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Research

Evaluation of Exenatide Versus Insulin Glargine Treatment's Impact on Brown Adipose Tissue Markers and Epicardial Adipose Tissue

Eksenatid ve İnsülin Glargin Tedavisinin Kahverengi Yağ Doku Belirteçleri ve Epikardiyal Yağ Doku Üzerine Etkisinin Karşılaştırmalı Olarak Değerlendirilmesi

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ABSTRACT

Objective: Bone morphogenetic protein-7 (BMP7), unique uncoupling protein-1 (UCP1), PR domain containing 16 (PRDM-16), and irisin are important brown adipose tissue (BAT) markers. This study aimed to evaluate the effects of insulin glargine and exenatide treatment on BAT markers and epicardial adipose tissue (EAT) volume in patients with type 2 diabetes mellitus (T2DM).

Methods: The study included 33 patients with T2DM. Patients with T2DM were randomized to the insulin glargine and exenatide arms. Before and 24 weeks after treatment, serum BAT markers and EAT levels were evaluated and compared in both treatment arms.

Results: EAT decreased in both groups with treatments (both groups $p<0.001$), but there was no significant difference between the two groups when compared. BMP7 significantly decreased with exenatide treatment ($p=0.03$). UCP1 significantly decreased with insulin glargine treatment ($p=0.008$). Pre- and post-treatment percentage changes in irisin, BMP7, UCP1, and PRDM-16 were similiar.

Conclusion: Weight loss and a decrease body fat mass occur with exenatide treatment, but this is probably unrelated to BAT activation.

Keywords: Type 2 diabetes mellitus, BMP7, epicardial adipose tissue, irisin, UCP1, PRDM-16

ÖZ

Amaç: Kemik morfojenik proteini-7 (BMP7), unique uncoupling protein-1 (UCP1), PR domain containing 16 (PRDM-16) ve irisin önemli kahverengi yağ doku (KYD) belirteçlerindendir. Bu çalışma tip 2 diabetes mellitus hastalarında (T2DM) insülin glargin ve eksenatid tedavisinin KYD belirteçleri ve epikardiyal yağ dokusu (EYD) üzerine etkilerini incelemeyi amaçlamıştır.

Gereç ve Yöntem: Çalışmaya 33 T2DM hastası alındı. T2DM hastaları, insülin glargin ve eksenatid kollarına randomize edildi. Her iki tedavi kolunda serum KYD belirteçlerinin ve EYD düzeylerinin tedaviden önce ve tedaviden 24 hafta sonraki verileri değerlendirildi ve karşılaştırıldı.

Bulgular: EYD tedavi ile her iki grupta da azaldı (her iki grupta da $p<0,001$), ancak her iki gruptaki değişimler karşılaştırıldığında aralarında anlamlı fark yoktu. BMP7 eksenatid tedavisi ile anlamlı azaldı ($p=0,03$). UCP1 insülin glargin tedavisi ile anlamlı azaldı ($p=0,008$). İrisin, BMP7, UCP1 ve PRDM-16'nın tedavi öncesi ve tedavi sonrası yüzde değişimleri benzerdi.

Sonuç: Eksenatid tedavisi ile vücut ağırlığında ve total vücut yağında anlamlı azalma oldu ancak bu muhtemelen KYD aktivasyonu bağlı değildi.

Anahtar Kelimeler: Tip 2 diabetes mellitus, BMP7, epikardiyal yağ dokusu, irisin, UCP1, PRDM-16

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INTRODUCTION

The frequency of diabetes and obesity has recently increased (1). Obesity causes insulin resistance, which further results in type 2 diabetes mellitus (T2DM) treatment difficulties. Recently, guidelines have focused on new anti-obesity drug options to break this vicious cycle. Glucagon-like peptide-1 (GLP-1) receptor analogs (GLP-1RAs) are anti-diabetic and anti-obesity drugs that provide a gate to break this vicious cycle by contributing to weight loss. GLP-1RAs exert weight loss effects through various mechanisms, such as central and peripheral effects. Weight loss potentials with brown adipose tissue (BAT) activation have become of particular interest after encouraging initial results (2,3). Humans have three morphological types of adipose tissue: white adipose tissue (WAT), beige adipose tissue, and BAT (4). BAT is an energy-wasting tissue that increases energy expenditure and chemical energy for thermogenesis (5,6). BAT activation can improve metabolic parameters such as hyperglycemia and dyslipidemia, thus making BAT activation a potential therapeutic target for obesity and other metabolic diseases (7,8). BAT contains high mitochondrial density and expresses high levels of uncoupling protein 1 (UCP1). UCP1, which is the most important marker of BAT, is also expressed in human BAT and can regulate thermogenesis (9,10). Bone morphogenic protein-7, PR domain containing 16 (PRDM-16), and irisin are BAT-related markers.

Bone morphogenesis proteins (BMPs) are members of the superfamily of transforming growth factor β (TGF-β). They participate in brown adipocyte development and insulin sensitivity and increase the expression of the PRDM-16. PRDM-16 is a key transcriptional regulator of brown adipose identity (11-13). PRDM-16 induces gene expression in BAT. Irisin is a newly discovered myokine that is secreted in response to exercise (14). Irisin increases PPARα and UCP1 expression, browns WAT (15), improves islet β-cell proliferation (16), and increases energy consumption and thermogenesis of both skeletal muscles and BAT (17).

There are different methods to evaluate BAT, such as 18F-fluorodeoxyglucose positron emission tomography integrated with computed tomography (18F-FDG PET-CT) and magnetic resonance imaging (MRI). Epicardial adipose tissue (EAT) is visceral fat surrounding the pericardium and myocardium; however, its biological characteristics are still not completely known (18). The main marker of BAT is a unique UCP1, which was detected in EAT. Therefore, EAT includes BAT components (19). Studies have shown that the reliability of transthoracic echocardiography (ECHO) in measuring EAT correlates well with MRI (20).

There are studies examining the effect of GLP-1RAs on BAT in animal studies. (3,21-23) However, there are very few human studies on this subject, and they are conflicted (2,24). Insulin glargine is a long-acting basal insulin analog used daily for the treatment of T2DM. To our knowledge, the effect of insulin treatment on BAT has not been investigated in the literature. To our knowledge, the comparative effect of treatment with exenatide versus insulin glargine on the serum levels of irisin, PRDM-16, BMP7, and UCP1 has not been studied.

This study investigated the potential roles of the GLP-1 agonist exenatide on metabolic parameters, EAT value, and serum levels of PRDM-16, irisin, UCP1, and BMP7 by comparing patients with diabetes treated with exenatide with those treated with insulin glargine.

METHODS

Study Design and Participants

This prospective, randomized, active-controlled study was conducted in the Kocaeli University School of Medicine Department of Endocrinology outpatient unit between 2016 and 2019. The study included 33 patients with T2DM. The age of patients with T2DM enrolled in the study was between 18 and 65 years, body mass index (BMI) was 25-35 kg/m^2, with hemoglobin A1c (HbA1c) >7% and <10%, who were on metformin 2×1 g/day alone in stable dose for at least 3 months during enrollment. Renal or hepatic impairment, thyroid dysfunction, coronary artery disease, cardiac failure, infectious or inflammatory disease, cancer and pregnancy was exclusion criteria. In addition, patients on insulin- or incretin-based therapy and patients with acute or chronic pancreatic disease were excluded from the study.

Patients with T2DM were randomized one to one to the exenatide or insulin glargine arm to investigate the effects of exenatide and insulin glargine treatment on BAT markers (irisin, PRDM-16, UCP1, and BMP7) and EAT. Twenty patients were included in the exenatide arm and 20 patients in the insulin glargine arm. Exenatide treatment was administered as 5 μg SC for the first month and titrated to 10 μg SC for the next 5 months. Insulin glargine was started at 0.2 IU/kg at night, and the dose was titrated according to fasting blood glucose levels. 0-, 4-, 12-, and 24-week visits of the patients were performed. Physical examinations, including vital signs and examination of all systems, were performed during these visits, and drug side effects were questioned. Height, weight, and BMI measurements were taken, and routine biochemistry tests were performed at 0- and 24-week visits. Blood samples for irisin, PRDM-16, UCP1, and BMP7 were collected. ECHO measured EAT at 0- and 24-

week visits. In the insulin glargine arm, two patients left the study because they wanted to stop injection therapy, and two patients were lost to follow-up. In the exenatide arm, two patients were excluded because of the side effect of vomiting, and one patient was lost follow-up. The insulin glargine arm was completed with 16 patients, and the arm with 17 patients. Pre- and post-treatment biochemical parameters, irisin, PRDM-16, UCP1, BMP7, and EAT levels were compared in both T2DM groups.

This study was approved by the Kocaeli University Non-Invasive Clinical Research Ethics Committee (decision no: KÜ GOKAEK 2017/820, project no: 2017/160, date: 07.06.2017). All experiments were conducted according to the Declaration of Helsinki. Written informed consent was obtained from all participants.

Biochemical Analysis

Blood samples were collected at 0 and 24 weeks after 8-10 hours (h) of fasting at 09.00 in the morning. Serum was obtained, and centrifuged blood samples were stored at -80 °C until analysis. The concentrations of UCP1, irisin, PRDM-16, and BMP7 were analyzed using a Radim Diagnostics Rome (Italy) device with a sandwich enzyme-linked immunosorbent assay method in accordance with the manufacturer's instructions (Elabscience).

Body Weight and Total Body Fat Mass Assessment

Body weight and total body fat mass were measured using the bioimpedance analysis technique with the Tanita BC-418 body composition analyzer device.

Baseline Echocardiography and Assessment of the Epicardial Adipose Tissue Thickness

All cases were evaluated with conventional ECHO in the left lateral decubitus position using a commercially available system (VIVID 7, General Electric-Vingmed Ultrasound, Horten, Norway). Measurements were performed by an experienced cardiologist blindly. EAT appeared as an echo-free space in the pericardial layers on a two-dimensional ECHO and was measured on the free wall of the right ventricle from a parasternal long-axis view, using the aortic annulus as an anatomic reference. EAT was measured perpendicularly in front of the right ventricular free wall at end-systole (20,25). The average value of three cardiac cycles was calculated.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) for Windows 23.0 (IBM SPSS Inc., Chicago, IL). The conformity of the variables to the normal distribution was examined visually (histogram and probability graphs) using the Shapiro-Wilk test. Descriptive data are presented as median and maximum-minimum values (median and minimum-maximum) for non-normally distributed variables and as mean and standard deviation for normally distributed data. The Mann-Whitney U test was used for independent variables, and the Wilcoxon signed-rank test was used for dependent variables to compare the numerical values of the two groups that were found to be non-normally distributed. An independent t-test was used for independent variables, and a paired t-test was used for dependent variables to compare the numerical values of the two groups that were found to have a normal distribution. The results were accepted as a 95% confidence interval, statistical significance $p<0.05$.

RESULTS

The demographic data, pre- and post-treatment biochemical parameters of the exenatide and insulin glargine groups are summarized in Table 1. The exenatide and insulin glargine groups were similar in terms of age, gender, age of diabetes, BMI, glucose, and HbA1c level. HbA1c levels significantly decreased after treatment in both groups; also, the pre- and post-treatment changes of HbA1c were similar between groups.

Effect on the Body Mass Index and Total Body Fat Mass

There was a significant reduction in BMI and total body fat mass with treatment in the exenatide group compared with glargine ($p<0.001$; $p=0.01$, respectively).

Effect on the Epicardial Adipose Tissue

The impact of exenatide versus insulin glargine treatment on EAT is shown in Table 2. EAT levels significantly decreased in both treatment groups. However, EAT differences were similar between the groups.

Effect on Brown Adipose Tissue Markers

The impact of exenatide versus insulin glargine treatment on BAT markers is shown in Table 2. Pre- and post-treatment serum irisin and PRDM-16 levels were similar in both treatment arms. BMP7 significantly decreased with exenatide treatment ($p=0.03$). UCP1 significantly decreased with insulin glargine treatment ($p=0.008$). Pre- and post-treatment percentage changes in irisin, BMP7, UCP1, and PRDM-16 were not significantly different between the groups.

DISCUSSION

In this study, although there was a significant improvement in BMI and total body fat mass with exenatide compared with insulin glargine treatment in patients with T2DM, no

Table 1. The demographic data, pre-, and post-treatment biochemical parameters of the exenatide and insulin glargine groups

Variables	Exenatide group (n=17)	Glargine group (n=16)	p-value
Age (years)	49.88±7.76	51.25±6.95	0.599
Gender (female/male)	15/2	10/6	0.095
DM age (years)	4.58±3.89	6.37±4.14	0.211
BMI (kg/m^2)-$_{pre}$	37.47±4.47	35.27±1.92	0.079
BMI (kg/m^2)-$_{post}$	35.89±4.71	35.23±1.76	0.605
p-value	**<0.001**	0.76	
Change from baseline (%)	-3.42 (-8.01 to -1.24)	0.13 (-0.81 to 0.5)	**<0.001**
Total body fat mass (kg)-$_{pre}$	40.72±10.38	35.71±5.60	0.100
Total body fat mass (kg)-$_{post}$	40.37.55±11.50	35.06±5.73	0.103
p-value	**<0.001**	0.06	
Change from baseline (%)	-9.11 (-13.17 to -3.49)	-0.72 (-5.93 to 0,56)	**0.01**
Glucose-$_{pre}$ (mg/dL)	147.52±39.44	142.81±15.83	0.656
Glucose-$_{post}$ (mg/dL)	132.29±36.08	114±18.15	0.093
p-value	0.02	**<0.001**	
Change from baseline (%)	-13.04 (-17.57 to -1.43)	-20.53 (-24.11 to -14.59)	**0.03**
Triglyceride-$_{pre}$ (mg/dL)	160.11±71.62	124.87±63.36	0.145
Triglyceride-$_{post}$ (mg/dL)	202.11±100.15	157.87±91.02	0.195
p-value	0.03	0.02	
Change from baseline (%)	22.5 (-8.19 to 58.5)	3.16 (0.00 to 55.64)	1.00
Total cholesterol-$_{pre}$ (mg/dL)	176.23±31.59	193.75±37.34	0.155
Total cholesterol-$_{post}$ (mg/dL)	191.23±21.60	187.46±29.00	0.677
p-value	0.085	0.39	
Change from baseline (%)	4.32 (-4.95 to31.97)	0.00 (-6.25 to 1.65)	0.26
LDL cholesterol-$_{pre}$ (mg/dL)	102.27±30.03	129.05±32.91	0.020
LDL cholesterol-$_{post}$ (mg/dL)	106.91±18.92	116.82±33.29	0.298
p-value	0.52	0.17	
Change from baseline (%)	-3.42 (-9.71 to 41.33)	-0.25 (-8.82 to 0.00)	0.65
HDL cholesterol-$_{pre}$ (mg/dL)	42.47±8.70	46.00±8.35	0.244
HDL cholesterol-$_{post}$ (mg/dL)	44.58±8.29	45.68±9.20	0.721
p-value	0.23	0.74	
Change from baseline (%)	0.00 (-5.4 to 12.07)	0.00 (-4.19 to 5.27)	0.53
HbA1c-$_{pre}$ (%)	8.43±0.99	8.10±0.45	0.236
HbA1c-$_{post}$ (%)	7.23±1.25	7.11±0.46	0.730
p-value	**0.002**	**≤0.001**	
Change from baseline (%)	-8.57 (-26.42 to -1.50)	-11.60 (-18.13 to -4.42)	1.00

Data was given as mean ± standard deviation or median (minimum-maximum) depending on the distribution.
DM: Diabetes mellitus, BMI: Body mass index, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, TSH: Thyroid-stimulating hormone, HbA1c: hemoglobin A1c

Table 2. Exenatide versus insulin glargine treatment's impact on EAT and brown adipose tissue markers

Variables	Exenatide group (n=17)	Glargine group (n=16)	p-value
PRDM-16-$_{pre}$	239.29±106.10	227.43±80.88	0.722
PRDM-16$_{-post}$	232.18±69.75	277.62±194.32	0.386
p-value	0.8	0.2	
Change from baseline (%)	-5.16 (-14.62 to 20)	9.94 (-16.96 to 54.45)	0.32
Irisin-$_{pre}$ (pg/mL)	6.62±3.37	5.71±2.49	0.386
Irisin$_{-post}$ (pg/mL)	6.09±3.48	5.84±2.84	0.820
p-value	0.2	0.4	
Change from baseline (%)	-3.07 (-23.11 to 6.48)	12.5 (-13.76 to 19.77)	0.16
UCP1-$_{pre}$ (ng/mL)	1.79±0.89	2.22±1.18	0.241
UCP1$_{-post}$ (ng/mL)	1.26±0.48	1.13±0.73	0.570
p-value	0.06	**0.008**	
Change from baseline (%)	-30.97 (-55.10 to 54.54)	-36.18 (-77.19 to 6.73)	0.23
BMP7-$_{pre}$ (pg/mL)	213.85±100.75	195.55±90.31	0.587
BMP7$_{-post}$ (pg/mL)	139.69±45.81	153.30±120.37	0.667
p-value	**0.03**	0.14	
Change from baseline (%)	-27.96 (-59.10 to 38.29)	-21.27 (-69.07 to 28.76)	0.87
EAT-$_{pre}$ cm	0.61±0.15	0.71±0.14	0.176
EAT-$_{post}$ cm	0.48±0.12	0.56±0.15	0.140
p-value	**0.000**	**0.000**	
Change from baseline (%)	-20 (-30.95 to -16.66)	-22.5 (-32.14 to -11.45)	0.81

Data was given as mean ± standard deviation or median (minimum-maximum) depending on the distribution.
Pre: Pretreatment, post: Post-treatment, PRDM-16: PR domain containing 16, UCP-1: Unique uncoupling protein 1, BMP-7: Bone morphogenetic protein 7, EAT: Epicardial adipose tissue

significant difference was observed between the groups in posttreatment BAT markers. EAT decreased in both treatment groups, but there was no significant difference between the two groups.

Brown fat mass in adults is positively related to weight loss and metabolic health (26,27) and can be activated (28). In a recent study, which compared liraglutide and placebo, BAT was measured from the supraclavicular fat depot using MRI, and no difference was found between the two groups. In this study, the GLP-1 agonist did not affect the activation of BAT, and a decreasing or changing supraclavicular fat store reflecting BAT was not observed (29). We evaluated BAT containing EAT using ECHO, and EAT decreased after exenatide and insulin glargine treatment. However, there was no significant change in EAT when the two groups were compared. Similar to our study, other studies have shown that EAT decreased with insulin glargine and exenatide treatment (30,31). In contrast to our study, Janssen et al. (32) studied the effects of exenatide treatment weekly in 24 patients who were not obese and without diabetes. They found that exenatide increased the volume and FDG uptake in cervical and supraclavicular upper mediastinal, axillary, and paravertebral BAT depots by 18-F FDG PET-CT. However, the same result was not achieved when they evaluated the supraclavicular region using MRI. The reason we could not obtain similar results may be that we evaluated a different BAT region or that our patients were diabetic.

UCP1 is a mitochondrial inner membrane protein considered as a marker of BAT activity and is significantly expressed in BAT. Wan et al. (33) reported that chronic peripheral treatment with the GLP-1R agonist supaglutide upregulates the expression of UCP1 in inguinal WAT, not in BAT and epididymal WAT. An animal study concluded that GLP-1 agonists did not affect UCP1 expression in BAT. They put forward that the GLP-1 agonist does not increase thermogenesis (24). In line with these studies, in our study, UCP1 differences were similar between the two treatment arms. In contrast to our study, a previous study showed that centrally administered liraglutide increases UCP1 expression in mice in BAT and WAT (2).

Irisin secreted in response to exercise is a newly discovered myokine. Animal studies have shown that irisin modulates energy metabolism (14). Serum irisin levels significantly increased after exenatide treatment in the study by Liu et al. (34). In our study, irisin differences were similar in the exenatide and glargine treatment groups. In Liu et al.'s study (34), exenatide treatment was used as the initial treatment for diabetes. In our study, both the exenatide and glargine groups used metformin as the initial treatment. Animal and human studies have shown that metformin increases serum irisin (35,36). Therefore, the use of metformin may be the reason why we cannot achieve improvement in the irisin level.

BMPs are members of the TGF-β superfamily (37). BMPs, especially BMP4, BMP7, and BMP8, can participate in the process of brown adipocyte development and the differentiation of white adipocytes to brown adipocytes (12). A rat study showed that BMP7 gene expression increased after GLP-1 agonist treatment (38). There has been no study on levels of BMP7 in patients receiving GLP-1 agonist therapy in humans. In this study, BMP7 levels significantly decreased with exenatide treatment, but BMP7 differences were not significant between the treatment groups. BMP7 increases the expression of PRDM-16, providing a balance between brown fat and skeletal muscle change (39,40). GLP-1 agonists increased the activity of insulin-suppressing lipolysis in subcutaneous adipose tissue (41). However, the benefits of GLP-1 agonists in BAT have not been clearly understood (42). A study on mice showed that GLP-1 agonist therapy increased both UCP1 and PRDM-16 expression in skeletal muscle but not in perigonadal fat (43). So far, we noticed no study on serum levels of PRDM-16 in patients with diabetes or related to GLP-1 agonist therapy in humans. Our results showed that the pre- and post-treatment serum PRDM-16 differences were similar in both treatment arms.

The limitations of our study are a relatively low number of participants, differences in the duration of follow-up, and the non-assessment of the time of physical activity and caloric intake. The absence of 4 and 8 weeks of evaluation was another limitation. In some studies evaluating REE, the REE increment seen in the first week were not seen in further weeks. It has been suggested that this was a mechanism to limit weight loss (29,44,45). Unfortunately, as we did not evaluate the first-week markers, we may have missed the increment. However, a longer treatment duration may be needed for further activation of BAT. Another reason for nonactivated BAT may be the different seasonal activation of BAT. We evaluated the results of the participants at 24 weeks in different seasons; as BAT is cold activated (26,46), seasonal changes may affect our results.

CONCLUSION

Weight loss and a decrease body fat mass occur with exenatide treatment, but this is probably not related to BAT activation. The effects of GLP-1s on BAT in humans are controversial. More comprehensive studies are needed with more patients and longer follow-up periods to clarify this situation.

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ETHICS

Ethics Committee Approval: Pre-study ethics committee approval was received from Kocaeli University Medical School Clinical Research Ethics Committee. Ethics committee project no is KÜ GOKAEK 2017/160 (decision no: KÜ GOKAEK 2017/820, date: 07.06.2017).

Informed Consent: Written consent was obtained from all patients or their relatives.

Authorship Contributions

Surgical and Medical Practices: Ö.Z.A., A.S., Y.Ç., Concept: Ö.Z.A., İ.T., Z.C., Y.Ç., Design: Ö.Z.A., İ.T., Y.Ç., Data Collection or Processing: Ö.Z.A., İ.T., B.Ç., Y.Ç., Analysis or Interpretation: T.Ş., C.B., Literature Search: Ö.Z.A., A.S., İ.T., Writing: Ö.Z.A., A.S., B.Ç., Y.Ç.

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REFERENCES

1. IDF Diabetes Atlas. 9th edition. 2019. Available from: URL: https://diabetesatlas.org/atlas/ninth-edition/
2. Beiroa D, Imbernon M, Gallego R, Senra A, Herranz D, Villarroya F, et al. GLP-1 agonism stimulates brown adipose tissue thermogenesis and browning through hypothalamic AMPK. Diabetes 2014;63:3346-58.
3. Horowitz M, Flint A, Jones KL, Hindsberger C, Rasmussen MF, Kapitza C, et al. Effect of the once-daily human GLP-1 analogue liraglutide on appetite, energy intake, energy expenditure and gastric emptying in type 2 diabetes. Diabetes Res Clin Pract 2012;97:258-66.
4. Chait A, den Hartigh LJ. Adipose Tissue Distribution, Inflammation and Its Metabolic Consequences, Including Diabetes and Cardiovascular Disease. Front Cardiovasc Med 2020;7:22.
5. Li Y, Fromme T. Uncoupling Protein 1 Does Not Produce Heat without Activation. Int J Mol Sci 2022;23:2406.
6. Crichton PG, Lee Y, Kunji ER. The molecular features of uncoupling protein 1 support a conventional mitochondrial carrier-like mechanism. Biochimie 2017;134:35-50.
7. McNeill BT, Suchacki KJ, Stimson RH. MECHANISMS IN ENDOCRINOLOGY: Human brown adipose tissue as a therapeutic target: warming up or cooling down? Eur J Endocrinol 2021;184:R243-59.

8. Leitner BP, Huang S, Brychta RJ, Duckworth CJ, Baskin AS, McGehee S, et al. Mapping of human brown adipose tissue in lean and obese young men. Proc Natl Acad Sci U S A 2017;114:8649-54.
9. Sharp LZ, Shinoda K, Ohno H, Scheel DW, Tomoda E, Ruiz L, et al. Human BAT possesses molecular signatures that resemble beige/brite cells. PLoS One 2012;7:e49452.
10. Virtanen KA, Lidell ME, Orava J, Heglind M, Westergren R, Niemi T, et al. Functional brown adipose tissue in healthy adults. N Engl J Med 2009;360:1518-25. Erratum in: N Engl J Med 2009;361:1123.
11. Cheng L, Wang J, Dai H, Duan Y, An Y, Shi L, et al. Brown and beige adipose tissue: a novel therapeutic strategy for obesity and type 2 diabetes mellitus. Adipocyte 2021;10:48-65.
12. Hogan BL. Bone morphogenetic proteins: multifunctional regulators of vertebrate development. Genes Dev 1996;10:1580-94.
13. Seale P, Kajimura S, Yang W, Chin S, Rohas LM, Uldry M, et al. Transcriptional control of brown fat determination by PRDM16. Cell Metab 2007;6:38-54.
14. Huh JY, Mougios V, Kabasakalis A, Fatouros I, Siopi A, Douroudos II, et al. Exercise-induced irisin secretion is independent of age or fitness level and increased irisin may directly modulate muscle metabolism through AMPK activation. J Clin Endocrinol Metab 2014;99:E2154-61.
15. Zhang Y, Li R, Meng Y, Li S, Donelan W, Zhao Y, et al. Irisin stimulates browning of white adipocytes through mitogen-activated protein kinase p38 MAP kinase and ERK MAP kinase signaling. Diabetes 2014;63:514-25.
16. Sanchis-Gomar F, Perez-Quilis C. The p38-PGC-1α-irisin-betatrophin axis: Exploring new pathways in insulin resistance. Adipocyte 2014;3:67-8.
17. Rodríguez A, Becerril S, Ezquerro S, Méndez-Giménez L, Frühbeck G. Crosstalk between adipokines and myokines in fat browning. Acta Physiol (Oxf) 2017;219:362-81.
18. Sacks HS, Fain JN. Human epicardial adipose tissue: a review. Am Heart J 2007;153:907-17.
19. Sacks HS, Fain JN, Holman B, Cheema P, Chary A, Parks F, et al. Uncoupling protein-1 and related messenger ribonucleic acids in human epicardial and other adipose tissues: epicardial fat functioning as brown fat. J Clin Endocrinol Metab 2009;94:3611-5.
20. Iacobellis G, Assael F, Ribaudo MC, Zappaterreno A, Alessi G, Di Mario U, et al. Epicardial fat from echocardiography: a new method for visceral adipose tissue prediction. Obes Res 2003;11:304-10.
21. Harder H, Nielsen L, Tu DT, Astrup A. The effect of liraglutide, a long-acting glucagon-like peptide 1 derivative, on glycemic control, body composition, and 24-h energy expenditure in patients with type 2 diabetes. Diabetes Care 2004;27:1915-21.
22. van Can J, Sloth B, Jensen CB, Flint A, Blaak EE, Saris WH. Effects of the once-daily GLP-1 analog liraglutide on gastric emptying, glycemic parameters, appetite and energy metabolism in obese, non-diabetic adults. Int J Obes (Lond) 2014;38:784-93.
23. Kooijman S, Wang Y, Parlevliet ET, Boon MR, Edelschaap D, Snaterse G, et al. Central GLP-1 receptor signalling accelerates plasma clearance of triacylglycerol and glucose by activating brown adipose tissue in mice. Diabetologia 2015;58:2637-46.
24. Stanford KI, Middelbeek RJ, Townsend KL, An D, Nygaard EB, Hitchcox KM, et al. Brown adipose tissue regulates glucose homeostasis and insulin sensitivity. J Clin Invest 2013;123:215-23.
25. Iacobellis G, Ribaudo MC, Assael F, Vecci E, Tiberti C, Zappaterreno A, et al. Echocardiographic epicardial adipose tissue is related to anthropometric and clinical parameters of metabolic syndrome: a new indicator of cardiovascular risk. J Clin Endocrinol Metab 2003;88:5163-8.
26. van Marken Lichtenbelt WD, Vanhommerig JW, Smulders NM, Drossaerts JM, Kemerink GJ, Bouvy ND, et al. Cold-activated brown adipose tissue in healthy men. N Engl J Med 2009;360:1500-8. Erratum in: N Engl J Med 2009;360:1917.
27. Cypess AM, Lehman S, Williams G, Tal I, Rodman D, Goldfine AB, et al. Identification and importance of brown adipose tissue in adult humans. N Engl J Med 2009;360:1509-17.
28. Cypess AM, Chen YC, Sze C, Wang K, English J, Chan O, et al. Cold but not sympathomimetics activates human brown adipose tissue in vivo. Proc Natl Acad Sci U S A 2012;109:10001-5.
29. van Eyk HJ, Paiman EHM, Bizino MB, IJzermans SL, Kleiburg F, Boers TGW, et al. Liraglutide decreases energy expenditure and does not affect the fat fraction of supraclavicular brown adipose tissue in patients with type 2 diabetes. Nutr Metab Cardiovasc Dis 2020;30:616-24.
30. Elisha B, Azar M, Taleb N, Bernard S, Iacobellis G, Rabasa-Lhoret R. Body Composition and Epicardial Fat in Type 2 Diabetes Patients Following Insulin Detemir Versus Insulin Glargine Initiation. Horm Metab Res 2016;48:42-7.
31. Dutour A, Abdesselam I, Ancel P, Kober F, Mrad G, Darmon P, et al. Exenatide decreases liver fat content and epicardial adipose tissue in patients with obesity and type 2 diabetes: a prospective randomized clinical trial using magnetic resonance imaging and spectroscopy. Diabetes Obes Metab 2016;18:882-91.
32. Janssen LGM, Nahon KJ, Bracké KFM, van den Broek D, Smit R, Sardjoe Mishre ASD, et al. Twelve weeks of exenatide treatment increases [18F]fluorodeoxyglucose uptake by brown adipose tissue without affecting oxidative resting energy expenditure in nondiabetic males. Metabolism 2020;106:154167.
33. Wan Y, Bao X, Huang J, Zhang X, Liu W, Cui Q, et al. Novel GLP-1 Analog Supaglutide Reduces HFD-Induced Obesity Associated with Increased Ucp-1 in White Adipose Tissue in Mice. Front Physiol 2017;8:294.
34. Liu J, Hu Y, Zhang H, Xu Y, Wang G. Exenatide treatment increases serum irisin levels in patients with obesity and newly diagnosed type 2 diabetes. J Diabetes Complications 2016;30:1555-9.
35. Li M, Yang M, Zhou X, Fang X, Hu W, Zhu W, et al. Elevated circulating levels of irisin and the effect of metformin treatment in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2015;100:1485-93. Erratum in: J Clin Endocrinol Metab 2015;100:3219.
36. Li DJ, Huang F, Lu WJ, Jiang GJ, Deng YP, Shen FM. Metformin promotes irisin release from murine skeletal muscle independently of AMP-activated protein kinase activation. Acta Physiol (Oxf) 2015;213:711-21.
37. Vukicevic S, Basic V, Rogic D, Basic N, Shih MS, Shepard A, et al. Osteogenic protein-1 (bone morphogenetic protein-7) reduces severity of injury after ischemic acute renal failure in rat. J Clin Invest 1998;102:202-14.
38. Ramzy MM, Abdalla AM, Zenhom NM, Okasha AM, Abdelkafy AE, Saleh RK. Therapeutic effect of liraglutide on expression of CTGF and BMP-7 in induced diabetic nephropathy. J Cell Biochem 2019;120:17512-9.
39. Harms M, Seale P. Brown and beige fat: development, function and therapeutic potential. Nat Med 2013;19:1252-63.
40. Harms MJ, Ishibashi J, Wang W, Lim HW, Goyama S, Sato T, et al. Prdm16 is required for the maintenance of brown adipocyte identity and function in adult mice. Cell Metab 2014;19:593-604.
41. Armstrong MJ, Hull D, Guo K, Barton D, Hazlehurst JM, Gathercole LL, et al. Glucagon-like peptide 1 decreases lipotoxicity in non-alcoholic steatohepatitis. J Hepatol 2016;64:399-408.
42. Heppner KM, Marks S, Holland J, Ottaway N, Smiley D, Dimarchi R, et al. Contribution of brown adipose tissue activity to the control of energy balance by GLP-1 receptor signalling in mice. Diabetologia 2015;58:2124-32.
43. Zhou JY, Poudel A, Welchko R, Mekala N, Chandramani-Shivalingappa P, Rosca MG, et al. Liraglutide improves insulin sensitivity in high fat diet induced diabetic mice through multiple pathways. Eur J Pharmacol 2019;861:172594.
44. Doré C, Hesp R, Wilkins D, Garrow JS. Prediction of energy requirements of obese patients after massive weight loss. Hum Nutr Clin Nutr 1982;36C:41-8.
45. Kiortsis DN, Durack I, Turpin G. Effects of a low-calorie diet on resting metabolic rate and serum tri-iodothyronine levels in obese children. Eur J Pediatr 1999;158:446-50.
46. Au-Yong IT, Thorn N, Ganatra R, Perkins AC, Symonds ME. Brown adipose tissue and seasonal variation in humans. Diabetes 2009;58:2583-7.