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Circulating irisin and rehabilitation: expanding cutting edge research of muscle-derivate endocrine profile to the physical activity/therapy in various ailments

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Abstract: One of the most spectacular topics in the field of exercise-related muscle activity is its endo-crine profile, particularly, exerkines. We aimed to analyze the most recent clinical data re-garding blood irisin after physical rehabilitation and/or physical activity/exercise in hu-mans with various diseases. We identified 20 original studies across an 18-month analysis of prior published data on PubMed, between 2024 and 2025. Except for two studies that en-rolled between 100 and 200 patients, and one large cohort of 1549 individuals, all the oth-ers showed a relative small sample size (from 13 to 63 subjects). Most ailments included cardio-metabolic disturbances. The type of rehabilitation varied: aerobic training, combined training, alternating aerobic and resistance training, complex programs amid post-stroke recovery, circuit training, and whole body vibration exercises. Except for one study which tested irisin minutes after a peak exercise, most studies addressed rehabilitation programs for weeks (between 4-to-6 and 12-to-24 weeks). Except for INTESITY cohort, only ELISA kit was used for testing (expressed in ng/mL, pg/mL or μg/mL). Overall, emerging data, while still being under the umbrella of a heterogeneous spectrum, showed that rehabilitation-related irisin might serve a biomarker for various improvements in terms of metabolic, cardiovascular, inflammatory, osseous or cognitive components or quality of life. Ongoing perspective of irisin as biomarker which is not yet definitive in the current practice and fur-ther research is mandatory to reduce the current gaps in the clinical use of circulating irisin.

Keywords: physical activity, muscle, bone, diabetes, obesity, training, myokines, intensity aerobic exercise, strengths training, resistive cycle ergometer, exerkine, resistance training

1. Introduction

One of the most spectacular topics in the field of exercise-related muscle activity is represented by the identification of an active endocrine profile, which might interplay and become a useful tool amidst the physical therapy and rehabilitation in various ailments [1-4]. Irisin, a muscle-secreted protein by the regulation of peroxisome proliferator-activated receptor γ coactivator-1α (PGC1α), belongs to the complex

group of adipo-miokines. This interesting exerkine has been discovered more than a decade ago, and since then, an increasing number of clinical studies have raised the issue of becoming a biomarker for every day practice across a multidisciplinary perspective [5-7].

The irisin-related biological correlations seem more than a translator of the physical exercise under physiological and pathological conditions, since they reflect the changes and the anomalies of the glucose metabolism and bone turnover, too, for instance, lower circulating levels have been found in diabetic versus non-diabetic patients, in osteoporotic versus non-osteoporotic adults, in females with prevalent fragility fractures versus uncomplicated osteoporosis [8-12].

Another key contribution of irisin has been found in aging, which generally represents a crossroad between autophagy (the degradation of the damaged cells and cells remnants, that declines across lifespan) and inflammasome (the mediator of inflammation that might cause a chronic low rate of inflammation amid aging, so called "inflammaging") [13-16]. Irisin inhibits inflammasome by activating mitophagy process, as a direct consequence of sustained physical activity (which otherwise improves not only the inflammatory status, but it reduces the cardiovascular and metabolic risks, helps the joints, muscle and skeletal health, and induces cognitive improvements) [17-22].

Overall, the scientific information we have so far in relationship with the physical rehabilitation and circulating (blood) irisin assays are continuously expanding, yet, many areas are still a matter of debate or unknown.

Objective

We aimed to analyze the most recent clinical data that have been published regarding the serum irisin assays after physical rehabilitation and/or physical activity/exercise in humans who were confirmed with various diseases.

2. Results: Sample-focused analysis of rehabilitation-related irisin outcomes

2.1. Cardio-metabolic disorders

Irisin was found to be positively correlated with cardiorespiratory fitness and negatively with the diagnosis of type 2 diabetes mellitus across the larger panel of metabolic ailments [23-25], while the protein secretion might improve the diabetic cardiomyopathy [26] or non-alcoholic fatty liver disease [27-29].

In addition, irisin might be connected to primary and secondary prevention of cardiovascular outcomes by being generated during physical activity and physical therapy after the first diagnosis of cardio-metabolic diseases. For instance, murine models have shown that resistance exercise may upregulate the protein irisin expression which, further on, will suppress the development of myocardial fibrosis after a myocardial infarction. One of the underlying mechanisms involves the activation of AMP-activated protein kinase (AMPK) and sirtuin 1 (AMPK-Sirt1) pathway and downregulation of the canonical signalling pathway of transforming growth factor-beta 1 (TGFβ1) (noting TGFβ1 further activates Smad2 and Smad3 proteins) [30,31]. Also, (exercise-generated) irisin might act synergistically with the channel piezo 1, which display an important role in the control of high blood pressure [32].

Currently, the association between irisin levels and the duration of type 2 diabetes is still less understood. A sub-analysis of INTESITY (The Improving Individual Glycemic Response with Exercise Intensity) study (NCT03787836) [33] conducted by Thomson et al. [34] explored the impact of the physical activity in 34 adults with a short history of diabetes (less than ten years) versus long-duration of the disease (at least ten years). They underwent a program of moderate-to-vigorous intensity aero-

bic training (150 minutes per week, 28 weeks), followed by moderate intensity exercise for 16 weeks, and then the patients were randomized either to follow a 12-week maintained-intensity or an increased-intensity exercise. Irisin statistically significant increased by 1.37 times ($p = 0.03$) only in the second category (for long-duration group), suggesting the impact of the physical activity is distinct and varies with diabetes duration and different levels of physical intensity [34].

One pilot study conducted by Bonfante et al. [35] aimed to analyze the combined training-related effects on **quality of life** and biomarkers in patients who were **overweight-type 2 diabetics**. Study group received strengths training followed by aerobic training, three times per week for 16 weeks (N = 13 patients) versus controls (N = 16 adults with similar demographic features who remained sedentary). The group with exposure to combined training showed a 20% improvement regarding the perception of general quality of life, both in the physical and social domain (of 12.7%, respectively, of 10.1%). Irisin levels correlated with general perception of health ($r = 0.91$, $p = 0.02$), so was brown adipose tissue (BAT) activity ($r = 0.9$, $p = 0.01$). Interleukin 6 (IL-6) and IL-10 negatively, respectively, positively, associated with the general perception of quality of life ($r = -0.92$, $p = 0.02$, respectively, $r = 0.99$, $p = 0.00001$), while bone morphogenic protein (BMP-4) associated with psychological, and social domains, respectively ($r = 0.67$, $p = 0.04$, and $r = 0.96$, $p = 0.03$) [35]. These findings supported the idea of biomarkers correlates amid different components of the quality of life's assessment (but not all), and irisin may serve as a surrogate for some of these components with concern to the evaluation of quality of life in patients with common disorders like obesity or diabetes [35-37].

While murine experiments showed an improvement of the insulin resistance due to muscle-related irisin, the results of clinical studies in humans with prediabetes or nondiabetic patients are less clear [38-41]. A prospective, randomized controlled trial (NCT04528693) enrolled 42 women with newly detected **insulin resistance** [33,42] who underwent either circuit training combined with strength training (50%-80% of one-repetition maximum) associated with endurance (50%-75% of heart rate reserve) exercises (12 weeks, three sessions of 33 minutes per week) versus controls (no additional physical activity). IL-6 statistically significant changed between the two groups ($p < 0.05$), while irisin [as well as IL-10, and fibroblast growth factor 21 (FGF21)] were stationary. These results suggested that irisin might not show clear correlations in subjects with insulin resistance or the fact that circuit training is potentially mediated by a more complex panel of (non-irisin, non-IL-10) adipo-myokines/exerkines or the need of using other more specific kits. In this instance, ELISA, BioVendor was used; e.g. irisin for the first group was; 6.6 ± 2.6 versus $7.6. \pm 2.9$ μg/mL, $p = 0.387$; respectively, for the second group: 6.1 ± 2.6 versus 6.5 ± 1.8 μg/m, $p = 0.592$ [42].

Obesity associates an increased adipose mass, insulin resistance, impaired muscle-bone crosstalk, and oxidative stress, etc. [43]. All these elements might be attenuated upon exercise or physical rehabilitation. Kilic-Toprak et al. [44] conducted a pilot study in 13 adults with **obesity** that underwent a 12-session exercise program using a whole body vibration exercise (for four weeks). Irisin and resistin statistically significant increased ($p < 0.05$), but not visfatin, while erythrocyte deformability and the level of oxidative stress also improved after a month [44].

Moreover, Bagheri et al. [45] conducted a randomized controlled study in resistance training and enrolled 60 overweight and **obese** adult males who received one of the following four programs (three sessions per week for 12 weeks): upper body or lower body or combined (upper and lower) exercises versus controls (N = 15 individuals per each group). The results showed a statistically significant improvement of the skeletal muscle mass, fat-free mass, an increase of the serum irisin levels,

as well as follistatin, follistatin/myostatin rate, and adiponectin, and a decrease of myostatin, C-reactive protein and tumor necrosis factor (TNF-α). The baseline irisin assays [Enzyme-Linked Immunosorbent Assay (ELISA) kit] showed 14.1 ± 1.7, 13.8 ± 2.3, 12.6 ± 1.8, and 14 ± 2.3 ng/mL. All these values statistically significant elevated in each training group, not in controls. However, after adjustment for training volume, no difference was observed between the groups ($p > 0.05$). Also, irisin negatively correlated with the change of fat mass ($r^2 = 0.181$, $p = 0.001$) [45]. Whether similar findings may be found in women, too, this is a work in progress.

Another study only in male population (1549 adults) analyzed three groups (with above-average muscle mass, **above-average fat mass**, and with average body composition). They all underwent a maximal physical effort and multiple biomarkers were tested five minutes before the physical activity and three minutes after the exercise. All groups showed a statistically significant post-effort increase of lipid peroxidation and resistin, and for the third group, of visfatin, too. Yet, circulating irisin (ELISA Kit RAG018R) showed no change versus baseline [46]. Moreover, Suder et al. [47] published a randomized controlled trial in 44 males with **abdominal obesity** that underwent a 6-week program of aerobic-resistance exercise. They were included in one of the following three groups: aerobic-resistance exercise, aerobic-resistance exercise combined with an ad libitum high-protein plus low-glycemic index carbohydrate diet, and controls. While different body composition metrics were registered in both study groups, only the second one showed a statistically significant reduction of irisin (ELISA kit, Shanghai, China) by 41% ($\eta p^2 = 0.03$, $p < 0.01$) [47].

We identified other two randomized controlled studies [48,49], and one of them included 63 adults with a **sedentary** lifestyle that showed across four groups of 8-week physical intervention (either high-intensity interval training, moderate-intensity continuous training or resistance exercise versus controls) an improvement of the macro- and micro-vascular endothelial functions (as reflected by the brachial artery flow-mediated dilation and fingertip reactive hyperemia index) and arterial stiffness (via carotid-femoral pulse wave velocity), as well as an increase of insulin-like growth factor 1 (IGF-1), brain-derived neurotrophic factor (BDNF), and irisin. Particularly, irisin assays (ELISA kit, Cusabio, Wuhan, China) reached statistical significance for the groups who underwent high-intensity and resistance exercise versus pre-intervention values (70.03 ± 11.24 versus 76.25 ± 12.9 ng/mL, respectively, 70.96 ± 7.4 versus 77.63 ± 11.06 ng/mL, $p < 0.05$ for each). Hence, amid other biomarkers, irisin might serve as a surrogate of cardiovascular improvement after different types of physical training [48]. Horváth et al. [49] published the results on 40 severely **obese** patients who followed a 6-week program of either moderate-intensity (40-60% heart rate reserve) or low-intensity (30-39% of heart rate reserve) aerobic training combined with resistance training. Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and apolipoprotein A and B improved in both groups, while C-reactive protein and lipocalin-2 decreased. Irisin (ELISA kit) statistically significant elevated only in the first group (insight group significance between pre- and post-physical therapy: $p = 0.014$, between group difference: $p = 0.01$) [49].

2.2. Rheumatologic and inflammatory diseases

Another important irisin chapter that is under exploration is represented by persistently increased **uric acid** levels and clinically manifested gout [50]. A retrospective, cross-sectional study conducted by Ozer et al. [51] in 44 adults with gout versus 44 age- and sex-matched healthy controls found that irisin was statistically significant higher in subjects with gout versus controls (405.6 ± 97.3 and 316 ± 80.8 pg/mL, $p < 0.01$) with lower IL-10 (90.8 ± 71.9 versus 172.7 ± 128.6 pg/mL, $p < 0.01$), and similar

concentrations of resistin, TNF-α, and total antioxidant status (TAS), thus suggesting the potential role of irisin as biomarker in gout [51].

In addition, Tüfekçi et al. [52] investigated 37 patients with systemic sclerosis amid applying the 12-weeks program of Cognitive Exercise Therapy Approach [Bilişsel Egzersiz Terapi Yaklaşımı (BETY)], which is a supervised model-based exercise intervention (versus 17 controls that followed a home exercise program). While some parameters improved, such as Scleroderma HAQ (SHAQ), and Modified Hand Mobility in Scleroderma (mHAMIS), irisin assays (ELISA kit, USCN Life Science, Wuhan, China) showed similar results, specifically: (BETY group: initial versus final) 2.32 versus 2.41 ng/mL ($p = 0.575$); (controls: initial versus final) 2.65 versus 2.63 ng/mL ($p = 0.723$); within the group change: 0.1 (0.71), respectively, -0.02(0.92) ng/mL ($p = 0.715$) [52].

2.3. Osteoporosis

Irisin has shown in murine models to stimulate bone formation and reduce bone resorption, thus, playing an important role in the overall bone status, including the muscle-bone cross-talk [53-55]. As previously found with regard to the bone formation marker osteocalcin, the physical activity-derivate irisin levels might represent one of the mechanisms which are prone to bone formation after exercise [56-58]. Moreover, irisin contributes to restoring the skeleton status in osteoporotic bone, including an improvement of the response to the mechanical stress [59-61]. It may, also, reduce the chronic inflammation and regulate the apoptosis of bone cells [62-64].

Also, muscle-derivate irisin might be involved in the recovery of post-traumatic osteoarthritis according to the rat models we have so far [65], or osteoarthritis in humans (with or without overlapping with osteoporosis or obesity) [66].

According to our methods, we identified one study on 29 menopausal women that analyzed the levels of irisin in relationship with long-term physical exercise (24-week program of alternating aerobic and resistance training) and bone assessments. Irisin, as well as osteocalcin, statistically significant increased ($p = 0.003$, respectively, $p < 0.001$), while osteoprotegerin and receptor activator of NF-κB ligand (RANKL) decreased ($p = 0.041$, respectively, $p < 0.001$). Irisin correlated with the change of upper and lower limb bone mineral density ($r = 0.462$, $p = 0.006$, respectively, $r = 0.566$, $p = 0.001$), according to Dual-Energy X-Ray Absorptiometry (DXA) assessment [67].

2.4. Oncologic conditions

Tuğral et al. [68] conducted a prospective study aiming to assess the effect of aerobic exercise on various biomarkers (including irisin) in 32 subjects who were prior diagnosed with **colon or breast cancer**, while they underwent chemotherapy (15 patients represented the study group and 17 were controls). The supervised physical activity was assessed by using stationary resistive cycle ergometer during chemotherapy (two times each week for 12 weeks; supervised exercise sessions of 35 min; maximum intensity of the physical exercise was measured at the point of reaching 50% of the maximal heart rate for each individual). The blood assays (irisin, leptin, adioponectin, and IL-6) were performed before and after each cycle of chemotherapy. The results showed that after the mentioned physical activity, IL-6, and adiponectin statistically significant increased ($t = -2.985$, $p = 0.011$, respectively, $z = -2.229$, $p = 0.026$), but not irisin (of note, a 10% irisin increase was found, but it did not reach the level of statistical significance). Further correlations were confirmed, between irisin and leptin, respectively, between leptin and adiponectin ($r = 0.802$, $p = 0.001$, and $r = -0.635$, $p = 0.015$). This suggested that specific/supervised physical exercise in oncologic patients may be safe and might help the overall status amid the effects on inflammatory markers (such as IL-6) or adipokines (like adiponectin) [68]. Regarding

irisin levels, we may conclude that either the sample size was not adequate, either its effects are more complex than previously described in healthy adults, thus, the circulating levels are not a direct reflection of its true influence, according to what we know at this point [69-71].
Notably, in 2024, Kim et al. [72] published MYEX trial launching in patients with prostate cancer (a single-group, cross-over design), which is meant to evaluate the circulatory myokines profile (including irisin) and the extracellular vesicle uptake upon targeted exercise [72]. On a general note, physical activity is recognized to improve the disease progression and reduce cancer-specific survival rates, but the involved mechanisms are less understood [73-75].

2.4. Neurologic and psychiatric diseases

It has been found that exercise-induced irisin might be prone to beneficial effects on the brain health in both physiological and pathological circumstances, noting its neuronal regulatory role and neuroprotective contribution [76-79]. While most clinical (human) studies we have so far associated a low sample size, most data agree that approximately 10% to 15% increase of the circulating irisin was detected after short-term physical activity, this peak being responsible for further positive cerebral effects on long-term in cases with sustained physical activity (even of short sessions) [79-81]. A recent meta-analysis on eleven studies found that a positive correlation with brain function might be registered via the interplay with BDNF since irisin helps the promotion of this factor [82]. Irisin is generated from fibronectin type III domain-containing protein 5 (FNDC5), and several studies found that exercise-induced FNDC5 improves cognition, particularly, at hippocampal area, and some authors suggested that irisin represents only an intermediate step amid this process of increasing brain activity [83-85].

According to our search, four studies addressed the issue of stroke-exercise-irisin [86-89]. A randomized clinical trial included two groups of patients after **first episode of ischemic stroke**. One group (N = 22) followed a moderate-intensity continuous training (four sessions of 45 minutes per week and two sessions of 45 minutes of standard neurorehabilitation each day) and the control group underwent four sessions of 45 minutes of low-intensity continuous training each week in addition to two sessions of 45 minutes of standard rehabilitation each day. After three weeks, the first group showed a statistically significant improvement of aerobic capacity and arm motor function versus controls. On the contrary, the panel of biomarkers at the end of the study did not show statistically significant changes of the factors that previously have been described as recovery predictors and prognostic factors of neurorehabilitation e.g. BDNF, glial cell line-derived neurotrophic factor (GDNF), IGF-1, as well as vascular endothelial growth factor A (VEGF-A). Circulating irisin was also tested and found similar after this 3-week program in both groups, with median between-group difference for the change of 40.7 [95% confidence interval (CI) between 62.6 and 143.9], hence, being inconclusive. Irisin correlated with patients' age (r = -0.316, 95% CI between -0.021 and -0.561), but not with the mentioned functional status, neither the specified blood markers (BDNF, GDNF, IGF-1, and VEGF-A) [86].

Another study aimed to analyze serum irisin assays as potential early prognostic marker in subjects diagnosed with an acute ischemic stroke with hemiplegia (who required rehabilitation). Ouyang et al. [87] enrolled 125 patients versus 135 controls and showed that irisin (ELISA, DY9420-05, USA) was statistically significant lower in the study group versus controls (1564 versus 1723 pg/mL, p = 0.012). The irisin increase [adjusted odds ratio (OR) of 0.938, 95% CI between 0.899 and 0.977 per 100 pg/mL increment] was associated with a reduced stroke risk [87]. García-Salazar et

al. [88] analyzed a 2-week program of rehabilitation in **post-stroke** subjects who received either a high-intensity aerobic exercise and a modified constraint-induced movement therapy (mCIMT) (N = 9, study group) or mCIMT alone (N = 7, controls). At the end of the study, irisin and BFNF were similar, while matrix metalloproteinase-9 (MMP-9) statistically significant increased (d = 0.67, p =0.033) [88]. Swank et al. [89] conducted another study in **stroke survivors**: this was a randomized controlled trial in patients with chronic stroke (more than 12 months) who either followed the Diabetes Prevention Program Group Lifestyle Balance-adapted for stroke (N = 24) or a wait-list control (N = 24) versus healthy controls (N = 19). After 6 months, irisin was similar between the groups and within the group [89].

Additionally, we mention a single-center cross-sectional study in 15 males with androgen deficiency following **spinal cord injury** who were admitted for a rehabilitation program explored the relationship between irisin (high-sensitivity ELISA kit; AVISCERA BIOSCIENCE, Santa Clara, CA) and androgen levels. 53% of the subjects were found with androgen deficiency (as defined by a blood testosterone level less than 3 ng/mL, and calculated free testosterone less than 64 ng/mL) and this subgroup presented lower irisin levels, as well as increased body mass index and serum triglycerides. Irisin positively correlated with calculated free testosterone (r = 0.55, p = 0.03), and negatively with triglycerides (r = -0.66, p = 0.009) and HOMA-IR (r = -0.55, p = 0.03), as well as erythrocyte sedimentation rate (ESR) (r = -0.64, p = 0.009), but not with the body mass index, and leisure time physical activity [90]. Under these circumstances, Venditti et al. [90] suggested that irisin might mediate male hypogonadism-related effects on the metabolism, as other studies has previously found, too [90-92].

Of note, in 2024, a pilot study in Parkinson disease-related brain connectivity has been launched in order to address the dose-response effects of physical activity and associated biomarkers, including irisin, and METEX-PD study is expected to be then implemented as a large multi-centric randomized controlled trial [93].

In addition, we briefly mention a recent meta-analysis from 2025 (n = 8 studies) showed that circulating irisin level is decreased in **depressive** individuals, the lower the level, the more severe depression was identified (with statistically significant correlations between irisin and depression scores, which might help in the clinical practice as prognostic factor) [94]. The protein helps the improvement of the depression after its release following physical activity by increasing the neurotransmitter dopamine, as well as BDNF, nerve growth factor (NGF), and IGF-1, and reducing IL-6 (which acts as inflammation mediator) [95].

2.6. Renal involvement and circulating irisin

Irisin was found to be involved not only in the improvement of the renal osteodystrophy, but, also, of the renal injury in patients confirmed with type 2 diabetes [96], while under physiological circumstances, the protein might be part of the renoprotective mechanisms that are triggered and sustained by the physical exercise [97]. Also, renal osteodystrophy in chronic kidney disease was studied in murine experiments in relationship with aerobic exercise, which increases PGC-1α, and, thus, circulating irisin levels. Further on, irisin activates osteoblasts (and not osteoclasts) by crosstalk with integrin $\alpha v\beta 5$ with bone benefits. The therapeutic approach involving irisin administration might represent a promising future in this specific ailment [98].

Franscescon et al. [99] analyzed the beneficial effects of resistance exercise (a program of 12 weeks) in 40 adults under hemodialysis (this was an experimental interventional study). Irisin (ELISA kit) statistically significant increased by 14.56% (p = 0.022), as opposite with adiponectin, which decreased by 55.7% (p = 0.0044), while leptin remained stationary. The authors found differences in the body weight and

handgrip strength between males and females, which correlated with an increase irisin in women (not in men). This suggested refining the interpretation of irisin assays based on gender distribution (as prior described in male obesity and male hypogonadism) [99].

2.7. Coronavirus infection: recent irisin findings

Another important chapter in the irisin-derivate domain that has been recently developed involves the COVID-19 pandemic experience and associated pathological conditions [100-103]. For instance, early rehabilitation after severe coronavirus infections showed an improvement of the physical and emotional status, which has been correlated with changes of irisin levels, as well [104-106]. We identified a single study according to our methods, which explored the assessment of exerkines in 167 **post-COVID-19** patients. They underwent a compressive rehabilitation program and showed lower irisin (Human irisin ELISA Kit, Shanghai, China) and myonectin and higher myostatin in those with longer recovery time. Irisin did not correlate with the length of hospitalization ($r = 0.02$, $p = 0.82$), as opposite to myostatin ($r = 0.24$, $p = 0.008$), but with the duration of rehabilitation ($r = -0.24$, $p = 0.002$), as similarly for myostatin ($r = 0.17$, $p = 0.029$), and myonectin ($r = -0.24$, $p = 0.001$). The findings of Mińko et al. [107] imply that irisin might serve as a surrogate marker for a good recovery after infection [107].

3. Discussion

3.1. Exploring novel irisin domains

In addition to multiple irisin-related outcomes (Figure 1), one of the controversial aspects that are yet to be understood involves the pattern of irisin secretion under prolonged or intermittent **fasting conditions** in apparently healthy individuals [108]. Some authors suggested clear benefits (e.g. 5-day fasting in terms of reducing body fat, insulin, glucose, and waist circumference), but a reduction in the lean mean correlated with irisin decrease, as well as an increase of impulsivity, especially in individuals with pre-fasting tension, was also identified. This suggests the need of a personalized approach in this type of lifestyle intervention, and irisin might be related to these distinct pathways of human body regulation [109].

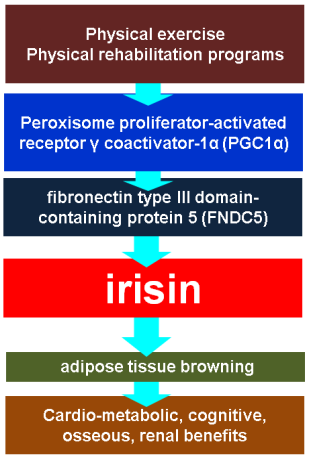

Figure 1. Irisin interplay with multi-organ involvement [34,35,42,44,45-49,51,52,67,68,86-90,99,107]

Other types of conditions that are still under evaluation are represented by **endocrine obesity** as found in complex syndromes (e.g. children diagnosed with Prader-Willi syndrome) [110-113] or the exposure to the physical exercise in patients

with severe **chronic** conditions such as cystic fibrosis [114]. Notably, a limited number of studies have been released so far with respect to the other traditional endocrine glands such as thyroid or adrenals and exercise-released irisin [115-120]. Topics such as gender-related differences in the interpretation of serum irisin testing are yet to be clarified [121-123].

In addition, other components of the complex rehabilitation landscape have been placed in relationship with the blood irisin testing. For instance, the effects of **electro-acupuncture** on vascular remodeling have been studied in murine models and irisin seems involved in recovery after cerebral ischemia by interfering with VEGF/Akt/eNOS pathway, a crossroad map that is still under research [124].

3.2. Irisin assays: from potential biases to the entire spectrum of exerkines

In the mentioned INTENSITY study [34], two types of irisin assays have been used: ELISA and western blotting techniques, while the others solely used ELISA kit with different origins [35,42,44,45-49,51,52,67,68,86-90,99,107]. Currently, there are insufficient data with regard to choosing the optimum irisin kit for specific disorders and this might bring a bias in the overall interpretation of these prior published studies. Further research is necessary to place the **hemorheological** evaluation (e.g. erythrocyte deformability, plasma viscosity, total oxidant/antioxidant status, oxidative stress index, etc. [125-135]) and the panel of other exerkines (visfatin, resistin, etc.) next to irisin testing as biomarkers and practical tools to be applied by the practitioners with distinct medical and surgical backgrounds.

3.3. Current limits

As limitations of the current analysis, we mention the single database search and narrative design, but, noting these heterogeneous assays and the small sample sized of the current trials, a systematic review might have limited the number of included studies. Also, we excluded healthy volunteers who performed different physical activities, and focused only on different ailments in order to provide a 360 degree updated perspective of the irisin assays, a domain which we expect to massively expend in the following years.

4. Methods

This was a narrative review based on searching upon using the combination of terms “irisin” and “rehabilitation”. Inclusion criteria were: English-published articles, full-length papers, time frame of publication: between 1st January 2024 and 1st September 2025; PubMed database, free access of the abstract and main text. Exclusion criteria were: non-human studies (including rat models); pregnant and pediatric population; clinical studies on healthy adults (no disease was registered by the authors); reviews and/or meta-analyses; conferences’ abstracts; duplicates; retractions; editorials; books and e-books. (Figure 2)

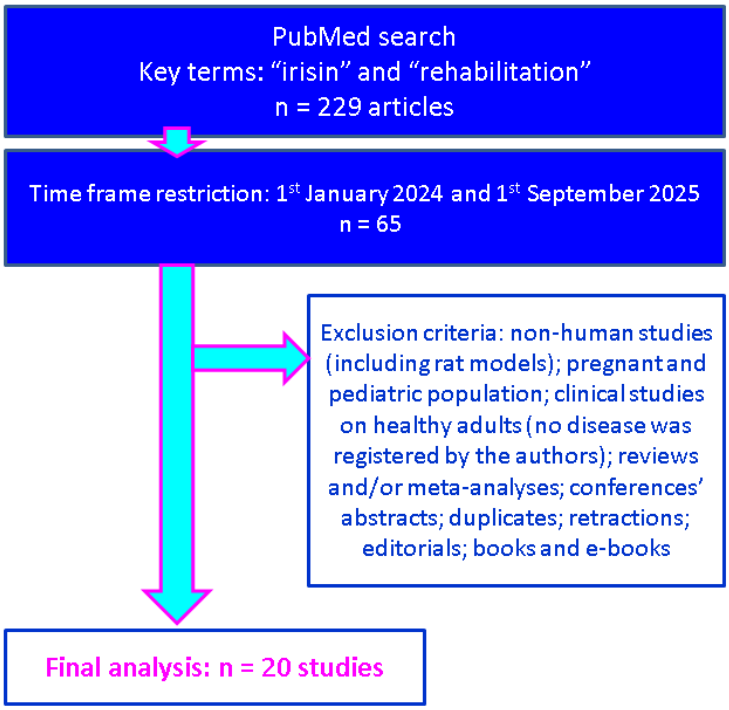

Figure 2. Flowchart of research according to our methods [35,42,44,45-49,51,52,67,68,86-90,99,107]

5. Conclusions

To summarize, we identified 20 original studies according across an 18-month analysis on prior published data (Table 1). Except for two studies that enrolled between 100 and 200 patients, and one large cohort of 1549 individuals, all the other studies showed a relative small sample size (from 13 to 63 subjects). The majority of the studied ailments in relationship with the physical rehabilitation included cardio-metabolic disturbances. The type of rehabilitation program varied, for instance, aerobic training, combined training, alternating aerobic and resistance training, complex rehabilitation programs amid post-stroke recovery, circuit training, whole body vibration exercises, etc. Except for one study which tested irisin minutes after a peak exercise, most studies addressed rehabilitation programs for several weeks (between 4-to-6 and 12-to-24 weeks). As mentioned, except for INTESITY study, ELISA kit was used with different origins and expressed in ng/mL, pg/mL μg/mL. Overall, emerging data, while still being under the umbrella of a heterogeneous spectrum, showed that rehabilitation-related irisin levels might be a biomarker of various improvements in terms of metabolic, cardiovascular, inflammatory, osseous or cognitive components or quality of life. Ongoing perspective of irisin as biomarker which is not yet definitive in the current practice and further research is mandatory to reduce the current gaps in the clinical use of circulating irisin.

Table 1. Study-focused analysis according to our methods [34,35,42,44,45-49,51,52,67,68,86-90,99,107]

Reference number	First author	Study design Study population	Study protocol (type of rehabilitation program)	Main findings: focus on irisin
34.	Thomson	INTESITY (The Improving Individual Glycemic Response with Exercise Intensity) prospective study 34 patients with type 2 diabetes mellitus	moderate-to-vigorous intensity aerobic training (28 weeks), followed by moderate intensity exercise (16 weeks), followed by maintained-intensity or an increased-intensity exercise (12 weeks)	irisin increased by 1.37 times ($p = 0.03$) only in the category with increased-intensity exercise in patients with a long-duration group of type diabetes (≥ 10 years)
35.	Bonfante	pilot study 29 overweight-type 2 diabetic adults (13 patients followed the physical training versus 16 control without physical activity)	combined training and assessment of quality of life	irisin correlated with general perception of health amid quality of life questionnaire ($r = 0.91$, $p = 0.02$)
42.	Karolkiewicz	randomized controlled trial 42 women with newly detected insulin resistance	12-week program of circuit training combined with strength training (50%-80% of one-repetition maximum) associated with endurance (50%-75% of heart rate reserve) exercises versus controls	irisin was stationary at the end of the study
44.	Kilic-Toprak	pilot study 13 patients with obesity	whole body vibration exercise (4 weeks)	irisin and resistin statistically significant increased ($p < 0.05$) after 4 weeks
45.	Bagheri	randomized controlled study 60 overweight and obese adult males	resistance training across 4 groups: upper body, lower body, combined exercises versus controls	irisin statistically significant increased after 12 weeks in each group, but not in controls irisin correlated with the change of fat mass ($r^2 = 0.181$, $p = 0.001$).
46.	Wiecek	clinical study 1549 adult males (3 groups: with above-average muscle mass, above-average fat mass, and with average body composition)	patients underwent a maximal physical effort	irisin showed no statistically significant difference between baseline and post-effort ($p > 0.5$)
47	Suder	randomized controlled trial 44 male patients with abdominal obesity	6-week program of aerobic-resistance exercise: aerobic-resistance exercise (group 1), aerobic-resistance exercise combined with an ad libitum high-protein plus low-glycemic index carbohydrate diet (group 2) versus controls	group 2: irisin statistically significant increased by 41% ($\eta p^2 = 0.03$, $p < 0.01$)
48.	Huang	randomized controlled study 63 sedentary adults	8-weeek program of high-intensity interval training, moderate-intensity continuous training or resistance exercise versus controls	irisin statistically significant increase in the high-intensity and resistance exercise groups

				versus pre-intervention values (70.03 ± 11.24 versus 76.25 ± 12.9 ng/mL, respectively, 70.96 ± 7.4 versus 77.63 ± 11.06 ng/mL, $p < 0.05$ for each)
49.	Horváth	randomized controlled trial 40 severely obese patients	6-week program of moderate-intensity (40-60% heart rate reserve) or low-intensity (30-39% of heart rate reserve) aerobic training combined with resistance training	irisin statistically significant elevated only in the first group (insight group significance between pre- and post-physical therapy $p = 0.014$, between group difference $p = 0.01$)
51.	Ozer	retrospective, cross-sectional study 44 patients with gout versus 44 age- and sex-matched healthy controls	irisin assay as biomarker in gout	patients with gout versus controls: increased irisin: 405.6 ± 97.3 and 316 ± 80.8 pg/mL, $p < 0.01$ reduced IL-10 (90.8 ± 71.9 versus 172.7 ± 128.6 pg/mL, $p < 0.01$)
52.	Tüfekçi	prospective study 37 patients with systemic sclerosis	12-week program of either Cognitive Exercise Therapy Approach [Bilişsel Egzersiz Terapi Yaklaşımı (BETY) or home exercise program	irisin was stationary at the end of the study in each group
67.	Chen	prospective study 29 menopausal women	24-week program of alternating aerobic and resistance training	irisin statistically significant increased ($p = 0.003$)
68.	Tuğral A	single-blind, prospective, controlled clinical trial 32 patients (15 patients with colon or breast cancer versus 17 controls)	aerobic physical exercise before and after chemotherapy	irisin increased by 10% after physical exercise (not statistically significant) irisin correlated with leptin ($r = 0.802$, $p = 0.001$)
86.	Górna	randomized clinical trial 44 patients after first episode of stroke	study group (N = 22): moderate-intensity continuous training (4 sessions of 45 minutes per week and two sessions of 45 minutes of standard neurorehabilitation each day) + control group (N = 22) 4 sessions of 45 minutes of low-intensity continuous training each week in addition to 2 sessions of 45 minutes of standard rehabilitation each day)	irisin was similar 3-week program in both groups (median between-group difference for the change of 40.7, 95% CI: -62.6 and 143.9)
87	Ouyang	cross-sectional study 125 patients with acute ischemic stroke with hemiplegia versus 135 controls	rehabilitation for hemiplegia	irisin was statistically significant lower in the study group (1564 versus 1723 pg/mL, $p = 0.012$)

88	García-Salazar	prospective study 16 post-stroke patients	2-week program of either high-intensity aerobic exercise and modified constraint-induced movement therapy or single modified constraint-induced movement therapy	irisin was stationary at the end of the study
89	Swank	randomized controlled trial 48 stroke survivors	6-month program of either Diabetes Prevention Program Group Lifestyle Balance-adapted for stroke or a wait-list control	irisin was stationary at the end of the study
90	Venditti	single-center, cross-sectional study 15 males with androgen deficiency following spinal cord injury	biomarkers assays during rehabilitation program	irisin positively correlated with calculated free testosterone (r = 0.55, p = 0.03), and negatively with triglycerides (r = -0.66, p = 0.009) and homeostatic model assessment of insulin resistance (HOMA-IR) (r = -0.55, p = 0.03)
99	Franscescon	experimental interventional study 40 patients under hemodialysis	12-week program of resistance exercise	irisin statistically significant increased by 14.56% (p = 0.022
107.	Mińko	single-center, prospective study 167 post-COVID-19 patients	compressive rehabilitation program	irisin correlated with the duration of rehabilitation (r = -0.24, p = 0.002)

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