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Insulin analogue with reduced weight gain effect in diabetic patients: detemir

Diabetes mellitus is a progressive condition in which the glycated hemoglobin level (i.e. marker of average blood glucose levels) rises inexorably over time. Strict glucose control in patients with type 1 or type 2 diabetes mellitus reduces the occurrence and progression of microvascular and macrovascular disease, even though intensive approaches required to achieve adequate glucose control often need insulin therapy. However, patients and healthcare providers are frequently reluctant to initiate insulin therapy also because this is perceived as complex and an added burden to diabetes management. In addition to the fear of needles and hypoglycaemia, the risk of weight gain remains one of the major obstacle towards initiation and titration of insulin treatment. Moreover, insulin associated weight gain is of particular concern in type 2 diabetes, a condition in which 80% to 90% of the population is already overweight or obese. The predominantly central or visceral distribution of insulin-associated weight gain is correlated with increased insulin resistance and cardiovascular risk, further undermining the benefits of improved glucose control.

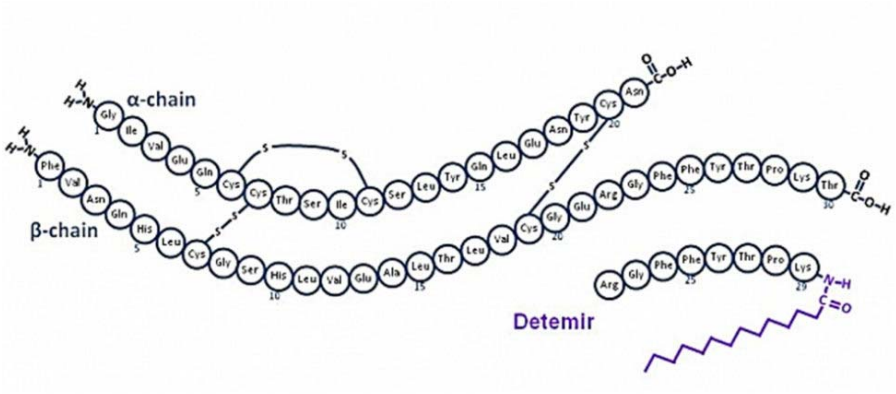

Fig. 1. Human Insulin and Detemir molecular structure..

In recent years, the basal insulin analogue B29Lys-myristoyl des-B30 human insulin (NN-304), known as Detemir, has been introduced. This was developed to improve upon the limitations of conventional basal insulins, which have an inadequate duration of action, a marked peak glucose-lowering effect and variability in response from one injection to another. Detemir represents human insulin with a B-chain shortened by the C-terminal threonine B30 and conjugated to a myristic acid molecule at the ε-amino group of lysine B29 (Fig. 1). The protracted action of this soluble insulin analogue in vivo is due to self-association into hexamers and dihexamers at the injection site and to reversible binding of the molecule to serum albumin in the circulation (97-98% of circulating Detemir is estimated to be albumin-bound), and both are mediated by the myristic acid moiety. Despite similar glucose-lowering effects, a series of clinical studies in type 1 and type 2 diabetic patients has demonstrated that Detemir, as compared to other long-acting insulins, e.g. neutral protamine

Hagedorn insulin (NPH), is weight-neutral or provokes only minor body weight gain. The mechanism behind Detemir's weight-sparing effect is however not completely elucidated.

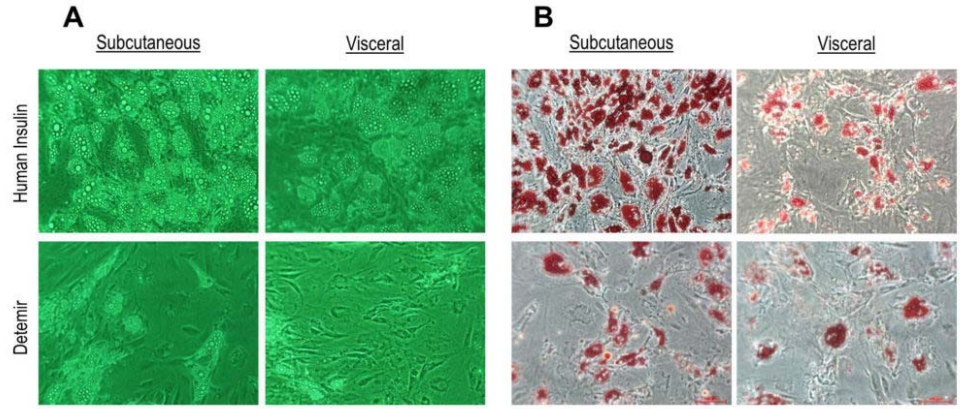

Fig. 2. Differentiation of human adipocytes. A. Microscopical appearance of subcutaneous (Sc)-ASC (left) and visceral (V)-ASC (right) after differentiation in the presence of 100 nM human insulin or 100 nM insulin detemir, respectively. Magnification 10x.B. Oil-Red-O staining of the cell cultures to visualize lipids. Magnification 10 x.

To this end, the pro-adipogenic potential of Detemir compared to Human Insulin was directly assessed for the first time in an *in vitro* model of human subcutaneous and visceral adipose stem cells. In this study, a lower adipocyte differentiation was demonstrated when adipose stem cells were treated with Detemir as compared to human insulin (Fig. 2). Other Authors have previously shown that Detemir displays reduced adipogenity, although in this human model this phenomenon occurs without changes in insulin signaling transduction. In fact, even though Detemir was described as 50% less potent at binding insulin receptor in vitro when compared with Human Insulin, for the first time in this human model of adipocyte precursor cells, Detemir-induced activation of proteins downstream the insulin receptor (i.e. Erk-1/2 and Akt) occurred in a comparable dose-dependent manner to Human Insulin; likewise, induction of early as well as adipogenic/lipogenic genes at various phases of differentiation appeared to be comparable between the two insulins. Interestingly, though, when late phase of adipocyte differentiation was evaluated in terms of adipocyte conversion, lipid accumulation and lipid droplet size, a clear reduction of adipocyte maturation in cells treated with Detemir was found, and this was associated to a reduced expression of critical adipogenic genes (i.e. PPARγ2, GLUT4, Adiponectin). Thus, Detemir affects the expression profile of late phase of differentiation genes in human adipocytes; down-regulation of adipogenic genes expression results in impairment of adipogenesis, and this could explain the weight-neutrality of this analogue observed in clinical studies.

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