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REVIEW ARTICLE

EFFECT OF PHYSICAL ACTIVITY ON IGF-1 AND IGFBP LEVELS IN THE CONTEXT OF CIVILIZATION DISEASES PREVENTION

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ABSTRACT

Background. Insulin-like growth factor 1 (IGF-1) is known as somatomedin C. This polypeptide hormone is functionally and structurally similar to insulin. IGF-1 effects on tissue by the IGF-1R and the insulin-like growth factor-binding protein also known as IGFBP. Abnormal IGF-1 and IGFBP signaling are positively correlated with a high risk of selected civilization diseases development. Physical inactivity is a one of the main causes of majority of chronic diseases and it is associated with eg. IGF-1 and IGFBPs level.

Objective. The aim of the study was to explanation the effect of physical activity on IGF-1 and its binding protein – IGFBPs concentration in the context of selected civilization diseases prevention. The review of clinical trial.

Material and Methods. The review of articles had published in databases: MEDLINE, EMBASE, Scopus and Web of Science until December 2015. The selected prospective studies about the effect of exercise on IGF-1 level and its binding protein IGFBP in the context of selected civilization diseases prevention were collected.

Results. The majority of the included studies indicate that mechanical loading is a key mechanism linking IGF-1/IGFBPs concentration and selected chronic diseases development. The duration and intensity of physical activity have a significant impact on IGF-1 and IGFBP serum. The highest concentration of IGF-1 in serum was after eccentric training. "Overtraining" increases unfavorable and unbound IGF-1 levels and contributes to the increased incidence of hormone-cancer and osteoarthritis.

Conclusions. Irregularity of the GH/IGF-1 axis may affect on the development of rheumatic diseases, cardiovascular diseases (regulate cardiac growth and metabolism) and metabolic syndrome.

Key words: *insulin-like growth factor 1, physical activity, rheumatic diseases, cardiovascular diseases*

STRESZCZENIE

Wprowadzenie. Insulinopodobny czynnik wzrostu 1 (IGF-1, *insulin-like growth factor 1*), zwany inaczej somatomedyną C. IGF-1 to hormon polipeptydowy, który funkcjonalnie i strukturalnie jest podobny do insuliny. IGF-1 oddziałuje na tkanki za pomocą receptora IGF-1R i białek wiążących IGFBP. Nieprawidłowości w produkcji IGF-1 i IGFBP są związane z wysokim ryzykiem rozwoju wielu chorób cywilizacyjnych. Brak aktywności fizycznej i związany z tym nieprawidłowy poziom krążącego IGF-1 przyczyniają się do rozwoju wielu przewlekłych chorób.

Cel. Celem badania była próba wyjaśnienia wpływu zmian stężenia IGF-1 i jego białka wiążącego IGFBP pod wpływem aktywności fizycznej na profilaktykę chorób cywilizacyjnych na podstawie analizy badań klinicznych.

Materiał i metody. Dokonano przeglądu artykułów opublikowanych do grudnia 2015 i zamieszczonych w bazach: MEDLINE, EMBASE, Scopus i Web of Science. Zebrano najnowsze badania prospektywne dotyczące znaczenia wysiłku fizycznego dla utrzymania prawidłowego poziomu IGF-1 i jego białka wiążącego IGFBP w kontekście profilaktyki wybranych chorób cywilizacyjnych.

Wyniki. Większość analizowanych badań wskazuje, że aktywność fizyczna regulując stężenie IGF-1 i IGFBPs wpływa na rozwój wybranych chorób cywilizacyjnych. Długość trwania i intensywność wysiłku fizycznego ma istotne znaczenie dla stężenia IGF-1 i IGFBPs. Największy wzrost IGF-1 obserwuje się w wyniku escentrycznej pracy mięśni. Stan „przetrenowania" powoduje wzrost niekorzystnego, niezwiązanego IGF-1 w surowicy. Wzrost poziomu IGF-1 niezwiązanego przyczynia się do zwiększonej zachorowalności na nowotwory hormonozależne i chorobę zwyrodnieniową stawów.

Wnioski. Nieprawidłowości osi GH/IGF-1 mogą wpływać na rozwój chorób reumatycznych, chorób układu krążenia i zespołu metabolicznego.

Słowa kluczowe*: IGF-1, aktywność fizyczna, choroby reumatyczne, schorzenia sercowo-naczyniowe*

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INTRODUCTION

Civilization diseases are an chronic diseases. 70% of all deaths in the U.S. are the patients with chronic diseases. These diseases are associated with many limitations of daily living among approximately 25 million people in U.S. [10].

Insulin-like growth factor 1 (IGF-1, insulin-like growth factor 1) is known as somatomedin C. IGF-1 belongs to polypeptide hormones, which are functionally and structurally similar to the insulin. IGF-1 is metabolic mediates of growth hormone (GH). Growth hormone is produced by the anterior pituitary gland, is essential for growth in the postnatal period. Growth hormone affects the tissue by the IGF1. IGF-1 stimulates all growth processes. Researches show that IGF-1 can be synthesized in vivo and in vitro in some tissues, but the main IGF-1 synthesizing organ is the liver. IGF-1 is secreted from hepatocytes into the serum, where it binds to insulin-like growth factor binding protein –IGFBP. Six types of IGFBPs is known. In human, IGF-binding protein-1 (IGFBP-1) is the basis. IGFBPs play an integral role in involving storage of IGF-1 by extending the period of its disintegration and protect tissues from undesirable effects of IGF-1. These proteins modulate the cellular response to IGF [1, 14, 16]. IGFBP-3 regulates growth independently of IGF-1 [2, 14, 16]. IGFBP-3 acting (independently of IGF-1) can bind specifically to the proteins or membrane receptors. In the central region of molecule IGFBP-3 is a fragment capable of binding to the membrane receptor in breast cancer cells [3, 14].

IGF-1 plays a key role in exercises associated muscle growth and development. IGF-I response is related to the intensity and duration of exercise. After short-term (20 min) ergometer exercise reported increased IGF-I but after 3 h endurance exercise, IGF-1 level was decreased and no change after interval training. In the same study, IGFBP-3 seems to increase during exercise [47]. This suggests that more prolonged exercise causes decreasing in total IGF-1 level. In the study involving children has been shown that exercise stimulates anabolic components like GH-IGF-1 axis. On the other side, exercise increases catabolic pro-inflammatory cytokines such as interleukin-6 (IL-6), IL-1 and tumor necrosis factor-α (TNF-α) what could be associated with rheumatic diseases development. This balance between anabolic and catabolic components depends on individual predisposition to the training load and to tolerate it. Hypokinesia or excessive exercise too much burden the body and cause adverse hormonal changes that affect the body systems [45].

The aim of this study was to review the literature about correlation between IGF-1 and IGFBPs level, physical activity and selected civilization diseases development.

MATERIALS AND METHODS

Search strategy. The review of published articles in databases: MEDLINE, EMBASE, Scopus and Web of Science and contained. The recent prospective studies about the effect of exercise on IGF-1 level and its binding protein IGFBP in the context of prevention of civilization diseases were collected. While searching the database, the following key words were used: insulin-like growth factor 1, physical activity, osteoarthritis, rheumatoid arthritis, metabolic syndrome, insulin tolerance, cardiovascular diseases. Publications until December 2015 were included. Only English and Polish articles or foreign language articles with English abstract were included.

Articles selection. All prospective studies and cross-sectional studies of the effects of physical activity on IGF-1 and IGFBP levels in context of prevention of the selected civilization diseases were selected from the search results and included in this review. Case reports were excluded. Only some of meta-analyses and systematic reviews were included. In conclusion, the 73 publications was included in this review. The publications identified include 69 published as full articles and 4 abstracts.

RESULTS

IGF-1 levels and several types of exercises

IGF-1 is not only related to growth hormone. Growth hormone (GH) stimulates IGF in skeletal muscle, promoting satellite cell activation, proliferation and differentiation [18]. It results increased levels of IGF-1 during exercise [15]. Reduced physical activity may influence on decreasing IGF-1. Myostatin and insulin like growth factor-I plays a key role in regulation of muscle homeostasis. The study comparing the types of training among *Sprague-Dawley* rats indicates that higher concentration of IGF-1 in serum was after eccentric training (Ecc) and isometric training (Iso) than after concentric (Con) training ($p < 0.05$) [19, 42]. Studies among people confirmed that total serum IGF-1 concentrations increase with endurance and strength exercise [13, 48]. The level of IGF should be considered as locally (in tissue) and peripherally (in serum). In the case of a local increase (ex. muscle), IGF-1 constantly increase after exercise, regardless of the length and intensity of exercise. However results for peripheral IGF-1 have been more differential (increases, decreases and no changes) [49, 50, 61]. Moreover, IGFBP-3 level changes in serum following exercise also are differential [62]. Some studies have shown that circulating levels of IGFBP-1 and IGFBP-3 are also modulated by several types of exercise [18, 40]. Another study demonstrates no effects in

IGF-1 level after moderate-intensity aerobic exercise or strength training [43]. Several of clinical studies have shown increased [35], decreased [14], or unchanged levels of IGF-I after endurance or resistance training [17]. Another study showed that resistance exercises changes concentrations of IGFBPs that influence on biological activity of IGF-1 [37]. It is interesting that if IGF-1 level is higher after marathon run, than after one day the IGFBP-1 level had returned to baseline [34]. IGF-1 stimulates the proliferation and differentiation of stem cells which are located at the periphery of muscle fibers and called satellite cells [22].

Japanese study evaluating the effect of a low-intensity exercise program on circulating levels of IGF-I, IGFBP-1, and IGFBP-3, in previously sedentary males. After aerobic training, insulin sensitivity improved by 20%, decreased the circulating levels of IGF-I by 9% ($p<0,01$) and IGFBP-1 levels increased by 16% ($p<0,05$) while IGFBP-3 levels were not changed. The study involved 14 healthy men (22.6+/-0.5 years) participated in cycle ergometer training at lactate threshold intensity for 60 min/day, 5 days/week for 6 weeks. Higher pre-training IGF-1 level was associated with greater decline in IGF-1 after training. [51].

IGF-1 and cancer development

IGF-1 is a central regulator of somatic, anabolic (growth) processes, metabolism, and cellular proliferation, differentiation and survival [60]. On the one hand, some studies indicate that IGF-1 has important role in neoplasia regulation [21, 63]. In study with mice (n=156), the low IGF1 concentration inhibits the growth of colon cancer and reduce cancer spreading [72]. On the other hand, IGF-1 was identified in very early phase of tumor development but they did not confirm that IGF-1 was reason of this cancer [40]. It suggests that IGF-1 level in the blood of people may be an early important indicator that can confirm a tumor is developing in the body. The studies that compared the levels of tumor markers and the level of IGF in serum, demonstrated the relationship between the risk of colorectal cancer and levels of IGF-I and IGFBP-3 in serum [27, 56, 63]. Increased circulating concentrations of insulin-like growth factor 1 (IGF-1) are associated with increased risks for colorectal, prostate, and premenopausal breast cancers [57, 63]. Higher concentrations of IGF binding protein 3 (IGFBP-3) are associated with increased risk of premenopausal breast cancer [57]. There is many scientific evidence indicates that apart from IGF and IGFBPs levels, a diet and sedentary lifestyle contributes to an increased risk of hormone-cancers development, including colon, prostate, breast, and endometrial cancers [67, 70]. IGF-I participates in the protective mechanism of physical activity against several sites of cancer [71]. Genes related to the IGF pathway expression is modified by overweight and a lack of physical activity that increases colorectal cancer risk [30]. Women who engage in regular physical activity have a reduced risk for both colon and breast cancers compared with inactive women. The hypothesis is that reduction of circulating free IGF-1 and increasing IGFBP-3 level decrease breast and colon cancer risk [6]. The combination of a low fat diet and physical activity reduces IGF serum concentration and increase IGFBP-1 level. It effects cancer cell growth reduction and induces apoptosis pathway in LNCaP prostate cancer cells. Cancer prevention is highly dependent on the intensity and type of training. High intensity exercise stimulate to acute increase in circulating IGF-1 concentration and it contributes to the cancer growth. Low or moderate intensity cause IGF-I level reduction [36]. Researchers have proposed several biological mechanisms to explain the relationship between physical activity and breast cancer development. Physical activity may prevent tumor development by lowering hormone levels, particularly in premenopausal women; low level of insulin and insulin-like growth factor I (IGF-1), improve the immune response and weight maintenance to avoid a high body mass index (BMI) [28].

IGF-1, physical exercises and rheumatic diseases

Several studies show that IGF-1 has a key role in the maintenance of a cartilage metabolism. IGF-1 stimulates the synthesis and decreases the degradation of proteoglycans in cartilage in laboratory tests [68]. Dynamic exercise normalize IGF-1 level among patients with rheumatoid arthritis (RA). It has a positive impact on their health by lowering indicators of disease activity and pain [44, 68]. Abnormalities in IGF-1 level are associated with dwarfism in children, muscle disorders, lipids and bone mineral density in adults (BMD). Optimal training speeds up the growth process, improves the structure of trabecular bone and bone chemical composition (increased mineral salts) [41]. In the study of the relation between serum IGF-1 and BMD, 16-wk strength training program was used in the group 61+/-1 yr and showed that strength training can increase femoral neck BMD and this affect does not appear to be accompanied by changes in anabolic hormones or markers of bone formation and resorption. There are no significant changes in GH and IGF-1 [54, 58].

In the *Snow* et al. study, they examine the levels of IGF-1 and BMD in gymnasts and runners adults. Excessive training load causes an increase in IGF-1 and IGFBP-3 level. Lean and bone mass at the hip and spine were higher in gymnasts and runners compared

to control group [64]. Optimal physical activity in the school age is a strategic action that leads to increase bone mass and prevent the osteopenia and osteoporosis development in adulthood. This physical activity must be optimal and not leads to overloading of the musculoskeletal system [41]. GH-IGF-1 system works locally at the epiphyseal plate and it is essential for normal growth. Over-activity among children brings them too fast ossification of the epiphysis which inhibits growth, reduces mobility and causes premature and osteoarthritis. Over-physical activity is associated with numerous injuries. The most prevalence of epiphyseal growth plate injuries is to children ages 10 to 16 years [24, 26]. Over-physical activity is not also beneficial for middle aged and older people. Sports with repetitive high level of impact and torsional loading cause cartilage degeneration and osteoarthritis but moderate habitual exercises inhibits osteoarthritis development [7]. The study of 174 healthy, inactive, pubertal children aged 11–15 years explained that hormonal variations and IGF1 are associated with bone mass, including anthropometric parameters such as weight, fat mass (FM), and muscle mass [73].

IGF-1 levels, physical activity and elderly people

The effects of exercise on health is more clearly among elderly people, where exercise improve learn, memory and executive function. This prevents age-related disease in brain areas, which have key role for higher cognitive processes [23]. Furthermore, IGF-1 as a similar to pro-insulin, is a potent survival factor for neurons and oligodendrocytes. IGF-1 is involved in the development and differentiation neurons in the brain. In addition, IGF-1 may effects on neurogenesis process and sirtuin 1 pathway. It can contribute to a brain injury protection [38]. IGF-1 initiates a cascade anabolic process in the brain, improve the brain plastic mechanism [20, 39], and start neuroprotectives paths [4, 20].

In elderly observed occurrence of depressed mood and depressive states. In a study of 20 people aged 60-65 years showed that the resistance training helps to increase IGF-1 levels. It negative correlated with a visual analogue scale (VAS) of mood results [9]. In rodent study exercises improved several major brain parameters especially in hippocampus. Moderate long term exercises induced and increase IGF1 level and also in energy parameters such as PGC-1 alpha and the OXPHOS [5].

IGF-1, physical activity and metabolic syndrome (MetS)

IGF level and inflammatory mediators have implicated in the pathogenesis of cardiovascular disease and glucose intolerance. Adipocytes stimulate proinflammatory cytokines production and resulting in insulin resistance. These cytokines have an inflammatory effect on hepatocytes. IGF-1 production in liver is disrupted and the level is reduced [33]. IGF-1 has anti-inflammatory effects and decreases expression of proinflammatory cytokines [66]. Type 2 diabetes mellitus (T2DM) is associated with metabolic disorders and chronic inflammation. Exercises have anti-inflammatory effects by IGF-1 level and may decrease proinflammatory cytokines inT2DM [32]. In cross-sectional study consisted of 186 Caucasian nondiabetic subjects reported inverse relationship between plasma IGF-1 and IL-6 and risk of having MetS. Higher IL-6 and lower IGF-1 levels correlate with increased risk of MetS development and related diseases: visceral obesity and insulin resistance [65]. The another cross-sectional study with random subsample (n=922) of the Cardiovascular Health Study (CHS) had a similar results [55].

IGF1 has important survival roles in myocardial cells to promote it survival. IGF-1 survival pathway in the young rat's heart can be increased through exercise training [11]. IGF-1 also influence on cardiac adaptation to strenuous exercise among athletes. Compensatory myocardial hypertrophy is mediated via increased IGF-1 expression [46]. However, moderate physical activity decrease cardiometabolic risk [25].

The role of insulin-like growth factor 1 in the Coronary artery atherosclerotic formation is not clear. On the one hand, IGF-1 has chemotactic action on macrophages, intensifying their local concentration, which underlies the process of atherosclerotic plaque formation [12]. On the other hand, the 15-year follow-up period study shows that low circulating IGF-1 levels and high IGFBP-3 levels significantly increase risk of developing atherosclerosis and ischemic heart disease [29]. Higher IGF-1 level in patients with advanced atherosclerosis according to the *Gensini* scale (231.4 [ng/mL] ± 59.3 [ng/mL]) compared to those with 0 points in the scale (181 [ng/mL] ± 37.8 [ng/mL], $p = 0.01$) was observed. High level of IGF-1 protein stabilizing atherosclerotic plaque and patients with advanced coronary atherosclerosis was spared before myocardial infarction (MI) [8]. In some prospective studies, low levels of circulating IGF-1 were associated with increased risk of ischemic heart disease (IHD), myocardial infarction (MI) [31, 69] and stroke [31]. In the large-scale cohort study (10600 subjects), the patients with higher IGF-1 level had a 55% reduction in the relative risk of developing myocardial infarction and 45% decrease for all-combined acute coronary syndromes [59]. Significant positive correlation between low-density lipoprotein cholesterol, systolic blood pressure and IGF-1 was found in the bench step exercise group [52]. Another prospective study among adult women showed that multivariable adjusted analyses (physical activity was measured by questionnaires: hs/week), IGF1 was not linearly related to the risk of MI in women [53].

CONCLUSIONS

The majority of the included studies indicate that mechanical loading is a key mechanism linking IGF-1/IGFBPs concentration and selected chronic diseases development. The duration and intensity of physical activity have a significant impact on IGF-1 and IGFBP serum. The highest concentration of IGF-1 in serum was after eccentric training. Physical activity increase IGF-1, IGFBPs levels and has a protective influence on IHD and MI development. IGF-1 is one of the leading growth factors implicated in bone remodeling and moderate strength training influence positively on increases bone density. "Overtraining" increases unfavorable and unbound IGF-1 levels and leads to hormone-cancer development and osteoarthritis. Irregularity of the GH / IGF-1 axis may affect on the development of rheumatic diseases, cardiovascular diseases (regulate cardiac growth and metabolism) and metabolic syndrome. Physical inactivity is a one of the reason of civilization diseases. Moderate, well-planned exercises benefit by increase in IGF-1, IGFBP-3 levels. Hippocrates said: "Walking is man's best medicine".

Conflict of interest

The authors declare no conflict of interest.

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