Medical Hypotheses 131 (2019) 109308

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

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

T. Režić[a,*], K. Blaslov[b,c], I. Kruljac[b,c], D. Rahelić[c,d], M. Vrkljan[b,c], I.P. Renar[c]

[a] Department of Endocrinology, Diabetes and Clinical Pharmacology, Dubrava University Hospital, Zagreb, Croatia
[b] Department of Endocrinology, Diabetes and Metabolic Diseases "Mladen Sekso", University Hospital Centre "Sestre Milosrdnice", Zagreb, Croatia
[c] University of Zagreb School of Medicine, Zagreb, Croatia
[d] Department of Diabetes and Endocrinology, Vuk Vrhovac University Clinic for Diabetes, Endocrinology and Metabolic Diseases, Merkur University Hospital, Zagreb, Croatia

ARTICLE INFO

Attribution to: Department of Endocrinology, Diabetes and Metabolic Diseases "Mladen Sekso", University Hospital Centre "Sestre Milosrdnice", Vinogradska cesta 29, Zagreb, Croatia.

Keywords:
Adiposity
Diabetes mellitus
Sex hormones
Glucagon-like peptide-1 agonist

ABSTRACT

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 glucagone-like peptide-1 (GLP-1) agonists have demonstrated benefitial 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/m^2 refers to overweight and BMI over 30 kg/m^2 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 reabsorption), and brain (insulin resistance) [4]. Adiposity in T2DM diminishes glucoregulation 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

* Corresponding author at: Department of Endocrinology, Diabetes and Clinical Pharmacology, Dubrava University Hospital, Avenija Gojka Šuška 6, 10000 Zagreb, Croatia.
E-mail address: tanjarezic1@gmail.com (T. Režić).

https://doi.org/10.1016/j.mehy.2019.109308
Received 3 June 2019; Received in revised form 7 July 2019; Accepted 12 July 2019

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, estradiole and testosterone, and GLP-1 analogues on body weight reduction by binding to their receptors in supramammilary 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 (estradiole 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 gluteofemoral 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 ovariectomized 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 oestrogen reduced body weight, food intake and food reward more than either of these agents applied separately. This might be partially explained by supramammilary nucleus (SUM); GLP-1-estrogen 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.

Funding/grant

The authors did not receive any financial support for this work.

Declaration of Competing Interest

None declared.

Acknowledgements

We acknowledge the project principal investigator, Ivana Pavlic Renar, for unique approach to our professional development, both clinical and scientific, but also for the active support many years after. This scientific project is a great recognition to our capacities in diabetology and metabolism. The funding source of our work is the project 'The possible synergistic effect of sex hormones and glucagon-like peptide-1 (GLP-1) on body mass decline in patients with type 2 diabetes mellitus' at University of Zagreb.

References

[1] Yumuk V, Tsigos C, Fried M, et al. European guidelines for management of obesity in adults. Obes Facts 2015;8(6):402–24.
[2] Zhu S, Wang Z, Heshka S, Heo M, Faith MS, Heymsfield SB. Waist circumference and obesity associated risk factors among whites in the third National Health and Nutrition Examination Survey: clinical action thresholds. Am J Clin Nutr 2002;76:743–9.
[3] Purnell JQ: Definitions, classification and epidemiology of obesity. Endotext (Internet).
[4] De Fronzo RA. Banting lecture: from the triumvirate to the omnious octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes 2009;58(4):773–95.
[5] Resnick H, Valsania P, Halter J, Lin X. Relation of weight gain and weight loss on subsequent diabetes risk in overweight adults. J Epidemiol Commun Health 2000;54(8):596–602.
[6] Bays HE, González-Campoy JM, Bray GA, et al. Pathogenic potential of adipose tissue and metabolic consequences of adipocyte hypertrophy and increased visceral adiposity. Expert Rev Cardiovasc Ther 2008;6:343–68.
[7] https://www.hzjz.hr/wp-content/uploads/2013/11/DM-bilten-2005_2014.pdf.
[8] Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in Type 2 diabetes. Lancet 2006;2006(368):1696–705.
[9] Wessels L, Keigan S, O'Brien SV, Hardy KJ. What proportion of patients fail NICE criteria for continuing GLP-1 treatment beyond six months, and why? Pract Diab 2013;30(5):196–8.
[10] Vogel H, Wolf S, Rabasa C, et al. GLP-1 and estrogen conjugate acts in the supramammillary nucleus to reduce food-reward and body weight. Neuropharmacology 2016;110(Pt A):396–406.
[11] Singh R, Artaza JN, Taylor WE, Gonzalez-Cadavid NF, Bhasin S. Androgens

stimulate myogenic differentiation and inhibit adipogenesis in C3H 10T1/2 pluripotent cells through an androgen receptor-mediated pathway. Endocrinology 2003;144(11):5081–8.
[12] Andersson B, Mårin P, Lissner L, Vermeulen A, Björntorp P. Testosterone concentrations in women and men with NIDDM. Diab Care 1994;17(5):405–11.
[13] Giagulli VA, Kaufmann JM, Vermeulen A. Pathogenesis of decreased androgen levels in obese men. J Clin Endocrinol Metab 1994;79(4):997–1000.
[14] Wu FC, Tajar A, Pye SR, et al. Hypothalamic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: the European Male Aging Study. J Clin Endocrinol Metab 2008;93(7):2737–45.
[15] Corona G, Rastrelli G, Monami M, et al. Body weight loss reverts obesity-associated hypogonadotropic hypogonadism: a systematic review and meta-analysis. Eur J Endocrinol 2013;168(6):829–43.
[16] Zitzmann M, Mattern A, Hanisch J, Gooren L, Jones H, Maggi M. IPASS: a study on the tolerability and effectiveness of injectable testosterone undecanoate for the treatment of male hypogonadism in a worldwide sample of 1,438 men. J Sex Med 2013;10(2):579–88.
[17] Saad F, Haider A, Doros G, Traish A. Long-term treatment of hypogonadal men with testosterone produces substantial and sustained weight loss. Obesity 2013;21(10):1975–81.
[18] Lapauw B, Ouwens M, Thart LM, et al. Sex steroids affect triglyceride handling, glucose-dependent insulinotropic polypeptide, and insulin sensitivity. Diab Care 2010;33(8):1831–3.
[19] Giagulli VA, Carbone MD, Ramunni MI, et al. Adding liraglutide to lifestyle changes, metformin and testosterone therapy boosts erectile function in diabetic obese men with overt hypogonadism. Andrology 2015;3(6):1094–103.
[20] Leeners B, Geary N, Tobler PN, Asarian L. Ovarian hormones and obesity. Hum Reprod Update 2017;23(3):300–21.
[21] Gong EJ, Garrel D, Calloway DH. Menstrual cycle and voluntary food intake. Am J Clin Nutr 1989;49(2):252–8.
[22] Asarian L, Geary N. Sex differences in the physiology of eating. Am J Physiol Regul Integr Comp Physiol 2013;305(11):R1215–67.
[23] Finan B, Yang B, Ottaway N, et al. Targeted estrogen delivery reverses the metabolic syndrome. Nat Med 2012;18(12):1847–56.