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MAJOR APPROACHES THE USE OF GH SECRETAGOGUE (MK-677) FOR MUSCLE MASS GAIN IN ELDERLY: A BRIEF SYSTEMATIC REVIEW

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ABSTRACT

Introduction: The number of disabilities due to age is expected to double by 2060. In this scenario, the development of sarcopenia is an important risk factor for the development of frailty, loss of independence and physical disability in the elderly and is associated with lower survival in critically ill patients. In this sense, the decline in fat-free mass correlates with the decline associated with the age of growth hormone (GH) secretion. Thus, GH secretagogue (MK-677) as the first orally active ghrelin mimetic may increase pulsatile GH secretion in the elderly. **Objective:** The main objectives were to determine whether oral MK-677 in healthy elderly would increase GH and IGF-I levels, prevent the decline of FFM and decrease abdominal visceral fat (AVF) with acceptable tolerability. **Methods:** A total of 18 articles were found involving MK-677, GH secretagogue, sarcopenia, insulin-like growth factor-1, safety, and efficacy. Initially, it was held the existing exclusion title and duplications following the interest described in this work. After this process, 5 articles were included and discussed in this study. The present study was elaborated according to the rules of systematic review- PRISMA (Transparent reporting of systematic reviews and meta-analysis- <http://www.prisma-statement.org/>). **Results:** In a clinical study, MK-677 neutralized three important factors contributing to the development of sarcopenia, which is reduced GH secretion, fat-free mass loss, and inadequate food intake. A recent study looked at the safety and efficacy of the oral GH secretagogue (MK-677) in humans, showing that MK-677 promotes pulsatile GH release that is subject to negative feedback and may prevent supra-therapeutic levels. of GH and its sequelae. Available studies indicate that MK-677 is well tolerated, however, there is a bias in decreased insulin sensitivity. There were no adverse effects attributable to MK-677. However, MK-677 had an unfavorable safety profile in individuals with congestive heart failure. **Conclusion:** The most confirmed sarcopenia treatment methods are nutritional overfeeding and resistance training, but studies have shown that supplementation with MK-677 can significantly reduce three important factors contributing to the development of sarcopenia, which is reduced secretion. GH loss, fat-free mass loss, and inadequate food intake, safely and effectively. However, it is imperative to increase randomized clinical trials to establish a consensus treatment.

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INTRODUCTION

In humans, muscle mass decreases after its peak in the third decade of life (Melmed, 2008). Muscle mass is important for physical and metabolic fitness regulation. The development of sarcopenia is an important risk factor for the development of frailty, loss of independence and physical disability in the elderly and is associated with shorter survival in critically ill

Patients (Brooks, 2010). In the 8th decade, men and women can lose about 7 and 3.8 kg of muscle mass, respectively, with increased intra-abdominal fat (FDA). In this context, the number of disabilities due to age is expected to double by 2060. Muscle mass is important for physical fitness and metabolic regulation (Plotkin, 1997). In this scenario, the development of sarcopenia is an important risk factor for the development of frailty, loss of independence and physical

disability in the elderly and is associated with lower survival in critically ill patients. The pathophysiology of sarcopenia is multifactorial and maybe influenced by reduced caloric intake, neurodegenerative diseases, intracellular oxidative stress, hormonal disorders, and others. In this sense, the decline in fat-free mass correlates with the decline associated with the age of growth hormone (GH) secretion. Thus, GH secretagogue (Ibutamoren - MK-677) as the first orally active ghrelin mimetic may increase pulsatile GH secretion in the elderly (Blackman, 2002). Therefore, the present study aimed to determine whether oral MK-677 in healthy elderly would increase GH and insulin-like growth factor I (IGF-I) levels, prevent the decline of muscle mass, and decrease abdominal visceral fat (AVF) with acceptable tolerability.

MATERIALS AND METHODS

Data sources and search strategy: A total of 24 articles were found involving MK-677, GH secretagogue, sarcopenia, insulin-like growth factor-1, safety, and efficacy. Initially, it was held the existing exclusion title and duplications following the interest described in this work. After this process, 14 articles were included and discussed in this study (Figure 1). PUBMED, EMBASE, OVID AND COCHRANE LIBRARY databases were searched. Initially, the descriptors were determined by searching the DeCS tool and later verified and validated by the MeSH Terms System (US National Library of Medicine). The present study was elaborated according to the rules of systematic review- PRISMA (Transparent reporting of systematic reviews and meta-analyses- <http://www.prisma-statement.org/>).

Study selection and risk of bias in each study: Two independent reviewers (1 and 2) performed research and study selection. The data extraction was performed by reviewer 1 and fully reviewed by reviewer 2. A third investigator decided some conflicting points and made the final decision to choose the articles. Only studies reported in Portuguese and English were evaluated. The Cochrane instrument was adopted to assess the quality of the included studies.

Risk of bias: Considering the Cochrane tool for risk of bias, the overall evaluation resulted in 4 studies with a high risk of bias and 2 studies with uncertain risk. Five studies had a limited number of participants. Also, the absence of the source of financing in 1 studies. Further, 2 studies did not disclose the information on the conflict of interest statement.

DEVELOPMENT AND DISCUSSION

In the stimulating scenario of GH production, the long-term safety of growth hormone (GH) treatment is an area of much debate. Healthy elderly subjects who took the MK-677 ghrelin mimetic experienced a sustained increase in the amplitude of GH and IGF-I pulsatile secretion to levels observed in young adults (Del Rincon, 2007 and Turzańska, 2019). The likely mechanism was ghrelin receptor activation by MK-677, with feedback from IGF-I. MK-677 increased the Fat-Free Mass (FFM) by 1.6 kg compared to placebo. To provide perspective, the average life loss in an adult's average lifespan is ~ 5.5 kg. A concomitant increase in intracellular water, which reflects body cell mass, is the likely mechanism for increased FFM

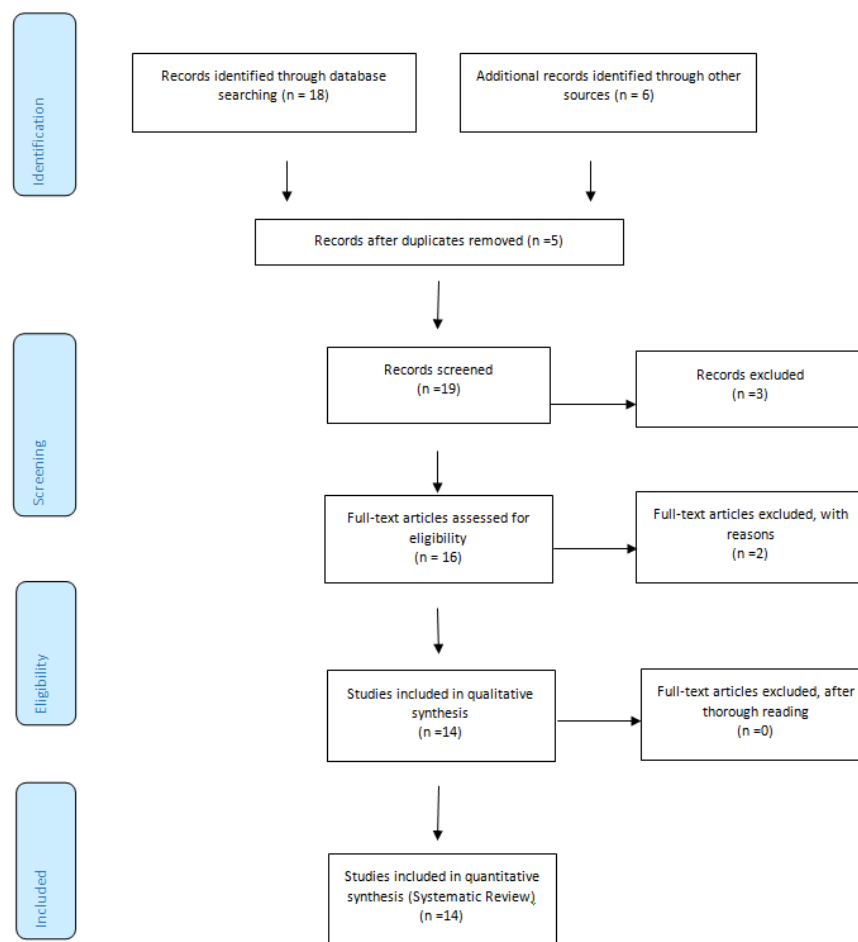


Figure 1. Flow Chart of the article selection process

(Nass, 2008). Ghrelin stimulates GH secretion but also has effects that are not attributable to GH increase. In this study, a ghrelin mimetic transiently increased appetite, a new effect that can counteract physiological anorexia, which is a cause of weight loss in the elderly, ghrelin increases fat stores, unlike lipolytic GH. Bodyweight was found to increase more after MK-677 than the placebo. Although total fat mass increased in both groups, lean fat and limb lean mass increased more with MK-677 than with placebo. Surprisingly, the cross-sectional area of the thigh muscle did not increase, although the study was not designed to detect small but potentially important differences with the inaccurate single slice CT method we use (Nass, 2009). GH reduces abdominal visceral fat (AVF) in GH-deficient and obese adults, postmenopausal women (29), but not in normal elderly. Despite increased GH levels, MK-677 did not affect AVF, perhaps because its combined orexigenic and adipogenic effects neutralized the lipolytic effects of increased GH. Finally, although MK-677 did not reduce AVF, it reduced LDL levels at 12 months, and the unobserved effect on GH in normal elderly (Nass, 2008). Although strength has improved in elderly hypopituitary patients following daily GH injections for two to three years, GH alone does not increase strength in healthy elderly. In fact, strength has improved in healthy older men who take GH alone in combination with testosterone for 26 weeks. Finally, the relationship between strength and physical strength performance is nonlinear. Increasing physical capacity has been found to substantially improve performance in fragile adults, but not in healthy adults (Sigalos, 2018). In this sense, sarcopenia is a characteristic of frailty and is associated with increased mortality in the elderly. In our study of healthy older adults, MK-677 neutralized three important factors contributing to the development of sarcopenia: reduced GH secretion, loss of FFM, and inadequate food intake. Both GH and MK-677 increase insulin resistance and blood glucose in the elderly (Campbell, 2018). Small increases in fasting glucose and HbA1c were found at 12 months. Based on the results of short-term studies with MK-677, which did not find a statistically significant increase in serum cortisol, it cannot be stated that the small increase in serum cortisol found in our study may underlie the increase in fasting glucose (Campbell, 2018).

In patients treated with GH, bone mineral density initially decreases and treatment is required for at least 18 months to demonstrate increased bone density. Femoral neck bone mineral density decreased at 12 months with MK-677, which is consistent with increased bone remodeling, as with GH. The risk of fracture would be the best measure of the effects of MK-677 on bone, but this result would require studies of a large number of individuals over many years (Turzańska, 2019). In addition, in one clinical study, MK-677 neutralized three important factors contributing to the development of sarcopenia, which is reduced GH secretion, fat-free mass loss and inadequate food intake (Sigalos, 2018). A recent study looked at the safety and efficacy of the oral GH secretagogue (MK-677) in humans, showing that MK-677 promotes pulsatile GH release that is subject to negative feedback and may prevent supra-therapeutic levels of GH and its sequelae. Available studies indicate that MK-677 is well tolerated, however, there is a bias in decreased insulin sensitivity (Campbell, 2018). In addition, a randomized double-blind crossover study evaluated the effect of MK-677 versus placebo on IGF-1 levels in 22 hemodialysis patients. The average IGF-1 was 1.07 times higher after placebo ($p > 0.001$). In patients

receiving MK-0677, the mean IGF-1 was 1.76 times higher after MK-677 ($p < 0.001$). These data demonstrate a 65% greater increase in IGF-1 in subjects treated with MK-677 compared with placebo. There were no adverse effects attributable to MK-677 (Campbell, 2018). Another randomized, double-blind study looked at 123 elderly hip fracture patients assigned to receive 25mg/day of MK-677 ($n = 62$) or placebo ($n = 61$). After 24 weeks, the average power of climbing stairs at 12.5 W in the MK-677 group increased considerably compared to placebo, as well as increased gait speed with a 0.7 point difference in averages. Also, the MK-677 group experienced fewer falls during the study compared to the placebo. Also, IGF-1 levels in treated patients increased by 51.4 ng/mL compared to placebo. However, MK-677 had an unfavorable safety profile in individuals with congestive heart failure (Adunsky, 2011). In this context, it was necessary to evaluate the effects of MK-677 on hip fracture functional recovery in previously mobile elderly individuals. Thus, it conducted a placebo-controlled, randomized, double-blind study. Thirteen medical centers in England, Sweden, Denmark, Belgium, Switzerland, Canada, and the United States. Patients were recruited between 3 and 14 days postoperatively, or at most 18 days after fracture, in acute care hospitals and rehabilitation centers. One hundred and sixty-one (161) hip fracture patients were included. Entry criteria included hip fracture patients with consent aged 65 years and older and outpatient clinically stable postoperative fractures and mentally competent (Bach, 2004). Patients were excluded if they had multiple fractures or severe trauma, diabetes mellitus, cancer, uncontrolled hypertension, congestive heart failure or total hip replacement at the involved extremity. Random assignment to 6 months of daily treatment with MK-677 or placebo. Patients were followed for a further 6 months after the end of therapy. MK-677 treatment increased serum IGF-I levels by 84% (95% confidence interval (CI) = 63-107) compared with a 17% increase (95% CI = 8-28) in placebo. There were no significant differences between MK-677 and placebo in improving functional performance measures or overall SIP-NH scores (Bach, 2004). In this study, although patients MK-677 showed greater improvement over placebo in three of the four measures of lower limb functional performance, physical domain and ability to live independently, these differences were not statistically significant. Although treatment with MK-677 increased serum IGF-I, it is not known whether clinically significant effects on physical function have been achieved. Measurement function in clinical trials in hip fracture patients is difficult due to the lack of validated outcome measures, high variability and lack of initial evaluation. Current functional performance measures may not be sufficiently responsive for use as the primary objective of small intervention studies; alternatively, GH stimulation may not result in significant functional improvement (Bach, 2004).

In this sense, growth hormone (GH) stimulates osteoblasts in vitro and increases bone turnover and stimulates osteoblast activity when administered to elderly individuals. Probably a large effect of GH on bone is mediated by stimulation of circulating or locally produced IGF-I. We determined the effect of chronic administration of GH secretagogue MK-677 on serum IGF-I and bone turnover markers in 187 elderly (65 years and over) enrolled in three randomized, double-blind, placebo-controlled clinical trials. 2-9 weeks. Urine was collected for determination of N-telopeptide (NTXs) cross-links, a bone resorption marker, and blood was collected for

determination of serum osteocalcin and bone-specific alkaline phosphatase (BSAP) as markers of bone formation and IGF. - Pre and post-treatment levels. Dose-response data were initially obtained in healthy elderly subjects who received oral doses of 10 mg or 25 mg MK-677 or placebo for 2 weeks (n = 10-12/group). Treatment with 10 mg and 25 mg MK-677 for 2 weeks increased average urinary NTXs by 10% and 17%, respectively (p <0.05 vs. placebo). In addition, 50 healthy elderly people received a placebo (n = 20) for 4 weeks or 25 mg of MK-677 (n = 30) daily for 2 weeks, followed by 50 mg daily for 2 weeks. MK-677 increased mean serum osteocalcin by 8% (p <0.05 vs. placebo) (Murphy, 1999).

Thus, in both studies, MK-677 significantly increased serum IGF-I levels (55-94%). Subsequently, the biological effects of MK-677 were studied in 105 elderly people who met objective criteria for functional impairment. Subjects were randomized to receive oral placebo doses for 9 weeks or 5, 10 or 25 mg of MK-677 daily for the initial 2 weeks, followed by 25 mg of MK-677 daily for the next 7 weeks (n = 63 in MK-677). 677 and n = 28 in placebo completed 9 weeks of therapy). Treatment with MK-677 (all combined MK-677 groups) for 9 weeks increased mean serum osteocalcin by 29.4% and BSAP by 10.4% (p <0.001 vs. placebo) and mean urinary excretion of NTX at 22.6% (p <0.05 vs. placebo). The change in basal serum osteocalcin correlated with the change in basal serum IGF-I in the MK-677 group (r = 0.37; p <0.01). In conclusion, a daily dose of MK-677, an orally active GH secretagogue, stimulates bone turnover in the elderly based on elevations in biochemical markers of bone resorption and formation (Murphy, 1999). Thus, more significant increases in IGF-1 levels were observed in the ibutamoren group compared to placebo (84% vs. 17%, respectively). In assessing functional outcomes, the ibutamoren group did not show a significant impact on quality of life, although three out of four lower extremity performance measures improved in this group. There was also a tendency towards a more independent life in the ibutamoren group in all patients, and in particular in 70% of those who were independent before hip fracture (p=0.036). A second smaller study (n=123), with a similar design assessing ibutamoren compared to placebo in hip fracture recovery, found an improvement in stair climbing power and gait speed in the ibutamoren group. However, these increases were so small that they were not considered a significant improvement. Although the above work suggests a positive impact of ibutamoren on anabolism, further studies are needed to determine whether slowing down ibutamoren catabolism affects mortality, length of hospital stay or results in functional improvements, reducing protein breakdown and increasing anabolism (Chapman, 1996). Within the limits of current literature, growth hormone secretagogues appear to be safe, with few studies cited in this review looking at serious adverse events with the use of ibutamoren. However, safety data are limited due to the short overall lengths and small sizes of most studies. Long term studies with ibutamoren are available. Adunsky et al. (Adunsky, 2011) examined the role of ibutamoren in hip fracture recovery in 123 elderly patients during 24 weeks of treatment and was the only randomized, double-blind, placebo-controlled study that was discontinued early due to concerns that ibutamoren could increase the rate of congestive heart failure (CHF). Four patients in the ibutamoren group (6.5%) and one in the placebo group (1.7%) developed CHF during the study, although the higher rate of CHF in the ibutamoren group may have been due in part to lower basal blood pressures. high in this group (Chapman,

1996). These findings contrast with a similar, randomized, double-blind, placebo-controlled study by Bach et al. (Bach, 2004) who also examined the use of ibutamoren for 6 months in 161 elderly patients recovering from hip fracture. However, more patients discontinued treatment due to a clinical adverse effect in the ibutamoren group than in the placebo group (p<0.05). Nevertheless, a randomized, double-blind, placebo-controlled study evaluating the 4-week effects of ibutamoren administration in 32 healthy elderly patients did not observe adverse effects (Chapman, 1996). There are currently few studies examining the effects of ibutamoren, although existing studies support beneficial roles for these drugs in elevating GH levels and impacting patient outcomes. There are currently few studies evaluating large cohorts for prolonged durations of ibutamoren treatments (Turzańska, 2019). Available data support increases in GH and IGF-1 levels with ibutamoren treatment, but provide little objective insight into the effects of these drugs on body composition or other important parameters. Although available studies support a beneficial effect of ibutamoren on growth velocity in children, appetite stimulation, positive effects on states of loss and in obese individuals, bone turnover, MLG, and sleep, the parameters that should be further investigated include hospital recovery, functional muscle parameters or adiposity changes in the context of an exercise program and large long-term safety data (Turzańska, 2019). In this sense, the current literature supports an increased risk of hyperglycemia in the context of ibutamoren use, with few other adverse effects directly attributable to ibutamoren use. However, larger safety studies are needed to accurately compare the safety of ibutamoren with exogenous GH. Future work should also focus on determining the effects of ibutamoren on patient outcomes under a variety of conditions, as well as on body composition in the catabolic exercise and recovery scenario. Therefore, based on the literature, current indications for the use of ibutamoren include waste treatment and as treatment for GH deficiency. An initial dose of 25 mg orally daily is recommended for ibutamoren, as this is the dose studied in randomized controlled trials. These patients should be followed with regular examinations for changes in body composition and IGF-1 levels during treatment with ibutamoren, as well as glycemia and HbA1c monitoring (Sigalos, 2018).

Conclusion

The most confirmed methods of treating sarcopenia are nutritional overfeeding and resistance training, but studies have shown that supplementation with MK-677 can significantly reduce three important factors contributing to the development of sarcopenia, which are reduced GH secretion, fat-free mass loss and inadequate food intake, safely and effectively. However, it is imperative to increase randomized clinical trials to establish a consensus treatment.

Declaration of conflicts of interest: The authors declare nothing.

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