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Sarcopenia: Pharmacology of Today and Tomorrow

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Abbreviations: ADL=activities of daily living; GH=growth hormone; KO=knock out DHEA=dehydroepiandrosterone; EPA= eicosapentaenoic acid; DHA= docosahexaenoic acid; ALA=alpha-linolenic acid; ACE=angiotensin-converting enzyme; MyoD=myoblast determination protein 1; Myf-5=myogenic factor 5; CyPD=cycliphilin D; PGC-1α= Peroxisome proliferator-activated receptor γ coactivator α; AICAR=5-amino-1-β-D-ribofuranosyl-imidazole-4-carboxamide; ROS=reactive oxygen species; AO=antisense oligonucleotides; PEMS=pulsed-electromagnetic stimulation

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ABSTRACT

Sarcopenia remains largely undiagnosed and undertreated, because of the lack of a universally accepted definition, effective ways to measure it, and identification of the outcomes that should guide treatment efficacy. An ever growing number of clinicians and researchers along with funding and regulatory agencies have gradually recognized that sarcopenia is a human condition that requires both prevention and treatment. In this “Pharmacology in Perspective” article, we briefly reviewed sarcopenia; its common and less known pharmacological treatments, and attempted to define sarcopenia in its broader context, and presented some new ideas for potential future treatment for this devastating condition.

Introduction

To a large extent the term “sarcopenia”, coined in 1988 by Dr. Irwin Rosenberg (Rosenberg, 1997), has been very valuable in bringing needed attention to a pathological condition that has as devastating consequences as osteoporosis (Cooper et al., 2012; Malafarina et al., 2012; Verschueren et al., 2012) . Despite its importance and growing clinical recognition, sarcopenia remains largely undiagnosed and undertreated, because of the lack of a universally accepted definition, effective ways to measure it, and what outcomes should guide treatment efficacy (Fielding et al., 2011; Morley et al., 2011).

Notwithstanding all these limitations, a larger number of clinicians and researchers along with funding and regulatory agencies have recognized that sarcopenia is a human condition that requires both prevention and treatment (Cruz-Jentoft et al., 2010; Chumlea et al., 2011; Morley et al., 2011; Biomarkers-Consortium-FNIH, 2012). While many questions still remain unanswered, this should not limit us from moving this field of research and clinical practice forward by recognizing sarcopenia as a clinical entity for which treatments and interventions should be designed to limit its rather serious consequences (Chumlea et al., 2011; Morley et al., 2011). Our “Pharmacology in Perspective” article does not claim to provide a comprehensive review of sarcopenia, rather we will focus on a brief working definition of this important condition and then highlight some of the most promising preventive measures and pharmacological interventions.

Sarcopenia: A working definition

A feasible, working definition of sarcopenia that we propose here, which literally means poverty of flesh, is “an aging-related condition that normally manifests during or after the 4th decade of life where the overall quality of skeletal muscle decreases, ultimately leading to muscle weakness”. It is fascinating to note that in rodents, primates, and humans muscle strength/power decrease significantly more than muscle mass itself, suggesting that it is the

overall quality of the muscle that is affected and not necessarily the size or quantity of muscle (Rosenberg, 1997; Visser and Schaap, 2011). For the individual, his family, and the clinician, perhaps the most important fact is that the sarcopenic individual is becoming weaker. In fact, grip strength, one of the best functional indicators of muscle weakness, strongly correlates with disability, morbidity, and mortality in the elderly (Ling et al., 2010; Taekema et al., 2010; Chen et al., 2012).

Why prevent and treat sarcopenia?

Skeletal muscles are the largest organ system in the body, second to only water itself (Lukaski, 1997; Close et al., 2005; Gissel, 2005). Skeletal muscles are also endocrine organs, and secrete myokines and other factors that influence distant organs and general health (Febbraio and Pedersen, 2005; Pedersen and Febbraio, 2008; Pedersen, 2011; Pedersen and Febbraio, 2012). Fat and overall body metabolism are dependent on the quality of skeletal muscle and the load that skeletal muscles exert on bones along with the biochemical signaling from muscle to bone cells and vice-versa. Weaker individuals translate into weaker societies that are predisposed to a myriad of secondary diseases or at least at a higher risk of developing these diseases. In addition, muscle weakness leads or predisposes to mobility disability re-enforcing the loss of muscle function. Significantly less mobile individuals, particularly when basic activities of daily living (ADL) are affected, become less independent and depressed. Since it seems that we have evolved to only focus on problems that have a monetary consequence, the direct cost of sarcopenia was estimated to be in the 18-30 billion dollars range in 2004. In the turn of the 20th century life expectancy in the US was ~49 years and in 2003 ~78 years. It is not an exaggeration to suggest that the real cost of sarcopenia in the US is in the hundreds of billions of dollars when accounting for both direct and indirect costs (Janssen et al., 2004).

In **Fig. 1** a model is proposed where the main influences on the development of sarcopenia during aging are highlighted and the potential outcomes on its progression when this disease is

treated or not treated. Clearly, the non-treatment of sarcopenia due to the lack of global recognition, sadly, leads to very serious consequences ranging from mobility disability to increased mortality. It is striking to observe that 24 years after its initial definition, sarcopenia remains undiagnosed, undertreated, and treatment efficacies for several of its most popular interventions have not been fully validated.

Can resistance exercise prevent or treat sarcopenia?

While the mechanisms responsible for the decline in muscle function during aging are not fully understood, there is a substantial body of knowledge related to how strength training in older adults appreciably increases strength and muscle cross-sectional area following even very short-term exercise programs. Some of these studies have become classic in the literature and were performed in the early 1990's. Frontera et al (Frontera et al., 1990) conducted a 12-week progressive resistance training program with 60 to 72 year-old men, while Fiatarone et al (Fiatarone et al., 1990) conducted a similar program but in men and women 87 to 96 years old that only lasted eight weeks. It is very interesting that in both studies the strength enhancement surpassed 170%, while muscle area increased by approximately 10%. Fiatarone conducted a second study in a larger sample of older adults (37 men and 63 women, mean age of 87 years) and was able to demonstrate a 113% increase in muscle strength and 11.8% increase in gait velocity in the exercise groups (Fiatarone et al., 1994). One cannot avoid commenting on the astronomical disconnect between muscle area and strength gains in these studies, which is what we call the corollary of all muscle aging studies in rodents and humans; the loss in strength/power is always significantly more than the loss of muscle mass in sedentary subjects, while the increase in strength/power is also more than the gain in muscle size when subjects are exercising, strongly suggesting that the key to muscle function is its quality and not necessarily its size. In fact, the myostatin knockout mouse model was a great disappointment (Gissel, 2005), since the extremely larger muscles in those animals were not stronger as muscle physiologists had hoped for, certainly teaching us a lesson that more subtle, intrinsic

mechanisms within muscles themselves, such as calcium homeostasis disruption, might be the culprit of these potent adaptations during aging (Gissel, 2005; Weisleder et al., 2006; Zhao et al., 2008; Romero-Suarez et al., 2010; Brotto, 2011; Thornton et al., 2011).

Malafarina (Malafarina et al., 2012) has recently reviewed resistance exercise as an intervention and confirmed earlier studies through his extensive review of the literature that resistance exercise does improve muscle mass and strength, but alerts for three very important limitations: a) resistance exercise cannot be discontinued, otherwise the benefits are quickly lost; b) there are some intrinsic difficulties in exercising regularly, particularly for older individuals, and in special for those that lack social support; c) resistance exercise might not be sufficient to all subjects to reverse loss of muscle function, particularly in the elderly frail individuals (Liu and Latham, 2009). Therefore, it is critical to develop pharmacological interventions that can be more effective than exercise, while being safer and broader in its spectrum of utilization. The next section reviews some of the most current interventions used for the treatment of sarcopenia.

How is sarcopenia being treated pharmacologically?

Active research on the use of pharmacological interventions against sarcopenia has grown significantly in the last decade, leading so far to more questions than answers with some controversial results. The most studied drugs have been:

a) Testosterone: Testosterone (figure 2A) has proven effects to increase muscle mass and muscle function, but along with these beneficial effects there are also problematic side effects. Reported side effects for testosterone are very diverse, some are quite mild: acne; bitter or strange taste in mouth; change in sex drive; fatigue; gum or mouth irritation; gum pain; gum tenderness or swelling; hair loss; headache. However, severe side effects can occur such as: severe allergic reactions; change in the size or shape of the testicles; dark urine or light-colored bowel movements; depression or mood changes; dizziness; gingivitis; sleep apnea; loss of

appetite; nausea; painful or prolonged erection; stomach pain; swelling of the ankles or legs; urination problems; and weight gain.

b) Growth hormone (GH): Growth hormone is obviously highly effective in promoting bone and muscle growth and it has been approved by the FDA for a number of applications, which in practical terms means that the drug has acceptable safety in light of its benefits when used in the approved way. A common application of GH replacement therapy in adults is GH deficiency of either childhood-onset or adult-onset (usually as a result of an acquired pituitary tumor). GH can also be used to treat conditions that produce short stature but are not related to deficiencies in GH. Interestingly, outcomes are not as dramatic when compared to short stature that is exclusively attributable to deficiency of GH. It is as well very interesting that the FDA has approved the use of GH for muscle wasting associated with chronic HIV infection (Gilden, 1995). Perhaps this application for a specific type of muscle wasting could be seen as a strong sign that GH could be useful in frail elderly subjects, but likely the major limitation of GH in clinical practice for the treatment of sarcopenia is the fact that the efficacy and safety of this use for GH has not been tested in a double-blind clinical trial. Obviously a complex hormone that acts in the entire body in a myriad of systems will have important side effects (e.g., injection-site reaction joint swelling, joint pain, carpal tunnel syndrome, increased risk of diabetes (Liu et al., 2007). While rare, patients can sometimes produce an immune response against GH, and GH may also be a risk factor for Hodgkin's lymphoma) (Freedman et al., 2005). Certainly the complex biology of GH, the lack of clinical trials, and its side effects have limited its utilization for the treatment of sarcopenia.

c) Dehydroepiandrosterone (DHEA): Supplementation with DHEA (figure 2B) was reviewed in details by Malafarina and colleagues (Malafarina et al., 2012). DHEA is an essential in the biosynthesis of androgen and estrogen sex steroids by functioning as a metabolic intermediate in pathway for the generation of these hormones, but more recent evidence also suggests that DHEA has its own biological activities independent of its functions related to sexual hormones

(Mo et al., 2006). It is likely because of these other cell biological functions that the use of DHEA became popular for example as a co-adjuvant to increase muscle strength. It is interesting that while DHEA is legal to sell in the United States as a dietary supplement, and it is specifically exempted from the Anabolic Steroid Control Act of 1990 and 2004 (http://www.deadiversion.usdoj.gov/fed_regs/rules/2005/fr1216.htm), it is banned by the World Anti-Doping Code of the World Anti-Doping Agency, which manages drug testing for Olympics and other sports (http://www.wada-ama.org/en/Resources/Q-and-A/2012-Prohibited-List/), making this supplement even more fascinating. If as recently reviewed, DHEA mostly lacks any known positive effects on muscle performance, why is it banned from sports competitions? Is it possible that the lack of effects findings is related to the different formulations and different levels of purity available on commercially available supplements? We do know that regular exercise elevates DHEA production in the body (Filaire et al., 1998; Copeland et al., 2002), but in one randomized controlled clinical trial DHEA failed to show improvements in muscle lean mass and muscle strength in middle age men. Perhaps the best we can say for now is that the evidence is inconclusive in regards to the effect of DHEA on strength in the elderly (Baker et al., 2011), and as beautifully summarized in paper by Tokish and colleagues: "The marketing of this supplement's effectiveness far exceeds its science" (Tokish et al., 2004). In conclusion, DHEA is a supplement that might deserve a new look in clinical trials designed to combine resistance exercise plus DHEA, and even resistance exercise plus DHEA plus protein intake supplementation.

d) Vitamin D: It is now very well established that low levels of blood vitamin D levels are associated with decreased muscle strength and statin-induced myopathy, but vitamin D supplementation results are still under investigation. Given the beneficial results of calcium + vitamin D supplementation on bone function (Recker et al., 2006), it is expected that correcting vitamin D levels will also be beneficial for muscle function. Furthermore, results might also be dependent on the form of Vitamin D used and whether vitamin D intake is combined or not with

calcium. We believe that it will be important to follow individuals longitudinally and test their muscle function as a function of age and levels of calcium plus vitamin D. In addition, vitamin D supplementation might be beneficial for overall health, since Lappe and colleagues have recently reported a 63% reduction in all types of cancers in subjects receiving vitamin D3 (figure 2C) supplementation (Lappe et al., 2007).

e) Myostatin: Myostatin is the most potent negative regulator of muscle growth, and its inhibition is required for muscle growth and development. Resistance exercise for example inhibits myostatin thereby releasing muscle from "the myostatin grip", hence allowing the dominance of muscle regulatory factors leading to muscle growth. Animal studies have revealed that myostatin effects are very complex. The mouse model of myostatin knockout (KO) created significant excitement since skeletal muscles were at least 3 times larger in volume as compared to control muscles, but these significantly larger muscles were not stronger (Gentry et al., 2011). Is oxygen and nutrient supply, particularly to the core of very large muscles deficient? Are these animals naturally more inactive due to their higher body weights? Researchers from the University of Missouri have published tantalizing data demonstrating that positive effects of myostatin KO might be dose dependent, since they found that the heterozygous mice (i.e., one gene was still active), had improved muscle performance (Gentry et al., 2011). In humans thus far, myostatin has shown only therapeutic potential, but as the cell biology of myostatin effects are better understood this scenario could easily change.

f) Ursolic acid: A very interesting acid present in apples, bilberries, cranberries, prunes, and also in several medicinal plants such as peppermint, rosemary, lavender, oregano, and thyme. It is very interesting that this acid has very potent anti-tumorigenic effects and is found in very large amounts in the apple peels (Shishodia et al., 2003; Pathak et al., 2007). Ursolic acid (figure 2D) has also been found to be effective in treating mice with atrophy (Kunkel et al., 2011). In this report, Kunkel and colleagues used a very clever combination of mice and human models of muscle research to show the beneficial effects of ursolic acid not only in muscle mass

maintenance, but also on fat metabolism. In addition, there have been suggestions that humans that ingest animal protein sources along with apples may get additional benefits for muscle growth (Kunkel et al., 2011). Since apple consumption has also been found to extend life span by 10% in drosophila, the old saying that “an apple a day may keep the doctor away” seems to have very deep scientific roots (Peng et al., 2011).

g) Omega-3 acids: The three main forms of omega-3 acids are: alpha-linolenic acid (ALA, figure 2G), docosahexaenoic acid (DHA, figure 2H), and eicosapentaenoic acid (EPA, figure 2I). While EPA and DHA are considered long-chain forms of omega-3 found in fish, some types of algae extracts, and fish oil supplements, ALA, the short-chain form, is found in plant sources like flax seed, walnuts, canola, and soybean oil. Omega-3 acids are generally recognized as anti-inflammatory agents (Calder, 2003), having been shown to prevent the damaging effects of TNF-α on muscle differentiation *in vitro* (Magee et al., 2008) Thus, it is possible to postulate that these acids could have unspecific beneficial effects linked to reduction of inflammation states that might characterize at least part of the aging process and the aging muscle. Yet another possibility is that these agents prevent the overall imbalance towards catabolism that develops during aging.

h) Angiotensin-converting enzyme (ACE) inhibitors: A beneficial role in skeletal muscles (Onder et al., 2002; Onder et al., 2006), including the prevention of sarcopenia (Sumukadas et al., 2006; Carter and Groban, 2008) has been suggested. It is interesting to note that benefits are more related to increased ability to exercise (Onder et al., 2006). Are such effects related to improvement of cardiac function, or do ACE inhibitors (e.g., enalapril, figure 2E) have direct effects on skeletal muscles? Here, it will be very interesting to consider the important work of Andrew Marks and colleagues. They have demonstrated that cardiac diseases lead to calcium leak mechanisms in skeletal muscles, suggesting important biochemical crosstalk between heart and skeletal muscle (Andersson and Marks, 2010). Our groups have also recently found potential crosstalk mechanisms between heart and skeletal muscle as well as bone-muscle,

muscle-bone, tendon-muscle. As we better understand the biological meaning of tissue crosstalk, new therapies for a host of diseases might be developed.

i) Proteasome inhibitors: Bortezomib a common proteasome inhibitor has been found to upregulate MyoD and Myf-5. Interestingly, the effects on muscle degeneration are dependent on muscle-fiber type (Beehler et al., 2006). In this report, the authors stated that "strangely, there is no rodent study examining the effect of these proteasome inhibitors to prevent muscle atrophy with aging", but the final conclusion is that proteasome inhibitors may not attenuate sarcopenia (for review see (Husom et al., 2004; Attaix et al., 2005; Bossola et al., 2008; Combaret et al., 2009).

j) Cyclophilin D (CyPD) inhibitor: Debio-025 (figure 2J) is a mitochondrial matrix isomerase that directly regulates mitochondrial calcium metabolism by inhibiting CyPD and consequently blocking mitochondrial calcium channels that have been implicated in deregulated calcium metabolism and muscle fiber death. This agent has been researched as a potential treatment of Duchene muscular dystrophy in the *mdx* mouse model, having demonstrated increased muscle function and shown to be as effective, or slightly more effective, than prednisone with the advantage of being non-immunosupressant (Wissing et al., 2010). Can it counteract sarcopenia symptoms? Specific clinical trials to answer this question are still lacking.

l) Peroxisome proliferator-activated receptor γ coactivator α (PGC-1α): There has been renewed interest in the PGC1-α pathway in skeletal muscle since the discovery of resveratrol, and also more recently the utilization of AICAR (figure 2K) and its mimetic equivalents (Lagouge et al., 2006; Tadaishi et al., 2011). These small compounds have the ability to stimulate the activity of the master regulator of mitochondrial biogenesis PGC-1α, leading to overall adaptations that mimic exercise training without exercise, enhanced utilization of glucose by muscle cells, and resistance in animal models to the development of obesity (Brault et al., 2010; Momken et al., 2011). More recently some of the first reports on benefic effects of resveratrol in humans have appeared (Timmers et al., 2011), but a double-blind controlled trial of resveratrol,

or AICAR, or similar agents is still missing for the potential treatment of sarcopenia. Both endurance training and resistance exercise have shown promising effects to offset at least part of the effects of the decline in muscle function with aging. Since mitochondrial dysregulation and ROS-mediated damage are thought to contribute to sarcopenia, it is seems plausible that mitochondrial protection or enhancement of mitochondrial replacement through biogenesis may confer protection against mitochondrial related muscle damage during aging.

m) Protein supplementation: Sakuma and Yamaguchi provided an interesting review of sarcopenia and the relative importance of what we call “bad trade of aging” whereas muscle is replaced by fat (Sakuma and Yamaguchi, 2012). Sakuma and Yamaguchi pointed to the fact that resistance training combined with essential amino acids has shown good results, and reviewed some of the supplements currently used to prevent muscle atrophy, which have been highlighted and expanded in this Pharmacology in Perspective article.

New Perspectives and a good “dose” of postulation:

The last 10 years have witnessed significant progress in antisense therapy for Duchenne muscular dystrophy (For a Review see (Nelson et al., 2009)). Early studies demonstrated the feasibility of antisense oligonucleotides (AO) to remove a targeted dystrophin exon in mouse and human cells (Cole-Strauss et al., 1996; Cole-Strauss et al., 1997; Cole-Strauss et al., 1999; Albuquerque-Silva et al., 2001; Kren et al., 2002; Hu and Gatti, 2008; Nelson et al., 2009). On-going clinical trials for Duchenne muscular dystrophy are currently testing antisense-mediated exon skipping and forced read-through of premature stop codons (www.clinicaltrials.gov). Interestingly, these approaches target the gene product rather than the gene itself. Thus, chimeric RNA/DNA oligonucleotides (chimeraplasts) may provide an alternative approach to treat muscle diseases caused by specific mutations, and this knowledge could be useful for the treatment of sarcopenia. Furthermore, in large screening studies it has been recently suggested that potential therapeutic approaches to target missense mutations are the use of tunicamycin, catanospermine, glycosylation inhibitors, or glycosidases (Hu and Gatti, 2008). With these

advances in different diseases and the sophistication of very large scale small compounds screening, there is significant hope that one or more of these agents will be effective to at least partially treat sarcopenia.

Equally promising will be the utilization of muscle stem cells to enhance the regenerative capacity of “old muscle”. The new emerging field of bone-muscle crosstalk also promises to shed light into the twin diseases of aging, osteoporosis and sarcopenia. This new concept that bone and muscle cells can communicate biochemically and not only through physical forces is certainly paradigm shifting and as bone and muscle factors continue to be identified, one would expect that new therapeutical agents will be developed for sarcopenia (Brotto et al., 2010; Lang, 2011; Jähn et al., In Press). Our labs have been experimenting with both heat shock therapy and a new device we developed to generate both electrical stimulation and pulsed-electromagnetic stimulation (PEMS). In vitro studies in our labs are very intriguing with these treatments being able to enhance myogenic differentiation and to produce larger muscle cells.

In conclusion, advances in our understanding of muscle biology (over the past decade) have led to potential new therapeutic approaches. When possible, these treatments should be combined with exercise and dietary supplements. Supplementation studies in rodents are urgently needed, and careful studies designed to understand the disconnect between muscle mass and muscle strength might hold the ultimate key for us to fully understand the biology, how to treat, and hopefully one day how to prevent sarcopenia, so that we might age graciously and strong, free from the devastating effects of muscle weakness. At last we will be able to say: “Live longer and stronger”!

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Brotto and Abreu

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FOOTNOTES

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LEGENDS FOR FIGURES

Fig. 1. Schematic drawing of a proposed model illustrating the known influences on the development of sarcopenia and the consequences of treating and not treating this human disease.

Fig. 2. Chemical structures of key drugs, compounds, and supplements discussed in this Pharmacology in Perspective are shown in details above (A- Testosterone; B- DHEA; C- Vitamin D3; D- Ursolic Acid; E- Enalapril; F- Bortezomib; G- ALA; H- DHA; I- EPA; J- Debio-025; K- AICAR).

Fig. 3. Schematic drawing illustrating some of the essential molecular pathways that can lead to anabolism or catabolism in skeletal muscles. Effective modulation of these pathways by existing and in-development agents could favor the balance towards anabolism and hypertrophy. It is important to observed that mechanisms that are not currently addressed by any of the compounds but seem to be affected by resistance exercise training are those that enhance muscle strength without necessarily increasing muscle mass.

Figure 1

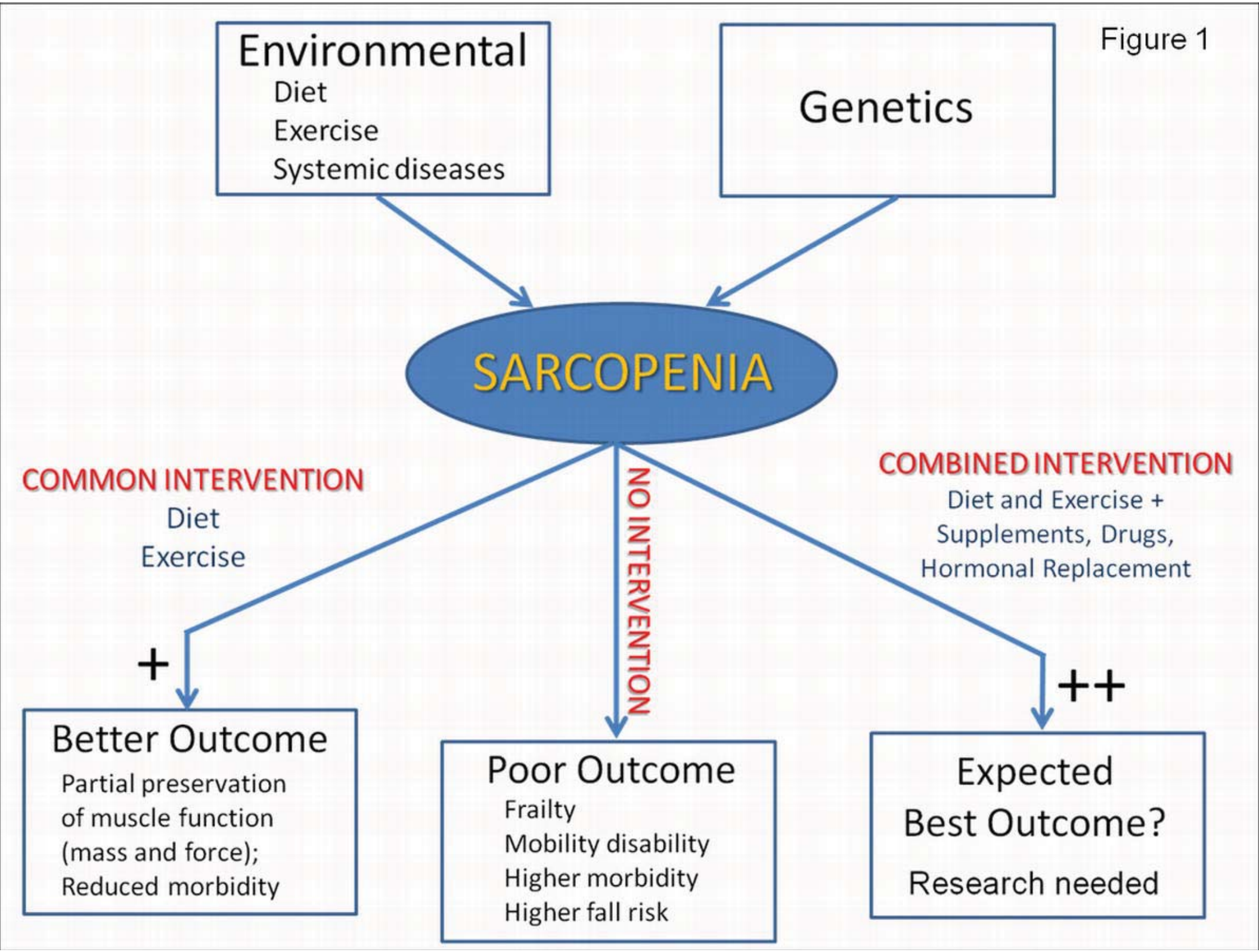

Environmental
Diet
Exercise
Systemic diseases
Genetics
SARCOPENIA
COMMON INTERVENTION
Diet
Exercise
NO INTERVENTION
COMBINED INTERVENTION
Diet and Exercise +
Supplements, Drugs,
Hormonal Replacement
+
++
Better Outcome
Partial preservation
of muscle function
(mass and force);
Reduced morbidity
Poor Outcome
Frailty
Mobility disability
Higher morbidity
Higher fall risk
Expected
Best Outcome?
Research needed

Figure 2

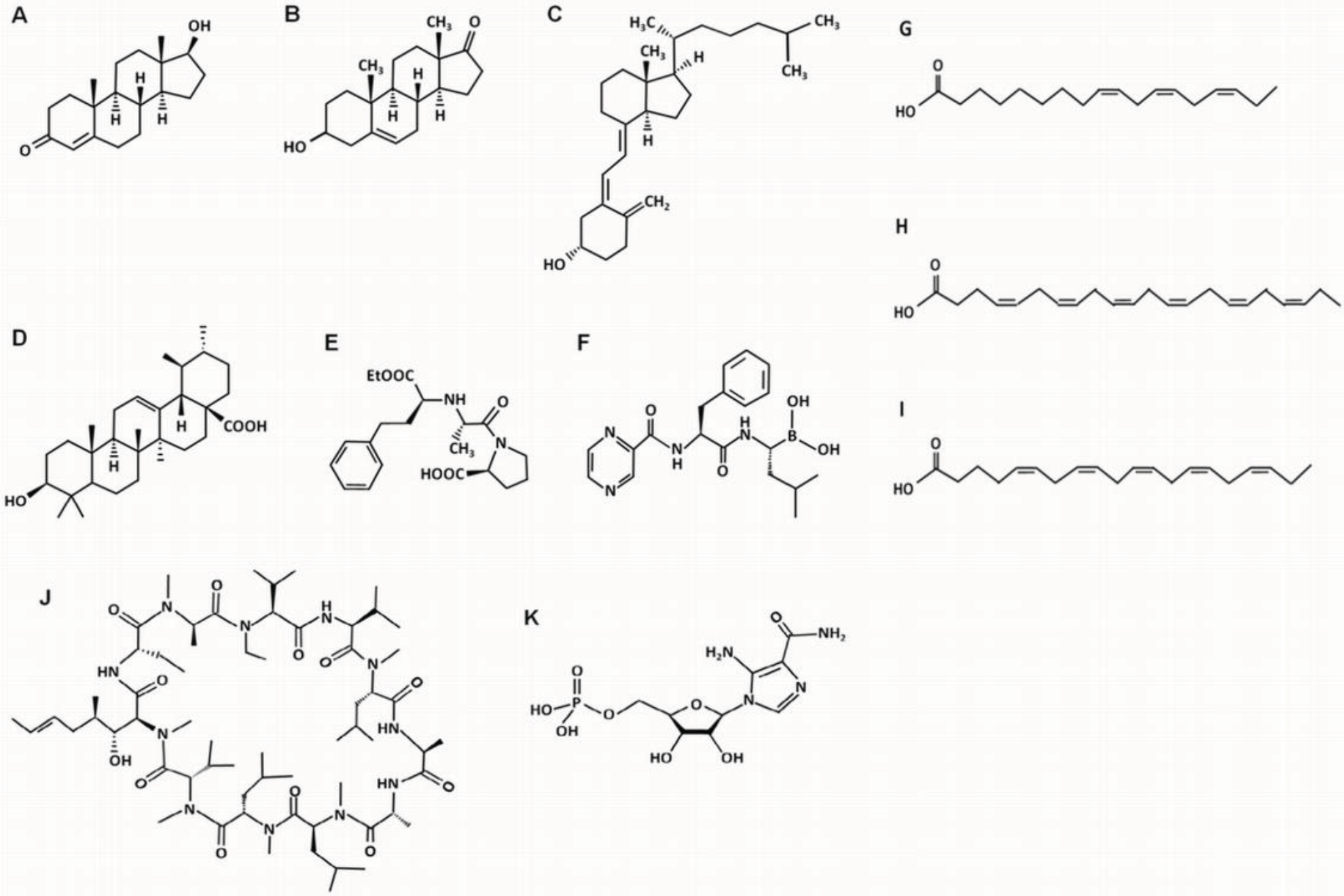
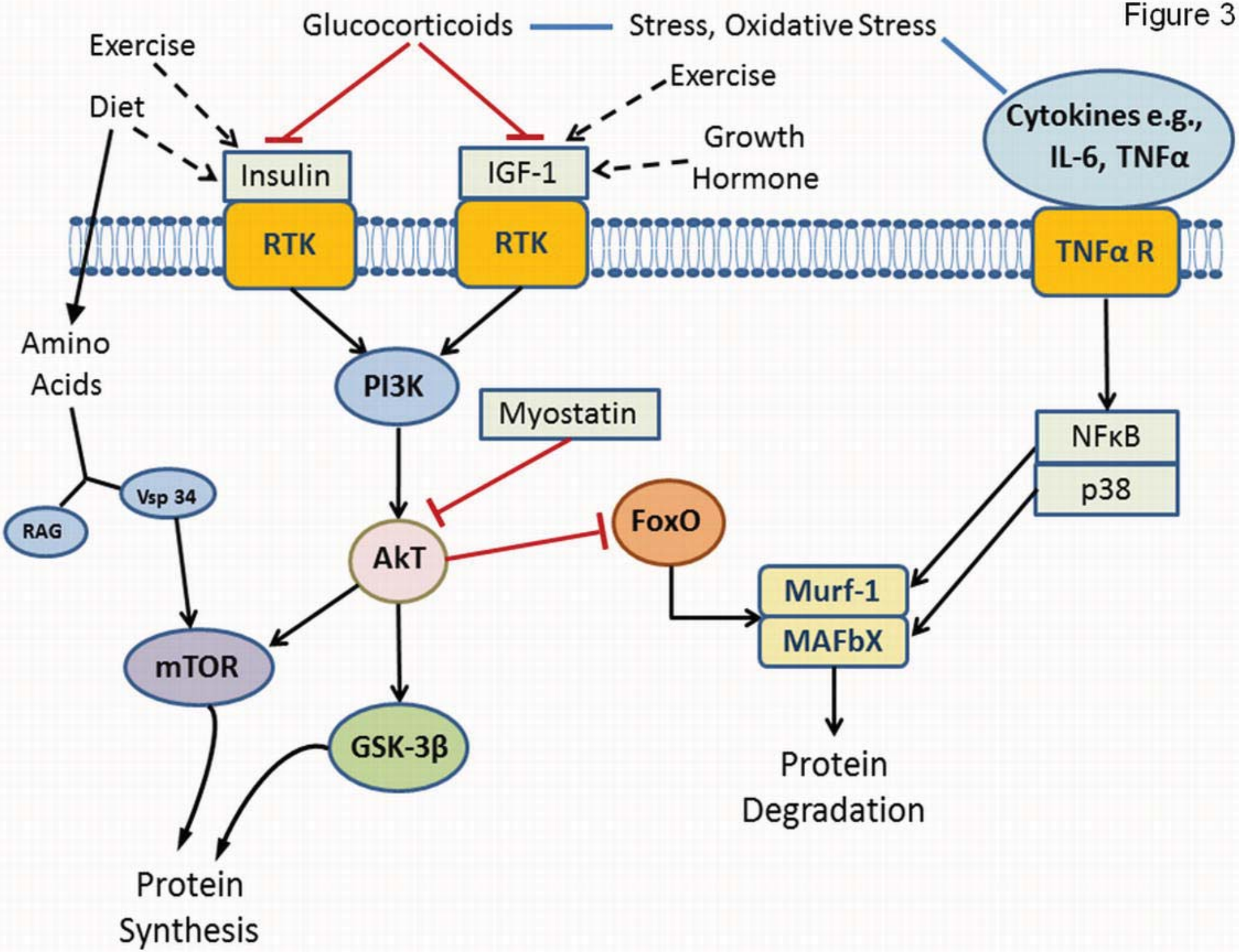


Figure 3


Glucocorticoids
Stress, Oxidative Stress
Exercise
Diet
Exercise
Growth Hormone
Cytokines e.g., IL-6, TNFα
Insulin
IGF-1
RTK
RTK
TNFα R
Amino Acids
PI3K
Myostatin
NFκB
p38
Vsp 34
RAG
AkT
FoxO
Murf-1
MAFbX
mTOR
GSK-3β
Protein Synthesis
Protein Degradation