The possible synergistic action of sex hormones and glucagon-like peptide-1 (GLP-1) agonists on body mass decline in patients with type 2 diabetes mellitus

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A R T I C L E   I N F O

Adiposity is a chronic disease and one of the major modifiable risk factors for the development of type 2 diabetes mellitus (T2DM). Its prevalence in the world could be considered epidemic with 80% of patients with T2DM being obese. Novel antidiabetic drugs, such as glucagon-like peptide-1 (GLP-1) agonists have demonstrated beneficial effect on weight reduction. Nevertheless, in the last decades the need for new therapeutic strategies in the management of adiposity have emerged. Both adiposity and T2DM have negative effect on hypothalamic-pituitary-gonadal axis. Conversely, it has been known that sex hormone replacement therapy improves metabolic parameters in hypogonadal subjects. Recent research has found potential therapeutic effect of combination therapies with sex hormones and GLP-1 agonists in reducing body weight. Based on the aforementioned, we hypothesize that there is a possible synergistic effect of GLP-1 agonists and sex hormones on body mass reduction in patients with type 2 diabetes. The possible additional effect of sex hormones on weight loss could contribute to more effective treatment of T2DM and its complications.

Background

Adiposity represents a condition resulting from excess accumulation of fat distributed generally or centralised or both. Thus, it is a common risk factor for the development of treatment outcomes in the pathophysiology of metabolic i.e. cardiometabolic diseases, frequently compromised in type 2 diabetes mellitus (T2DM). Despite anthropological limitations, body mass index (BMI) is a gold standard in grading scale of adiposity. According to the World Health Organization (WHO) BMI of 25–29.9 kg/m² refers to overweight and BMI over 30 kg/m² to obese. Higher BMI increases the risk of comorbid conditions [1]. Every obtained kg of body mass in one year over a 10 year period increases the risk for T2DM development over the next 10 years up to 49% [5]. However, the central fat distribution (waist circumference greater than 102 cm in men and greater than 88 cm in women for Europeans) is associated with greater risk for cardiovascular and metabolic diseases, even in normal weight individuals [2,3]. Type 2 diabetes (T2DM) represents dysregulation in fat, protein and glucose metabolism that clinically presents with hyperglycaemia. However, its pathogenesis has not been elucidated so far although it became evident there is a complex interplay among β-cell (decreased insulin secretion), muscle (decreased glucose uptake), liver (increased hepatic glucose production), fat cell (accelerated lipolysis), gastrointestinal tract (decreased incretin effect), α-cell (hyperglucagonemia), kidney (increased glucose re-absorption), and brain (insulin resistance) [4]. Adiposity in T2DM diminishes glucose regulation importance in micro- and macro-vascular complications development and progression [7]. Adipose tissue is potentiating the state of inflammation in the organism by producing pro-inflammatory adipokines [6]. Therefore, adiposity is one of the major targets in T2DM treatment, beyond glucoregulation. The development of pharmacological agents that demonstrate efficacy on both targets has made them a part of scientific and professional interest. Glucagon-like peptide-1 (GLP-1) belongs to the group of incretin hormones secreted from the endocrine intestinal cells in response to food intake [8]. Glucagon-like peptide-1 binds to G-protein associated receptors (GLP-1R). These are mainly expressed in the pancreas and their activation
results in increased insulin and decreased glucagon secretion, thus regulating blood glucose levels. Besides pancreas, GLP-1R are widely distributed. Consistent with this, GLP-1 exhibits various effects: delayed gastric emptying and bowel intestine mobility. Recently it has been demonstrated that GLP-1R in the hypothalamus mediate appetite reduction and food intake i.e. increase satiety [8]. Thus, the group of noninsulin injectable hypoglycaemic agents: GLP-1 agonists have been recognized in the treatment of adiposity and T2DM. Despite that, it remains unclear why approximately 30% of patients fail to achieve adequate glucoregulation and/or expected weight reduction with GLP-1 analogues treatment [9]. Gradually it became clear that GLP-1 agonists are not effective secretagogues in the lack of viable β cells number, but the mechanism of appetite suppression in CNS accompanied by weight loss are yet to be clarified. Recent study results suggest that there might be a synergistic effect of sex hormones, estradiol and testosterone, and GLP-1 analogues on body weight reduction by binding to their receptors in supramamillary region of the posterior pituitary gland [10,11].

The hypothesis

We hypothesise that it would be of special scientific and clinical interest to investigate if there is a difference between endogenous sex hormones (estradiol and testosterone) together with endogenous postprandial GLP-1 concentration in T2DM subjects with mild to moderate and severe adiposity. Secondly, it would be of special interest to elucidate whether the concentration of sex hormones could affect body mass reduction accompanied to GLP-1 receptor analogue therapy. To summarise, the ultimate goal is to clarify whether and to what extent endogenous sex hormones and GLP-1 analogues achieve synergistic effect on appetite suppression, nutritional habits and weight loss in subjects with T2DM.

Evaluation of the hypothesis

Adiposity is one of the most common phenotype characteristics in hypogonadism and metabolic diseases. It disrupts hypothalamic-pituitary-testicular axis leading to decrease in serum testosterone concentration [12–15]. Adiposity is a modifiable factor and serum testosterone levels rise with weight loss [15]. Studies have shown that testosterone replacement therapy in obese subjects leads to better metabolic control and fat loss [16,17]. Hence, the question arises whether correction of both appetite and hypogonadism would lead to weight loss and better metabolic control. GLP-1 agonists exert multifactorial beneficial metabolic effects, including weight loss, lowering blood pressure and triglycerides and improving insulin sensitivity in obese patients. In addition, it was shown that increase in serum testosterone levels induced by letrozole increased insulin sensitivity in healthy young men [18]. Experimental studies suggest that testosterone treatment might promote the differentiation of pluripotent cells into the myogenic lineage and inhibit their differentiation into adipocytes [11]. Giagulli et al. showed that addition of liraglutide (a long acting GLP-1 agonist) to standard non pharmacologic and pharmacologic treatment in obese men with T2DM and overt hypogonadism resulted in improved clinical, anthropometric (weight, BMI, waist circumference, systolic blood pressure) and laboratory parameters (glucose, HbA1c, total cholesterol, triglycerides, LDL) along with International Index of Erectile Function (IIEF) score [19]. Oestrogen has protective metabolic effect by decreasing central adipose tissue mass and increasing glucose-femoral subcutaneous adipose tissue mass. In addition, oestrogen exhibits its effect on food intake and energy expenditure through different peripheral and central mechanisms [20]. Moreover, several studies have shown changes in food intake during different phases of menstrual cycle, with lowest energy intake during periovulatory phase [20,21]. Oestrogen was shown to increase cholecystokinin mediated satiation by acting on caudal medial nucleus of the solitary tract (cmNTS) in rats [20]. Moreover, it was demonstrated that GLP-1 satiating effect increased in ovariecotimized rats [22]. Consequently, recent research papers presented that higher weight loss could be achieved by combining multiple aforementioned agents: hormones and GLP-receptor agonists in one molecule [23]. Vogel et al. reported that conjugated GLP-1 agonist and oestradiol reduced body weight, food intake and food reward more than either of these agents applied separately. This might be partially explained by supramamillary nucleus (SUM); GLP-1-estradione conjugate reduced food reward behaviour in rats, discovering new area in brain responsible for food-motivated behaviour [10]. For that reason, it seems to be of special clinical and scientific interest to investigate if there is a synergistic effect of sex hormones and GLP-1 agonists on weight loss in obese individuals.

Consequences of the hypothesis and discussion

The reduction of body weight through CNS might represent one of the basic therapeutic effects of the GLP-1 analogues, focusing mostly on appetite. Thus, it is of special interest to elucidate new biological factors involved in the mechanism of action of GLP-1 analogues and their therapeutic potential. It might be of a great importance to find possible interventions for effective treatment of obesity in T2DM.

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Declaration of Competing Interest

None declared.

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References

stimulate myogenic differentiation and inhibit adipogenesis in C3H 10T1/2 pluripotent cells through an androgen receptor-mediated pathway. Endocrinology 2003;144(11):5081–8.


