Int J Clin Exp Med 2020;13(4):2846-2853
www.ijcem.com /ISSN:1940-5901/IJCEM0107276

Original Article

Effects of exercise on sex hormones and glucose metabolism among male patients with type-2 diabetes mellitus

Wen Cao[1], Hongping Sun[2], Yongxin Hu[2], Shaofeng Xie[2], Kun Wang[1], Yaofu Fan[2]

[1]Endocrinology Department, The Affiliated Jiangning Hospital of Nanjing Medical University, Nanjing 211100, China; [2]Endocrine and Diabetes Center, Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine, Nanjing 210028, China

Received November 1, 2019; Accepted January 13, 2020; Epub April 15, 2020; Published April 30, 2020

Abstract: Objective: This study aims to reveal the influence of regular physical activity on sex hormones and glucose regulation in males with type-2 diabetes mellitus (T2DM). Methods: We enrolled 159 males with T2DM that were divided into two groups: physical activity group (n=124) and no physical activity group (n=35). The general indicators included weight, BMI, blood pressure and waist circumference. The biochemical indicators (renal function, blood glucose, insulin and glycosylated hemoglobin) and sex hormone index (total testosterone [TT], luteinizing hormone, follicle stimulating hormone, estradiol, and sex hormones binding globulin) were also determined. Furthermore, free testosterone (FT), bioactive testosterone (BT) and the homeostasis model assessment-insulin resistance index (HOMA-IR) were also calculated. The differences in general indicators and sex hormone indicators between groups were compared using different exercise times and body mass indices. Results: The levels of TT and BT were significantly higher in the activity group (P < 0.05). Furthermore, the HOMA-IR of T2DM patients differed across both groups (P < 0.05). Patients with a daily activity time of 0.5-1.0 hour had a lower HOMA-IR index, and physical activity time influenced the HOMA-IR of these patients. In addition, the FT and BT values differed between these two groups (P < 0.05), with patients with a daily activity time of less than 30 minutes showing higher levels of testosterone. TT levels were also higher in patients with normal BMI (P < 0.01). Conclusion: Hypogonadism is common amongst T2DM males. Physical activity can improve the testosterone levels of males with T2DM. The levels of testosterone are higher in individuals with normal BMI *vs.* obese individuals.

Keywords: Exercise, type-2 diabetes mellitus, sex hormones, metabolism

Introduction

Diabetes mellitus (DM) encompasses a range of metabolic diseases characterized by hyperglycemia and glucose intolerance [1]. In parallel to the worldwide increase in incidence and prevalence of DM, this has become an epidemic in China [2]. DM can lead to a variety of acute and chronic complications, resulting in a huge economic burden on society [3]. A study revealed that gonadal dysfunction was more common among men with type-2 diabetes mellitus (T2DM) as patients had decreased serum testosterone levels, and some patients had clinical symptoms of decreased libido and reduced sexual function, which had a further negative effect on the lives of these patients [4]. This might be due to diet-induced hypothalamic inflammatory reactions, which reduce the secretion of gonadotropin-releasing hormones [5]. Since a variety of metabolic abnormalities can induce male gonadal dysfunction [6, 7], the present study focused on finding effective interventions to treat gonadal function in diabetic patients.

Physical activity or exercise is an integral part of lifestyle interventions for the prevention or delay of DM [8]. The 2018 Standards in Medical Care of Diabetes issued by the American Diabetes Association (ADA) recommend that adult patients with DM should engage in moderate intensity of aerobic activity (50-70% of maximum heart rate) for 150 minutes per week, for at least three days a week, and should avoid two consecutive days of inactivity, in order to decrease insulin resistance [9]. Physical activity can control obesity, help in losing weight [10], increase bone density and muscle strength [11], improve body reactivity, and improve insulin sensitivity [12]. On the other hand, obesity [13] and insulin resistance [14] are also known risk factors for gonadal dysfunction. A study that evaluated the effects of an 8-week aerobic exercise program on obese men with T2DM revealed that physical activity can improve physical capacity and quality of life [15]. Thus, the present study aimed to determine whether physical activity can improve sex hormone levels in male patients with T2DM. Furthermore, the effects of regular physical activity on sex hormones and glucose metabolism in men with T2DM was investigated.

Methods

Subjects

A total of 1,107 male patients with T2DM, who were hospitalized between January 2015 and June 2018 in our institute, were eligible for inclusion. All patients conformed to the 1999 World Health Organization (WHO) Diabetes Diagnostic criteria [16].

Exclusion criteria: (1) patients with liver or renal insufficiency; (2) patients with decreased cardiac function; (3) patients with acute diabetes; (4) patients with diseases of sex glands, such as testicular dysfunction and primary male gonadal dysfunction; (5) patients with autoimmune and infectious diseases; (6) patients with hypertension and/or diuretics, or high blood pressure (≥ 40/90 mmHg); (7) patients with a history of rehabilitation sports; (8) patients with contraindications for physical activity; (9) patients with concomitant administration of testosterone therapy. Finally, 325 patients with liver and kidney dysfunction, 11 patients with cardiac dysfunction, 156 patients with acute complications of DM, eight patients with gonadal disease, 143 patients with infectious or immune diseases, 260 patients with poor control of hypertension or that used diuretics, 34 patients with a history of rehabilitation, and 11 patients who received testosterone replacement therapy were excluded. A total of 159 patients were included, and their age ranged within 28-78 years old. All patients provided a signed informed consent.

General Indices

Waist circumference was horizontally measured midway between the lowest rib and iliac crest. Height, body mass index (BMI), body weight and blood pressure were also assessed.

Physical activity history

Patients were inquired about regular exercise through a questionnaire, which mentioned about their daily physical activity, including physical activity time, type of physical activity, and so on. The most common physical activity among the included patients was walking, followed by light and moderate aerobic activity, such as jogging, popular calisthenics and swimming. The physical activity history of all patients was at least one year.

Blood indices

Blood was collected from 6 am to 7 am after overnight fasting for 8-10 hours. Fasting blood glucose (FBG), fasting insulin (FINS), glycosylated hemoglobin (HbA_{1c}), blood urea nitrogen (BUN), serum creatinine (Cr), and sex hormone (total testosterone [TT], luteinizing [LH], follicle stimulating hormone [FSH], estradiol [E2], and sex hormone binding globulin [SHBG]) levels were measured. The post prandial glucose levels were estimated after two hours of intake of anhydrous glucose (75 g in 200 mL of water). The levels of free testosterone (FT) and bioactive testosterone (BT) (http://www.issam.ch/freetesto.ht) were calculated using the software by measuring the serum SHBG, testosterone and serum albumin levels. Biochemical indicators were detected using a Swiss Roche C8000 biochemical analyzer. The HbA1c assay was performed with a US Bole D10 glycated hemoglobin analyzer, and assay used chromatography. The hormonal correlation was detected using a Swiss Roche E601 automatic electrochemiluminescence analyzer. All test kits were equipped with the corresponding instrument kit. HOMA-IR was calculated as follows: fasting blood glucose level (mmol/L) × fasting insulin level (mIU/L)/22.5.

Grouping methods

Depending on the routine physical activity, patients were sub-grouped according to physical (n=124) and non-physical activity (n=35).

Table 1. Effect of physical activity on the general indices and glucose metabolism index in men with T2DM

Group	No physical activity	Physical activity	t/Z	P-value
n	35	124		
Age (years)	48.06±11.35	51.06±11.38	-1.38	0.173
BMI (Kg/m^2)	25.59±3.73	25.24±3.47	0.642	0.524
WC (cm)	90	90	1.108	0.273
SBP (mmHg)	120	130	-0.944	0.134
DBP (mmHg)	78	80	-1.628	0.104
BUN (mmol/L)	5.56	5.14	-1.183	0.237
Cr (μmol/L)	65	67	-0.944	0.345
HbA_{1c} (%)	9.77±1.86	9.78±2.32	-0.034	0.973
FBG (mmol/L)	8.97	8.15	-1.189	0.234
PBG (mmol/L)	15.06	16.18	-1.858	0.063
HOMA-IR	2.87	2.57	-1.320	0.187

Data: mean ± SD. BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; BUN: urea nitrogen; Cr: creatinine; HbA_{1c}, glycated hemoglobin; FBG: fasting blood-glucose; PBG: postprandial blood glucose; HOMA-IR: homeostasis model assessment, insulin resistance index.

Table 2. Effect of physical activity on sex hormones in male patients with T2DM

Group	No physical activity	Physical activity	t/Z	P-value
n	35	124		
TT (nmol/L)	13.58	15.57	-2.029	0.042
FT	0.29	0.34	-1.673	0.094
BT	6.67	7.70	-2.284	0.022
LH (mIU/L)	5.61	5.99	-0.087	0.930
FSH (mIU/L)	5.27	5.77	-0.056	0.955
E2 (pmol/L)	98.32±40.06	93.28±37.76	0.665	0.509
SHBG (nmol/L)	26.40	25.97	-0.170	0.865

Data: mean ± SD or median. TT: total testosterone; BT: bioactive testosterone; FT: free testosterone; LH: luteinizing hormone; FSH: follicle-stimulating hormone; E2: estradiol; SHBG: sex hormone-binding globulin.

In the physical activity group, according to the different times of activity, patients were divided into four sub-groups: Q1 group (physical activity time: < 30 minutes, *n*=12), Q2 group (physical activity time: 30-60 minutes/day, *n*=51), Q3 group (exercise time: 60-120 minutes/day, *n*=47), and Q4 group (exercise time: > 120 minutes/day, *n*=14).

In the exercise group, patients were divided into three sub-groups according to BMI: Q1 group (BMI < 25 kg/m^2, *n*=58), Q2 group (25≤ BMI < 28 kg/m^2, *n*=39), and Q3 group (BMI ≥ 28 kg/m^2, *n*=27).

Statistical analysis

SPSS 19.0 software was used for all analyses. Normally distributed variables were expressed as mean ± standard deviation (SD). *T*-test was used for single group comparisons. Multiple groups were compared using single-factor variance analysis. For non-normal data, and through median representation, the comparison between these two groups was performed using the Kolmogorov-Smirnov test, while for multi-group comparisons, Kruskal-Wallis test was performed. If there were differences among groups, the Student-Newman-Keuls multi-comparison test was performed to analyze these groups and compare these in pairs. $P < 0.05$ was considered statistically significant.

Results

Effect of physical activity on glucose metabolism in male patients with T2DM

The two groups were compared for age, BMI, abdominal circumference, blood glucose, HbA_{1c}, blood pressure and renal function. No significant differences in these parameters were observed between these groups ($P > 0.05$, **Table 1**).

Effect of physical activity on sex hormones in male patients with T2DM

Compared with the non-physical activity group, TT and BT levels significantly increased ($P < 0.05$). However, no significant difference was observed among FT, LH, FSH, E2 and SHBG levels ($P > 0.05$, **Table 2**).

Effect of different physical activity times on glucose metabolism in male patients with T2DM

No significant differences in age, BMI, blood pressure, renal function, blood glucose and HbA_{1c} levels ($P > 0.05$) were observed between these groups. However, there were statistical differences between the HOMA-IR groups ($P < 0.05$, **Table 3**). Furthermore, there was a signifi-

Table 3. Effect of different physical activity times on glucose metabolism in male patients with T2DM

Group	Q1	Q2	Q3	Q4	χ^2/F	*P-value*
n	12	51	47	14		
Age (years)	47.67±9.41	51.73±11.25	51.02±12.44	51.64±10.14	0.420	0.739
BMI (Kg/m^2)	26.89	25.69	25.36	24.11	3.465	0.325
WC (cm)	90	90	91	89	1.560	0.669
SBP (mmHg)	134	126	124	130	3.465	0.325
DBP (mmHg)	84	80	80	79	5.089	0.165
BUN (mmol/L)	5.34	4.94	5.20	5.22	0.134	0.988
Cr (μmol/L)	67	67	67	67	0.232	0.972
HbA_{1c} (%)	9.53±2.07	9.77±2.48	9.78±2.18	10.04±2.57	0.100	0.960
FBG (mmol/L)	8.06	7.91	8.25	8.50	1.738	0.325
PBG (mmol/L)	16.51±2.31	15.79±3.94	16.66±4.08	16.22±4.10	0.433	0.730
HOMA-IR	3.61	2.16	2.12	3.37	8.499	0.037

Data: mean ± SD. BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; BUN: urea nitrogen; Cr: creatinine; HbA1c, glycated hemoglobin; FBG: fasting blood-glucose; PBG: postprandial blood glucose; HOMA-IR: homeostasis model assessment, insulin resistance index.

Table 4. Effect of different physical activity times on sex hormone levels in male patients with T2DM

Group	Q1	Q2	Q3	Q4	χ^2	*P-value*
n	12	51	47	14		
TT (nmol/L)	15.26	14.16	12.50	13.18	6.467	0.091
FT	0.39	0.30	0.27	0.29	15.770	0.001
BT	8.86	7.04	5.87	6.47	16.198	0.001
LH (mIU/L)	6.53	6.09	5.48	5.18	0.614	0.893
FSH (mIU/L)	5.95	4.83	6.16	7.15	2.037	0.565
E2 (pmol/L)	92.50	101.10	87.69	86.69	5.660	0.129
SHBG (nmol/L)	24.90	25.33	23.61	31.03	2.027	0.567

Data: mean ± SD or median. TT: total testosterone; BT: bioactive testosterone; FT: free testosterone; LH: luteinizing hormone; FSH: follicle-stimulating hormone; E2: estradiol; SHBG: sex hormone-binding globulin.

cant difference between the Q2 group and Q1 group (P=0.049), and between the Q2 group and Q4 group (P=0.013).

Effect of different physical activity times on sex hormones in male patients with T2DM

The FT and BT levels significantly differed between these groups ($P < 0.05$). The testosterone levels were higher in patients with less than 30 minutes of daily physical activity time, when compared to the other groups (**Table 4**).

Sex hormone levels in T2DM patients with different BMIs in the physical activity group

According to BMI, patients were subdivided, as follows: (1) Q1 (n=58), (2) Q2 (n=39), and (3) Q3 (n=27). The TT levels were sub-divided according to BMI. TT was highest in T2DM males with normal BMIs ($P < 0.01$). However, the LH and E2 levels significantly differed between these groups ($P < 0.01$), and there were no significant differences in FT, BT, FSH and SHBG levels (**Table 5**).

Discussion

Male gonadal dysfunction is common during T2DM [17]. The incidence of this dysfunction among DM patients influences the quality of life of afflicted patients [18]. Thus, the early identification of dysfunction and effective measures of intervention can improve the quality of life of these patients. At present, the treatment of male gonadal dysfunctions remains limited, and testosterone substitution is one of the intervention strategies [19]. However, testosterone replacement treatment should be preceded by a prior examination of prostate cancer, and the risks of adverse effects of testosterone should be evaluated before initiating the treatment [20]. At present, large sample size studies are still needed to clarify the benefits and risks of testosterone substitution [21]. Studies in obese mice have revealed that long-term moderate-intensity physical activity can improve the negative effects of obesity on sexual development, and increase testosterone levels in mice [22]. A meta-analysis revealed that aerobic training

Table 5. Sex hormone levels in T2DM patients with different BMIs in the physical activity group

Group	Q1	Q2	Q3	χ^2/F	*P-value*
n	58	39	27		
TT (nmol/L)	14.73	13.40	12.32	9.556	0.008
FT	0.30	0.31	0.29	0.586	0.746
BT	6.59	7.05	7.04	0.310	0.856
LH (mIU/L)	6.57	5.63	4.24	13.321	0.001
FSH (mIU/L)	6.55	5.54	4.59	5.379	0.068
E2 (pmol/L)	91.44±31.73	88.16±38.21	107.79±42.64	3.749	0.026
SHBG (nmol/L)	31.03	23.31	20.06	21.740	< 0.001

Data: mean ± SD or median. TT: total testosterone; BT: bioactive testosterone; FT: free testosterone; LH: luteinizing hormone; FSH: follicle-stimulating hormone; E2: estradiol; SHBG: sex hormone-binding globulin.

and interval training can improve basal testosterone levels [23].

Therefore, the investigators attempted to observe the effect of physical activity on testosterone levels among male patients with T2DM. A total of 159 male patients with T2DM were investigated, which included 124 patients who engaged in regular physical activity and 35 patients who did not do any physical activity. It was found that the levels of TT and BT were significantly higher in patients who engaged in physical activity for a longer period of time. Furthermore, FT and BT levels were higher in patients with less than 30 minutes of daily physical activity *vs*. other groups. Thus, physical activity increases testosterone levels [24]. The proposed mechanism may be as follows: physical activity stimulates the sympathetic system, and the secretion of gonads is associated with the sympathetic nerves [25]. That is, sympathetic stimulation occurs with physical activity, and leads to the increase in gonadal hormone secretion [26]. At the same time, testosterone stimulates the synthesis of protein in the body [27], which leads to muscle hypertrophy and the improvement of motor ability [28].

In the present study, it was found that according to the length of different physical activity times, male patients with T2DM had significant differences in HOMA-IR levels. These levels were lower among those who did physical activity for 30-60 minutes daily, indicating that moderate physical activity can improve insulin resistance. Researchers, such as Kim [29], also reported similar results. That is, six weeks of combined exercise was effective in improving fitness and HOMA-IR in T2DM patients. Another study also concluded that decreased testosterone levels were closely correlated with insulin resistance and hyperglycemia [30]. The skeletal muscle is an important site of insulin resistance manifestations [31], muscle cell mitochondrial dysfunction, intracellular glycerol and ceramide accumulation, as well as excessive reactive oxygen generation and other damages to insulin cascade signals [32]. Physical activity can enhance the synthesis and oxidation ability of muscle cell mitochondria [33], adjust the fission and fusion of mitochondria [34], and increase the insulin-mediated glucose intake of skeletal muscles [35], thereby improving insulin resistance. As a result, it was speculated that moderate physical activity may inhibit decreased testosterone levels, and thereby improve insulin resistance in the body.

The present study also revealed that T2DM male patients with a BMI of < 25 kg/m^2 in the physical activity group had significantly higher levels of TT *vs.* overweight patients. Estradiol levels also increased in patients with a high BMI, and this is consistent with previous studies, in which testosterone levels were shown to significantly decrease in obese patients [36]. First, obesity results in the dysfunction of the hypothalamus-pituitary-gonadal axis [37]. Second, obesity causes the accumulation of white fat in the body [38]. These fat cells produce excessive aromatic enzymes, which result in the conversion of testosterone into estradiol, and the further increase in estradiol can inhibit the function of the gonadal axis, and reduce the synthesis and secretion of testosterone [39]. Third, leptin levels are altered among obese patients [40]. Leptin influences the release of gonadotropin-releasing hormones (GnRh) from the hypothalamus, which affects the synthesis of testosterone and decreases androgen secretion [41]. In addition, the present results revealed that serum SHBG levels decreased in obese patients. It has been proposed that hyperinsulinemia and insulin resistance inhibit the formation of SHBG [42]. Thus, it can be assumed that physical activity improves gonadal function by reducing weight, increasing insulin sensitivity, and promoting the synthesis and secretion of testosterone and SHBG levels.

In the present study, no positive effects in physical activity on blood glucose or glycated hemoglobin were observed in T2DM patients, which differed from the findings of Liu *et al.* [43]. The small sample size and use of hypoglycemic drugs may have contributed to these discrepancies. The present study was a single-center study with 159 patients, and the effects on gonadal dysfunction were only dependent on TT levels, without the consideration of clinical symptoms. The limitations of the present study include the following: the patients were mainly engaged in aerobic physical activity alone, and it was not determined whether other forms of physical activity have any distinct influence on hormone levels; the glucose metabolism was not monitored. Studies with a larger sample size can help to better analyze the association among physical activity, gonadal hormone levels and glycemic control.

Conclusion

Physical activity improves the testosterone levels in male patients with T2DM. Testosterone levels are higher in patients engaged in daily physical activity for less than 30 minutes *vs.* other groups. Furthermore, testosterone levels are significantly higher in patients engaged in physical activity with normal BMI *vs.* obese patients. These results show that regular physical activity can help in improving the testosterone levels of men with T2DM and normal BMI.

Acknowledgements

The authors gratefully acknowledge the grand support of the Jiangsu Province Chinese Medicine Bureau Science and Technology Project (Grant no. FY201808). This present work was also supported by grants from the National Natural Science Foundation of China (No. 81870542; No.81603585).

Disclosure of conflict of interest

None.

Abbreviations

T2DM, Type-2 diabetes mellitus; FBG, Fasting blood glucose; PBG, Postprandial blood sugar; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; HbA1c, Glycated hemoglobin; BUN, Urea nitrogen; Cr, Creatinine; TT, Total testosterone; LH, Luteinizing hormone; FSH, Follicle-stimulating hormone; E2, Estradiol; SHBG, Sex hormone-blinding globulin; FINS, Fasting insulin; BT, Bioactive testosterone; FT, Free testosterone; HOMA-IR, Homeostasis model assessment-insulin resistance index.

Address correspondence to: Kun Wang, Endocrinology Department, The Affiliated Jiangning Hospital of Nanjing Medical University, 169 Hu-shan Road, Jiangning District, Nanjing 211100, China. E-mail: goldinnanjing@163.com; Yaofu Fan, Endocrine and Diabetes Center, Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine, 8 Hua-Dian Road, Qixia District, Nanjing 210028, China. E-mail: fanyaofu2010@163.com

References

[1] American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes-Care 2004; 27 Suppl 1: s5-s10.
[2] Wang H and Lai Y. Urban-rural differences in diabetes in China. JAMA 2017; 317: 1688-1689.
[3] Bommer C, Heesemann E, Sagalova V, Manne-Goehler J, Atun R, Bärnighausen T and Vollmer S. The global economic burden of diabetes in adults aged 20-79 years: a cost-of-illness study. Lancet Diabetes Endocrinol 2017; 5: 423-430.
[4] Shigehara K, Konaka H, Kato Y, Lijima M, Nakashima K, Kawaguchi S, Nohara T, Lzumi K, Namiki M and Mizokami A. Effect of testosterone replacement therapy on sexual function and glycemic control among hypogonadal men with type 2 daibetes mellitus. Int J Impot Res 2019; 31: 25-30.
[5] Chen D, Cao S, Chang B, Ma T, Gao H, Tong Y, Li T, Han J and Yi X. Increasing hypothalamic nucleobindin 2 levels and decreasing hypothalamic inflammation in obese male mice via diet and exercies alleviate obesity-associated hypogonadism. Neuropeptides 2019; 74: 34-43.
[6] Cao W, Zheng RD, Xu SH, Fan YF, Sun HP and Liu C. Association between sex hormone and blood uric acid in male patients with type 2 diabetes. J Diabetes Res 2017; 2017: 4375253.

[7] Cao W, Zheng RD, Fan YF and Liu C. Correlation between testosterone and metabolic index in male patients with type 2 diabetes mellitus. Sichuan Da Xue Xue Bao Yi Xue Ban 2018; 49: 235-238.

[8] Litchfield I, Andrews RC, Narendran P and Greenfield S. Patient and healthcare professionals perspectives on the delivery of exercise education for patients with type 1 diabetes. Front Endocrinol (Lausanne) 2019; 10: 76.

[9] Chamberlain JJ, Johnson EL, Leal S, Rhinehart AS, Shubrook JH and Peterson L. Cardiovascular disease and risk management: review of the amercan diabetes association standards of medical care in diabetes 2018. Ann Intern Med 2018; 168: 640-650.

[10] Moran LJ, Noakes M, Clifton P, Buckley J, Brinkworth G, Thomson R and Norman RJ. Predictors of lifestyle intervention attrition or weight loss success in women with polycystic ovary syndrome who are overweight or obese. Nutrients 2019; 11: E492.

[11] Lwanoto J. Calcium and bone metabolism across women's life stages. Exercise and sport to increase bone strength in accordance with female lifecycle. Clin Calcium 2017; 27: 715-721.

[12] Hanssen H, Minghetti A, Faude O, Schmidt-Trucksäss A, Zahner L, Beck J and Donath L. Effects of endurance exercise modalities on arterial stiffness in patients suffering from unipolar depression: a randomized controlled trial. Front Psychiatry 2018; 8: 311.

[13] Niederberger C. Re: effects of clomiphene citrate on male obesity-associated hypogonadism. J Urol 2019; 201: 427-428.

[14] Contreras PH, Serrano FG, Salgado AM and Vigil P. Insulin sensitivity and testicular function in a cohort of adult males suspected of being insulin-resistant. Front Med (Lausanne) 2018; 5: 190.

[15] Baillot A, Vibarel-Rebot N, Amiot V, Emy P and Collomp K. Effects of an 8-week aerobic exercise training on saliva steroid hormones, physical capacity, and quality of life in diabetic obese men. Horm Metab Res 2012; 44: 146-151.

[16] American Diabetes Association. Classification and diagnosis of diabetes: standards of medical care in diabetes-2018. Diabetes Care 2018; 41 Suppl 1: S13-S27.

[17] Yassin A, Haider A, Haider KS, Caliber M, Doros G, Saad F and Garvey WT. Testosterone therapy in men with hypogonadism prevents progression from prediabetes to type 2 diabetes: eight-year data from a registry study. Diabetes Care 2019; 42: 1104-1111.

[18] Herrero A, Marcos M, Galindo P, Miralles JM and Corrales JJ. Clinical and biochemical correlates of male hypogonadism in type 2 diabetes. Andrology 2018; 6: 58-63.

[19] Saad F, Caliber M, Doros G, Haider KS and Haider A. Long-term treatment with testosterone undercanoate injections in men with hypogonadism alleviates erectile dysfunction and reduces risk of major adverse cardiovascular events, prostate cancer, and mortality. Aging Male 2019; 20: 1-12.

[20] Elliott J, Kelly SE, Millar AC, Peterson J, Chen L, Johnston A, Kotb A, Skidmore B, Bai Z, Mamdani M and Wells GA. Testosterone therapy in hypogonadal men: a systematic review and network meta-analysis. BMJ Open 2017; 7: e015284.

[21] Fink J, Matsumoto M and Tamura Y. Potential application of testosterone replacement therapy as treatment for obesity and type 2 diabetes in men. Steroids 2018; 138: 161-166.

[22] Wang JM, Gong TY and Zhao ZJ. Effects of exercise on sex hormones and expression of relevant genes in the hypothalamus in obese mice. J Biol Regul Homeost Agents 2019; 33: 517-523.

[23] Hayes LD and Elliott BT. Short-Term exercise training inconsistently influences basal testosterone in older men: a systematic review and meta-analysis. Front Physiol 2019; 9: 1878.

[24] Zekarias K and Shrestha RT. Role relative malnutrition in exercise hypogonadal male condition. Med Sci Sports Exerc 2019; 51: 234-236.

[25] Espinoza JA, Alvarado W, Venegas B, Dominguez R and Morales-Ledesma L. Pharmacological sympathetic denervation prevents the development of polycystic ovarian syndrome in rats injected with estradiol valerate. Reprod Biol Endocrinol 2018; 16: 86.

[26] Dos Santos MR, Sayegh AL, Bacurau AV, Arap MA, Brum PC, Pereira RM, Takayama L, Barretto AC, Negrão CE and Alves MJ. Effect of exercise training and testosterone replacement on skeletal muscle wasting in patients with heart failure with testosterone deficiency. Mayo Clin Proc 2016; 91: 575-86.

[27] Lam T, Poljak A, Mclean M, Bahl N, Ho KKY and Birzniece V. Testosterone prevents protein loss via the hepatic urea cycle in human. Eur J Endocrinol 2017; 176: 489-496.

[28] Storer TW, Basaria S, Traustadottir T, Harman SM, Pencina K, Li Z, Travison TG, Miciek R, Tsitouras P, Hally K, Huang G and Bhasin S. Effects of testosterone supplementation for 3 years on muscle performance and physical function in older men. J Clin Endocrinol Metab 2017; 102: 583-593.

[29] Kim DI, Lee DH, Hong S, Jo SW, Won YS and Jeon JY. Six weeks of combined aerobic and resistance exercise using outdoor exercise machines improves fitness, insulin resistance,

and cheerin in the Korean elderly: a pilot randomized controlled trial. Arch Gerontol Geriatr 2018; 75: 59-64.

[30] Schianca GP, Fra GP, Brustia F, Bellan M, Pirovano A, Gualerzi A, Gentile M, Gibbin A, Menegatti M, Bartoli E and Pirisi M. Testosterone plasma concentration is associated with insulin resistance in male hypertensive patients. Exp Clin Endocrinol Diabetes 2017; 125: 171-175.

[31] Hirasawa Y, Matsuki R, Ebisu T, Kurose T, Hamamoto Y and Seino Y. Evaluation of skeletal muscle mass indices, assessed by bioelectrical impedance, as indicators of insulin resistance in patients with type 2 diabetes. J Phys Ther Sci 2019; 31: 190-194.

[32] Pattanakuhar S, Sutham W, Sripetchwandee J, Minta W, Mantor D, Palee S, Pratchayasakul W, Chattipakorn N and Chattipakorn SC. Combined exercise and calorie restriction therapies restore contractile and mitochondrial functions in skeletal muscle of obese-insulin resistant rats. Nutrition 2018; 62: 74-84.

[33] Fritzen AM, Thøgersen FB, Thybo K,Vissing CR, Krag TO, Ruiz-Ruiz C, Risom L, Wibrand F, Høeg LD, Kiens B, Duno M, Vissing J and Jeppesen TD. Adaptations in mitochondrial enzymatic activity occurs independent of genomic dosage in response to aerobic exercise training and deconditioning in human skeletal muscle. Cells 2019; 8: E237.

[34] Yoo SZ, No MH, Heo JW, Park DH, Kang JH, Kim JH, Seo DY, Han J, Jung SJ and Kwak HB. Effects of acute exercise on mitochondrial function, dynamics, and mitophagy in rat cardiac and skeletal muscles. Int Neurourol J 2019; 23 Suppl 1: S22-31.

[35] Sylow L, Kleinert M, Richter EA and Jensen TE. Exercise-stimulated glucose uptake-regulation and implications for glycaemic control. Nat Rev Endocrinol 2017; 13: 133-148.

[36] Zheng Rendong, Cao Lin, Cao Wen, Chu X, Hu Y, Zhang H, Xu J, Sun H, Bao W, Liu K and Liu C. Risk factors for hypogonadism in male patients with type 2 diabetes. J Diabetes Res 2016; 2016: 5162167.

[37] Kahn BE and Brannigan RE. Obesity and male infertility. Curr Opin Urol 2017; 27: 441-445.

[38] Giolo De Carvalho F and Sparks LM. Targeting white adipose tissue with exercise or bariatric surgery as therapeutic strategies in obesity. Biology (Basel) 2019; 8: E16.

[39] Xu X, Wang L, Luo D, Zhang M, Chen S, Wang Y, Zheng D, Feng L, Gao L, Yu C and Guan Q. Effect of testosterone synthesis and conversion on serum testosterone levels in obese men. Horm Metab Res 2018; 50: 661-670.

[40] Foglesong G, Queen N, Huang W, Widstrom KJ and Cao L. Enriched environment inhibits breast cancer progression in obese models with intact leptin signaling. Endocr Relat Cancer 2019; 26: 483-495.

[41] Abuzzahab MJ, Roth CL and Shoemaker AH. Hypothalamic obesity: prologue and promise. Horm Res Paediatr 2019; 18: 1-9.

[42] Amjad S, Baig M, Zahid N, Tarig S and Rehman R. Association between leptin, obesity, hormonal interplay and male infertility. Andrologia 2019; 51: e13147.

[43] Liu Y, Ye W, Chen Q, Zhang Y, Kuo CH and Korivi M. Resistance exercise intensity is correlated with attenuation of HbA1c and insulin in patients with type 2 daibetes: a systematic review and meta-analysis. Int J Environ Res Public Health 2019; 16: E140.