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Title Page

The effects of different types of exercise on circulating irisin levels in healthy individuals and in people with overweight, metabolic syndrome and type 2 diabetes

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Short title: Effect of physical training on irisin concentration

SUMMARY

Irisin is a myokine secreted during exercise. It has drawn the attention of researchers as it regulates several effects of exercise that are considered beneficial. It has also been proposed as a therapeutic tool to treat metabolic disorders. In recent years, the effect of different types of training on circulating irisin has been studied in large populations. An overall beneficial result has been shown, however, the outcome of the investigations has raised some controversy. Herein we evaluated the existing literature on the effects of different types of training on the circulating irisin levels in healthy subjects and in those displaying different metabolic condition. We conducted queries in the PubMed and Web of Science databases for literature published between January 2010 and January 2021. Thirty-seven original articles were retrieved and they were included in this review. Any letter to the editor, meta-analyses, reviews, and systematic review articles were excluded. From these 37 articles, 19 of them reported increased levels of circulating irisin. The interventions encompassed aerobic, resistance, combined, circuit, and interval training types. Such increase of circulating irisin was reported for healthy subjects and for those displaying different metabolic condition. A training that is steadily kept with a moderate to high intensity, including that characterized by brief highly intense intervals, were distinguishable from the rest. Nevertheless, the training effectiveness as evaluated by the increased circulating irisin levels depends on the subject's metabolic condition and age.

Key words

Exercise

FNDC5

Metabolic Syndrome

Obesity

Type 2 Diabetes

Introduction

Irisin has acquired some relevance in research studies as it may represent a therapeutic target in the context of disorders such as obesity and impaired glucose metabolism.

Irisin is a polypeptide hormone secreted by skeletal muscle cells derived from the FNDC5 gene (Fibronectin Type III Domain-Containing 5). It is induced by the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) [1] and it is released during exercise. Irisin immediately enters into the circulatory system and into some organs. Studies conducted in murine models identified that irisin is associated with a higher energy expenditure because of its ability to stimulate the browning of the white adipose tissue, to regulate glucose uptake, to increase lipolysis, and to decrease lipid accumulation. In the muscle of diabetic mice, irisin stimulates glucose uptake and it down-regulates gluconeogenesis and glycogenolysis [2]. It has been reported that irisin is positively correlated with insulin sensitivity and weight loss, and its circulating levels increase with training [3].

In murine models it has been observed that PGC1α stimulates the expression of FNDC5 and it promotes irisin release in the muscle during exercise [2]. Furthermore, an intracellular muscle ATP deprivation triggers FNDC5 synthesis and consequently the release of irisin. After reviewing the physiology and the role of irisin in glucose homeostasis, Perakakis et al. (2017) suggested that the duration of exercise may be important to observe increased irisin levels [2]. It has been reported that different types of training, such as aerobic [3-8], resistance [9-11], combined [8,12-15], circuits [16-18] and intervals [19,20] stimulate higher circulating irisin concentrations.

The latter effect of physical training on circulating irisin concentration is contradictory [4,11,12,21-23]. It has been suggested that such differences may be caused by the variable metabolic condition of the subjects, the method used to assess irisin concentration, and the type of training [24]. The purpose of this review was to evaluate the existing literature regarding the effects of different types of training on the circulating irisin levels in healthy subjects and in those displaying different metabolic condition, i.e., overweight, insulin resistance and MetSx (Metabolic Syndrome).

Methods

Research design

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) items were used to prepare this review.

Inclusion and exclusion criteria

The inclusion criteria were the following: original studies, those characterized by a longitudinal design regarding the physical training intervention, those published in English language after the year 2010, those where the target populations were healthy participants or diagnosed with overweight/obesity, type 2 diabetes mellitus (T2D), or MetSx. The following were excluded: studies conducted in animals, those where the participants displayed kidney or lung diseases, multiple sclerosis, hemodialysis, hypothyroidism, or pregnancy, those with interventions conducted in water, with cryostimulation or in controlled oxygen and/or temperature environments, including interventions where the participants followed a controlled diet in combination with training.

Search strategy and study selection

Queries were conducted in the following electronic databases between January 2020 and February 2021: PubMed and Web of Science. The search terms were designed to include the hormone's name ("irisin") and the type of training intervention ("aerobic", "endurance", "resistance", "concurrent", "combined", "HIIT", "High Intensity Interval Training", "SIT", "Sprint Interval Training", "program"," exercise" and "training"). Only full-text articles that met the inclusion criteria were retrieved.

Results

A total of 506 articles were identified. Duplicates were eliminated, then the titles and abstracts of 146 articles were examined. Of these, 109 were excluded and finally 37 full-text articles met the inclusion criteria. The flow of studies and the reasons for exclusion at each stage are summarized in a PRISMA diagram (Fig. 1).

Among the 37 articles, and in those where aerobic training was reported: eight included a healthy population and seven contemplated a population displaying different metabolic condition. Those where resistance training was reported: 10 included a healthy population and five studied a population displaying different metabolic condition; 12 articles were focused on combined training, four of them on a healthy population and eight on a population displaying different metabolic condition. Three articles dealt with circuit trainin using a healthy population and six articles contemplated interval training: four of them focused on a healthy population and two were focused on those displaying a different metabolic condition.

Subject features, their metabolic condition, and the interventions are shown in **Table 1**.

Discussion

Effect of aerobic training on irisin concentration in healthy subjects and in those displaying different metabolic condition

Eight interventions consisting of aerobic training by a healthy population were analyzed. In three of these studies, an increased irisin concentration was observed [3-5]. Sedentary and moderately active males and/or females, ages between 59 and 75 years old, were included in these studies. After performing training for 6-10 weeks, either by cycling or walking, with an intensity between 50 and 75% of the maximum heart rate (HRmax), 3-5 times a week, circulating irisin levels increased in the 14.0 – 83.0% range.

Increased irisin levels were also observed in the population displaying different metabolic condition: in three of the seven interventions evaluated [6-8]. Sedentary males and/or females with ages between 24 and 61 years old, that exhibited overweight, obesity, or those with MetSx were contemplated for these interventions. After 12 weeks of cycling, Nordic walking, regular walking, or running, with an intensity of 55-80% of the HRmax, 3 times/week, circulating irisin level increased in the 5.72-14.3% range.

The circulating irisin levels did not change in the rest of these studies, either in the healthy population [6,23,25-28] or in the population displaying overweight, obesity, MetSx or T2D [6,11,28-30] (Table 1). It is noteworthy that such studies that failed to report increased irisin levels were characterized by including younger subjects, even children.

Therefore, it may be stated that aerobic training promoted increased irisin circulating levels in a population of healthy adults and older adults, with an intensity of 50-75% of the HRmax, and a 3-5 times/week frequency. Such an increase was observed when the blood sample was obtained between the weeks 6 and 10 of the training. When the overweighted/obese population (either with or without MetSx) was considered, a greater training intensity (55-82% of the HRmax) was required to attain an increase. In this case, the increase was observed at the week 12 of the training.

Effect of resistance training on irisin concentration in healthy subjects and in those displaying a different metabolic condition

Two [9,10] of the10 analyzed articles reported an increased irisin concentration (Table 1). The subjects in these interventions were healthy men or women, older than 62 years old. All

subjects trained the main body muscles for 12 weeks with a light intensity, 2 times/week. In this case, the irisin concentration increased in the 22.5-93.7% range.

In the population displaying different metabolic condition, only one of five articles reported an increased circulating irisin levels [11]. Overweighted or obese 25.8-year-old male and female subjects entered the study and they trained the body main muscles for 8 weeks with an intensity between 65 and 80% 1RM, 5 days/week. In this case the circulating irisin levels increased by 18.3%.

Conversely, three interventions were analyzed [21,22,31] where circulating irisin levels significantly decreased (Table 1). Sedentary women of ages between 21 and > 60 years old were included in these trials. The subjects trained the main body muscles during 8-16 weeks with a 40-90% intensity 1RM, 2-3 times/week. Circulating irisin concentration decreased within a 5.4-34.3% range. However, the results were a function of the metabolic condition, the intensity, and periodization. The intervention studied by Tibana et al. (2017) a decreased irisin concentration was observed only for the non-obese women group, whereas the obese women group showed no change [22]. The training program established by Moienneia et al. (2016), induced a decrease of irisin concentration that was detected only for the group that trained between 70-90% of 1RM when compared to the group that trained at low intensity, where no changes were observed [21]. Finally, the intervention performed by Prestes et al. (2015) the group that trained with a linear periodization displayed lower levels of irisin, and the group that trained with undulating periodization showed no changes [31]. It is important to highlight that the main difference between the above three studies and those that report increased irisin levels in healthy populations is the intensity of training. Higher irisin levels were reported in studies where training intensity was light [9,10], whereas those studies that reported decreased irisin concentrations, the training was between moderately and highly intense.

The rest of the studies observed no significant changes regarding circulating irisin levels in healthy subjects [21,23,26,31-34] or in those displaying overweight, obesity or MetSx [7,8,22,30] (Table 1). The most striking aspect of these studies are the inclusion of trained younger subjects, even elite athletes, as well as the training period: 8 weeks or more than 24 weeks.

Therefore, healthy adults with older ages that trained with a light intensity 2 times/week, the increased irisin concentrations appeared within 12 weeks of a resistance training. For the overweight/obese younger population, a more intense training with higher frequency was necessary to attain such increase, however, this effect may be observed from the week 8.

Effect of combined training on irisin concentration in healthy subjects and those displaying different metabolic condition

Five interventions where a healthy population was submitted to combined training were analyzed. Two of such studies showed increased irisin concentrations [12,13]. These levels increased in a 4.3-65.4% range for sedentary and active men and women, with ages between 25-65 years, when they performed aerobic or resistance training for 10-12 weeks combined with a high-intensity interval training (HIIT) with a 95-98% intensity of the HRmax (aerobic), 40-85% 1RM (resistance), and 85 to > 90% of the HRmax (HIIT).

Increased irisin concentrations were also observed in three of eight interventions that considered a population displaying different metabolic condition [8,14,15]. Such studies included male and/or female subjects with ages between 7 and 61 years, affected by obesity or T2D, or showing overweight/obesity and MetSx. Irisin levels increased in a 9.6-22.2% range after performing 12-48 weeks of resistance training combined with HIIT or aerobic training with a 40-80% intensity of 1RM (resistance), 40-95% of the HRmax (HIIT) and 60-75% of the HRmax (aerobic), 2-3 times/week.

Conversely, irisin levels decreased in one intervention that contemplated a healthy population [26]. Irisin concentration decreased by 12.7% in women with ages 26.60 ± 4.00 years, and untrained, after they performed 8 weeks of aerobic training combined with resistance training, with a 55-75% intensity of the HR_{max} and 55-75% 1RM, respectively, 3 times/week. All other studies showed no change of circulating irisin levels in neither the healthy population [13,27] or those displaying overweight, obesity, MetSx or T2D [30,35-38] (Table 1).

Of note, HIIT has an important role to increase irisin concentration in a healthy population. However, the greatest increase was observed when HIIT and resistance training were combined. This was also observed for the T2D population. Additionally, aerobic combined with resistance training was also effective to induce a rise in irisin levels for subjects displaying obesity or MetSx.

Effect of circuit training on irisin concentration in healthy subjects and in those displaying different metabolic condition

Three interventions were analyzed where circuit training was performed. Increased irisin levels were detected in these studies [17,18]. An increase within the 4.1-34.0%. range was observed for female subjects with ages between 26 and 60 years. They were not active or sedentary postmenopausal. After performing a training for 5-8 weeks: either 1 or 3 circuits that combined aerobic and muscle-strengthening training with an 80-90% intensity of the HRmax or resistance training only with a 55% intensity of 1 RM, 3 times/week. The irisin increase depended on the assessed VO_{2max} (Maximal Oxygen Uptake) values [17] or if they were older than 30 years [18]. Therefore the same training program induced a 10.0% decrease of irisin levels in younger subjects < 30 years old [18].

It is noteworthy that only 5 weeks were sufficient to detect increased irisin levels. However, more studies are required where this type of training is executed. Such trials should also include both sexes and a population displaying metabolic disorders.

Effect of interval training on the irisin concentration in healthy subjects and I those displaying different metabolic condition

Four interventions were analyzed where an interval training was performed by a healthy population. An increase of irisin concentration was detected in two of these studies [19,20]. Male or female subjects with ages between 23 and 38 years, characterized by performing low physical activity, were included in this study. Irisin levels increased within a 22.3-29.7% range after performing bicycle or resistance training for 3-8 weeks with a maximum effort, 2-3 times/week.

Increased irisin levels were also observed in a population with T2D. In one of the two analyzed interventions [29], circulating irisin levels increased by 7.0% in male and female subjects with ages of 59.6±5.7 years, and after performing a training on a cycle ergometer for 4 weeks with a 70-95% intensity of the HRmax, 3 times/week.

On the other hand, irisin levels decreased in a healthy population as reported in three of the analyzed interventions [19,39,40]. Irisin decreased within a 19.2-38.6% range in physically active male subjects, ages between 13 and 25 years, after they performed a training on a cycle ergometer or if they practiced basketball for 3-8 weeks with a maximum effort.

However, another study reported unmodified circulating irisin levels in a population displaying T2D [38].

Regarding interval training it is important to note that changes in circulating irisin concentrations were reported right from week 3. Although some authors indicate that higher irisin levels depend on sex [19], Scalzo et al. (2014) [19] reported that a interval training program induced higher irisin levels in young females whereas it triggered a decreased in males. This agrees with other studies that showed that irisin levels depend on sex [41,42]. Consequently, more studies are needed to understand this aspect.

General focus points

Huh et al. (2014) suggest that irisin secretion is independent of age and the level of physical conditioning [43]. However, increased circulating irisin levels were reported, especially in the adult population and it is generally observed that this myokine increases mainly in sedentary participants or in those exhibiting a low conditioning level.

Low ATP levels and/or increased phosphate (Pi) or adenosine diphosphate levels promote irisin release, thus ATP homeostasis is restored in working muscle [44]. Consequently, as physical conditioning improves, ATP levels remains steady and circulating irisin does not increase. This suggests that the lower irisin level observed in active subjects is the consequence of an adaptive response towards a greater muscle capacity. This may explain why circulating irisin levels did not increase in active subjects or when it is measured after 12 weeks of training, scenarios where an improved muscle capacity is possible. It is probable that irisin concentration increased when the interventions entailing long periods of training were performed, although it was not timely detected. However, Blüher et al (2014) [14] reported a 12.0% increase in circulating irisin levels after 48 weeks of combined training. It is possible that this increase may be a consequence of studying only a pediatric population, although the authors ruled out that the increase was exclusively caused by age.

Furthermore, a few weeks of training may not be sufficient to attain a muscle adaptation with a measurable increase of irisin. In fact, it has been observed that additional weeks or a higher frequency of aerobic resistance or combined training are needed to increase irisin levels in a population displaying a different metabolic condition. Although, if circuit and interval training is performed, only 5 and 3 weeks, respectively, were enough to observe an increase of irisin. It is also important to note that the irisin increase observed in combined

training was mainly observed when a HIIT was implemented. These types of training are distinguishable because of their high and/or sustained intensity. This may be a key variable as previous articles have reported that a greater increase of irisin was attainable only when the intensity of aerobic exercise was higher [45-47]. Additionally, it has been reported that a HIIT produces beneficial effects as it promotes increased concentrations of circulating irisin [20], and those subjects that perform a HIIT may obtain a benefit on their body composition [48]. It is important to note that benefits may be achieved in less time by performing a HIIT than when medium or low-intensity training is implemented [49].

Moreover, some authors indicate that a higher volume of intervals entails more benefits for glucose metabolism in patients with prediabetes when compared to lower volumes and it is more useful to achieve a glycemic control [50]. This was demonstrated in subjects with T2D; as increased circulating irisin levels were reported in one study when a high volume training was performed [29], whereas in another study irisin remained unchanged after a low volume training [38] (Table 1).

Studies have shown that irisin significantly increases within the first 120 min after an exercise load [27,37,45,51,52] and it decreases after 180 min [53]. A little more than 50% of the studies analyzed herein that reported increased circulating irisin levels, they established a sampling ≥ 24 h after the last exercise load. The increased irisin levels reported by these studies is between 4 and 65%. All other studies indicate that a final sample was taken right after the training period without specifying the time elapsed after the last exercise load. However, the increase extent they reported is similar to those studies that did report a sampling time. Nevertheless, those studies that described 83 and 93.7% increases of circulating irisin after the training program [3,9] do not specify a sampling time. This aspect that may cause a certain degree of heterogeneity regarding the results.

Finally, it is necessary to emphasize the role of the enzymatic assay kit used to quantify irisin levels. Although the Phoenix Pharmaceuticals kit was used in most of the studies and this kit has been previously validated by several researchers [54-56], the different kit brands may have an important role and in part this may explain the differences observed between the analyzed studies. Each one has a different sensitivity, detection range, and precision. It is important that future research should be focused on kit to be used to assess irisin levels as well as the sampling time.

Conclusions

The results indicate that all the types of training increase circulating irisin levels. However, the results may depend on the subjects' features, such as metabolic condition and age. Generally, training increases irisin concentration in a population of healthy adults and old people, whereas the increase is evident in population of young adults with overweight, obesity or T2D. Furthermore, in this population requires a greater intensity and a longer period of aerobic, resistance or combined training. Although generally the effect of the different types of training on the circulating irisin levels does not depend on sex, some results show sex-dependent changes in irisin levels. This deserver further investigation.

Certainly, the type of training plays a key role regarding the changes of circulating irisin. In this context, a training in which a moderately-highly intense is maintained and those routines characterized by high-intensity intervals are noteworthy.

Declaration of competing interest

The authors declare no conflicts of interest relevant to this article

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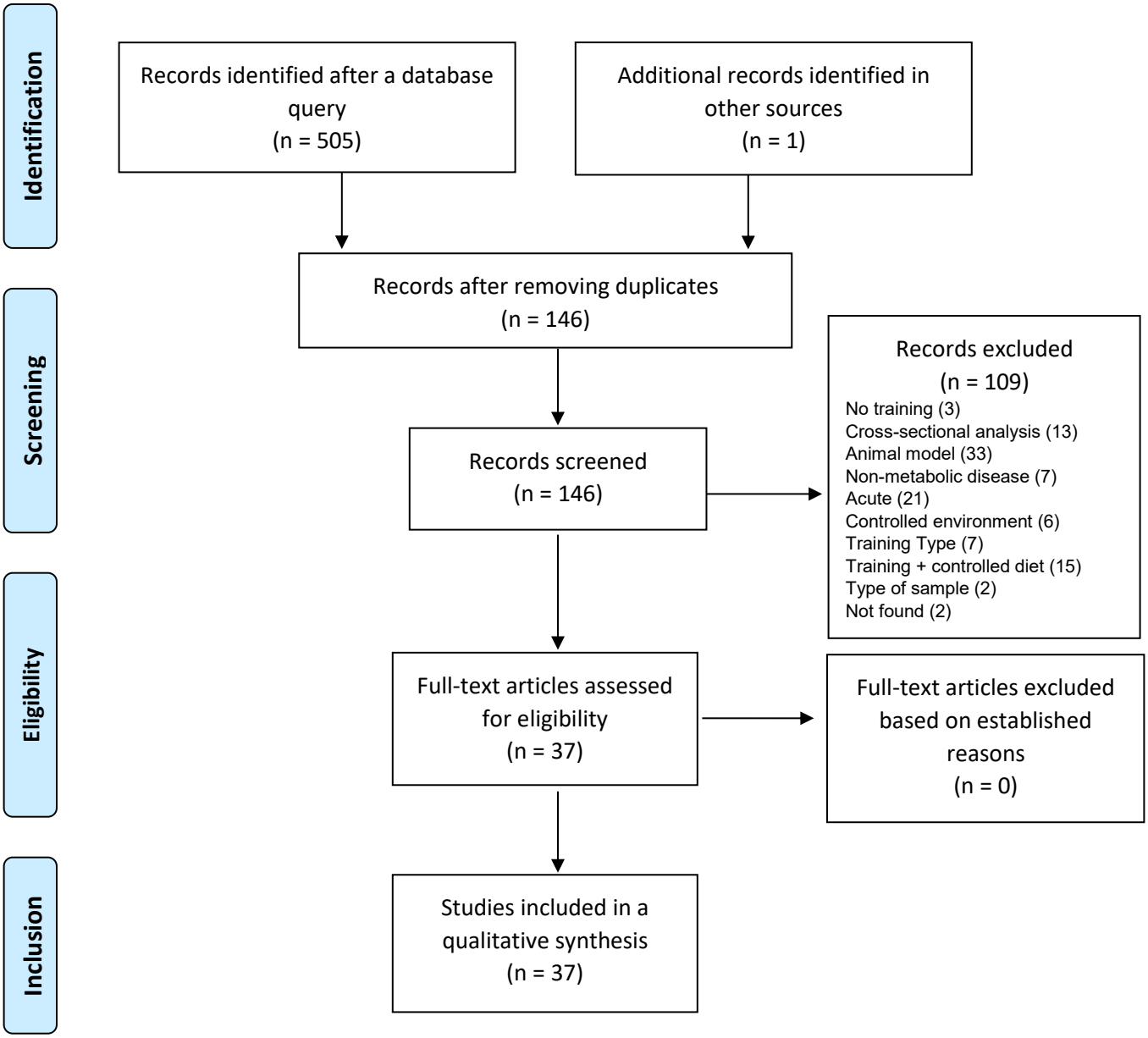

Figure 1: PRISMA flow diagram

Table 1. Subject features and details on the interventions

Training Type	Population	Training protocol	Sampling time	Irisin concentration	Irisin assay kit (Sample)
Aerobic					
Miyamoto-Mikami et al, (2015) [4]	25 young (9 females, 16 males) and 28 middle-aged/older adults (16 females, 12 males) sedentary or moderately active healthy subjects Age: 21 ± 1 67 ± 8 years	**M:** cycling on a leg ergometer **F:** 3 times/wk **D:** 55 min **I:** 70% VO_{2peak} **T:** 8 wks	At the baseline and at the end of the study period. Samples were drawn at least after a 48 h rest following the last exercise-training session	Middle-age/older adults cohort ↑ (19.9%)	ELISA kit (EK-067-16 Phoenix Pharmaceuticals, Burlingame, CA, USA) (Serum)
Hew-Butler et al, (2015) [25]	7 healthy non-runner women Age: 23.4 ± 6.9 years	**M:** walking/running **F:** 3 times/wk **D:** 20-30 min **I:** As the weeks elapsed, the running time gradually increased whereas the walking time decreased **T:** 10 wks	At the baseline and after the intervention	=	ELISA kit (EK-067-29 Phoenix Pharmaceuticals, Burlingame, CA) (Plasma)
Shabani et al, (2018) [26]	9 untrained healthy women Age: 24.66 ± 2.29 years	**M:** aerobic step training and running **F:** 3 times/wk **D:** 65 min **I:** 55-75% of the age-predicted HR_{max} **T:** 8 wks	At the baseline and after the exercise program	=	ELISA kit (ZellBio GmbH, Ulm, Germany) (Serum)
Böstrom et al, (2012) [3]	8 non-diabetic adult males Age: NS	**M:** cycling on stationary bikes **F:** 4-5 times/wk **D:** 20-30 min/wk **I:** ~ 65% VO_2max **T:** 10 wks	At the baseline and after 10 weeks	↑ (83.0%)	BCA-kit (Thermo Scientific) (Plasma)
Hecksteden et al, (2013) [23]	23 sedentary healthy subjects (15 females, 8 males) Age: 30-60 years	**M:** walking/running **F:** 3 times/wk **D:** 45 min **I:** 60% HR_{max} **T:** 26 wks	At the baseline and 2-7 days after the final training bout	=	ELISA kit (Phoenix Pharmaceuticals, Burlingame, CA, USA) (Serum)
Pekkala et al, (2013) [27]	9 sedentary healthy males. Age: 57 ±7 years	**M:** cycle ergometer **F:** 2 times/wk **D:** 30-90 min **I:** <75% - >90% HR_{max} **T:** 21 wks	At the baseline and 3 h post-exercise	=	EIA kit (Phoenix Pharmaceuticals, Inc., Burlingame, CA, USA) (Serum)

Kim et al, (2020) [5]	25 menopausal women Age: 60.28± 5.30 years	**M:** walking **F:** 3 times/wk **D:** 60 min **I:** 50-60% HR_{max} **T:** 6 wks	At baseline and after the exercise program	↑ (14.07%)	ELISA kit (BioVendor, Brno, Czech) (Plasma)
Otero-Díaz et al, (2018) [6]	33 sedentary healthy subjects: 13 with normal weight, 10 overweighted and 10 obese subjects (19 females, 14 males) Age: 30.4 ± 4.6 years	**M:** bicycle **F:** 3 times/wk **D:** 60 min **I:** 60-80% age-predicted HR_{max} **T:** 12 wks	At the baseline and after the exercise program	Normal weight group = Obesity group = Overweight group ↑ (5.72%)	ELISA kit (EK-067-29, Phoenix Pharmaceuticals, Burlingame, CA, United States) (Plasma)
Kim et al, (2016) [11]	10 sedentary obese/overweighted subjects (4 females, 6 males) Age: 19-35 years	**M:** cycling and treadmill mountain climber **F:** 5 times/wk **D:** 60 min **I:** 65-80% HR_{max} **T:** 8 wks	At the baseline and after 2 days of minimal physical activity	=	ELISA kit (Phoenix Pharmaceuticals, CA, USA), EK-067-16 (Plasma)
Korkmaz et al, (2018) [7]	39 overweighted/obese males Age:40-65 years	**M:** nordic walking **F:** 3 times/wk **D:** 60 min **I:** 55-75% HRR **T:** 12 wks	At the baseline and after the intervention	↑ (14.3%)	ELISA kit (EK-067–52 Phoenix Pharmaceuticals, Burlingame, California, USA) (Plasma)
Palacios-González et al, (2015) [28]	37 children with normal weight (10 female, 27 male) Age: 9.0 ± 0.86 years 25 obese children (15 females, 10 males) Age: 8.8 ± 0.86 years and 23 overweighted children (3 females, 20 male) Age: 9.5 ± 0.74 years	**M:** walking/running **F:** 5 times/wk **D:** 30 min **I:** <70% HR_{max} **T:** 32 wks	At the baseline and after the intervention	=	ELISA kit (CUSABIO BIOTECH) (Serum)
Dünnwald et al, (2019) [29]	6 subjects with T2D (2 females, 4 males) Age: 59.5 ± 6.0 years	**M:** cycle ergometer **F:** 3 times/wk **D:** 50.3 min **I:** 70% HR_{max} **T:** 4 wks	At the baseline and one day after the exercise intervention	=	ELISA kit (Biovendor R&D, BioVendor – Laboratorní Medicína a.s, Brno, Czech Republic) (Plasma)

Amanat et al, (2020) [8]	14 overweighted/obese women with metabolic syndrome Age: 54.5 ± 6.9 years	**M:** running on treadmill, stretching exercises, treadmill walking, stationary cycling and balance exercises **F:** 3 times/wk **D:** 60 min **I:** 60-75% age-predicted HR_{max} **T:** 12 wks	At the baseline and 24 h after the last intervention	↑ (6.8%)	ELISA kit (Phoenix Pharmaceuticals, Burlingame, USA) (Serum)
Dianatinasab et al, (2020) [30]	13 overweighted women with metabolic syndrome Age: 53.43 ± 6.53 years	**M:** running in treadmill **F:** 3 times/wk **D:** 60 min **I:** 60–75% HR_{max} **T:** 8 wks	At the baseline and 24 h after the last exercise of intervention	=	ELISA kit (Phoenix Pharmaceuticals, Burlingame, USA) (Serum)
Resistance					
Zhao et al, (2017) [9]	10 older adults (healthy males) Age: 62.3 ± 3.5 years	**M:** abdominal, hip flexor/extensor, back extensor muscles, leg press and knee extension **F:** 2 times/wk **D:** 55 min **I:** NS **T:** 12 wks	At the baseline and after the 12 wks of intervention	↑ (93.7%)	ELISA kit (BioVendor-Laboratomi Medicina, Karasek, Crech Republic) (Serum)
Bang et al, (2014) [32]	7 trained men Age: 28.71 ± 5.76 years	**M:** chin-up, lateral pull-down, bent over/up-right row, bench press, fly, cable cross-over, shoulder press, lateral raise, biceps curl, concentration curl, barbell elbow extension, kick back, squat, leg extension, leg press, sissy squat, leg curl, dead lift, stiff leg dead lift, lunges, back extension, seated/standing calf raise, sit-up, and abdominal crunch **F:** 6 times/wk **D:** 5 sets of 10-15 reps **I:** 60-80% 1RM **T:** 8 wks	At the baseline and after the exercise program	=	ELISA kit (Phoenix Pharmaceuticals, Inc., Burlingame, CA, USA) (Serum)
Shabani et al, (2018) [26]	10 non obese, untrained women Age: 24.60 ± 2.45 years	**M:** leg press, chest press, latissimus dorsi pull down, leg extension, leg curl, cable crossover, biceps curl, triceps extension, and abdominal crunches **F:** 3 times/wk **D:** 65 min, 3 – 4 sets of 8 – 12 reps	At the baseline and after the exercise program	=	ELISA kit (ZellBio GmbH, Ulm, Germany) (Serum)

		I: 55-75% 1RM **T:** 8 wks			
Ozan et al, (2020) [33]	9 elite boxers Age: 17.22 ± 3.35 years	**M:** sportive movement as static; direct hit, crochet, uppercut, elbow flexion, elbow extension, sideways lifting, rowing up, flapping, chest press, front lift, cross- lift, cross back cut, leg press, fall off, with resistance bands (thera-band®) **F:** 3 times/wk **D:** NS **I:** NS **T:** 8 wks	At the baseline and after the exercise program	=	ELISA kit (Mybiosourche, San Diego, USA) (Serum)
Hecksteden et al, (2013) [23]	40 untrained healthy subjects (23 females, 17 males) Age: 30-60 years	**M**: eight machine-based exercises, pulldown, seated row, seated leg curl, seated leg extension, seated chest press, and lying leg press **F:** 3 times/wk **D:** 2 sets of 15 repetitions **I:** 100% of the 20 RM and 60% HRR **T:** 26 wks	At the baseline and 2-7 days after the final training bout	=	ELISA kit (Phoenix Pharmaceuticals, Burlingame, CA, USA) (Serum)
Prestes et al, (2015) [31]	39 sedentary women Age: ≥ 60 years	**M:** bench press, 45° leg press, seated low row, leg extension, leg curl, triceps pulley extension, adduction and abduction machines, standing arm curl, and seated calf raise **F:** 2 times/wk **D:** 40-50 min, 3 sets of 12-14 RM, 10-12 RM, 8-10RM and 6-8RM Linear periodization: the training loads were maintained per week Undulating periodization: the training loads were changed on a daily basis **I:** 50-70% 1RM **T:** 16 wks	At the baseline and after the exercise program	Linear periodization group ↓ (5.4%) Undulating periodization group =	ELISA kit (MyBioSource Inc., San Diego, CA, USA) (Serum)
Moienneia et al, (2016) [21]	21 sedentary young women Age: 24.42 ± 2.95 years	**M:** leg extension, leg flexion, squat, and standing calf raise, high pull, elbow flexion, and elbow extension **F:** 3 session/wk **D:** low intensity: 3 sets of 20-30 repetitions in each station (45s);	At the baseline, right after one session, and 48 h after the end of the study	Low intensity = High intensity ↓ (34.31%)	ELISA (CSB-EQ027943HU, CASABIO and Japan) (Serum)

		high intensity: 3 sets of 5-15 repetitions in each station (20s) **I:** low: 40-60% 1RM high: 70-90% 1RM **T:** 8 wks			
Scharhag-Rosenberger et al, (2014) [34]	37 sedentary healthy subjects (20 females, 17 males) Age: 47 ± 7 years	**M:** back extension and crunch, pulldown machine, seated row machine, seated leg curl machine, seated leg extension machine, seated chest press machine, and lying leg press machine **F:** 3 times/wk **D:** 2 sets of 16, 18, and 20 repetitions **I:** 64 – 71% 1RM **T:** 24 wk (6-wk cycle)	At the baseline and ≥48 h after completing the training period	=	ELISA kit (Phoenix Pharmaceutics, Burlingame, CA) (Serum)
Kim et al, (2015) [10]	18 women Age: > 65 years	**M:** elastic band (green) **F:** 2 times/wk **D:** 2-3 sets of 12-15 repetitions per session (40 min) **I:** light **T:** 12 wk	NS	↑ (22.5%)	ELISA Kit (Phoenix Pharmaceuticals, CA, USA) (Serum)
Kim et al, (2016) [11]	10 young overweighted or obese adults (3 females, 7 males) Age: 25.8 years	**M:** shoulder press, seated rows, lat pull down, bench press, push up, pec deck fly, squat, leg extension, leg curls, leg press, crunch **F:** 5 times/wk **D:** 3 sets of 10-12 repetitions **I:** 65-80% 1RM **T:** 8 wks	At the baseline and after the exercise program	↑ (18.29%)	ELISA kit (EK-067-16 Phoenix Pharmaceuticals, CA, USA) (Plasma)
Tibana et al, (2017) [22]	49 older women with or without obesity Age: >60 years	**M:** barbell bench press, 45° leg press, seated row, knee extension, lateral raise, knee flexion, arm extension, hip adduction and abduction, arm curl and standing calf raise followed by abdominal crunches **F:** 2 session/wk **D:** 3 sets with 6-12 repetitions **I:** 60% 10RM **T:** 16 wks	At the baseline and five days after ending the training	Non obese group ↓ (14.25%) Obese group =	ELISA kit (MyBioSource Inc., San Diego, CA, USA) (Serum)
Korkmaz et al, (2018) [7]	36 overweighted and obese men Age:40-65 years	**M:** leg press, bench press, leg extension, lateral pull-down, leg flexion and shoulder flexion, explosive leg	At the baseline and after the intervention	=	ELISA kit (EK-067–52 Phoenix Pharmaceuticals,

		squats, squat jumps, standing calf jumps or heel raises, push-ups, abdominal flexions, and back extensions **F:** 3 times/wk **D:** 60 min **I:** 50-85% 1RM **T:** 12 wks			Burlingame, California, USA) (Plasma)
Amanat et al, (2020) [8]	14 overweighted/obese women with metabolic syndrome Age: 54.5 ± 6.9 years	**M:** bench press, seated row, shoulder press, chest press, lateral pull-down, abdominal crunches, leg press, leg extension, triceps pushdown, and seated bicep curls **F:** 2-3 sessions/wk **D:** 2 sets, 8-10 reps, 60 min **I:** 60-80% 1RM **T:** 12 wks	At the baseline and 24 h after the last intervention	=	ELISA kit (Phoenix Pharmaceuticals, Burlingame, USA) (Serum)
Dianatinasab et al, (2020) [30]	13 overweighted women with metabolic syndrome Age: 53.43 ± 6.53 years	**M:** bench press, seated row, shoulder press, chest press, lateral pull-down, abdominal crunches, leg press, leg extension, triceps pushdown, and seated bicep curls **F:** 3 session/wk **D:** 2 sets with 8-10 repetitions **I:** 60–80% 1RM **T:** 8 wks	At the baseline and after the last exercise of intervention	=	ELISA kit (Phoenix Pharmaceuticals, Burlingame, USA) (Serum)
Combined					
Shabani et al, (2018) [26]	10 non-obese, untrained women Age: 26.60 ± 4.00 years	**M:** Aerobic: aerobic step training and running Resistance: leg press, cable crossover, biceps curl, triceps extension and abdominal crunches or chest press, latissimus dorsi pull down, leg extension, leg curl, and abdominal crunches**.** They only performed five exercises in each session. Aerobic and resistance training were performed in the same session. **F:** 3 times/wk **D:** Aerobic: 25 min Resistance: 25 min	At the baseline and after the exercise program	↓ (12.68%)	ELISA kit (ZellBio GmbH, Ulm, Germany) (Serum)

		3 – 4 sets of 8-12 reps **I:** Aerobic: 55-75% age-predicted HR_{max} Resistance: 55-75% age-predicted 1RM **T:** 8 wks			
Pekkala et al, (2013) [27]	9 sedentary healthy males Age: 62 ± 5 years	**M:** Aerobic: cycle ergometer Resistance leg press, knee extension, bench press, triceps pushdown, lateral pull-down, sit-up, and elbow flexion. Aerobic and resistance training were performed in the same session. **F:** Aerobic: 2 times/wk Resistance: 2 times/wk **D:** Aerobic: 30-90 min Resistance: 60-90 min **I:** Aerobic: <75% - >90% HR_{max} Resistance: 40-90% 1 RM **T:** 21 wks	At the baseline and 3 h post-exercise	=	EIA Kit (Irisin/FNDC-5 Phoenix Pharmaceuticals, Inc., Burlingame, CA, USA) (Serum)
Jedrychowski et al, (2015) [12]	6 young healthy males Age: 25 ± 5 years	**M:** HIIT: cycle ergometer Aerobic: treadmill HIIT and aerobic training were performed in different days. **F:** HIIT:3 times/wk Aerobic: 2 times/wk **D:** HIIT: 25 min Aerobic: 45 min **I:** HIIT: 4 x 4 min intervals at >90% VO_{2peak} separated by a 3 min recovery Aerobic: 70% VO_{2peak} **T:** 12 wks	NS	↑ (~4.3%)	Anti-FNDC5 (Sigma) (Plasma)
Rashti et al, (2019) [13]	15 postmenopausal active and sedentary women Age: 45-65 years	**M:** Aerobic: on a treadmill HIIT: on a treadmill Resistance: leg press, chest press, lat pull-down, leg extension, leg curl, cable crossover, biceps curl, triceps extension, and abdominal crunches HIIT and resistance training were performed in different days. **F:** 3 times/wk **D:** Aerobic: 45-55 min	At the baseline and 24 h post-training	Aerobic + resistance = HIIT + resistance ↑ (65.41%)	Enzyme immunoassay (BioVendor, USA) (Serum)

		HIIT: 40-50 min Resistance: 35-45 min, 2–4 sets of 8–10 reps or 3–4 sets of 12–15 reps **I:** Aerobic: 50-75% HR_{max} HIIT: 4 x 4 min intervals at 85-95%HRM separated by a 4 min recovery at 65% HRM Resistance: 40-85% 1RM **T:** 10 wks			
Kurdiova et al, (2014) [35]	16 sedentary overweighted/obese subjects (6 females, 10 males). Age: 36.5 ± 1.1 years	**M:** Aerobic: aerobic dance, running and spinning Resistance: squat-ups, bench dips, back extensions, bench lift, inclined press-up, sit ups-lower abdominals, stomach crunch-upper abdominals, back extension, chest raise, jumps, astride jumps, step-ups, bench squats, burpees, squat thrusts, squat press, skipping. Aerobic and resistance training were performed in the same session **F:** 3 times/wk **D:** 60 min **I:** Aerobic: 70-85% HR_{max} Resistance: 50-60% 1RM **T:** 12 wks	At the baseline, immediately, 60 min and 3 months after exercise	=	Irisin/FNDC5 RIA kit (Phoenix Pharmaceuticals, USA) (Plasma)
Bonfante et al, (2017) [36]	22 middle-aged overweighted/obese men Age: 49.13 ± 5.75 years	**M:** Aerobic: walking/running Resistance: bench press, 45° leg press and arm curl exercises Aerobic and resistance training were performed in the same session **F:** 3 times/wk **D:** ~60 min for both exercises Resistance: 3 sets of 6 – 10 reps **I:** Aerobic: 55-85% VO_{2peak} Resistance: 6-10RM **T:** 24 wks	At the baseline and 72 h after the last training session	=	ELISA kit, (United States Biological, Massachusetts, USA) (Plasma)
Norheim et al, (2014) [37]	26 healthy and physically inactive men (with normal weight and overweighted with	**M:** Aerobic: treadmills or stationary bikes Resistance: for the whole body It is not indicated if the training was performed in the same session or in several	At the baseline, immediately after, and 2 h after 70% of the bicycle test 12 weeks after the training.	Control group (healthy) = Prediabetes group	ELISA kit (EK-067-52, y EK-067- 29 Phoenix Pharmaceuticals Inc., Burlingame, CA, USA) (Plasma)

	abnormal glucose metabolism) Age: 40-65 years	**F:** 2 times/wk **D:** Aerobic: 30 min Resistance: 30 min **I:** NS **T:** 12 wks	Biopsies from the VL muscle: at the baseline, directly after, and 2 h after 70% of the bicycle test 12 weeks after the training	=	
Blüher et al, (2014) [14]	77 obese children (34 females, 43 males) Age: 7-18 years	**M:** Aerobic: stationary bikes Resistance: chest press, leg press, leg extension, leg flexion, latissimus dorsi pull down, rowing, biceps curl, triceps extension with stack weight equipment. It is not indicated if the training was performed in the same session or in several. **F:** NS **D:** 8 – 12 reps, 150 min/wk **I:** NS **T:** 48 wks	At the baseline and after completing the program	↑ (12.0%)	ELISA kit (EK-067-52 Phoenix Pharmaceuticals, Burlingame, CA) (Serum)
Banitalebi et al, (2019) [38]	14 overweighted women with T2D Age: 54.14 ± 5.43 years	**M:** Aerobic: treadmill/cycle ergometer Resistance: bilateral leg press, lateral pull down, bench press, bilateral biceps curl, and bilateral triceps push down Aerobic and resistance training were performed in the same session **F:** 3 times/wk **D:** Aerobic: 20-30 min Resistance: 1-3 sets,15-10 reps **I:** Aerobic: 50-70% HR_{max} Resistance: 10-15 RM **T:** 10 wks	At the baseline and 48 h after the intervention	=	ELISA (Hangzhou East Biopharm Co, K-E90905) (Serum)
Motahari Rad et al, (2020) [15]	30 male patients with T2D Age: 43.9 ± 2.5 years and 44.0 ± 2.6 years	**M:** HIIT: walking/running on a treadmill Resistance: leg press, bench press, leg extension, lat pulldown, lying leg curl, and seated shoulder press with weight machines, both exercises in a same session HIIT and resistance training were performed in the same session One group performed HIIT + resistance and the other group in the opposite	At the baseline and 48 h after the last session of the intervention	HIIT + resistance ↑ (18.7%) Resistance + HIIT ↑ (22.2%)	ELISA kit (human irisin, ZellBio GmbH, Ulm, Lonsee, Germany) (Serum)

		order. **F:** 3 times/wk **D:** HIIT: 30 min Resistance: 3 sets, 15-18 to 8-10 reps. **I:** HIIT: 10 x 1 min intervals at 75–95% HR_{max} separated by a 1 min recovery at 40-60% HR_{max} Resistance: 40-50 to 70-80% 1RM **T:** 12 wks			
Dianatinasab et al, (2020) [30]	13 overweighted women with metabolic syndrome Age: 53.43 ± 6.53 years	**M:** Aerobic: walking in treadmill Resistance: bench press, seated row, shoulder press, chest press, lateral pull-down, abdominal crunches, leg press, leg extension, triceps pushdown, and seated bicep curls Aerobic and resistance training were performed in the same session **F:** 3 times/wk **D:** Aerobic: 20 min Resistance: 1 set with 8-10 repetitions **I:** Aerobic: 75% HR_{max} Resistance: 60–80% 1RM **T:** 8 wks	At the baseline and after the last exercise of intervention	=	ELISA kit (Phoenix Pharmaceuticals, Burlingame, USA) (Serum)
Amanat et al, (2020) [8]	15 overweighted/obese women with metabolic syndrome Age: 54.5 ± 6.9 years	**M:** Aerobic: running on a treadmill Resistance: bench press, seated row, shoulder press, chest press, lateral pull-down, abdominal crunches, leg press, leg extension, triceps pushdown, and seated bicep curls. Aerobic and resistance training were performed in the same session **F:** 2-3 times/wk **D:** Aerobic: 20 min Resistance: 2 sets, 8-10 reps.60 min total **I:** Aerobic: 60-75% HR_{max} Resistance: 60-80% 1RM **T:** 12 wks	At the baseline and 24 h after the last intervention	↑ (9.6%)	ELISA kit (Phoenix Pharmaceuticals, Burlingame, USA) (Serum)
Circuits					

Micielska et al, (2019) [17]	20 non-active women Age: 40 ± 11 years	**M**: 3 circuits consisted of: jumping jacks, push- ups, sit-ups, side plank, squats, plank, running in place, lunges and push-ups. With a 2 min break between circuits **F:** 3 times/wk **D:** 25 min **I:** 80-90 %FCM **T:** 5 wks	24 h after the first and last session	Women with a low VO_2max value ↑ (34.0%)	ELISA kit (EK 067-16 Phoenix Pharmaceuticals Inc.) (Serum)
Micielska et al, (2021) [18]	21 healthy, sedentary, adult females Age: 39 ± 13 years (Young < 30 years old Old > 30 years old)	**M:** 3 circuits consisting of: jumping jacks, push-ups, sit-ups, side plank, squats, plank, running in place, lunges and push-ups. With a 2 min break **F:** 3 times/wk **D:** 25 min **I:** 80-90% FCM **T:** 5 wks	24 h after the first and last session	< 30 years old ↓ (10.0%) > 30 years old ↑ (21.0%)	ELISA kit (EK 067–29 Phoenix Pharmaceuticals Inc.) (Serum)
Ghanbari-Niaki et al, (2018) [16]	12 untrained postmenopausal women Age: 55.7 ± 4.9 years	**M:** resistance circuit: squat, chest press, leg press, standing military press, knee extension, seated cable rowing, knee curl, biceps curl, standingcalf raise, triceps press, back extension, and abdominal crunch **F:** 3 times/wk **D:** 2 sets of 12 exercises **I:** 55% 1RM **T:** 8 wks	At baseline (48 h after) and 48 h before the last session	↑ (4.14%)	ELISA kit (CUSABIO, product number: CSB-EQ027943HU) (Serum)
Intervals					
Scalzo et al, (2014) [19]	19 young healthy adults (12 females, 7 males) Age: 24 ± 1 years	**M:** cycle ergometer **F:** 3 times/wk **D:** 12-32 min **I:** 4-8 x 30 s intervals at maximal efforts separated by a 4 min recovery **T:** 3 wks	At the baseline, right after concluding the training, after a 12-hour fast and a 48-h period of exercise abstention	Females ↑ (22.30%) Males ↓ (29.13%)	ELISA kit (Phoenix Pharmaceutical, Burlingame, CA, USA) (Plasma)
Tsuchiya et al, (2016) [39]	20 physically active males Age: 21.0 ± 2.9/22.2 ± 1.8 years	**M:** cycle ergometer **F:** Single: once daily 5 times/wk Repeat: two sessions on the same day with a 1-h rest between sessions, 2-3 times/wk **D:** 21.5 min **I:** 3 x 30 s intervals at maximal pedaling separated by a 10 min recovery	At the baseline and 48 h after completing the last training session	Single ↓ (38.6%) Repeat ↓ (28.9%)	ELISA kit (EK-067-52, Lot 604,197, Phoenix Pharmaceuticals, Germany) (Serum)

		T: 4 wks			
Dundar et al, (2019) [40]	17 physically active males Age: 14.47 ± 1.06 years	**M:** basketball **F:** 5 times/wk **D:** 120 min **I:** NS **T:** 8 wks	At the baseline and after 8 wks	↓ (19.2%)	ELISA kit (Cloud-Clone Corp., Katy, TX, USA) (Serum)
Murawska-Cialowicz et al, (2020) [20]	15 men with low physical activity Age: 32.39 ± 6.63 years	**M:** Squats with jumps, back extensions, crunches, push-ups, triceps dips, side crunch, military press with medicine ball and chin-ups **F:** 2 times/wk **D:** 60 min **I:** 8 x 4 min intervals at maximum intensity separated by a 1 min recovery **T:** 8 wks	At the baseline and after the exercise program	↑ (29.7%)	ELISA kit (BioVendor Laboratorni Medicina, Brno, Czech Republic) (Serum)
Banitalebi et al, (2019) [38]	14 overweighted women with T2D Age: 55.36 ± 5.94 years	**M:** cycle ergometer **F:** 3 times/wk **D:** 13 min **I:** 4 x 30 s intervals at maximum intensity separated by a 2 min recovery at 50 W. **T:** 10 wks	At the baseline and 48 h after the intervention	=	ELISA kit (Hangzhou East Biopharm Co, K-E90905) (Serum)
Dünnwald et al, (2019) [29]	8 subjects with T2D (2 females, 6 males) Age: 59.6 ± 5.7 years	**M:** cycle ergometer **F:** 3 times/wk **D:** 42 min **I:** 5 x 4 min intervals at 90–95% HR_{max} separated by a 3 min recovery at 70% HR_{max} **T:** 4 wks	At the baseline and one day after the exercise intervention	↑ (7.01%)	ELISA kit (Biovendor R&D, Laboratorni Medicína, Brno, Czech Republic) (Plasma)

Note: all trainings were performed under supervision.
D= duration; F= frequency; HIIT: High Intensity Interval Training; h= hour; HRR= Heart rate reserve; I= intensity; min= minute; M: Mode; HR_{max}= maximum heart rate; NS= not shown; R= repeated; RM= repetition maximum; S= single; T= weeks of training; T2D: type 2 diabetes; VO_2max= maximum oxygen uptake; VO_{2peak}= peak oxygen uptake; wk= week; ↑ increase; ↓ decrease; = no significant change.

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