours.

As mentioned (but not shown) in our communication, a trend for increased analogue (compared with NPH) insulin dose requirements (especially in obese patients on high total doses) to reach glucose targets was observed. The difference was significant in patients with a BMI of $>30 \text{ kg/m}^2$, as shown in Table 1.

In patients with type 2 diabetes, it has previously been reported that a higher dose of insulin analogues relative to NPH insulin is required to achieve similar glucose control, e.g. in the Treat-to-Target Trial, in which doses of insulin glargine were higher than those of NPH [3]. An increased insulin dose requirement compared with NPH insulin in patients with type 2 diabetes has also been reported for insulin detemir [4, 5]. Whereas such differences have not been found in all studies (e.g. in the LANMET study [6]), to the best of our knowledge, the opposite, i.e. a lower insulin dose requirement of the long-acting analogues compared with NPH insulin in patients with type 2 diabetes, has not been reported.

Good glycaemic control and prevention of cardiovascular disease remain major goals when treating patients with type 2 diabetes. Lifestyle changes are difficult to achieve,

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Table 1 Required insulin doses (units per patient) of insulin preparations injected at bedtime

BMI (kg/m ²)	<i>n</i>	Insulin detemir	vs (p value)	NPH	vs (p value)	Insulin glargine
<30	6	25±11	NS	27±12	NS	23±8
>30	14	37±12	0.004	30±10	0.048	35±11

Data are presented as mean±SD

p values were calculated by paired *t* test

and long-term exposure to high concentrations of insulin is common. Ease of application, single daily injections and a decreased risk of nocturnal hypoglycaemia have been praised as advantages of long-acting insulin analogues. Nocturnal hypoglycaemia is rather an infrequent clinically relevant problem when NPH insulin is appropriately dose-adjusted (which did not occur in some clinical trials) and handled. In obese patients with type 2 diabetes, required insulin doses tend to be lower with NPH insulin than with insulin analogues. If a dose-dependent effect of insulin on cancer risk is confirmed in future studies, this could be, apart from costs, another reason to favour NPH insulin over long-acting insulin analogues in the majority of obese patients with type 2 diabetes.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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