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METABOLIC DISORDERS

FGF21 analogue shows promise in the clinic

The circulating protein fibroblast growth factor 21 (FGF21) has emerged as a key metabolic regulator and its potential exploitation in the treatment of metabolic disorders is currently being investigated. Now, writing in *Cell Metabolism*, Moller and colleagues report promising results of the first clinical trial of an FGF21 analogue in obese patients with type 2 diabetes.

FGF21 is a 181-amino-acid secreted protein produced in the liver, adipose tissue and pancreas, with roles in the regulation of insulin sensitivity as well as lipid and energy metabolism. In preclinical animal models of obesity and type 2 diabetes, exogenous FGF21 and various analogues have demonstrated considerable promise as a future class of therapeutic agents, by positively modulating several key metabolic parameters. Furthermore, one analogue, LY2405319, has been reported to be safe, exhibiting favourable pharmacokinetics and exerting beneficial effects on cholesterol and triglyceride levels in healthy volunteers.

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The current study involved 46 obese individuals who had been diagnosed with type 2 diabetes for an average of 7.4 years prior to enrolment; 43 of these patients were being treated with metformin and 11 with a statin. The individuals were randomized to receive 3, 10 or 20 mg of LY2405319 or placebo daily for 28 days by subcutaneous injection.

At the end of the study period, LY2405319 had exerted significant beneficial effects on four lipid parameters compared to placebo: it lowered total cholesterol levels by 15% to 19%, low-density lipoprotein (LDL) levels by 20% to 30%, triglyceride levels by 26% to 46%; and raised high-density lipoprotein (HDL) levels by 15% to 20%. These effects occurred as early as 2 days after the initiation of dosing in the case of fasting triglycerides, and appeared to reach a maximum effect within 7 to 21 days. Notably, these improvements in dyslipidaemia were accompanied by a shift to a less atherogenic apolipoprotein profile.

Significant decreases of 1.5–1.75 kg in mean body weight were also noted following LY2405319 treatment, which the authors hypothesized may be due to increased energy expenditure. However, these weight changes were not statistically significant compared to placebo. In addition, a dose-dependent trend in the lowering of fasting glucose was observed over the treatment period, and fasting insulin levels were substantially reduced in the highest dose group compared to placebo. Interestingly, plasma levels of adiponectin — which has an important role in the propagation of the metabolic effects of FGF21 and is negatively correlated with obesity and insulin resistance — were increased in a dose-dependent manner.

Importantly, treatment with LY2405319 was generally well tolerated in all groups, with skin rash and hypersensitivity reported in two patients and injection site reactions reported in several other patients.

Together, these results demonstrate that daily administration of LY2405319 exhibited clinically meaningful effects on several metabolic comorbidities associated with type 2 diabetes. These findings support the further development of FGF21-based therapies for the potential future treatment of metabolic disorders.

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ORIGINAL RESEARCH PAPER Gaich, G. *et al.* The effects of LY2405319, an FGF21 analog, in obese human subjects with type 2 diabetes. *Cell Metab.* **18**, 333–340 (2013)