Acylated-based long-acting insulin analogues: Is “misfolding” the problem? Commentary letter on Hamasaki H and Yanai H. The switching from insulin glargine to insulin degludec reduced HbA1c, daily insulin doses and anti-insulin antibody in anti-insulin antibody-positive subjects with type 1 diabetes

In this issue of Diabetes & Metabolism, Hamasaki et al. raise the question of the possible benefits of insulin degludec compared with insulin glargine when tested in a subset of patients with type 1 diabetes positive for anti-insulin antibodies [1]. As these results were obtained in a small number of patients, they should be interpreted with caution and discussed on a broader basis.

Like all water-soluble hormones, insulin cannot diffuse across the plasma cell membrane, and its action depends on its binding to cell surface receptors. In addition, native insulin, which is secreted by human beta cells, has to be properly folded into alpha-helix (spiral) and beta-pleated sheet (laterally packed with parallel or antiparallel beta strands) conformations to be captured by specific receptors and to further exert its biological activity in insulin-sensitive tissues [2]. All chemical modifications of the insulin molecule, including elongation with two arginine residues at the C terminus of the B-chain (insulin glargine), and acylation of the hormone with a fatty acid either directly (insulin detemir) or indirectly (insulin degludec) added to the B-chain, can alter the effects of these long-acting insulin analogues on such parameters as glucose transport to cells, stimulation of multiple intracellular pathways and activation of mitogenic processes.

Furthermore, appropriate folding of the native human insulin molecule is important for preventing its aggregation and binding to other proteins, and for minimizing its immunogenicity. Therefore, the question arises as to whether the high level of binding to albumin and, thus, the high circulating insulin concentrations observed with detemir and degludec preparations may not be related to in-vivo misfolding of these acylated insulins. There is no reason to exclude the fact that non-physiological binding to albumin might be extended to other structural proteins such as those of the plasma membrane of endothelial cells and, more generally, of vascular walls [3].

Even though the study by Hamasaki et al. [1] does not provide an answer to the latter question, their findings are of importance, as they have observed that concentrations of anti-insulin antibodies decreased significantly when insulin degludec was substituted for insulin glargine in 10 patients with type 1 diabetes, who had preformed anti-insulin antibodies on treatment with glargine. This observation is in agreement with previous reports showing that insulin degludec does not stimulate formation of specific antibodies after a 16-week period of treatment with this analogue in type 1 diabetes [4]. However, we are more doubtful when Hamasaki et al. suggest that the decrement in anti-insulin antibodies could be an explanation for the improvement in diabetic control and reduction of insulin doses observed in their patients, albeit this hypothesis seems to be tenable.

Although these results are somewhat reassuring, it appears necessary to reiterate that the in-vivo metabolism and body distribution of the newer insulin preparations should be clearly understood prior to any phase-II or -III clinical trials and a fortiori before their large-scale marketing and use. Such a procedure has been used for insulin glargine, as its safety was clearly established by the results of the ORIGIN trial. Furthermore, it is now well known that its in-vivo biological and mitogenic activity is mainly due to its M1 metabolite [5], which only differs from native human insulin by the amino-acid residue at the N-terminus of the A chain. This M1 metabolite exhibits the same metabolic and mitogenic activity as does normal human insulin.

Returning to the chemical changes of long-acting insulin analogues, it would be of interest to evaluate the possible consequences on their three-dimensional structure on their lifespan and binding or cross-linking to other proteins, especially those present in vascular walls. So far, it has been demonstrated that the structural changes of insulin degludec result in modifications in binding to plasma albumin and in a protracted potency to form linear multi-hexamers in subcutaneous tissue [6]. Even though the protein-folding of insulin degludec in its monomeric configuration is very similar to that of human insulin, there remains the fact that its prolongation in subcutaneous tissue is accompanied by allosteric changes from “relaxed” to “tense” states, which are characterized by the disappearance of the alpha-helix conformation in some amino-acid sequences [7].

Such changes are triggered by removal of the phenolic ligand in subcutaneous tissue. However, such modifications have been neither confirmed nor refuted when insulin degludec has been absorbed into the systemic circulation after diffusion from its

http://dx.doi.org/10.1016/j.diabet.2014.10.001
1262-3636/© 2014 Elsevier Masson SAS. All rights reserved.
subcutaneous depot. In addition, it is thought that the fatty acid chain added to acylated long-acting insulins modifies the molecular surfaces used for linkage to its cognate receptor, for self-assembly and even for binding to plasma albumin [2,8]. Consequently, it is not surprising to observe a reduced potency with such insulin preparations compared with native human insulin. Thus, to compensate for its reduced metabolic activity, insulin detemir is formulated at a fourfold higher concentration per unit compared with other insulin preparations (24 vs 6 nmol).

In summary, given the fact that insulin and its analogues are multifaceted hormones [9], all current uncertainties related to their metabolism and modalities of action should be clearly removed prior to their large-scale clinical application.

Acknowledgements

The authors declare that this work has received no funding from academic or private sources and that they have no conflict of interest with the content of this letter.

References